CLL/SLL Treatment Highlights from ASH 2022

Roger A. Fleischman, MD, PhD

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Lexington, KY

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Zanubrutinib: Differentiating Features and Background

- Zanubrutinib is a second-generation Bruton tyrosine kinase inhibitor (BTKi)
  - Zanubrutinib was designed to have greater BTK specificity than ibrutinib
  - Zanubrutinib has exposure coverage above its IC_{50}
  - Higher drug-concentration/IC_{50} ratios would be expected to lead to more sustained and complete BTK inhibition to improve efficacy
- Zanubrutinib has demonstrated superior PFS by IRC over chemoimmunotherapy in treatment-naive CLL/SLL patients without del(17p)[1]

[1]Tam CS, Brown JB, Kahl BS, et al. *Lancet Oncol*. 2022. https://doi.org/10.1016/S1470-2045(22)00293-5

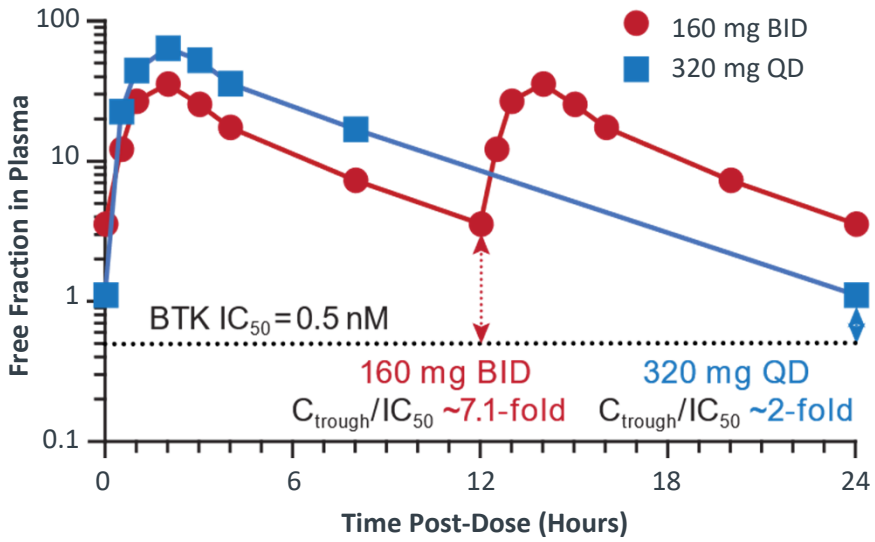

Figure modified from Ou YC, Tang Z, Novotny W, et al *Leukemia & Lymphoma.* 2021; 62(11):2612-2624.

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ALPINE Study Design

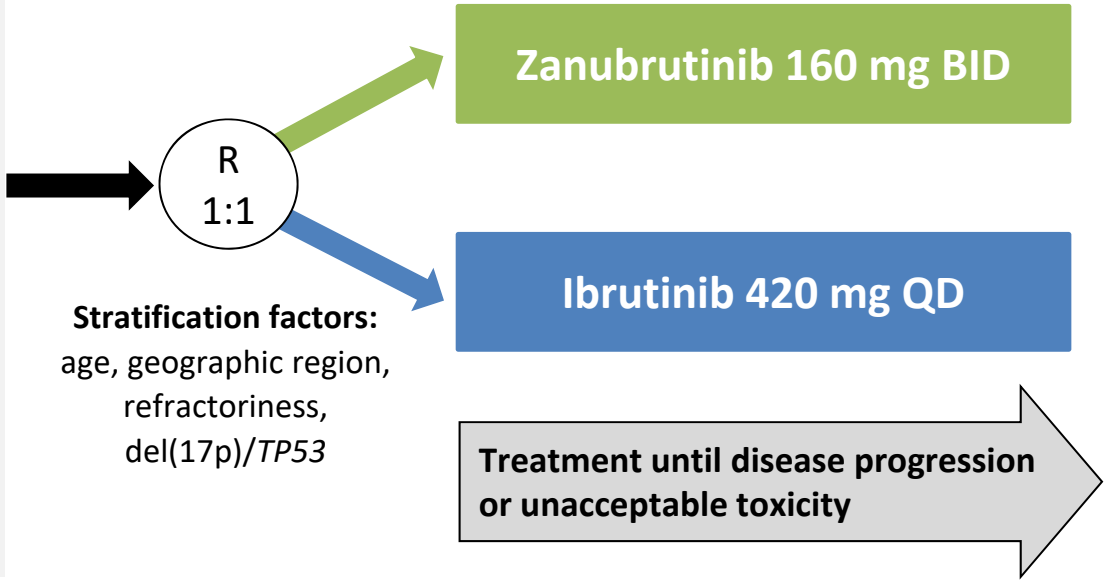
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

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



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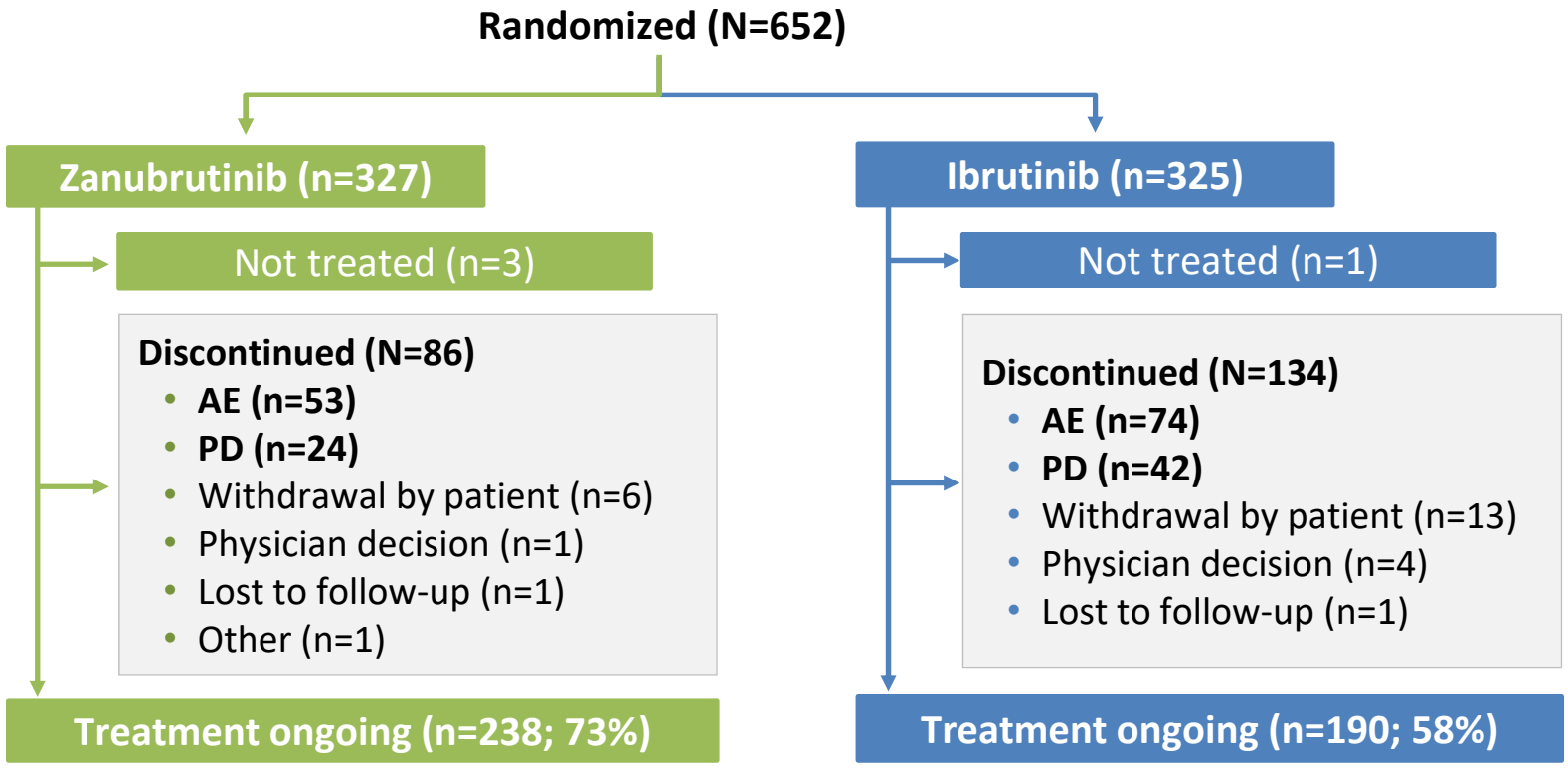
Patient Disposition



AE, adverse event; PD, progressive disease.

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Balanced Demographics and Disease Characteristics

	Zanubrutinib (n=327)	Ibrutinib (n=325)
Age, median (range) ≥65 years, n (%)	**67 (35-90)** 201 (61.5)	**68 (35-89)** 200 (61.5)
Male, n (%)	**213 (65.1)**	**232 (71.4)**
ECOG PS ≥1, n (%)	**198 (60.6)**	**203 (62.5)**
Prior lines of systemic therapy, median (range) >3 prior lines, n (%)	**1 (1-6)** 24 (7.3)	**1 (1-12)** 30 (9.2)
del(17p) and/or *TP53*^{mut}, n (%) del(17p) *TP53*^{mut} without del(17p)	**75 (22.9)** 45 (13.8) 30 (9.2)	**75 (23.1)** 50 (15.4) 25 (7.7)
del(11q), n (%)	**91 (27.8)**	**88 (27.1)**
IGHV mutational status, n (%) Mutated **Unmutated**	 79 (24.2) **239 (73.1)**	 70 (21.5) **239 (73.5)**
Complex karyotype*	**56 (17.1)**	**70 (21.5)**
Bulky disease (≥5 cm), n (%)	**145 (44.3)**	**149 (45.8)**

*Complex karyotype is defined as having ≥3 abnormalities.

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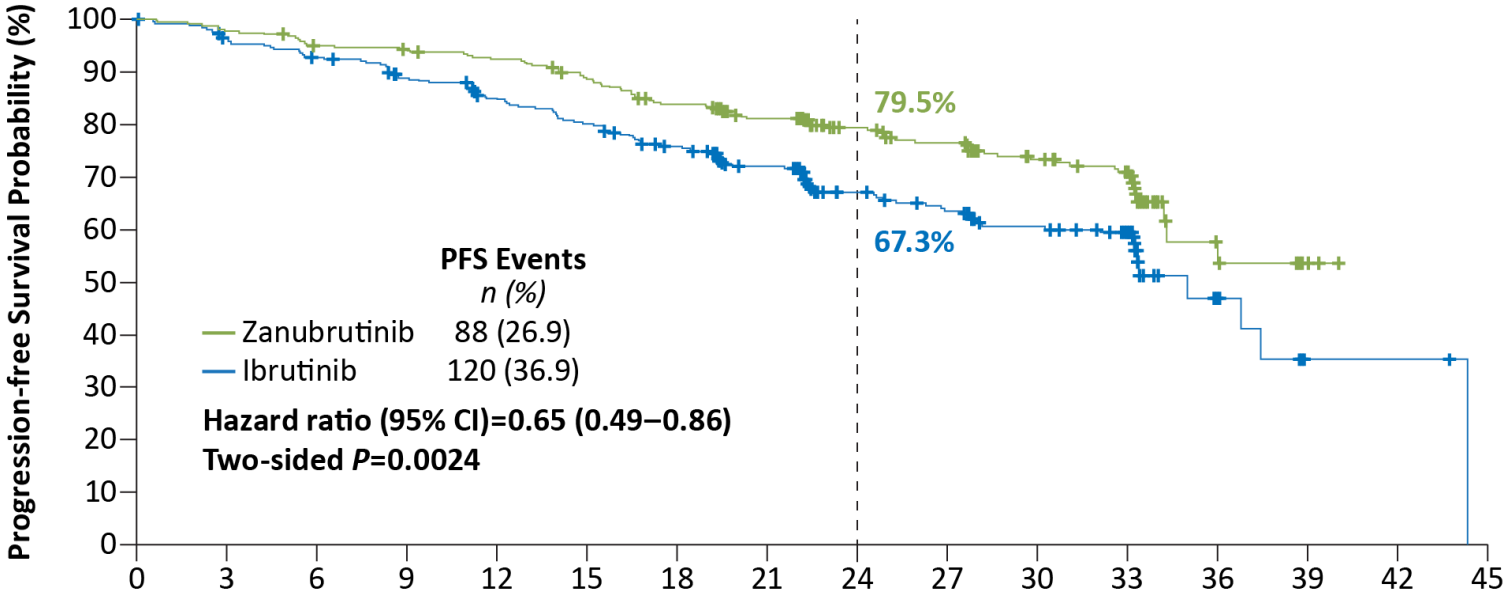
Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months



No. at Risk																
Zanubrutinib	327	315	304	301	294	280	263	226	172	161	125	113	14	2	0	
Ibrutinib	325	305	293	277	260	246	228	191	133	123	98	87	9	2	2	0

Data cutoff: 8 Aug 2022

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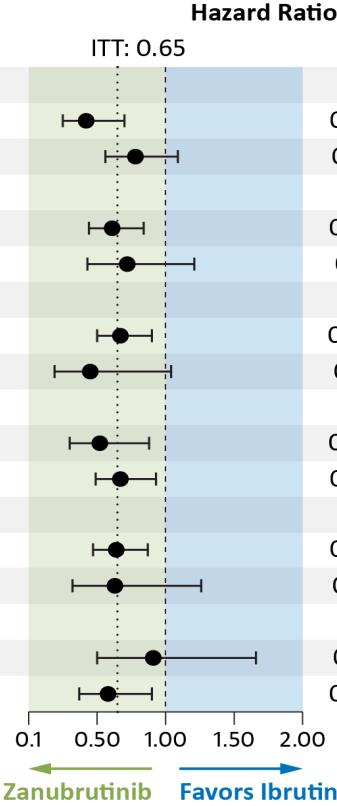
PFS Favored Zanubrutinib Across Subgroups

Subgroup	Zanubrutinib Response/Patients	Ibrutinib Response/Patients	Hazard Ratio (95% CI)[a]
Age group			
<65 years	23/126	43/125	0 42 (0.25, 0.70)
≥65 years	65/201	77/200	0.78 (0.56, 1.09)
Sex			
Male	59/213	91/232	0.61 (0.44, 0.84)
Female	29/114	29/93	0.72 (0.43, 1.21)
Prior lines of therapy			
1–3	80/303	102/295	0.67 (0.50, 0.90)
>3	8/24	18/30	0.45 (0.19, 1.04)
Baseline *del*(17p)/*TP53* mutation status			
Present	23/75	34/75	0.52 (0.30, 0.88)
Absent	65/251	86/250	0.67 (0.49, 0.93)
Baseline IGHV mutation status			
Unmutated	72/239	98/239	0.64 (0.47, 0.87)
Mutated	15/79	18/70	0.63 (0.32, 1.26)
Complex karyotype			
Yes	20/56	24/70	0.91 (0.50, 1.66)
No	37/153	45/130	0.58 (0.37, 0.90)



[a]Hazard ratio and 95% CI were unstratified for subgroups.

Data cutoff: 8 Aug 2022

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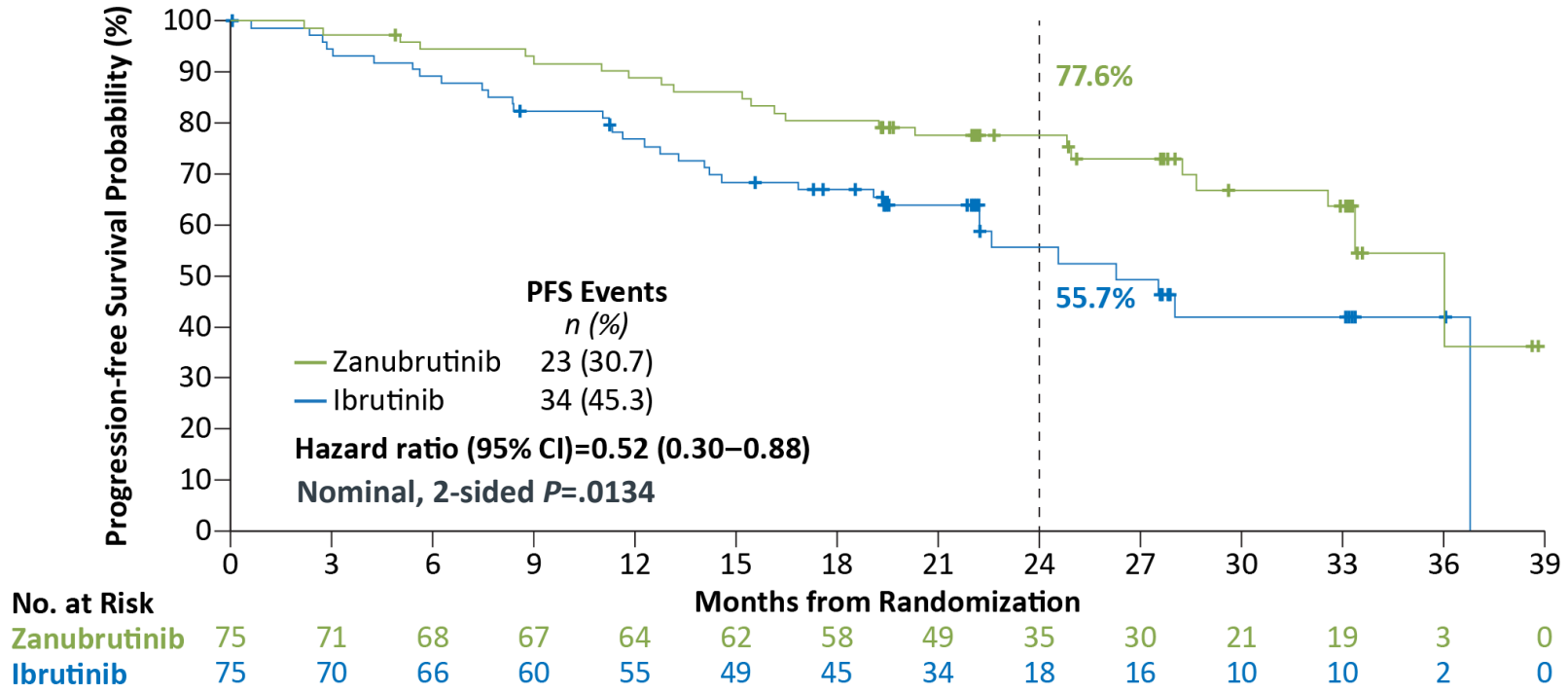
Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*^{mut}



PFS data assessed by IRC

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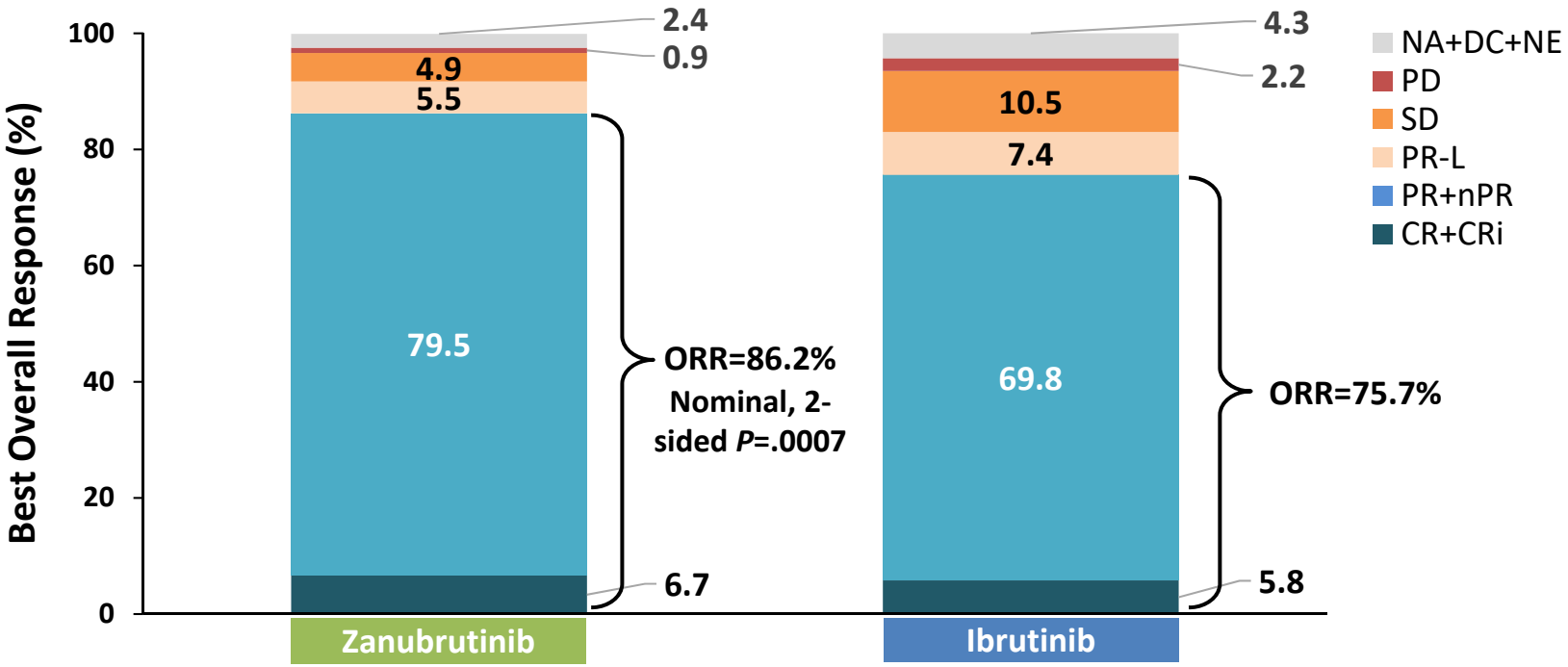
Zanubrutinib Showed Higher ORR Assessed by IRC



CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable response; PD, progressive disease; NA, not assessed; DC, discontinued prior to first assessment; NE, not evaluable.

Data cutoff: 8 Aug 2022

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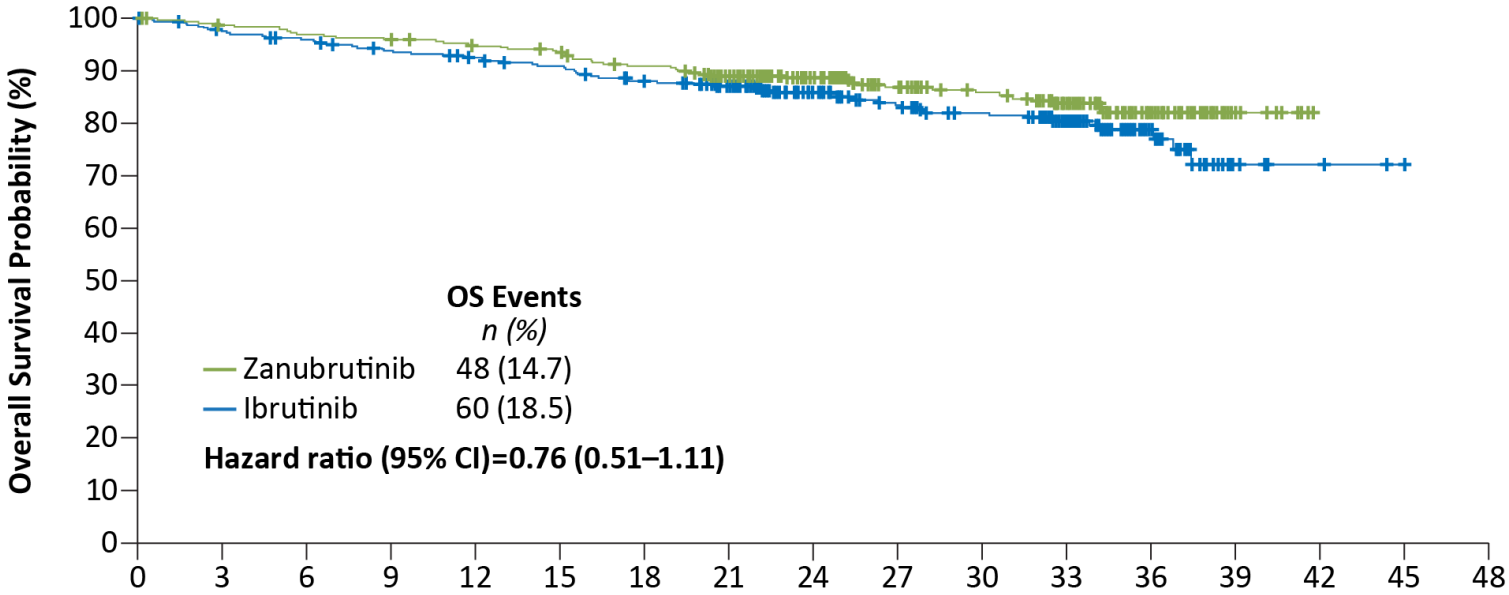
Overall Survival

Fewer deaths with zanubrutinib compared with ibrutinib



No. at Risk																	
Zanubrutinib	327	319	313	310	303	298	287	268	224	185	169	134	56	8	0		
Ibrutinib	325	314	307	297	290	283	271	255	200	171	156	124	50	7	3	1	0

Data cutoff: 8 Aug 2022

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Overall Safety/Tolerability Summary

Zanubrutinib safety profile was favorable to ibrutinib

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**28.4**	**24.3**
Any grade adverse event	**318 (98.1)**	**321 (99.1)**
Grade 3 to 5	218 (67.3)	228 (70.4)
Grade 5	33 (10.2)	36 (11.1)
Serious adverse event	**136 (42.0)**	**162 (50.0)**
Adverse events leading to		
Dose reduction	**40 (12.3)**	**55 (17.0)**
Dose interruption	**162 (50.0)**	**184 (56.8)**
Treatment discontinuation	**50 (15.4)**	**72 (22.2)**

Data cutoff: 8 Aug 2022

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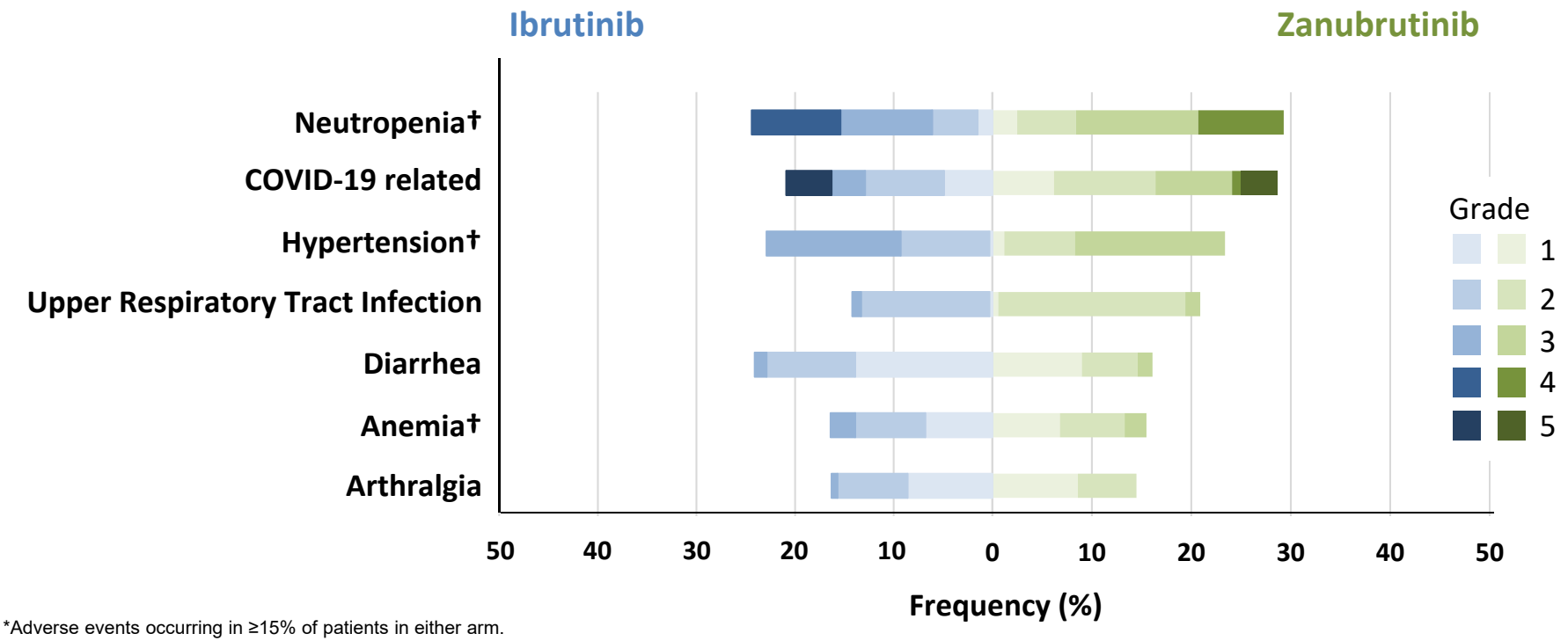
Most Common Adverse Events*



*Adverse events occurring in ≥15% of patients in either arm.
†Pooled terms.

Data cutoff: 8 Aug 2022

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Zanubrutinib Had A Favorable Cardiac Profile

Lower rate of cardiac events, serious cardiac events, treatment discontinuation, and deaths

- Lower rate of serious cardiac adverse events reported with zanubrutinib
  - A fib/flutter (n=2)
  - MI/ACS (n=2)
  - CHF (n=2)
- **Fatal cardiac events:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**69 (21.3%)**	**96 (29.6%)**
Serious cardiac adverse events	**6 (1.9%)**	**25 (7.7%)**
Cardiac adverse events leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)*
Cardiac failure	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)*
Congestive cardiomyopathy	0	1 (0.3)*
Myocardial infarction	0	1 (0.3)*
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

Data cutoff: 8 Aug 2022

*Cardiac deaths. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.

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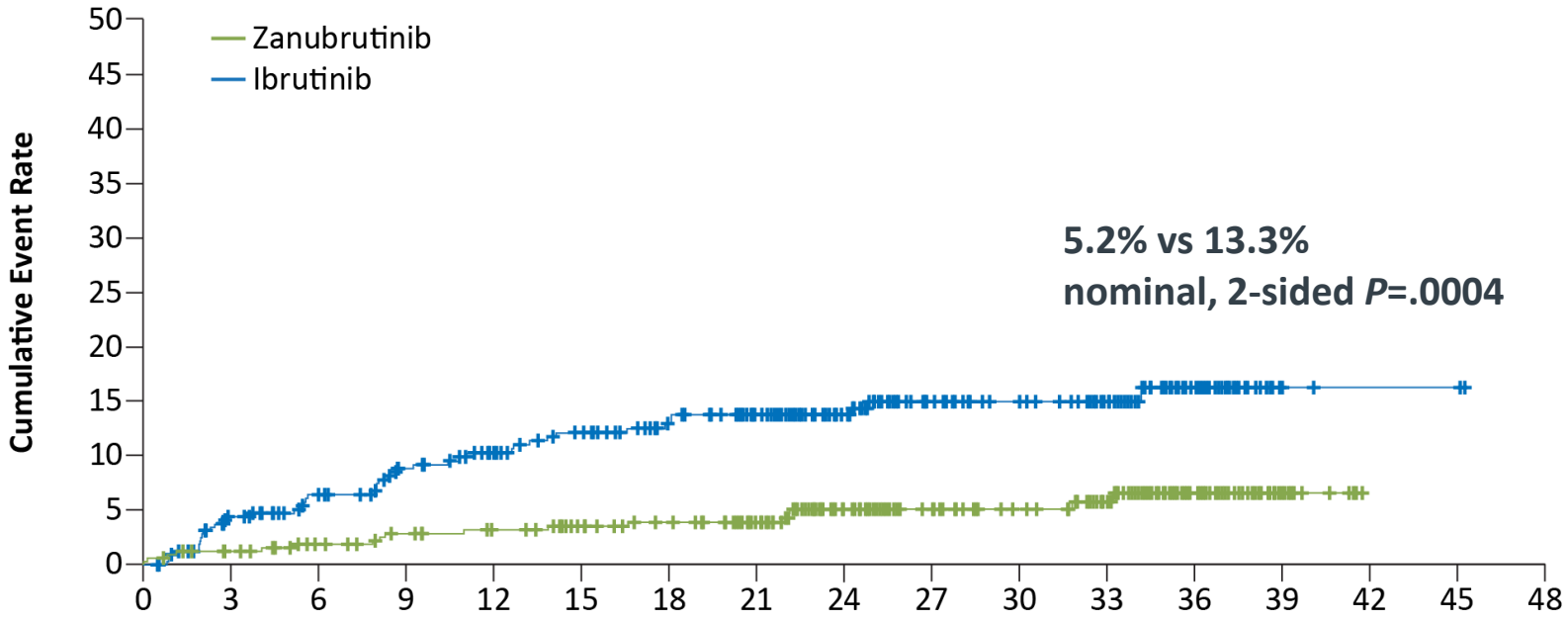
Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib



No. at Risk																	
Zanubrutinib	324	312	302	294	288	277	268	249	199	164	148	120	51	10	0		
Ibrutinib	324	295	278	260	247	230	211	193	153	121	108	89	40	3	2	1	0

Data cutoff: 8 Aug 2022

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Conclusions

- Zanubrutinib demonstrated superior PFS over ibrutinib in patients with relapsed/refractory CLL/SLL
  - PFS benefit seen across all major subgroups, including the del(17p)/*TP53*^{mut} population
- Zanubrutinib has a favorable safety profile compared with ibrutinib
  - Lower rate of grade ≥3 and serious AEs, fewer AEs leading to treatment discontinuation and dose reduction
  - Zanubrutinib has a better cardiac profile than ibrutinib with lower rates of atrial fibrillation, serious cardiac events, cardiac events leading to treatment discontinuation, and fatal cardiac events
- ALPINE is the first study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors in patients with relapsed/refractory CLL/SLL; **zanubrutinib has now proven superiority to ibrutinib in both PFS and ORR.**

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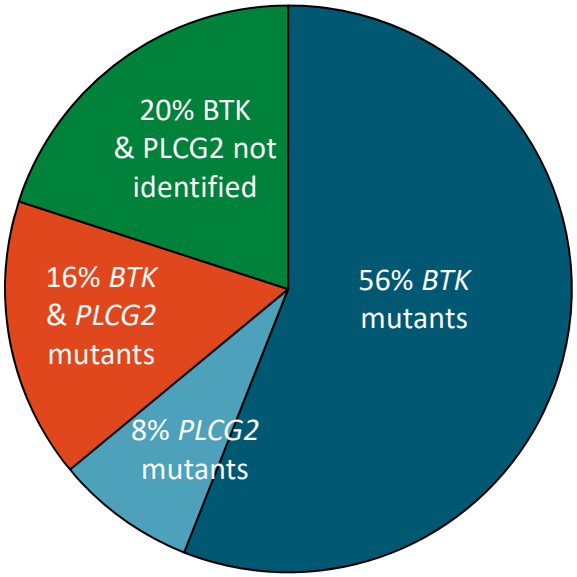
Resistance and Intolerance Limit Covalent BTK Inhibitor Outcomes

Ibrutinib Acquired Resistance in Patients With Progressive CLL[1]



- Ibrutinib discontinuation rate at 5 yr
  - Frontline: 41%[2]
  - R/R: 53.7%[6]
- Appearance of *BTK* C481 mutations dominant reason for progressive CLL after covalent BTKi[1-7]
- *BTK* C481 mutations prevent covalent BTKi from effective target inhibition[1-6]

1. Lampson. Expert Rev Hematol. 2018;11:185. 2. Woyach. JCO. 2017;35:1437. 3. Byrd. NEJM. 2016;374:323. 4. Xu. Blood. 2017;129:2519.
5. Hershkovitz-Rokah. Br. J. Haematol. 2018;181;306. 6. Burger. Leukemia. 2020;34:787. 7. Woyach. ASH 2019. Abstr 642.

Noncovalent BTK Inhibitors Are Active Against *BTK* C481 Mutations

Feature	Ibrutinib	Nemtabrutinib (ARQ-531)	Pirtobrutinib (LOXO-305)
Target	BTK	BTK	BTK
Bond type	Irreversible covalent	Reversible noncovalent	Reversible noncovalent
Requires C481 residue?	Yes	No	No
Active in C481 mutations?	No	Yes	Yes

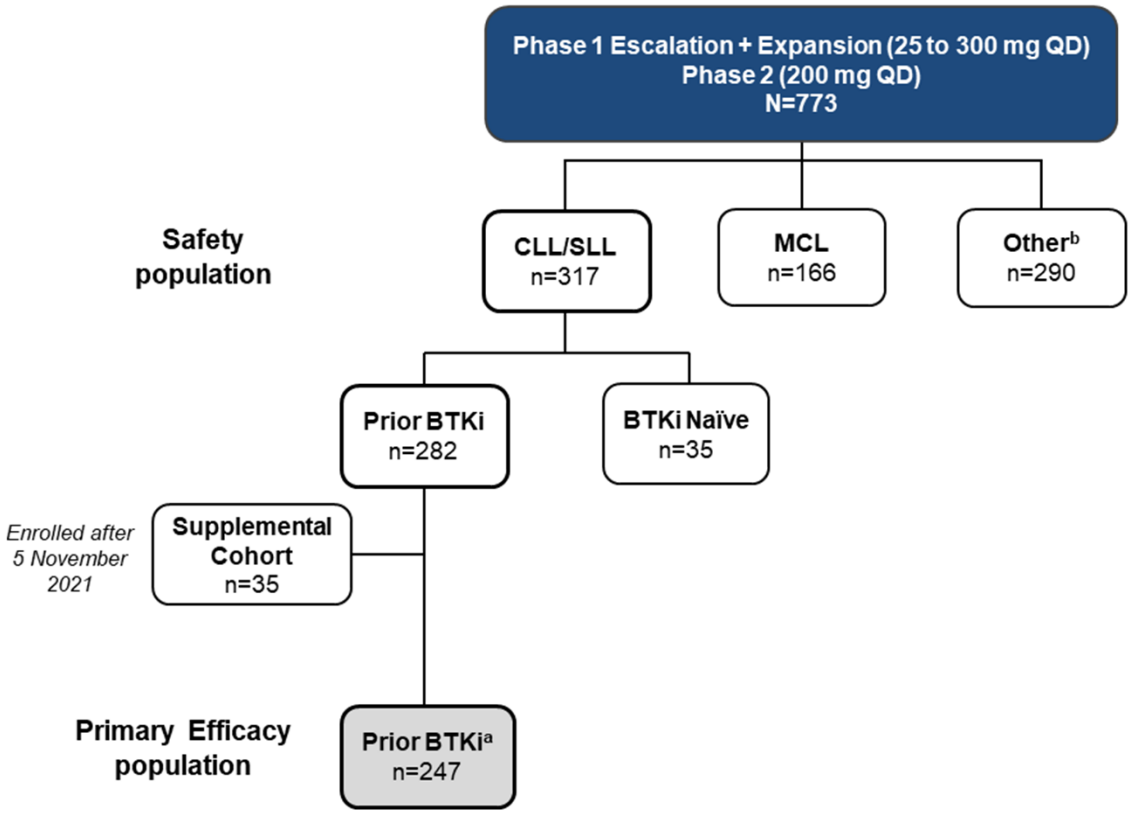
Slide credit: clinicaloptions.com

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

Anthony R. Mato[1], Jennifer A. Woyach[2], Jennifer R. Brown[3], Paolo Ghia[4], Krish Patel [5], Toby A. Eyre[6], Talha Munir[7], Ewa Lech-Maranda[8], Nicole Lamanna[9], Constantine S. Tam[10], Nirav N. Shah[11], Catherine C. Coombs[12], Chaitra S. Ujjani[13], Manish R. Patel[14], Bita Fakhri[15], Chan Y. Cheah[16], Alvaro J. Alencar[17], Jonathon B. Cohen[18], James N. Gerson[19], Ian W. Flinn[20], Shuo Ma[21], Deepa Jagadeesh[22], Joanna M. Rhodes[23], Francisco Hernandez-Ilizaliturri[24], John F. Seymour[10], Pier Luigi Zinzani[25], Minna Balbas[26], Binoj Nair[26], Paolo Abada[26], Chunxiao Wang[27], Amy S. Ruppert[27], Denise Wang[26], Donald E. Tsai[26], William G. Wierda[28], Wojciech Jurczak[29]

[1]Memorial Sloan Kettering Cancer Center, New York, USA; [2]The Ohio State University Comprehensive Cancer Center, Columbus, USA; [3]Dana-Farber Cancer Institute and Harvard Medical School, Boston, USA; [4]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [5]Center for Blood Disorders and Cellular Therapy, Swedish Cancer Institute, Seattle, USA; [6]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, UK; [7]Department of Haematology, St. James's University Hospital, Leeds, UK; [8]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [9]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, USA; [10]Peter MacCallum Cancer Centre and the University of Melbourne, Melbourne, Australia; [11]Medical College of Wisconsin, Milwaukee, USA; [12]University of North Carolina at Chapel Hill, Chapel Hill, USA; [13]Fred Hutchinson Cancer Center, University of Washington, Seattle, USA; [14]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, USA; [15]University of California San Francisco, San Francisco, USA; [16]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [17]University of Miami Miller School of Medicine, Miami, USA; [18]Winship Cancer Institute, Emory University, Atlanta, USA; [19]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, USA; [20]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, USA; [21]Robert H. Lurie Comprehensive Cancer Center, Division of Hematology-Oncology, Northwestern University Feinberg School of Medicine, Chicago USA; [22]Cleveland Clinic, Cleveland, USA; [23]Northwell Health Cancer Institute, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell Health, New Hyde Park, USA; [24]Lymphoma Section, Department of Medical Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, USAY; [25]Institute of Hematology Seràgnoli, University of Bologna, Bologna, Italy; [26]Loxo@Lilly, Indianapolis, USA; [27]Eli Lilly and Company, Indianapolis, USA; [28]MD Anderson Cancer Center, Houston, USA; [29]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland

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. [a]To ensure adequate follow-up, the primary efficacy population included all CLL/SLL patients who enrolled prior to 5 November 2021. [b]Other includes DLBCL, WM, FL, MZL, Richter transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

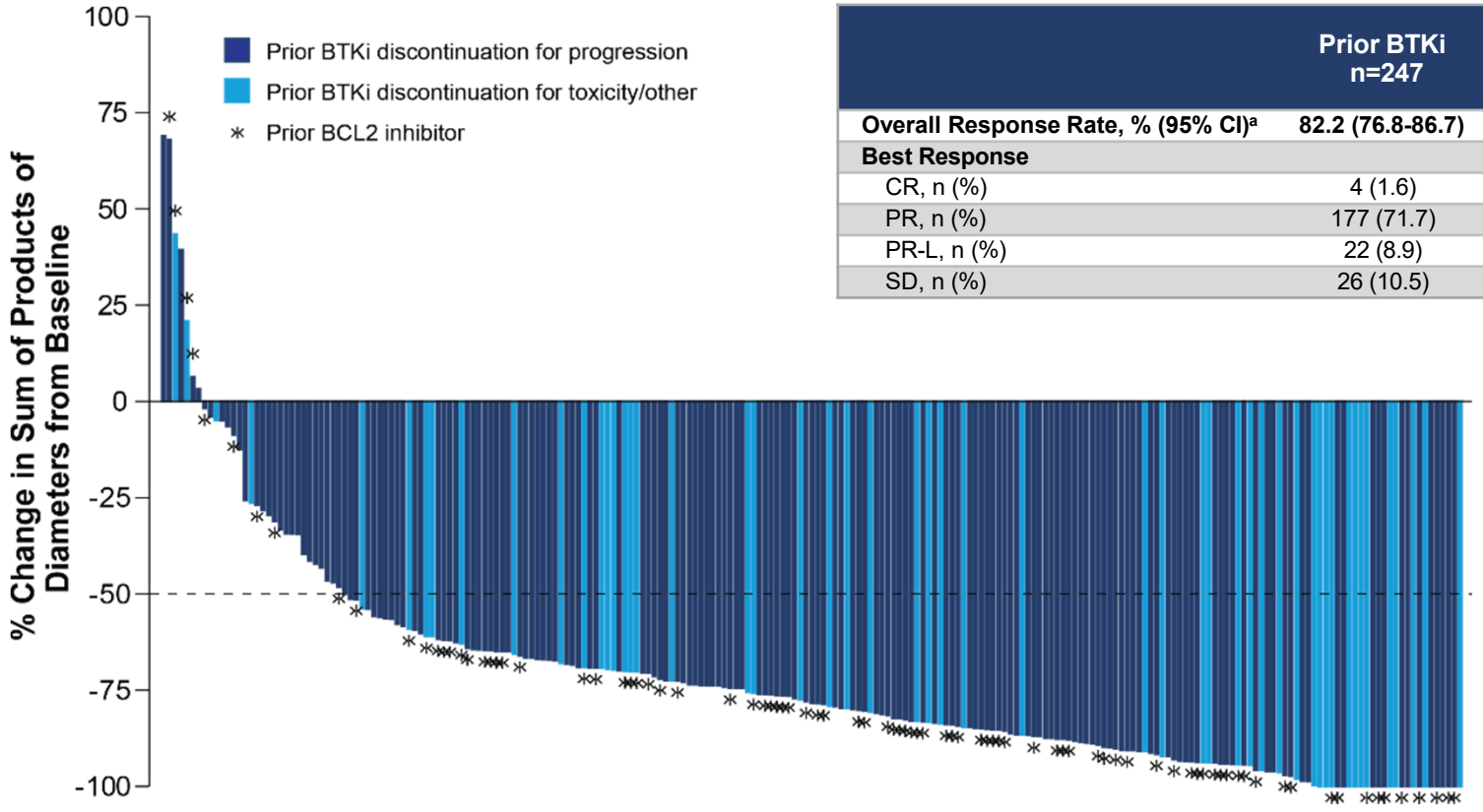
CLL/SLL Patient Characteristics

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 (%)	
BTK C481-mutant	84/222 (38)
BTK C481-wildtype	138/222 (62)
PLCG2-mutant	18/222 (8)
PLCG2-wildtype	204/222 (92)
High Risk Molecular Features, n/n available (%)	
17p deletion	51/176 (29)
TP53 mutation	87/222 (39)
17p deletion and/or *TP53* mutation	90/193 (47)
Both 17p deletion and *TP53* mutation	48/170 (28)
IGHV 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. [a]14 patients had missing data for Rai staging data. [b]Molecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control. [c]In 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

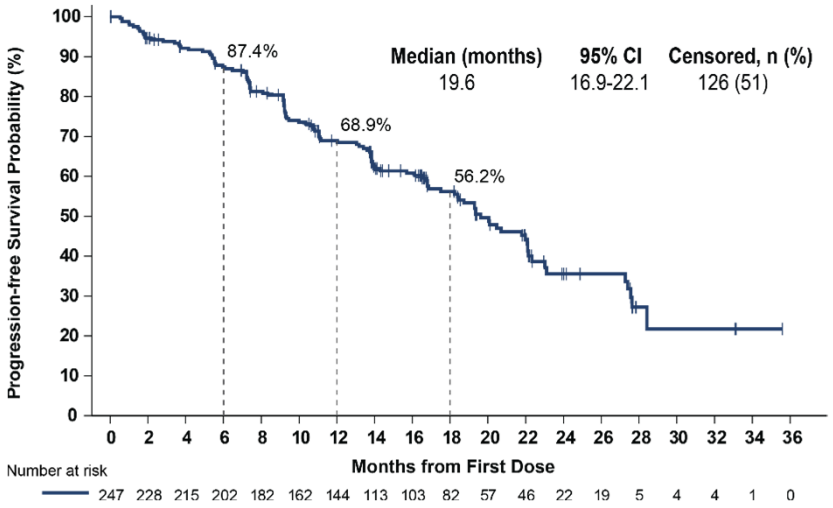


	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

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. [a]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.

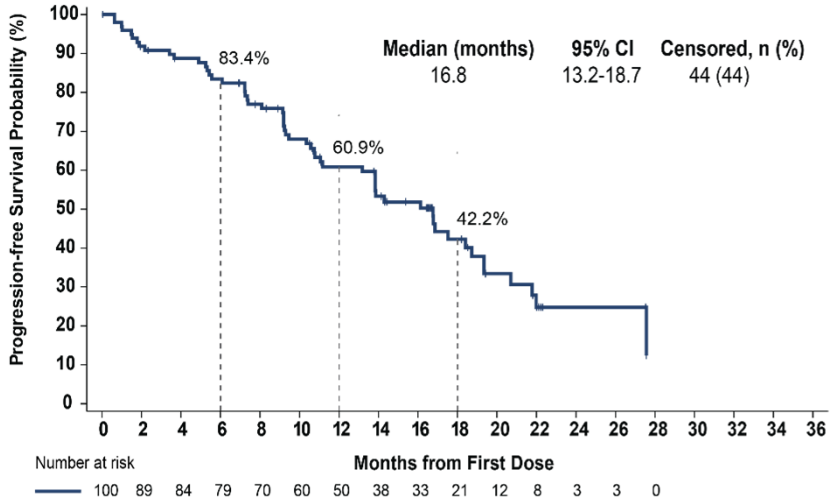
Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients
Median prior lines = 3



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

Prior BTKi and BCL2i patients
Median prior lines = 5

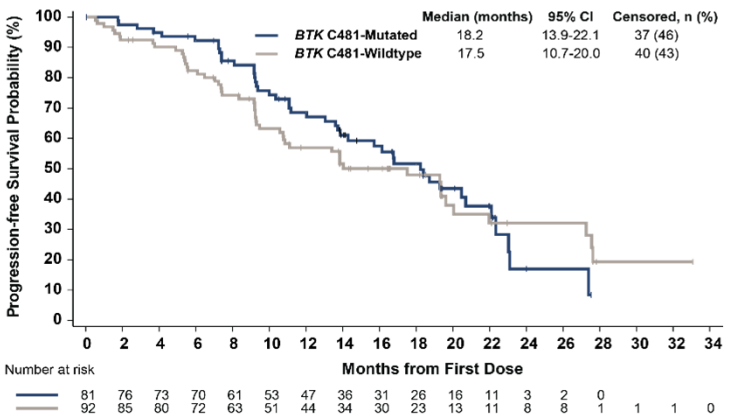


- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

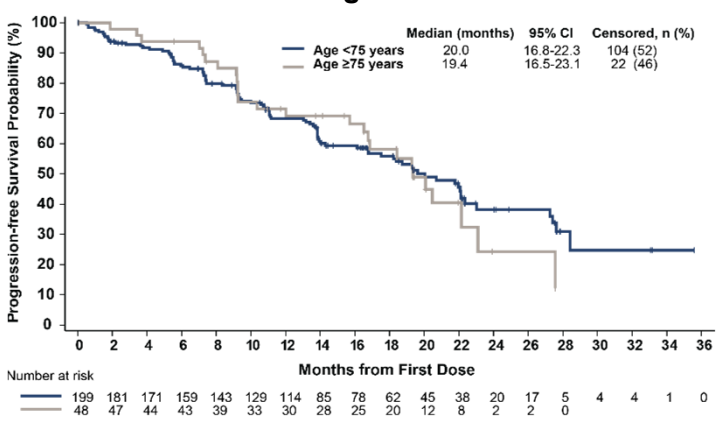
Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

Progression-Free Survival in CLL/SLL Subgroups

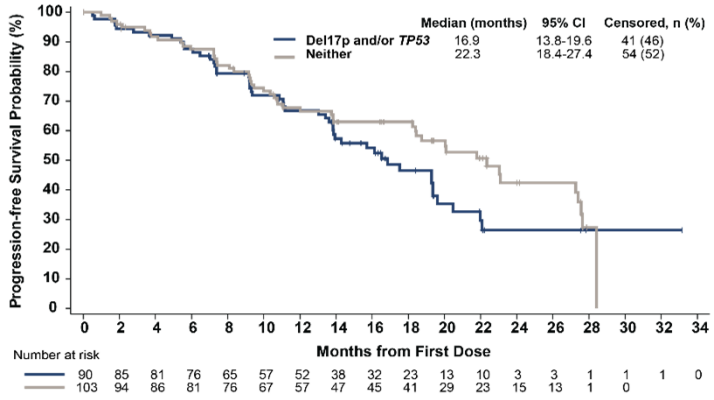
BTK C481 mutation status[a,b]



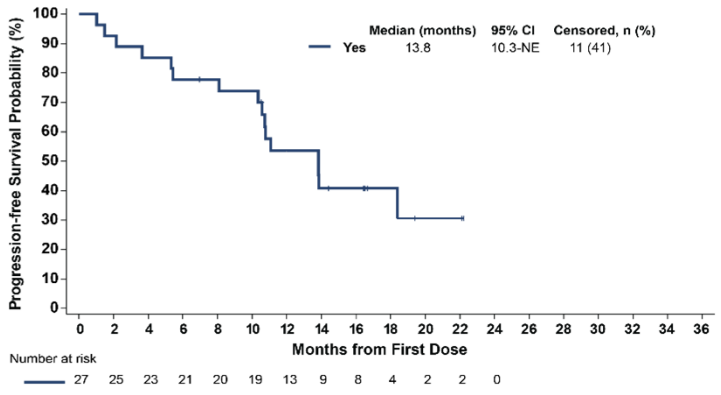
Age



del(17p) and/or *TP53* mutation[a]



Prior BTKi, CIT, BCL2i, and PI3Ki therapy



Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment. [a]*BTK* C481 mutation status, del(17p), and *TP53* mutation status were centrally determined and based on pre-treatment samples. [b]Patients with available mutation data who progressed on any prior BTKi.

Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

Median time on treatment for the overall safety population was 9.6 months
Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
Overall and CLL/SLL safety profiles are consistent[h]

Data cutoff date of 29 July 2022.. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]CLL/SLL safety population data can be found via QR code.

Conclusions

- With more than 2 years of additional data, pirtobrutinib continues to demonstrate clinically meaningful and durable efficacy in CLL/SLL patients previously treated with BTK inhibitors
- Favorable efficacy was observed regardless of BTK C481 mutation status, age, TP53 and/or del(17p) mutation status, and in those with additional lines of therapy
  - Notably, this was observed in patients with relapsed / refractory disease after prior treatment with BTKi and BCL2i
- Consistently high overall response rates were observed across all subgroups
- Pirtobrutinib continues to be well-tolerated with low-rates of Grade ≥3 AEs and discontinuation due to drug-related toxicity
- Four global, randomized, Phase 3 trials evaluating pirtobrutinib in CLL/SLL are ongoing:

BRUIN-CLL-313	BRUIN-CLL-314	BRUIN-CLL-321	BRUIN-CLL-322
Monotherapy vs. bendamustine + rituximab in treatment naïve CLL/SLL	Head-to-head vs. ibrutinib in CLL/SLL	Monotherapy vs. investigator's choice (IdelaR or BR) in post-BTKi CLL/SLL	Combo with venetoclax + rituximab vs. venetoclax + rituximab in CLL/SLL
NCT05023980	NCT05254743	NCT04666038	NCT04965493

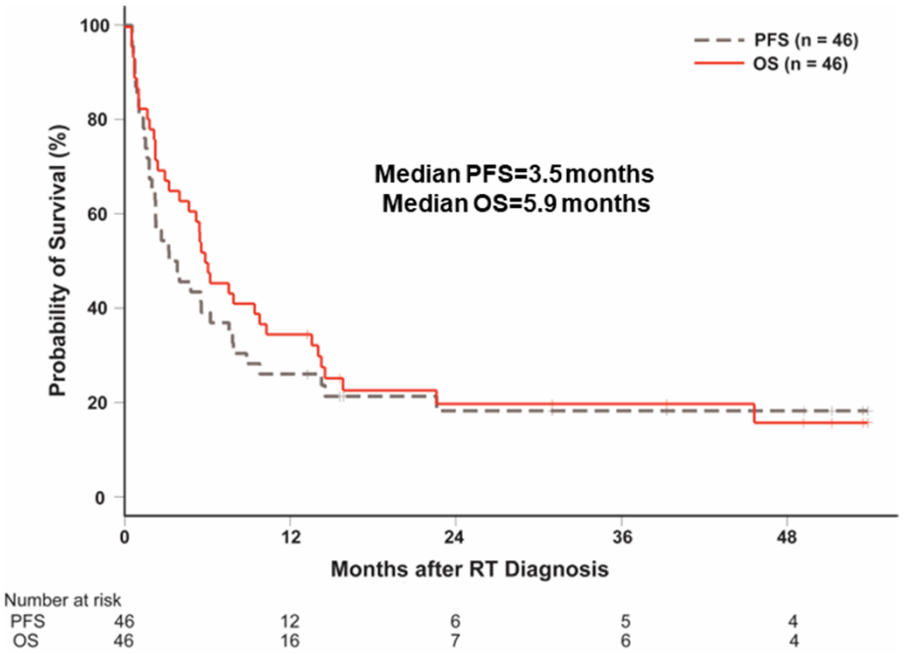
Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Richter Transformation: Results From the Phase 1/2 BRUIN Study

William G. Wierda[1], David Lewis[2], Paolo Ghia[3], Nirav N. Shah[4], Catherine C. Coombs[5], Chan Y. Cheah[6], Jennifer Woyach[7], Nicole Lamanna[8], Joanna M. Rhodes[9], Marc S. Hoffmann[10], Shuo Ma[11], Toby A. Eyre[12], Talha Munir[13], Manish R. Patel[14], Alvaro J. Alencar[15], Constantine S. Tam[16], Wojciech Jurczak[17], Ewa Lech-Maranda[18], John F. Seymour[16], Lindsey E. Roeker[19], Philip A. Thompson[1], Paolo B. Abada[20], Chunxiao Wang[21], Amy S. Ruppert[21], Binoj Nair[20], Hui Liu[20], Donald E. Tsai[20], Anthony R. Mato[19]

[1]The University of Texas, MD Anderson Cancer Center, Houston, USA; [2]Plymouth Hospitals NHS Trust – Derriford Hospital, Plymouth, UK; [3]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy; [4]Medical College of Wisconsin, Brookfield, USA; [5]University of North Carolina at Chapel Hill, Chapel Hill, USA; [6]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [7]The Ohio State University Comprehensive Cancer Center, Columbus, USA; [8]Herbert Irving Comprehensive Cancer Center, New York-Presbyterian/Columbia University Medical Center, New York, USA; [9]Northwell Health Cancer Institute, New Hyde Park, USA; [10]The University of Kansas Cancer Center, Kansas City, USA; [11]Robert H. Lurie Comprehensive Cancer Center, Feinberg School of Medicine, Northwestern University, Chicago, USA; [12]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, UK; [13]Department of Haematology, St. James's University Hospital, Leeds, UK; [14]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, USA; [15]Sylvester Comprehensive Cancer Center, University of Miami, Miller School of Medicine, Miami, USA; [16]Peter MacCallum Cancer Center, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia; [17]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [18]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [19]Memorial Sloan Kettering Cancer Center, New York, USA; [20]Loxo@Lilly, Indianapolis, USA; [21]Eli Lilly and Company, Indianapolis, USA

Richter Transformation is a Complication of CLL With Poor Prognosis

Progression-Free and Overall Survival after RT Diagnosis[a]

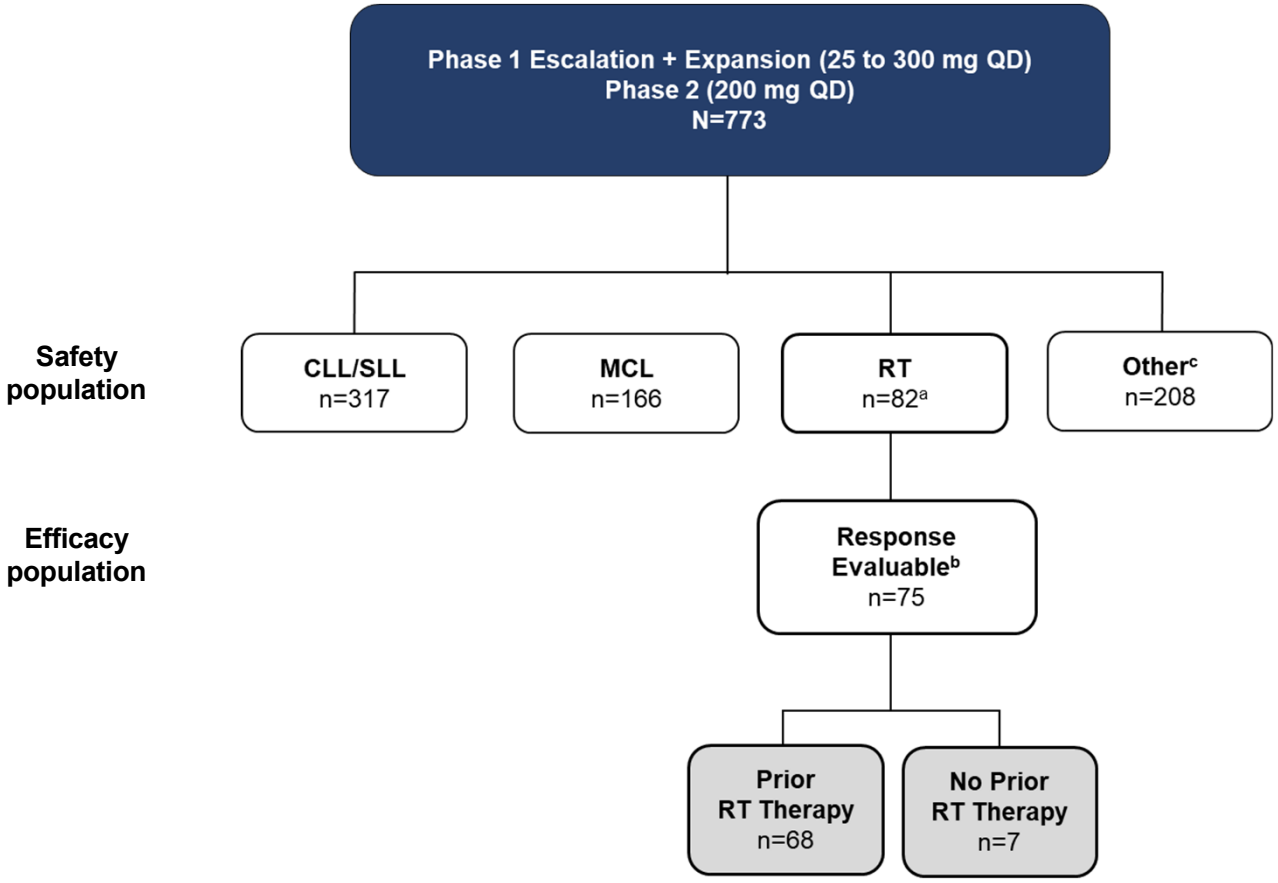


Data from Figure 1, Rogers KA, et al.[5]

- **RT occurs in up to 10% of patients with CLL[1,2]**
  - Estimated median OS of 3-12 months[1,3-5]
  - No approved therapies, clinical trial preferred as standard of care
  - cBTKi clinical trials have reported
    - Median OS of 4 months (95% CI, 0.9-5) for patients on ibrutinib monotherapy[6]
    - ORR of 40% (95% CI, 21.1-61.3) for patients on acalabrutinib monotherapy[7]

CLL, chronic lymphocytic leukemia. RT, Richter transformation. [1]Al-Sawaf et al. *Leukemia* 2021;35:169-76. [2]Tadmor and Levy *Cancers (Basel)* 2021;13:5141. [3]Ding *Hematology Am Soc Hematol Educ Program* 2018;30:256-63. [4]Wang et al. *Haematologica* 2020;105:765-73. [5]Rogers et al, *Br J Haematol* 2018;180:259-66. [6]Byrd et al, *Clin Cancer Res* 2020;26:3918-27. [7]Eyre et al, *Lancet Haematol* 2021;8:e912-21. [a]Patients receiving R-EPOCH.

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

RT eligibility

- Age ≥18
- ECOG PS 0-2
- Previously treated
- Histologically confirmed active RT (all DLBCL)
- No limit on prior lines of therapy
- Prior cBTKi permitted
- With Amendment 10, frontline RT patients were eligible[d]

Key endpoints

- Safety/tolerability
- Determine MTD and RP2D
- Pharmacokinetics
- Efficacy according to ORR and DoR based on Lugano criteria

Data cutoff date of 29 July 2022. [a]n=74 received prior RT therapy and n=8 did not. [b]Response evaluable patients are those who had ≥1 post-baseline response assessment or discontinued treatment prior to first post-baseline response assessment. [c]Other includes DLBCL, WM, FL, MZL, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation. [d]Prior to Amendment 10 (21 Jan 2022), patients required to be previously treated for RT.

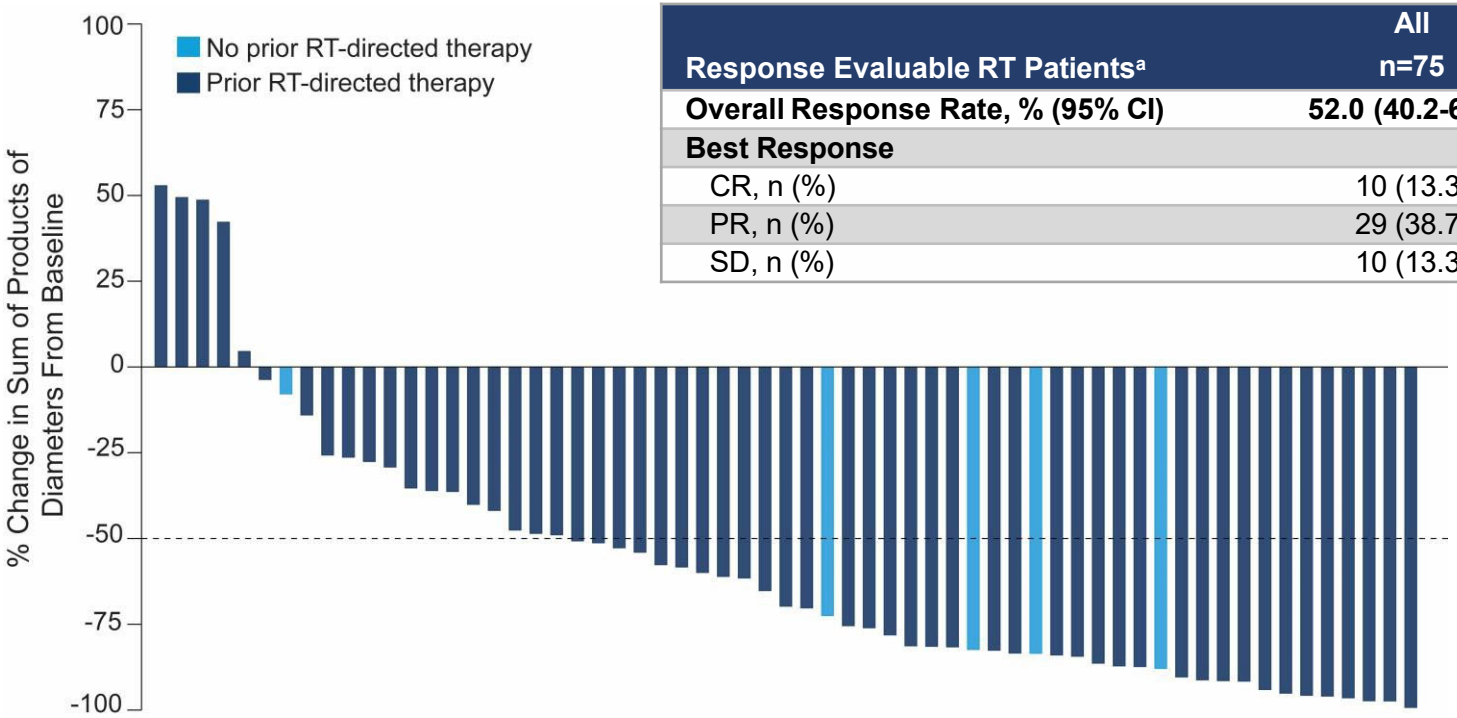
RT Patient Characteristics

Characteristics	All n=82	Prior RT Therapy n=74
Median age, years (range)	67 (26-95)	66 (26-95)
Male, n (%)	55 (67)	53 (72)
ECOG PS, n (%)		
0	32 (39)	29 (39)
1	38 (46)	34 (46)
2	12 (15)	11 (15)
Ann Arbor Stage		
Stage I-II	8 (10)	8 (11)
Stage III	15 (18)	13 (18)
Stage IV	42 (51)	38 (51)
Missing	17 (21)	15 (20)
Tumor bulk, cm, n (%)		
<5 cm	41 (50)	35 (47)
≥5 cm	31 (38)	31 (42)
Missing	10 (12)	8 (11)
Elevated LDH, n (%)		
Yes	66 (81)	60 (81)
No	16 (20)	14 (19)
Median time from initial CLL diagnosis to RT presentation (months, IQR)	60.8 (17.4-101.5)	60.8 (18.8-98.6)
Median time from transformation to first pirtobrutinib dose (months, IQR)	4.6 (1.8-13.1)	5.5 (2.2-15.6)

Characteristics	All n=82	Prior RT Therapy n=74
Median number of prior lines of CLL therapy (range)[a]	2 (0-13)	2 (0-11)
Median number of prior lines of RT therapy (range)	2 (0-8)	2 (1-8)
Median number of prior lines of CLL and RT therapy (range)	4 (0-13)	4 (1-12)
Prior RT therapies, n (%)		
Anti-CD20 antibody	64 (78)	64 (87)
Chemotherapy	62 (76)	62 (84)
BCL2 inhibitor	31 (38)	31 (42)
BTK inhibitor	28 (34)	28 (38)
CAR-T cell therapy	9 (11)	9 (12)
PI3K inhibitor	8 (10)	8 (11)
Stem cell transplant	5 (6)	5 (7)
Allogeneic	4 (5)	4 (5)
Autologous	1 (1)	1 (1)
Immunomodulator[b]	3 (4)	3 (4)
Other systemic therapy	25 (31)	25 (34)

Data cutoff date of 29 July 2022. [a]17 patients were CLL therapy naïve. [b]Includes IMID and lenalidomide.

Pirtobrutinib Efficacy in RT Patients

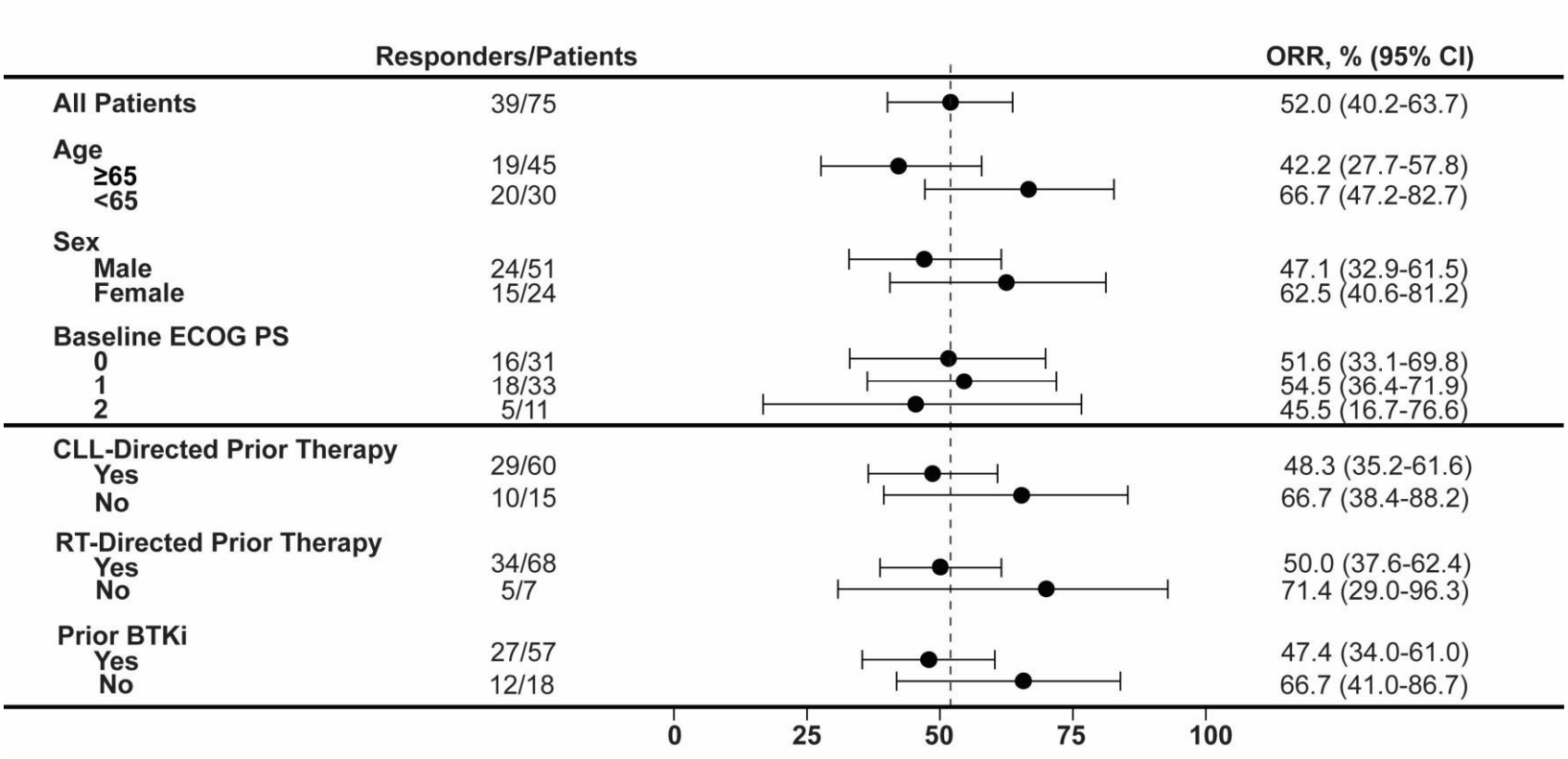


Response Evaluable RT Patients[a]	All n=75	Prior RT Therapy n=68
Overall Response Rate, % (95% CI)	**52.0 (40.2-63.7)**	**50.0 (37.6-62.4)**
Best Response		
CR, n (%)	10 (13.3)	9 (13.2)
PR, n (%)	29 (38.7)	25 (36.8)
SD, n (%)	10 (13.3)	10 (14.7)

- 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)

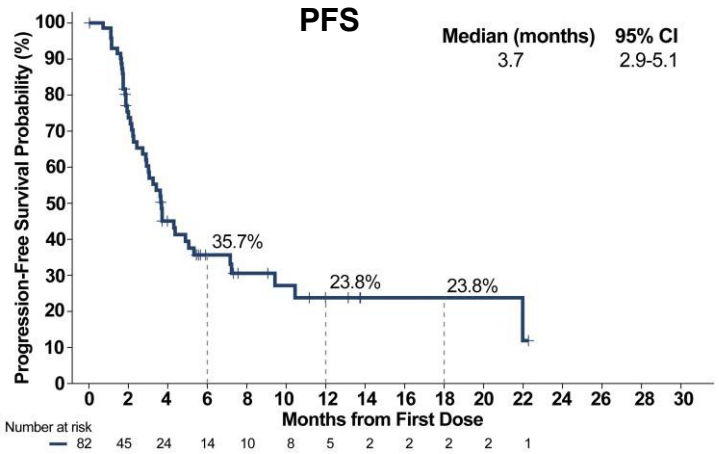
Data cutoff date of 29 July 2022. Data for 14 patients are not shown in the waterfall plot due to no baseline or post-baseline assessment. [a]Response evaluable patients are those who had at least 1 post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. Response as assessed by investigator based on Lugano criteria.

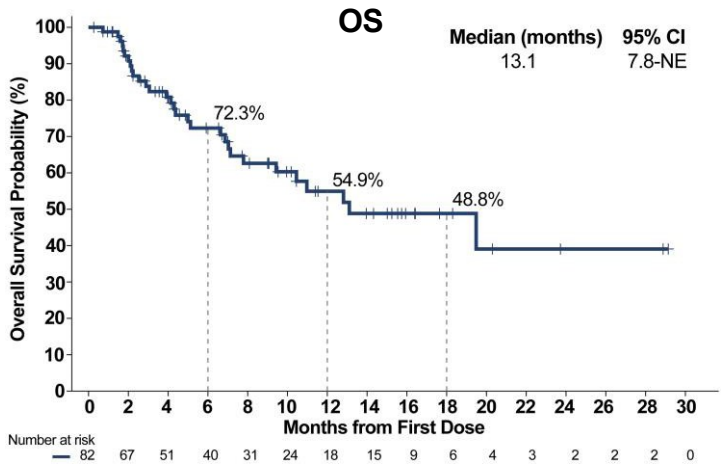
Overall Response Rate in RT Patient Subgroups



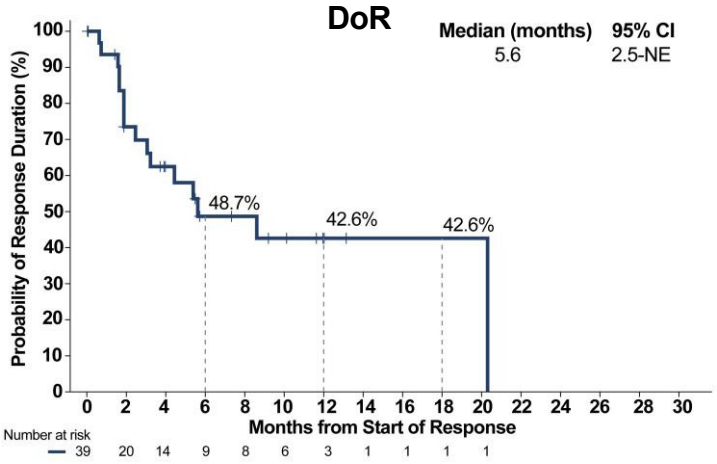
Data cutoff date of 29 July 2022. Response as assessed by investigator based on Lugano criteria.

PFS, OS, and DoR in All RT Patients



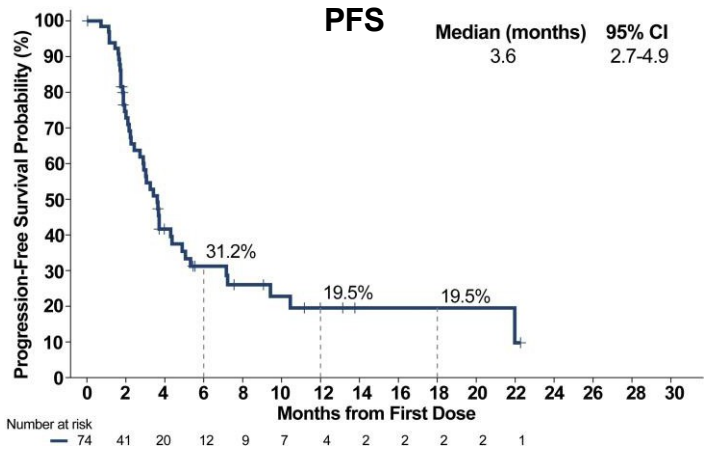


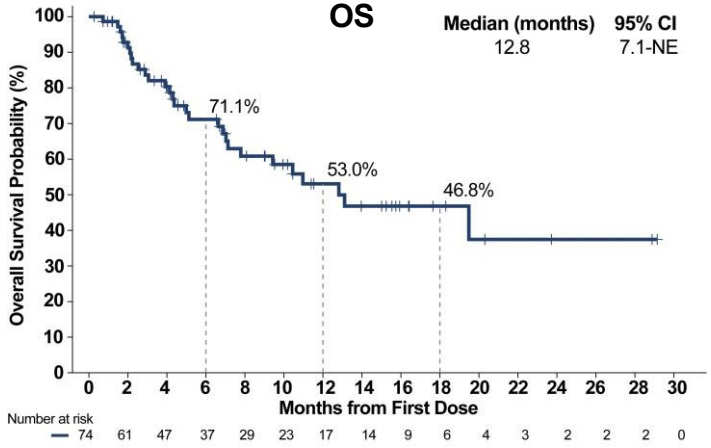
- 6 responding patients were censored for curative intent transplant therapy



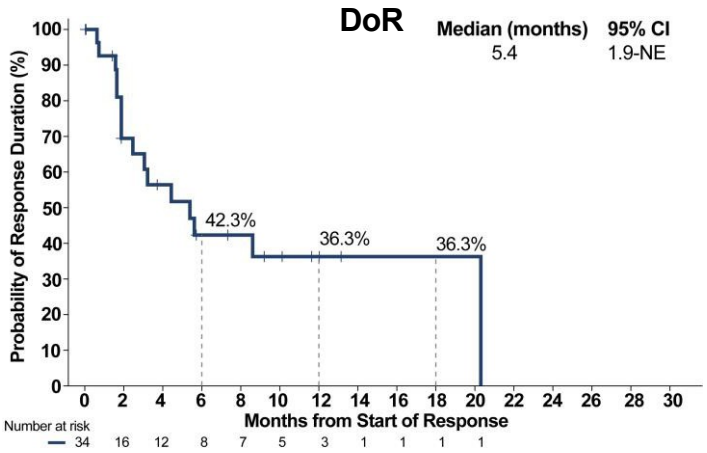
Data cutoff date of 29 July 2022. Response as assessed by investigator based on Lugano criteria.

PFS, OS, and DoR in Patients who Received Prior RT Therapy





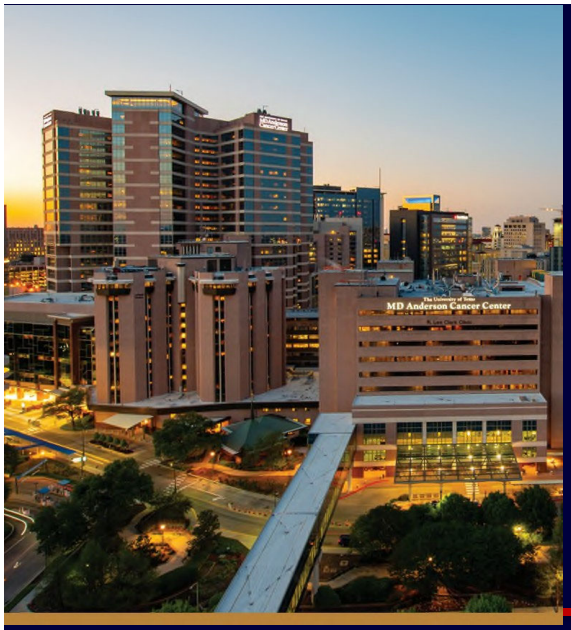
- 6 responding patients were censored for curative intent transplant therapy



Data cutoff date of 29 July 2022. Response as assessed by investigator based on Lugano criteria.

Conclusions

- This trial represents one of the largest prospective RT populations ever studied, comprised predominantly of heavily pretreated RT patients with an extremely poor expected overall survival
- Pirtobrutinib demonstrated promising efficacy, including among patients who received prior RT chemoimmunotherapy and cBTKi
  - Notably, pirtobrutinib demonstrated an ORR of 52% overall and 50% among patients who received prior RT therapy
  - Median OS was 13.1 months, regardless of prior RT therapy
  - DoR was 5.6 months, regardless of prior RT therapy
  - 6 responding patients discontinued in ongoing response to pursue curative intent transplant therapy
- Pirtobrutinib continues to be well-tolerated with low rates of Grade ≥3 AEs and discontinuation due to drug-related toxicity
  - Low rates of cBTKi-associated AEs were observed with pirtobrutinib



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

Background

- Ibrutinib (IBR), a BTK inhibitor, and Venetoclax (VEN), a BCL2 inhibitor, approved for CLL
- VEN + Obinutuzumab is approved for first-line CLL as 1-year time-limited therapy
- Preclinical studies support combination of IBR + VEN combination
- IBR + VEN combination have been investigated in several clinical trials
- We previously reported outcomes of 80 pts enrolled on this trial of first-line IBR + VEN

  Jain et al. N Engl J Med 2019; Jain et al. JAMA Onc 2021

- We provide updated results for these 80 pts and an additional 40 first-line pts (total 120 pts) with a median follow-up of 54.3 months

Byrd et al. NEJM. 2014;371(3):213-23; Burger et al. NEJM. 2015;373(25): 2425-37; Roberts et al. NEJM. 2016;374(4):311-22; Fischer et al. NEJM. 2019;380(23):2225-2236. Cervantes-Gomez et al. CCR. 2015; 21 (16):3705-15; Wierda et al. J Clin Oncol. 2021;39(34):3853-3865; Kater et al. NEJM Evid 2022;1(7).

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, IBR + VEN in CLL, ASH 2022, Abs 95

Treatment Schema

	C1	C2	C3	C4 --> 27 (24 cycles of Combined Rx)
Ibrutinib	420 mg 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

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

- Negative (<0.01%): Stop both IBR and VEN
- Positive (≥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/µL		76.3 [1.14-366]
PLT, K/µL		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)
IGHV status (n=116)	Unmutated	100 (86)
Cytogenetics (n=115)	Complex	15 (13)
Mutations (n=119)	*TP53*	19 (16)
	NOTCH1	35 (29)
	SF3B1	26 (22)
	BIRC3	10 (8)

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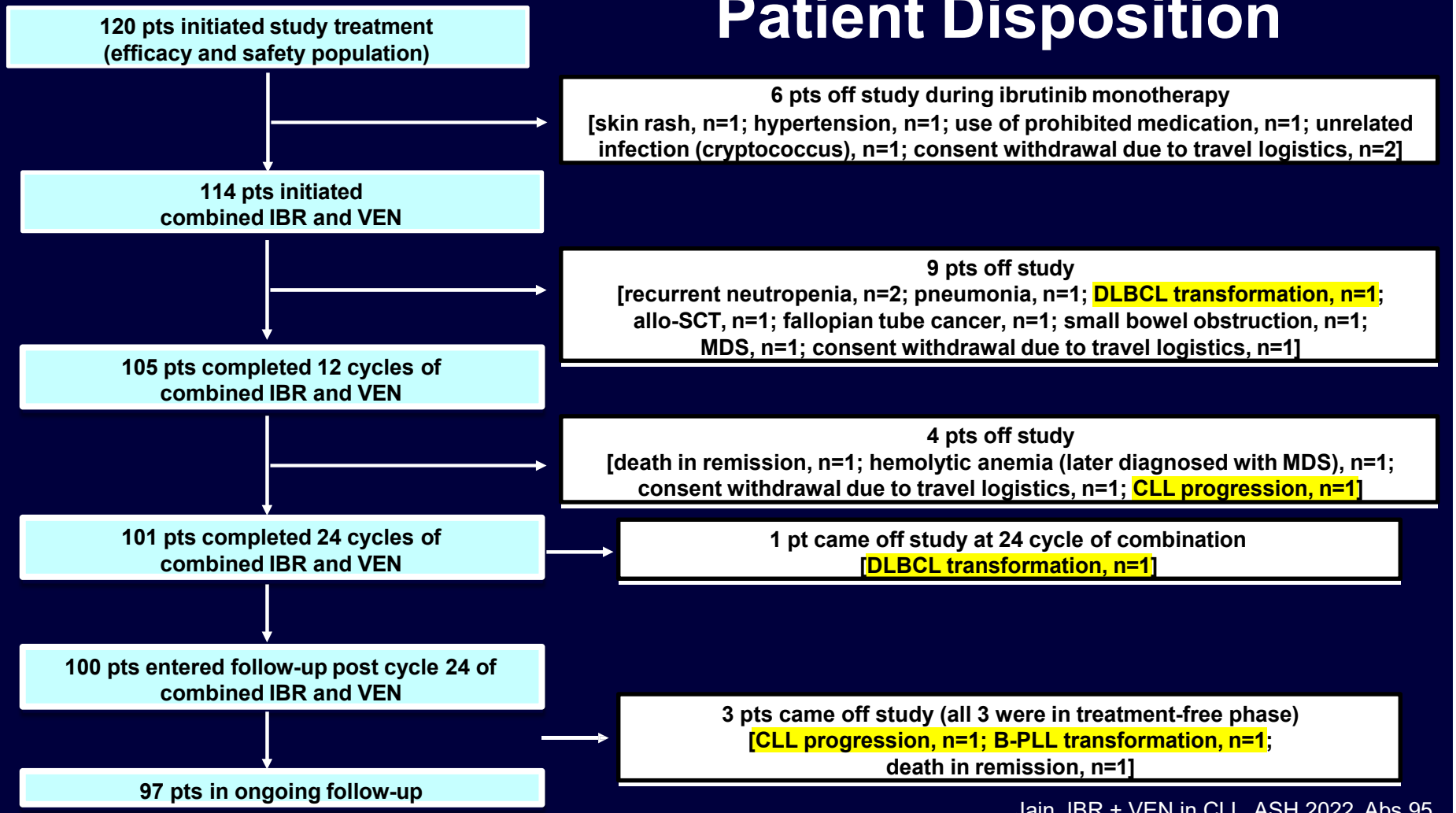
Patient Disposition



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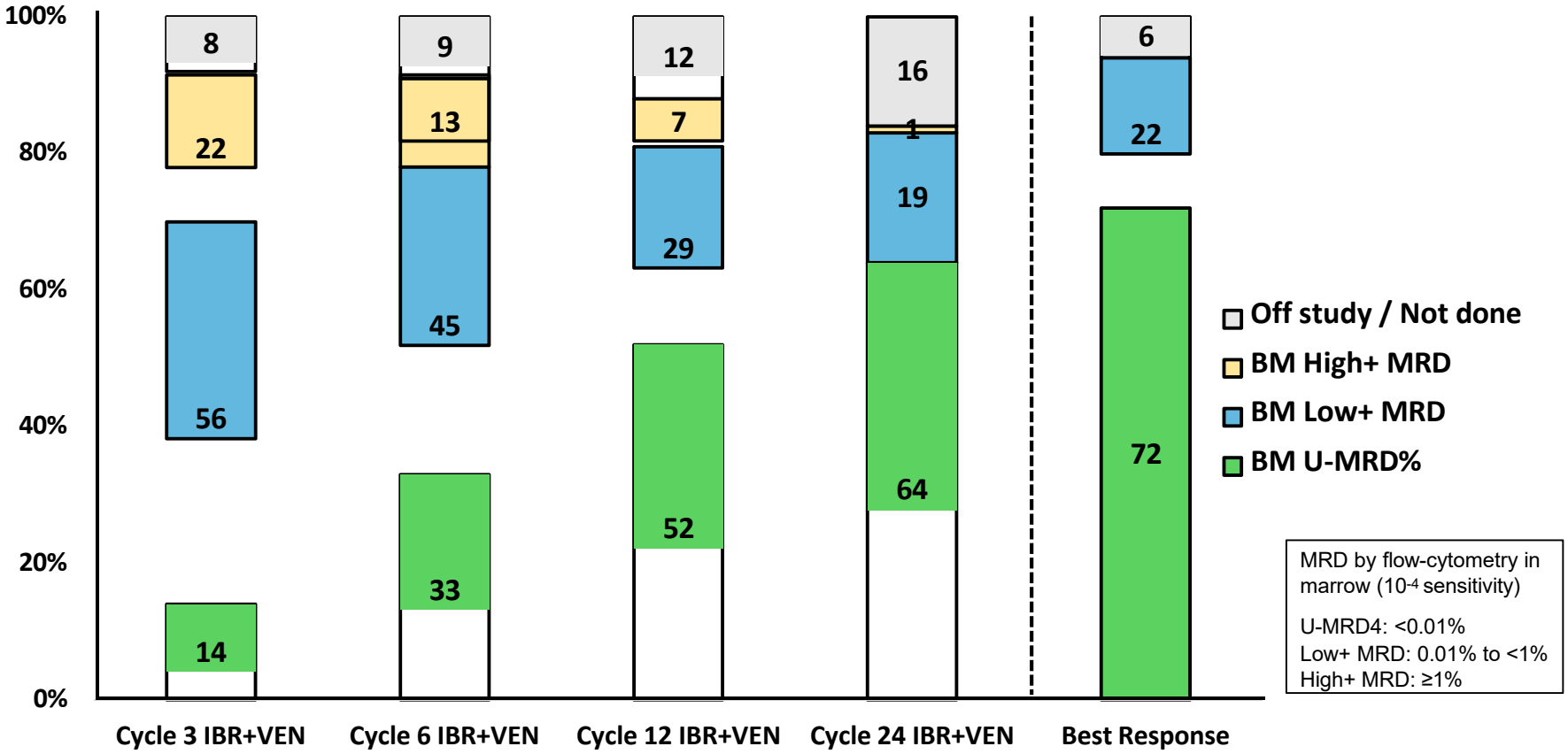
Marrow MRD Response at Serial Time-Points
Intent-to-Treat (N=120)



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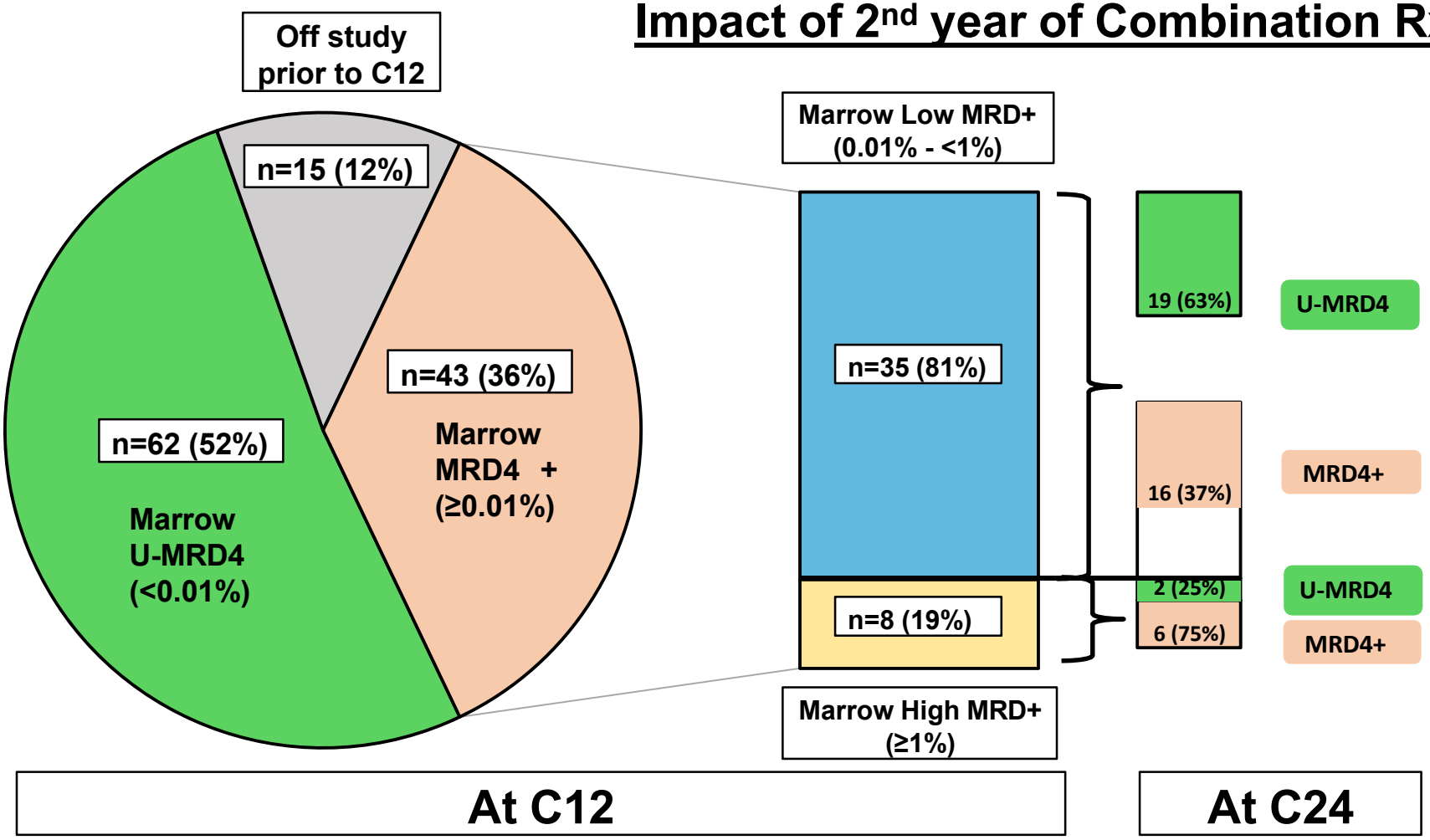
Impact of 2nd year of Combination Rx



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Baseline variables and odds of achieving U-MRD4 at different study time points

	U-MRD at 6 mo IBR+VEN		U-MRD at 12 mo IBR+VEN		U-MRD as best response	
Variables	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**
Age	1	0.91	0.98	0.25	0.98	0.25
IGHV-M	0.41	0.19	0.37	0.09	0.25	0.01
FISH [del(17p) vs others)	0.46	0.29	1.17	0.81	0.65	0.42
Cyto (CK vs others)	0.68	0.53	1.38	0.56	0.97	0.96
Del(17p) / *TP53*-m	0.39	0.08	0.83	0.68	0.56	0.21
SF3B1-m	1.7	0.24	0.77	0.56	1.36	0.55
NOTCH1-m	0.76	0.53	0.62	0.24	1.16	0.75

Follow-up Post Rx Discontinuation after 24 cycles of IBR +VEN

- 77 pts were marrow U-MRD at the end of cycle 24 of the combination
  - 73 discontinued all therapy (4 pts continued ibrutinib per physician discretion)
  - Among these 77 pts, with a median time of 30.8 months post Cycle 24
    - 18 pts had recurrence of blood MRD (defined as MRD ≥0.01% in 2 consecutive assessments)
      - 17 are being monitored without disease progression
      - 1 pt had CLL progression
    - 59 pts remain blood U-MRD in follow-up
      - 1 pt had B-PLL transformation

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Factors Predicting for blood MRD recurrence

Univariate Logistic regression for odds of MRD recurrence in patients who were UMRD4 at C24 (n=77)

Variables	Odds ratio	95% CI	P-value
Age	1	0.96-1.04	0.96
IGHV-M	1.36	0.24-7.78	0.73
FISH (Del17p vs others)	0.61	0.09-2.65	0.55
Cyto (CK vs others)	0.83	0.16-4.32	0.83
Del(17p) / *TP53*-m	0.78	0.19-3.15	0.73
SF3B1-m	0.9	0.26-3.15	0.87
NOTCH1-m	1.43	0.46-4.47	0.54
Early MRD negative*	0.2	0.04-0.68	0.02

* U-MRD4 in marrow by 6 months of combination therapy

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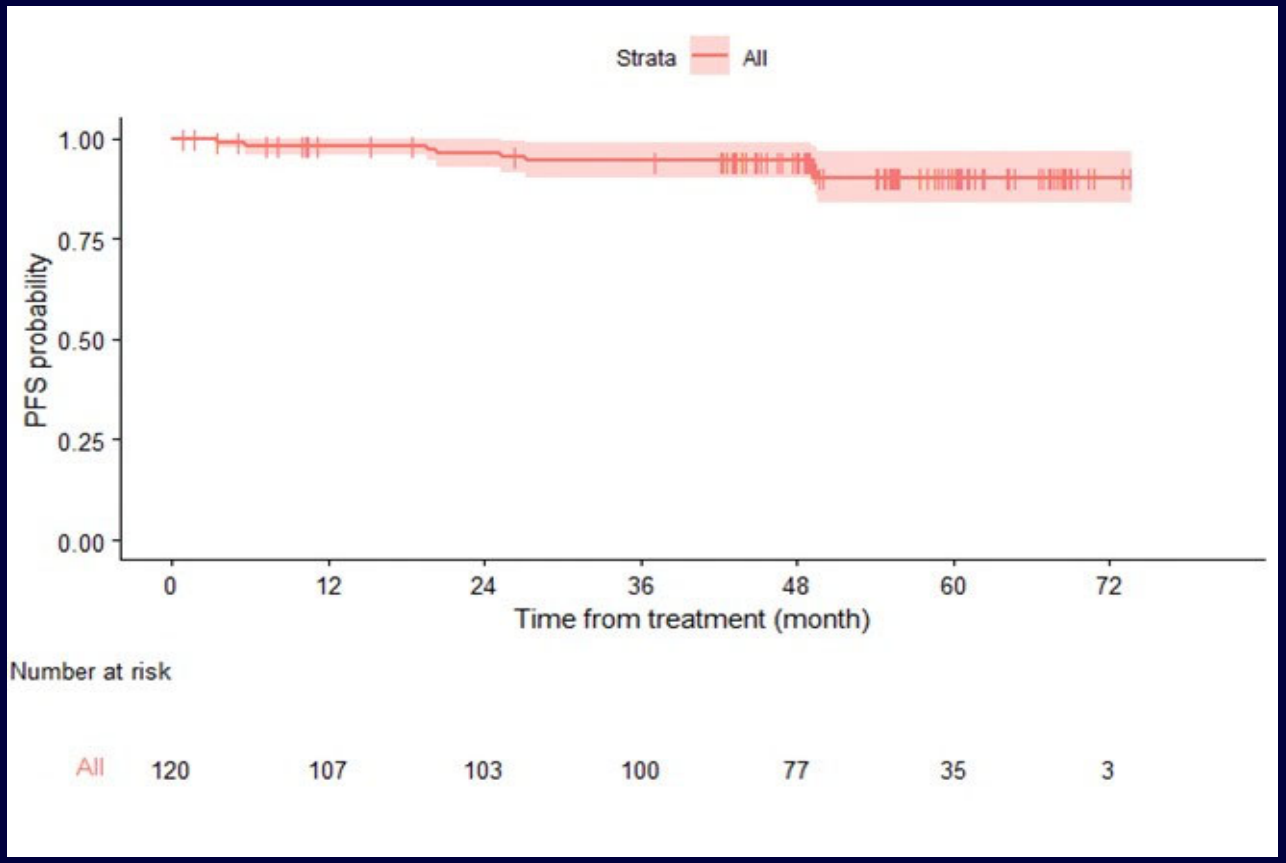
Outcomes of pts remaining MRD+ after 24 cycles of IBR + VEN

24 pts were marrow MRD+ at the end of C24 of combination

- Low MRD+, n=23; High MRD+, n=1
- Only pt with high-MRD+ at end of C24 had Richter transformation at that time
- The remaining 23 pts (low MRD+ in marrow, median 0.03%, range 0.01-0.95%) continued IBR monotherapy
- With a trial amendment, MRD+ pts after C24 could get 12 additional cycles of IBR + VEN combination
- 18/23 pts resumed combination for 12 additional cycles
  - 11/18 (61%) pts achieved U-MRD remission during the third year of combined Rx

Jain, IBR + VEN in CLL, ASH 2022, Abs 95

PFS for all Patients (N=120)



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

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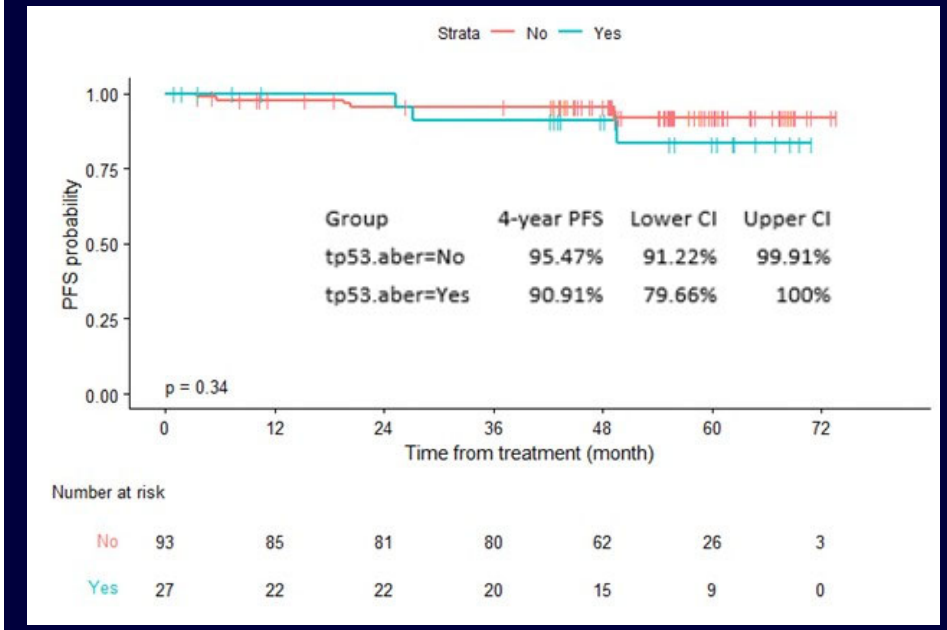
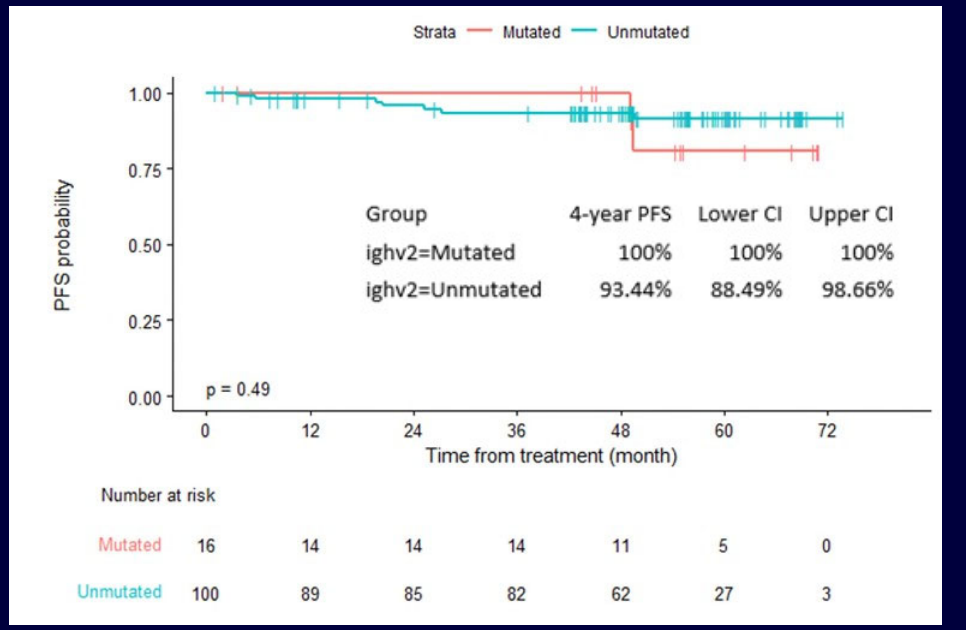
PFS by Genomic Subgroups



TP53 aberrant status



IGHV mutation status

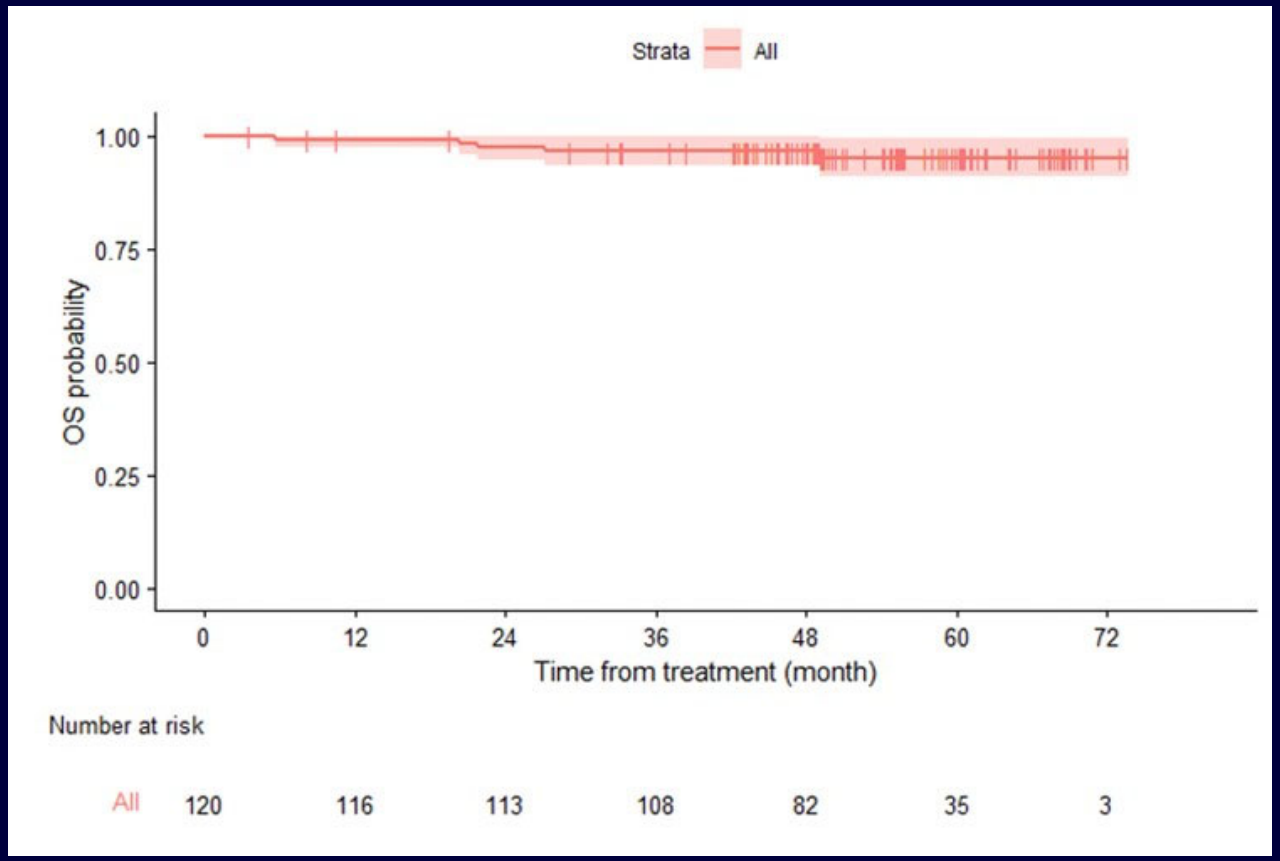
Jain, IBR + VEN in CLL, ASH 2022, Abs 95

Factors affecting PFS

Univariate Cox regression analysis for hazards of progression/death

Variables	HR	95% CI	P-value
Age	1.05	0.97-1.13	0.22
IGHV-M	1.72	0.36-8.29	0.50
Cyto (CK vs. others)	3.04	0.76-12.18	0.12
Del(17p) / *TP53*-m	1.95	0.49-7.8	0.35
NOTCH1 mut	2.11	0.57-7.87	0.27
SF3B1 mut	1.7	0.42-6.78	0.46

OS for all Patients (N=120)



4-year OS = 96.6%
(95% CI, 93.3-99.9%)

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Details of Patients with CLL Progression

2 pts had CLL progression

- 57-yr-old [*IGHV*-M; del(11q); *NOTCH1*-m, *BIRC3*-m]
  - Pt achieved U-MRD for the first time at the end of C24 of combination
  - Stopped both IBR and VEN per protocol
  - Noted to be MRD+ in blood 16 mos off therapy
  - CLL progression 22 months off therapy
  - BTK or PLCG2 or BCL2 mutations not detected
  - Currently in clinical remission 21+ mos on acalabrutinib
- 53-yr-old [*IGHV*-UM; trisomy 12]
  - Ibrutinib d/c in cycle 9 due to arthralgias/myalgias; Continued VEN single agent
  - Never achieved marrow U-MRD
  - Progressed during cycle 22 while on VEN monotherapy
  - Currently in clinical remission 27+ mos on acalabrutinib

Jain, IBR + VEN in CLL, ASH 2022, Abs 95

Details of Patients with Richter Transformation

2 pts developed Richter transformation

- 63-yr-old [*IGHV*-UM, del(13q), *NOTCH1*-m]
  - Noted to back pain during venetoclax dose escalation
  - Vertebral bone biopsy confirmed Richter transformation
  - For RT, pt received radiation, venetoclax-based therapy and then allo-SCT
- 67-yr-old [*IGHV*-UM, del(17p), complex karyotype, *TP53*-m]
  - Received 24 cycles of combined ibrutinib + venetoclax
  - Never achieved U-MRD
  - Noted to have Richter transformation at end of cycle 24 of combined therapy
  - BTK or PLCG2 or BCL2 mutations not detected
  - For RT, pt received PD1 inhibitor, R-EPOCH chemotherapy, and then allo-SCT

Jain, IBR + VEN in CLL, ASH 2022, Abs 95

Details of Patient with B-PLL Progression

1 pt developed B-PLL transformation

- 76-year-old [del(17p), complex karyotype, *IGHV*-UM, *SF3B1*-m, *NOTCH1*-m, *FBXW7*-m]
  - Pt achieved marrow U-MRD early at 3 months of the combination Rx; remained MRD negative at C24 of combination; Stopped both IBR and VEN per protocol
  - B-PLL transformation (noted on lymph node biopsy), 25-month in the off-treatment phase; notably, blood CLL MRD was negative 2-weeks prior to B-PLL diagnosis
  - BTK or PLCG2 or BCL2 mutation not detected in B-PLL tissue
  - Planned to start venetoclax + obinutuzumab

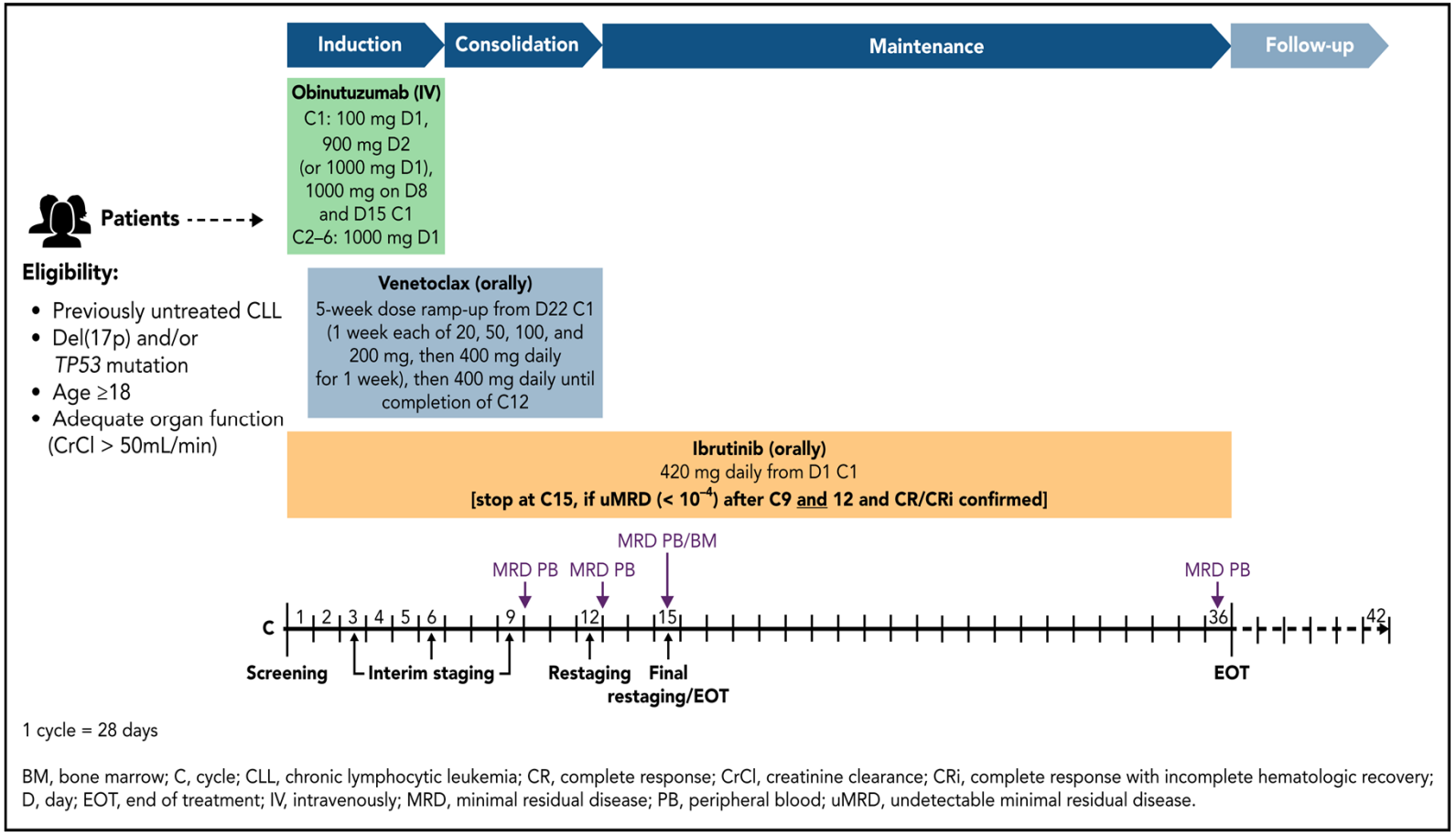
Jain, IBR + VEN in CLL, ASH 2022, Abs 95

Conclusions

- Combined ibrutinib and venetoclax is an effective chemotherapy-free oral regimen for patients with high-risk untreated CLL
- Best marrow U-MRD4 remission: 72%
- 4-year PFS is 94.5% and is independent of *IGHV*, FISH and *TP53* aberrant status
- Continuation of combined therapy among pts with marrow MRD+ disease for the second and the third year led to achievement of U-MRD remission in a subset of pts

Jain, IBR + VEN in CLL, ASH 2022, Abs 95

Huber et al. Obin/Ibr/Ven (GIVe) for frontline Rx for high-risk CLL. Blood, 2022



1 cycle = 28 days

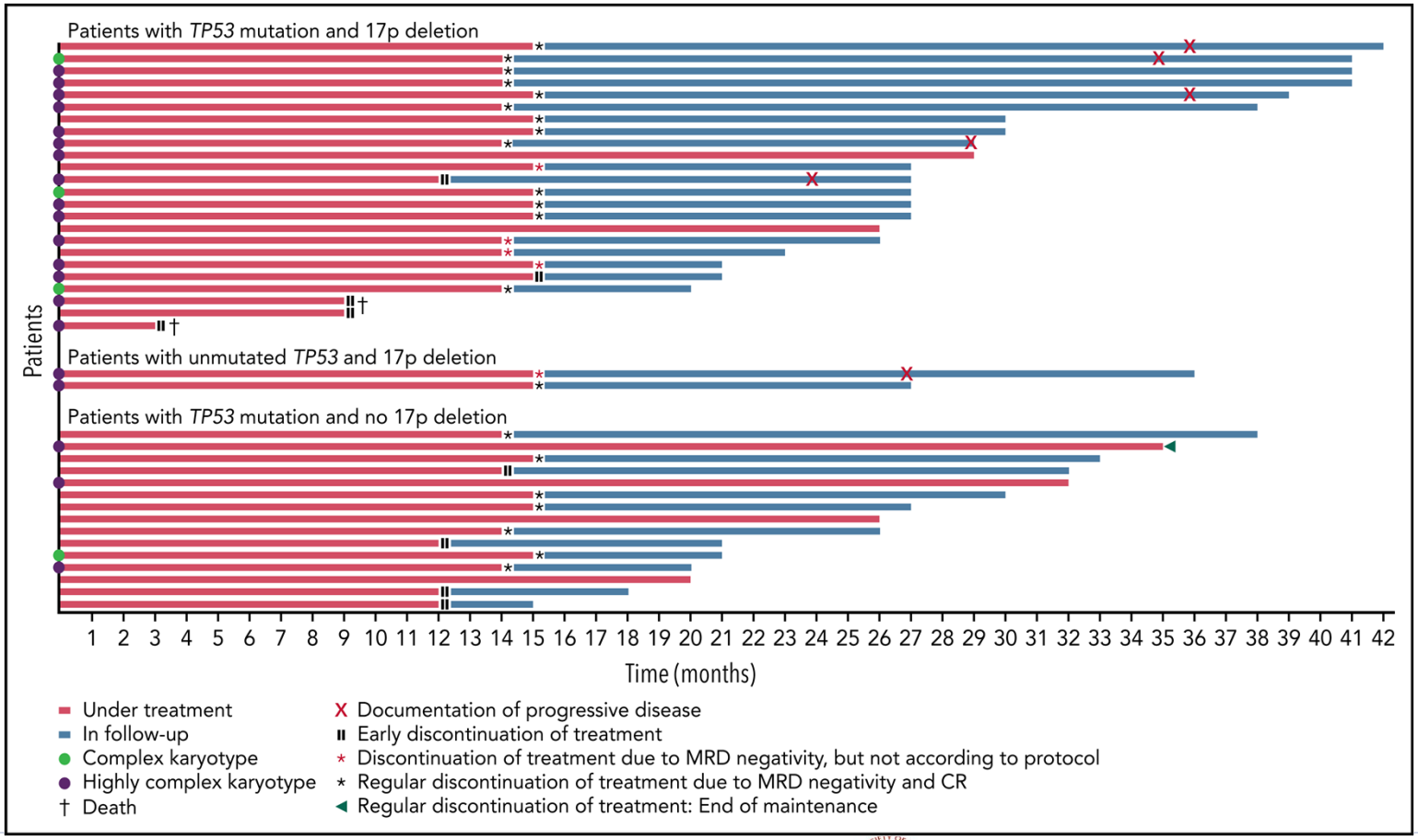
BM, bone marrow; C, cycle; CLL, chronic lymphocytic leukemia; CR, complete response; CrCl, creatinine clearance; CRi, complete response with incomplete hematologic recovery; D, day; EOT, end of treatment; IV, intravenously; MRD, minimal residual disease; PB, peripheral blood; uMRD, undetectable minimal residual disease.

Patient Characteristics and Toxicity

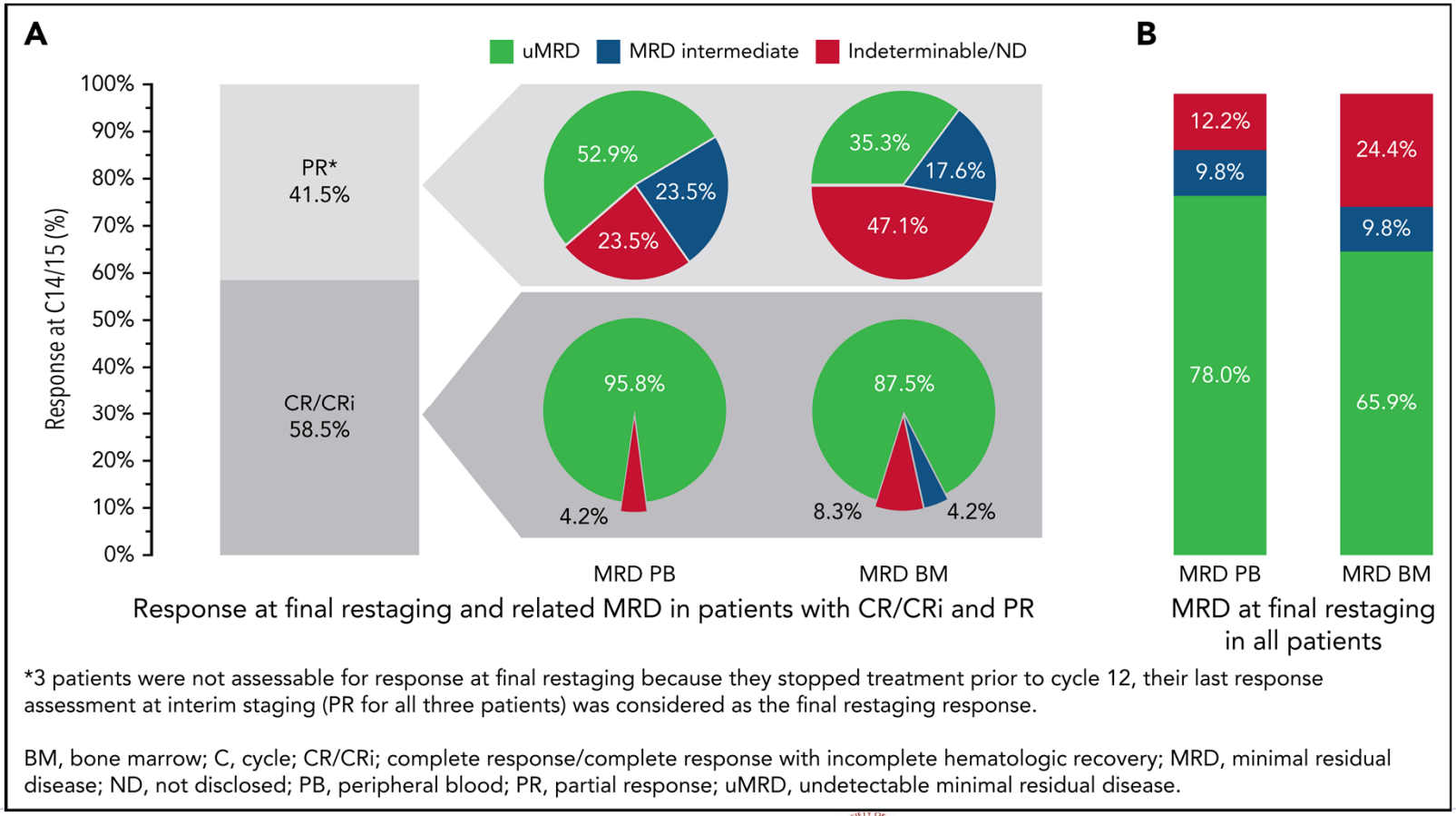
- **41 patients - median age 62 (35-85)**
- **del(17p) in 26 pts, *TP53*mut in 39 pts**
- **32 pts unmutated IgHV**

- **grade 3-5 AEs over entire study were neutropenia (48.8%), thrombocytopenia (17.1%), infections (19.5%)**
- **AEs of any grade in 85.4% were mostly low grade GI**
- **Any grade A-fib in 14.6% of pts.**

Huber et al. Obin/Ibr/Ven (GIVe) for frontline Rx for high-risk CLL, Blood, 2022



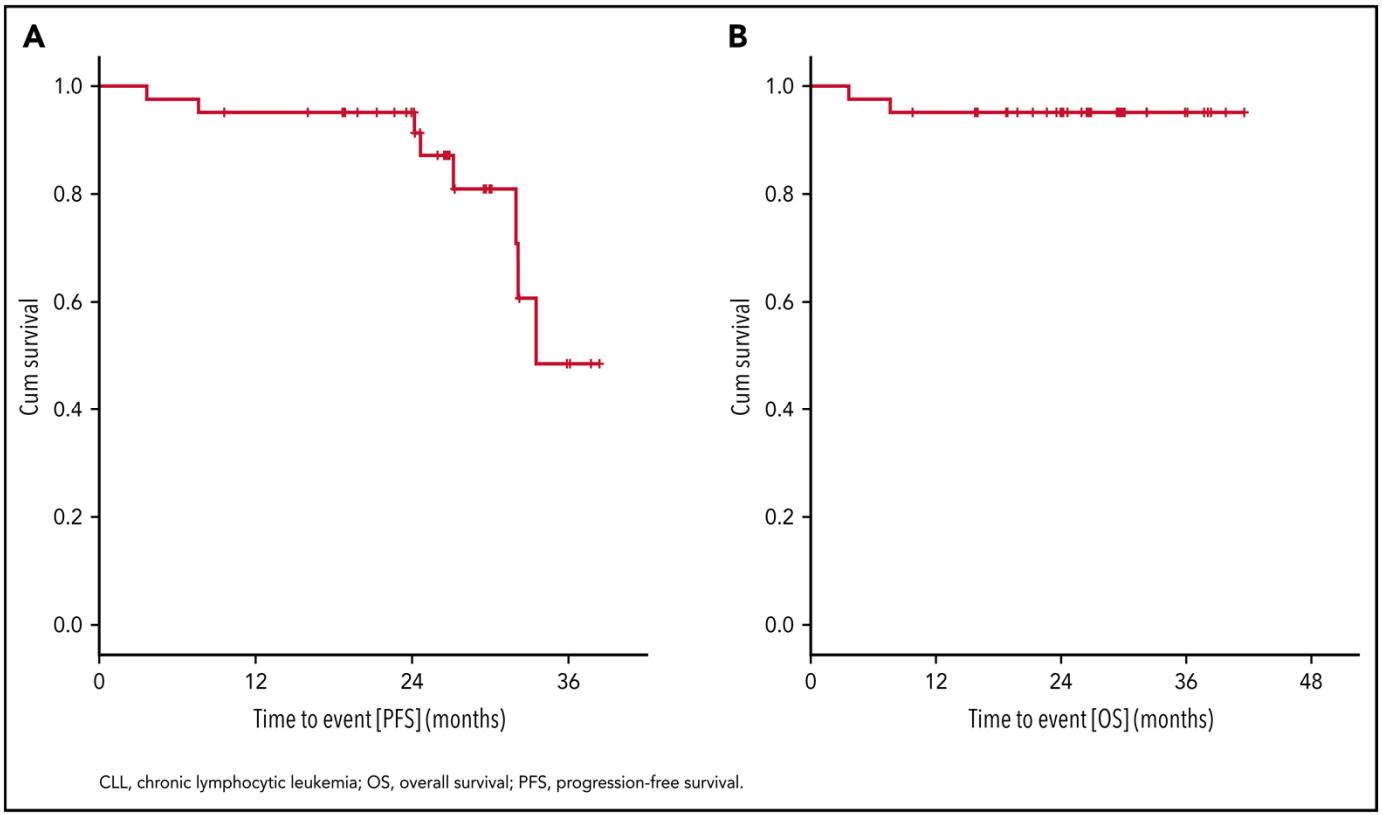
Huber et al. Obin/Ibr/Ven (GIVe) frontline Rx for high-risk CLL, Blood, 2022



*3 patients were not assessable for response at final restaging because they stopped treatment prior to cycle 12, their last response assessment at interim staging (PR for all three patients) was considered as the final restaging response.

BM, bone marrow; C, cycle; CR/CRi; complete response/complete response with incomplete hematologic recovery; MRD, minimal residual disease; ND, not disclosed; PB, peripheral blood; PR, partial response; uMRD, undetectable minimal residual disease.

Huber et al. Obinutuzumab, ibrutinib, and venetoclax (GIVe) frontline treatment for high-risk chronic lymphocytic leukemia, Blood, 2022



CLL, chronic lymphocytic leukemia; OS, overall survival; PFS, progression-free survival.

CLL: Therapeutic Agents

Chemotherapy	CD20 mAb	BTKi	PI3Ki	BCL-2i	Others
Chlorambucil	Rituximab	Ibrutinib	Idelalisib	Venetoclax	Lenalidomide
Fludarabine	~~Ofatumumab*~~	Acalabrutinib	Duvelisib		CD19-CAR T-cell
Cyclophosphamide	Obinutuzumab	Zanubrutinib	~~Umbralisib*~~		
Bendamustine	Ublituximab	Tirabrutinib			
		Vecabrutinib			
		Nemtabrutinib			
		Pirtobrutinib			
		Luxeptinib			

*Applications for approval in CLL/SLL withdrawn

- FDA approved for 1L treatment of CLL in US
- FDA approved for >1L treatment of CLL in US
- Not FDA approved for CLL

BTK Inhibitor vs Bcl-2 Inhibitor: Which to Pick First?

BTK Inhibitor[1-4]

- Logistically easier
- Continuous and indefinite therapy
- TLS not a concern
- More cardiac risk (A-fib)
- ? favored in del(17p)/*TP53* mutation
- long term efficacy data
- Phase III data compared to FCR or BR

Bcl-2 Inhibitor[4,5]

- Risk for TLS requires monitoring and has cumbersome initiation
- Includes CD20 mAb with higher risk of immunosuppression
- Fixed duration – Patient Preference
- Cost savings
- GFR sensitivity
- May not be best for high-risk 17p/ p53 patients

1. Acalabrutinib PI. 2. Ibrutinib PI. 3. Zanubrutinib PI. 4. Awan. Am Soc Clin Oncol Educ Book. 2020;40:1. 5. Venetoclax PI.

Conclusions and Questions for Frontline Therapy of CLL/SLL

- **BTKi can produce long remissions with continuous therapy**
- **Ven/Obin is finite 1 year of therapy with high rates of uMRD**
- **Small molecule BTKi/Ven combinations result in high rates of uMRD**

  - **Do we need anti-CD20 antibody with small molecule combinations?**
  - **Is Ibr/Ven/Obin better than Ven/Obin?**
  - **Results of re-treatment after finite duration regimens? Is the risk of resistance/transformation increased while off therapy o less likely with combination therapy?**
  - **Does uMRD matter for OS? Can we cure some cases with combinations?**

Summary of Treatment for Relapsed/Refractory CLL/SLL

- **2nd generation BTKi favored over 1st generation based on safety profile**
- **After frontline Bcl-2 therapy, BTKi effective vs. Ven re-treatment**
- **PI3K inhibitors poorly defined role in CLL post BTKi and Ven**
- **Still an option for BR, FCR, lenalidomide +/- rituximab**
- **Noncovalent BTK inhibitors coming soon!**
- **BTK degraders and CAR-T on horizon – refer for clinical trials!**