Updates in CLL

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American Society of Hematology
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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

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ALPINE Study Design

R/R CLL/SLL with ≥ 1 prior treatment

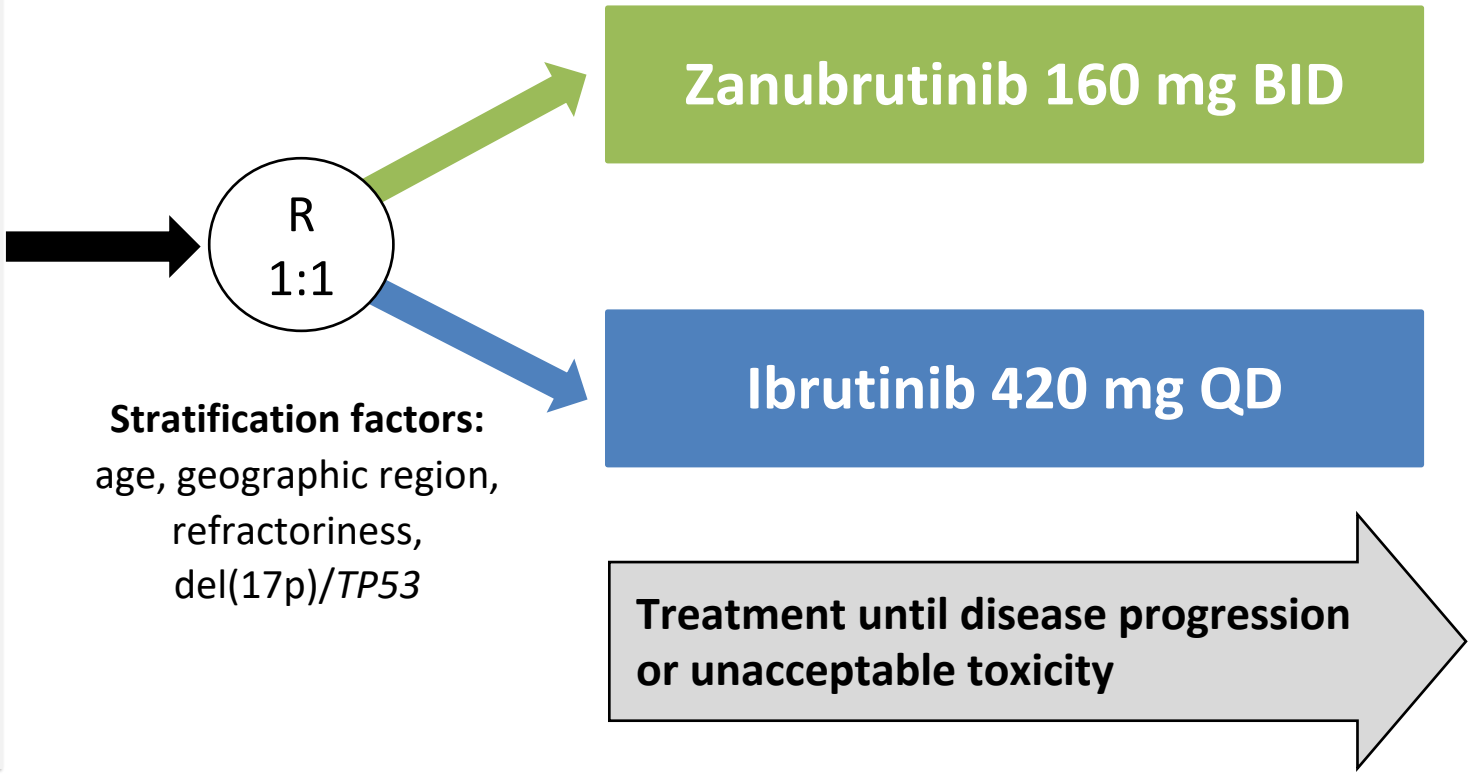
(Planned N=600, Actual N=652)

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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Endpoints and Statistical Design

Primary Endpoint

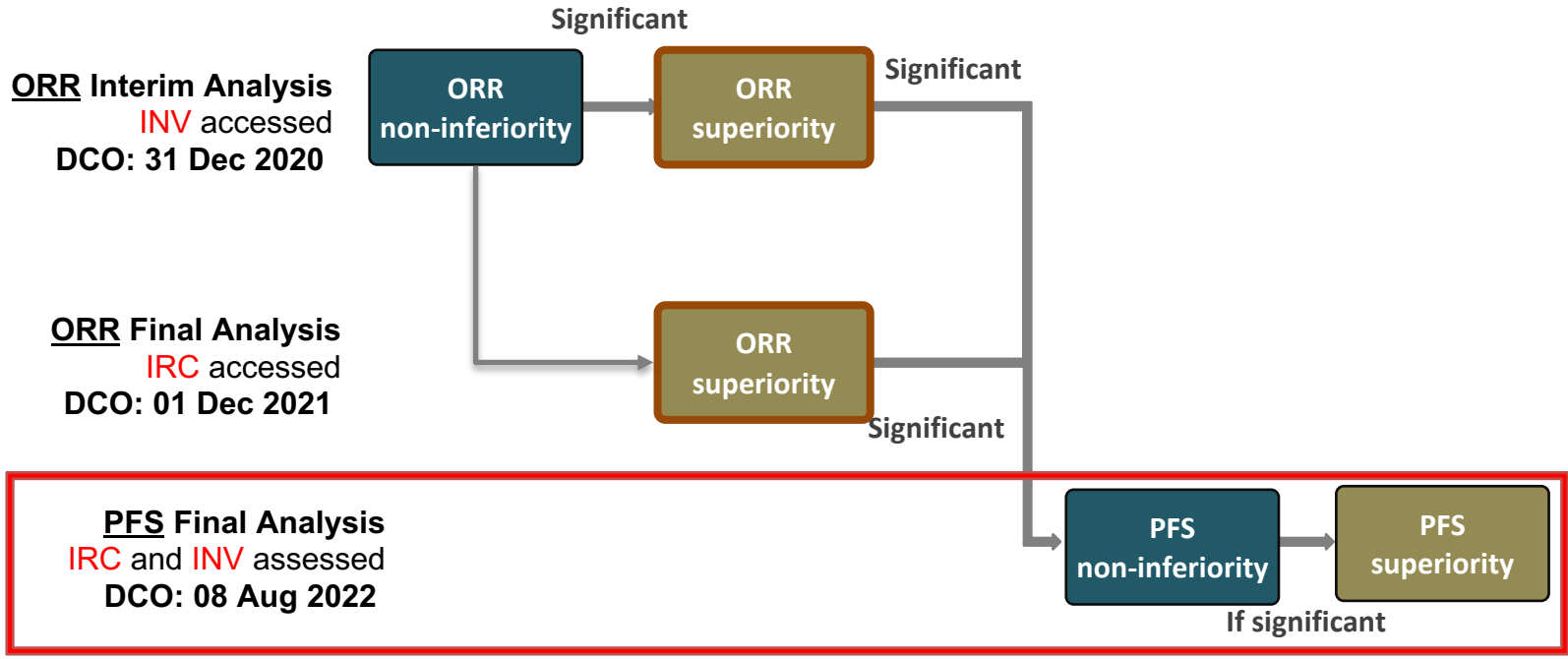
- ORR (PR+CR) noninferiority and superiority (by investigator)

Key Secondary Endpoints

- PFS
- Incidence of atrial fibrillation

Other Secondary Endpoints

- DoR, OS
- Time to treatment failure
- PR-L or higher
- Patient-reported outcomes
- Safety



Overall response rate noninferiority and superiority were demonstrated in the ORR interim and final analyses; PFS was tested for noninferiority under hierarchical testing when 205 events had occurred

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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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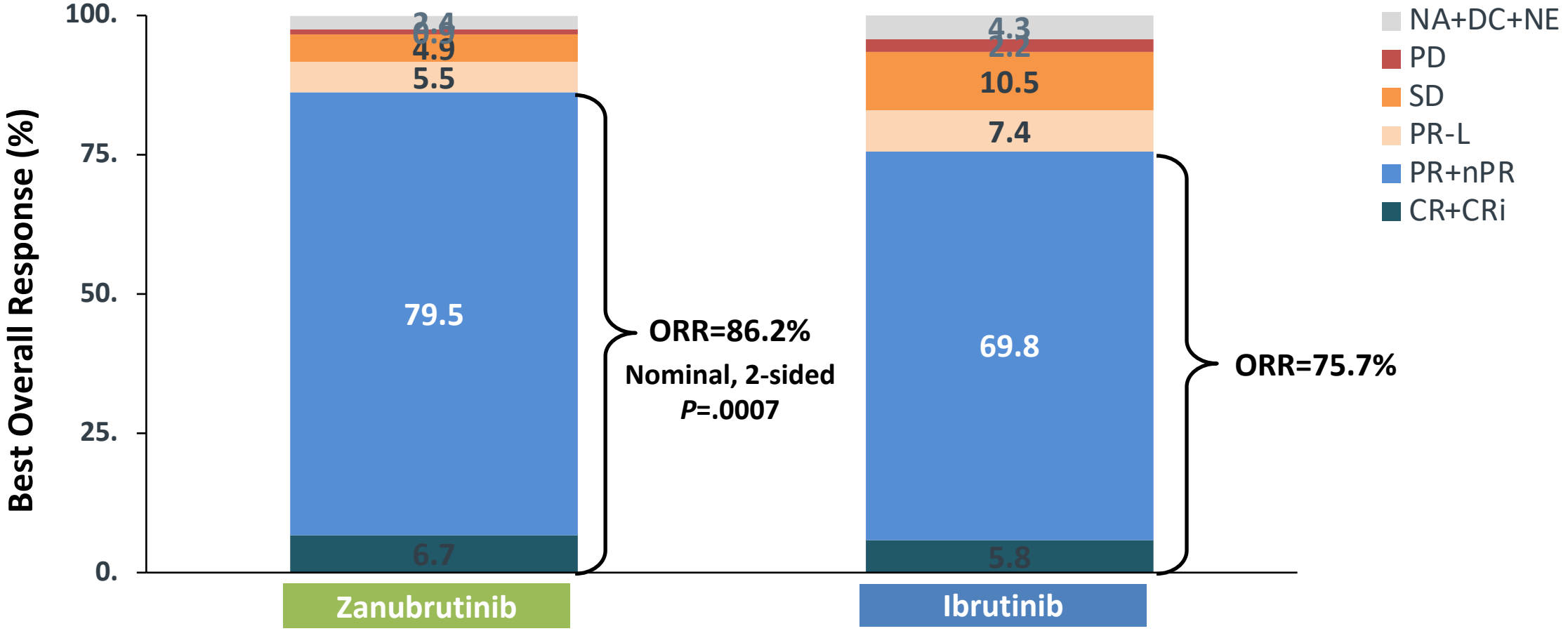
Zanubrutinib Showed Higher ORR Assessed by IRC



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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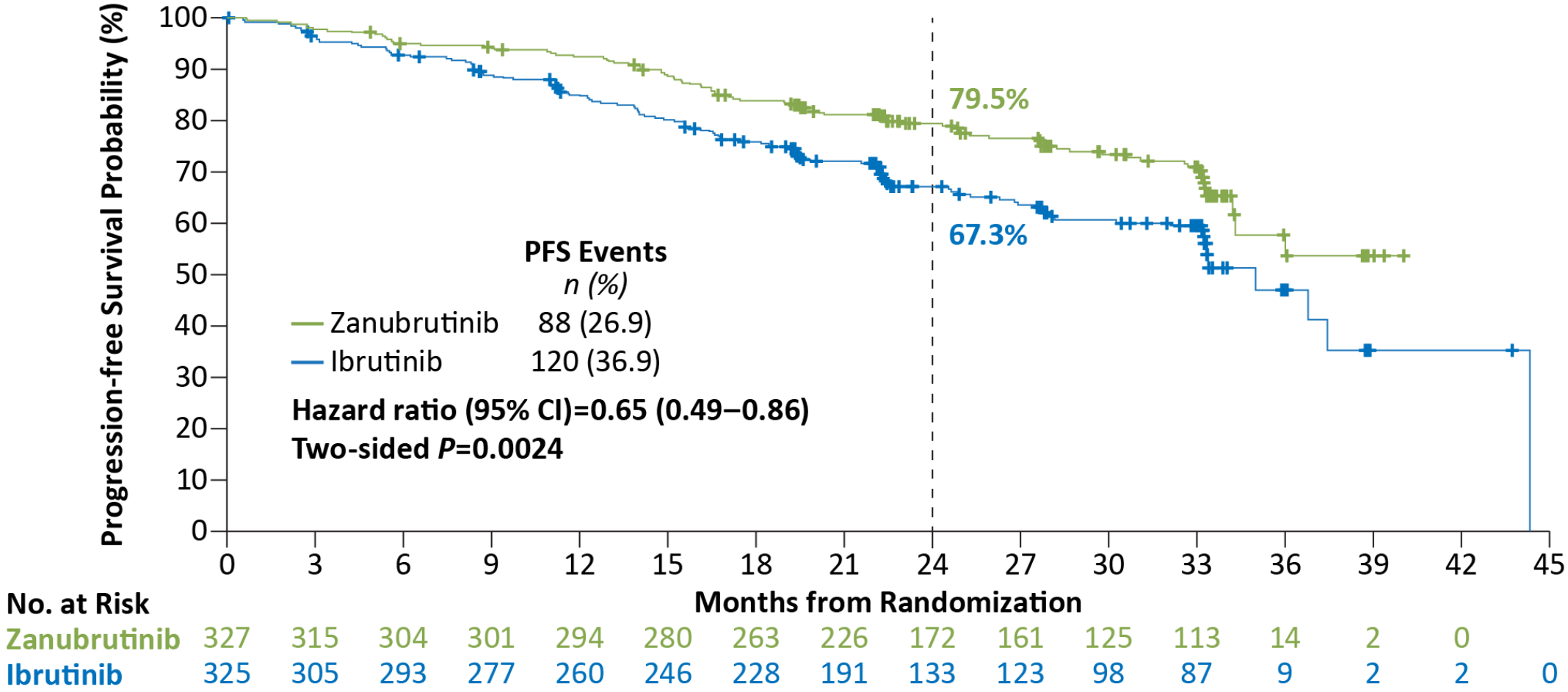
Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

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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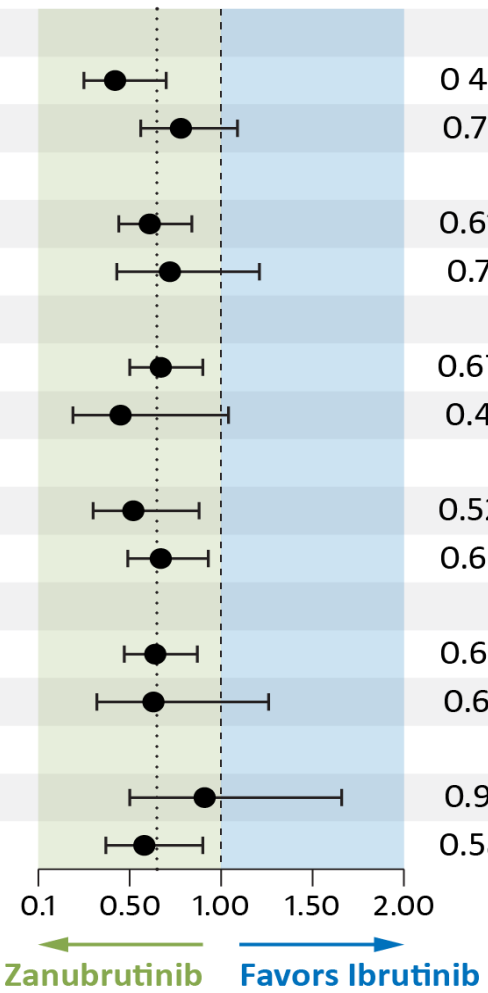
PFS Favored Zanubrutinib Across Subgroups

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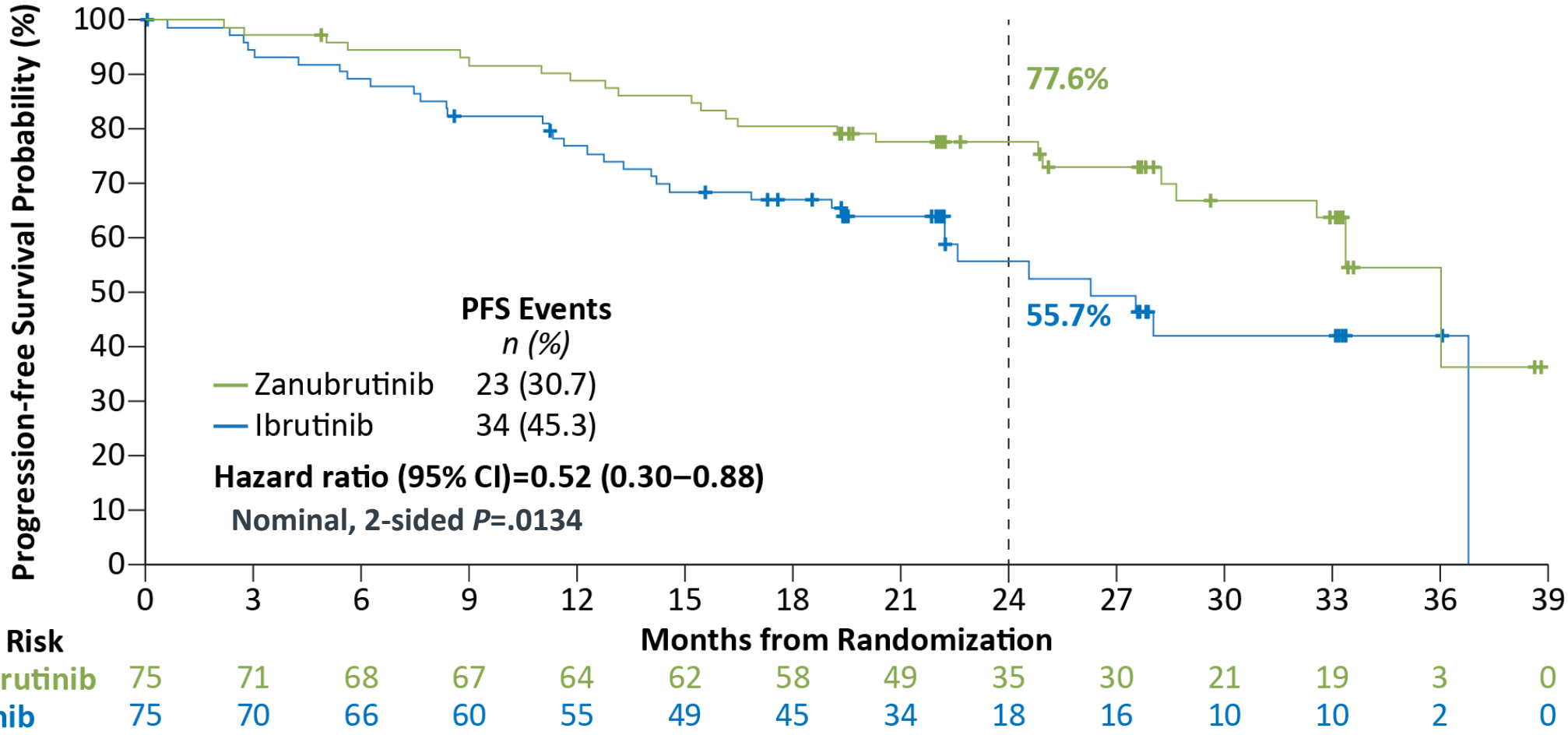
Zanubrutinib Improved PFS in Patients with del(17p)/*TP53*^{mut}



PFS data assessed by IRC

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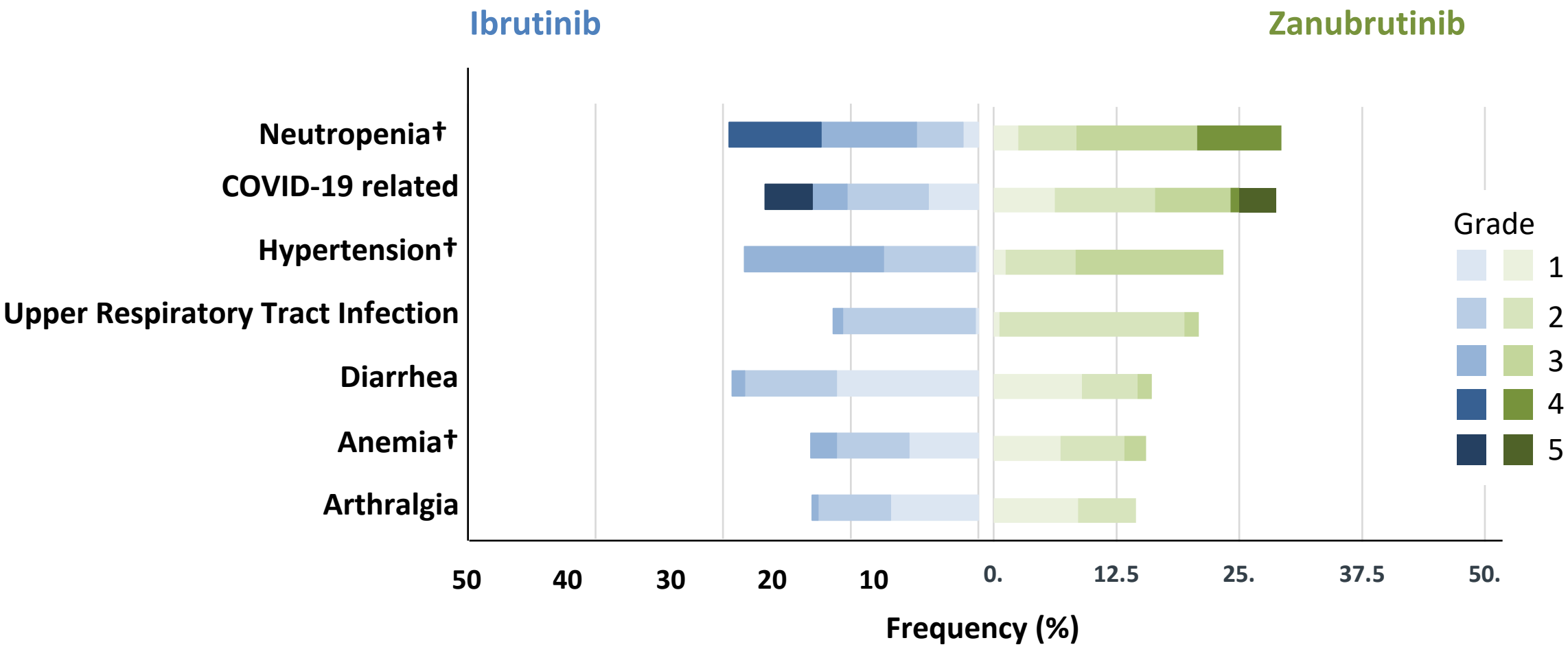
Most Common Adverse Events*



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

Data cutoff: 8 Aug 2022

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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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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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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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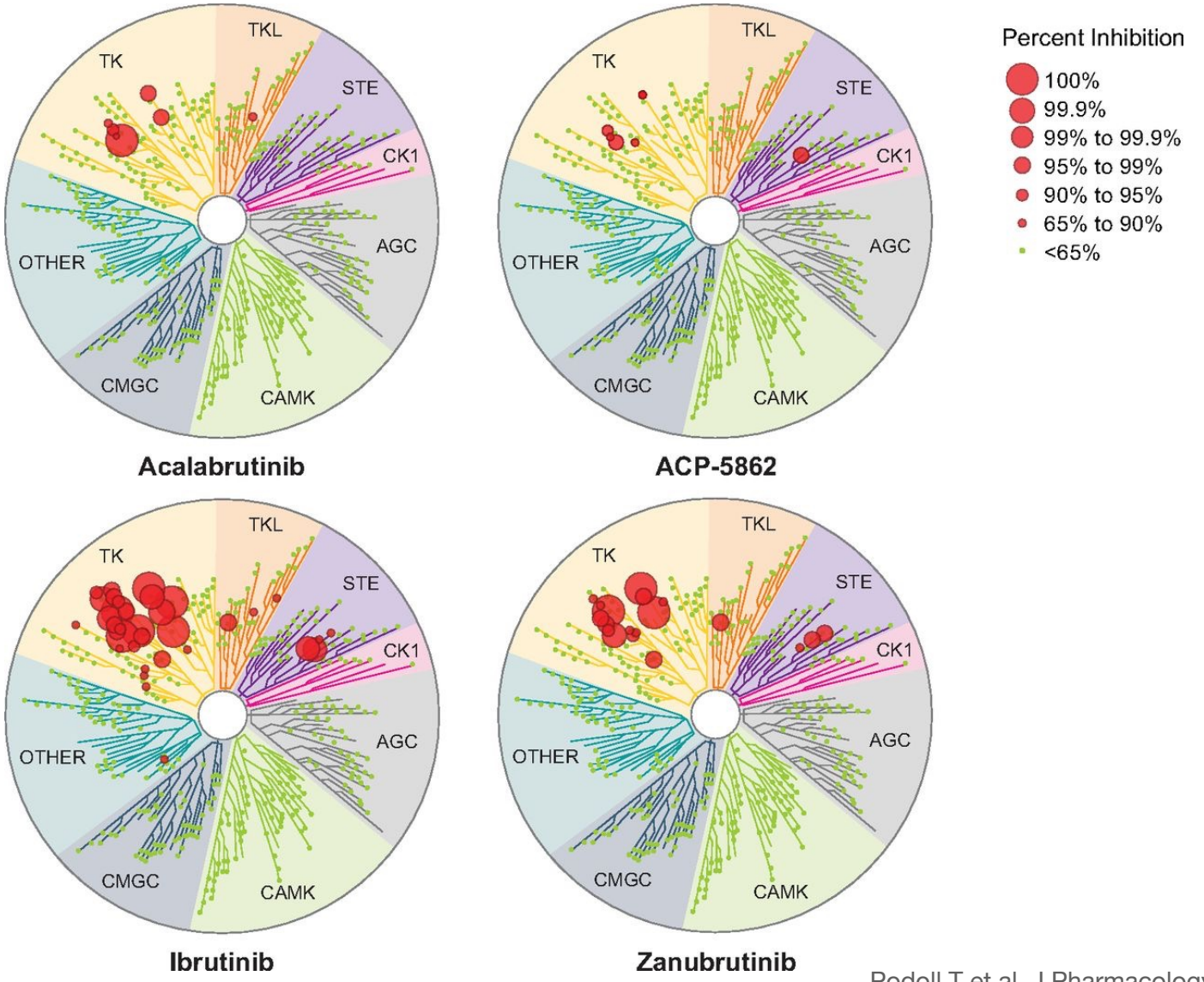
FDA approves zanubrutinib for chronic lymphocytic leukemia or small lymphocytic lymphoma

On January 19, 2023, the Food and Drug Administration (FDA) approved zanubrutinib (Brukinsa, BeiGene USA, Inc.) for chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).

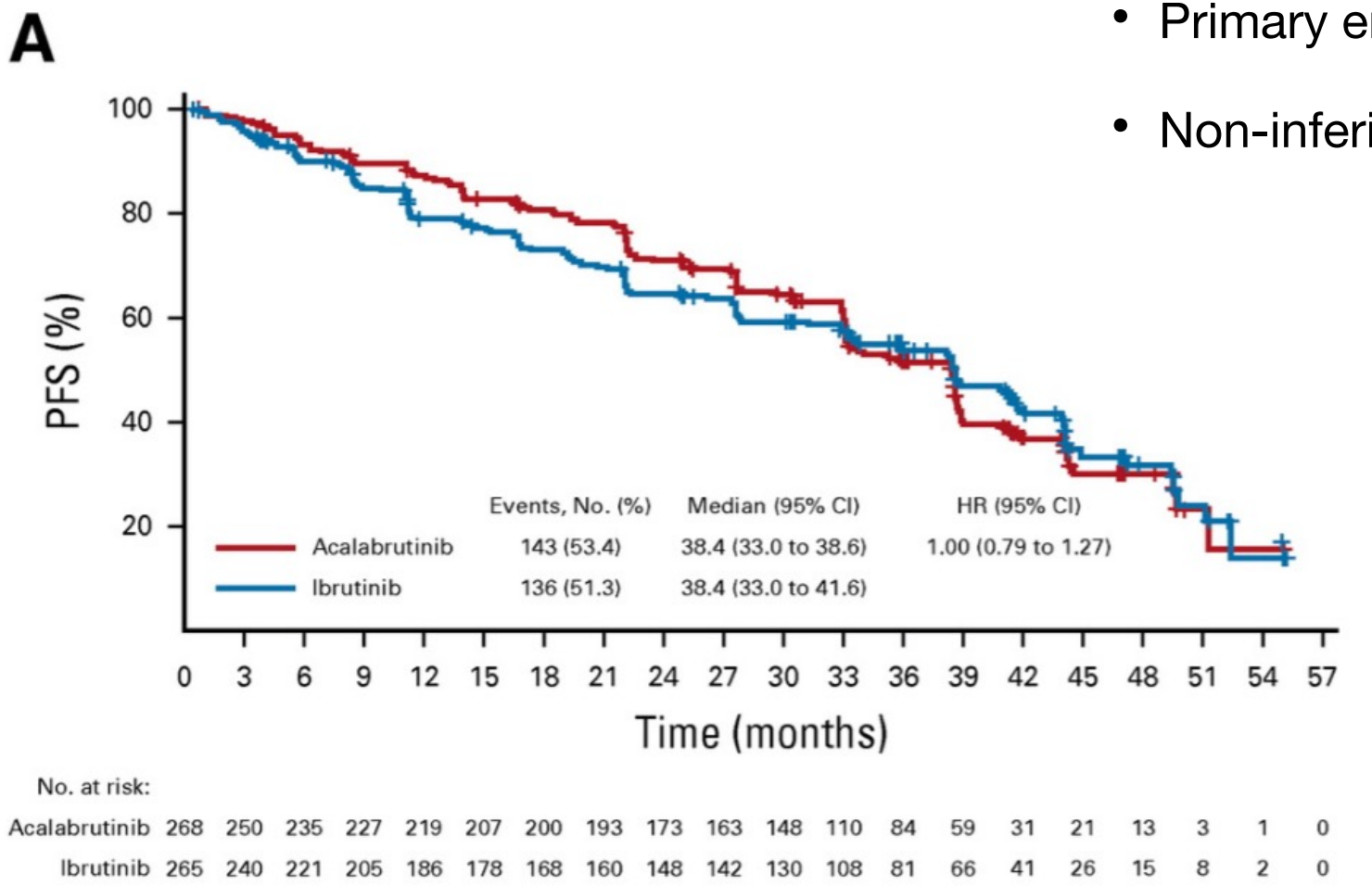
So - which BTKi do we use now?



Podoll T et al. J Pharmacology and Experimental Therapeutics, 2023.

So - which BTKi do we use now?

ELEVATE-RR



- Primary endpoint: PFS
- Non-inferiority

ELEVATE-RR; Byrd J et al, JCO. 2021.

So - which BTKi do we use now?

ELEVATE-RR

Events	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
Ventricular arrhythmia or cardiac arrest	1 (0.4)	1 (0.4)	5 (1.9)	3 (1.1)
Cardiorespiratory arrest	1 (0.4)	1 (0.4)	0	0
Cardiac arrest	0	0	2 (0.8)	2 (0.8)
Ventricular arrhythmia	0	0	1 (0.4)	0
Ventricular extrasystoles	0	0	1 (0.4)	0
Ventricular fibrillation	0	0	1 (0.4)	1 (0.4)
Atrial fibrillation[b]	25 (9.4)[c]	13 (4.9)	42 (16.0)	10 (3.8)
Events/100 person-months	0.366	0.155	0.721	0.124
Age 75 years or older	8 (32.0)	6 (46.2)	11 (26.2)	4 (40.0)
Patients with a history of atrial fibrillation	10 (40.0)	6 (46.2)	5 (11.9)	2 (20.0)
Patients with risk factors[d]	23 (92.0)	12 (92.3)	32 (76.2)	8 (80.0)
Hypertension	15 (60.0)	6 (46.2)	23 (54.8)	6 (60.0)
Diabetes mellitus[e]	10 (40.0)	5 (38.5)	4 (9.5)	2 (20.0)
Myocardial infarction/ischemia	3 (12.0)	3 (23.1)	4 (9.5)	0
Cardiac disease[f]	2 (8.0)	2 (15.4)	5 (11.9)	2 (20.0)

*Excluded “significant cardiovascular disease” and use of warfarin.

ELEVATE-RR; Byrd J et al, JCO. 2021.

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Data cutoff: 8 Aug 2022

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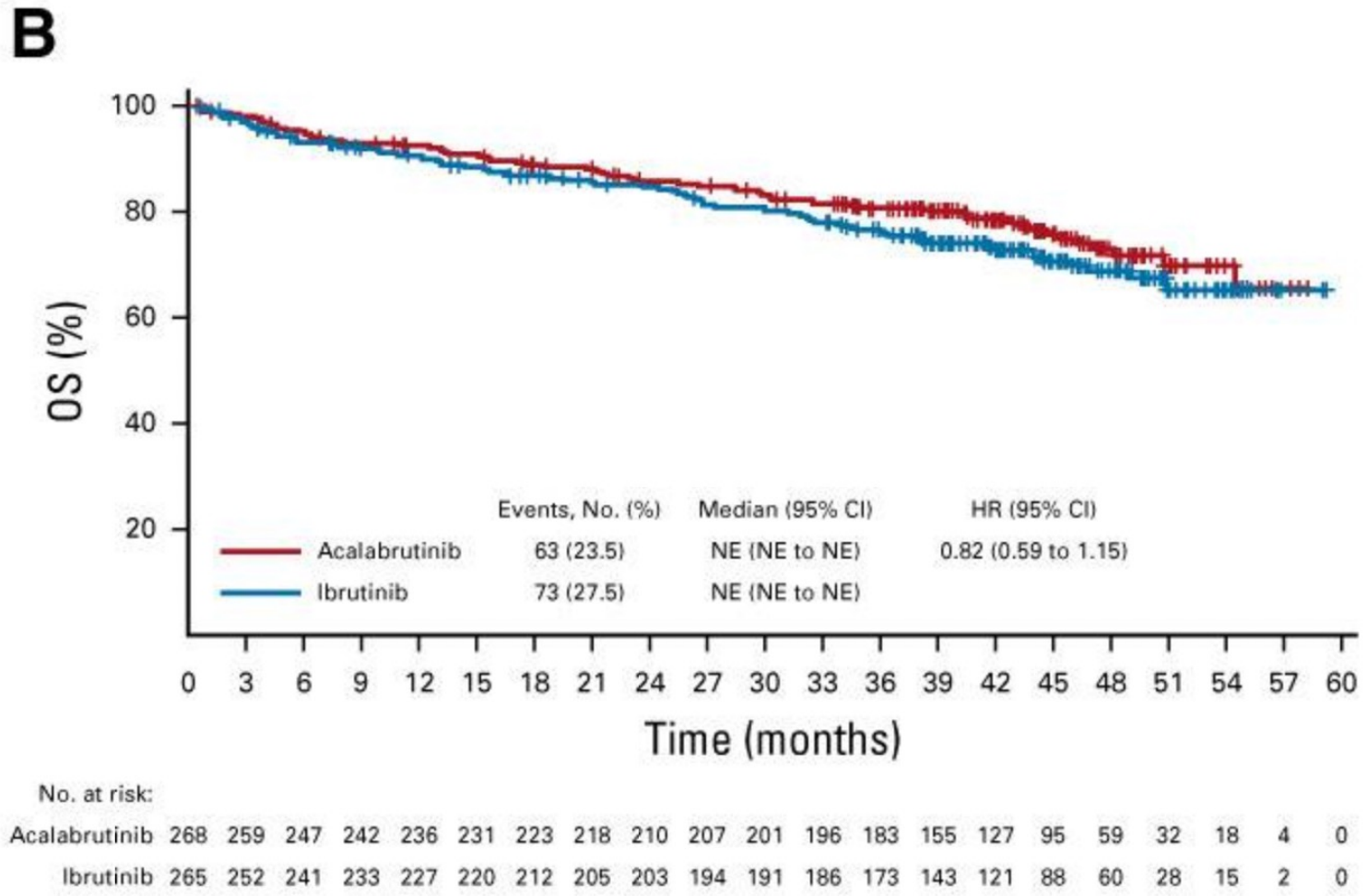
So - which BTKi do we use now?

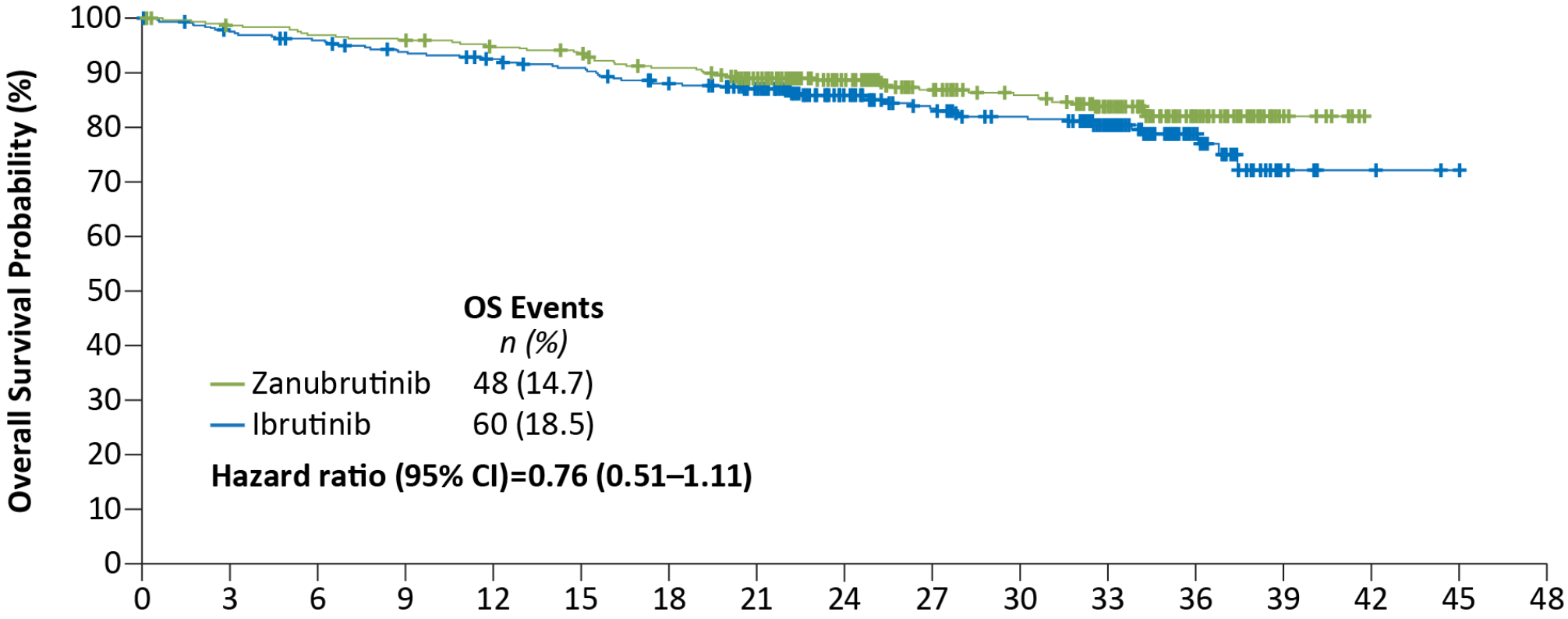
ELEVATE-RR



ELEVATE-RR; Byrd J et al, JCO. 2021.

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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So how will we decide?

- Zanu seems to have less cardiac tox, but NO DIRECT COMPARISON to acala.
  - Different patient populations? More time needed?
- Does BTK occupancy matter?
- Zanu = 4 capsules; acala = 2 tablets
- Option with give acala with obina (ELEVATE-TN)
- No PPI issue anymore with acala
- Will payers have a preference?

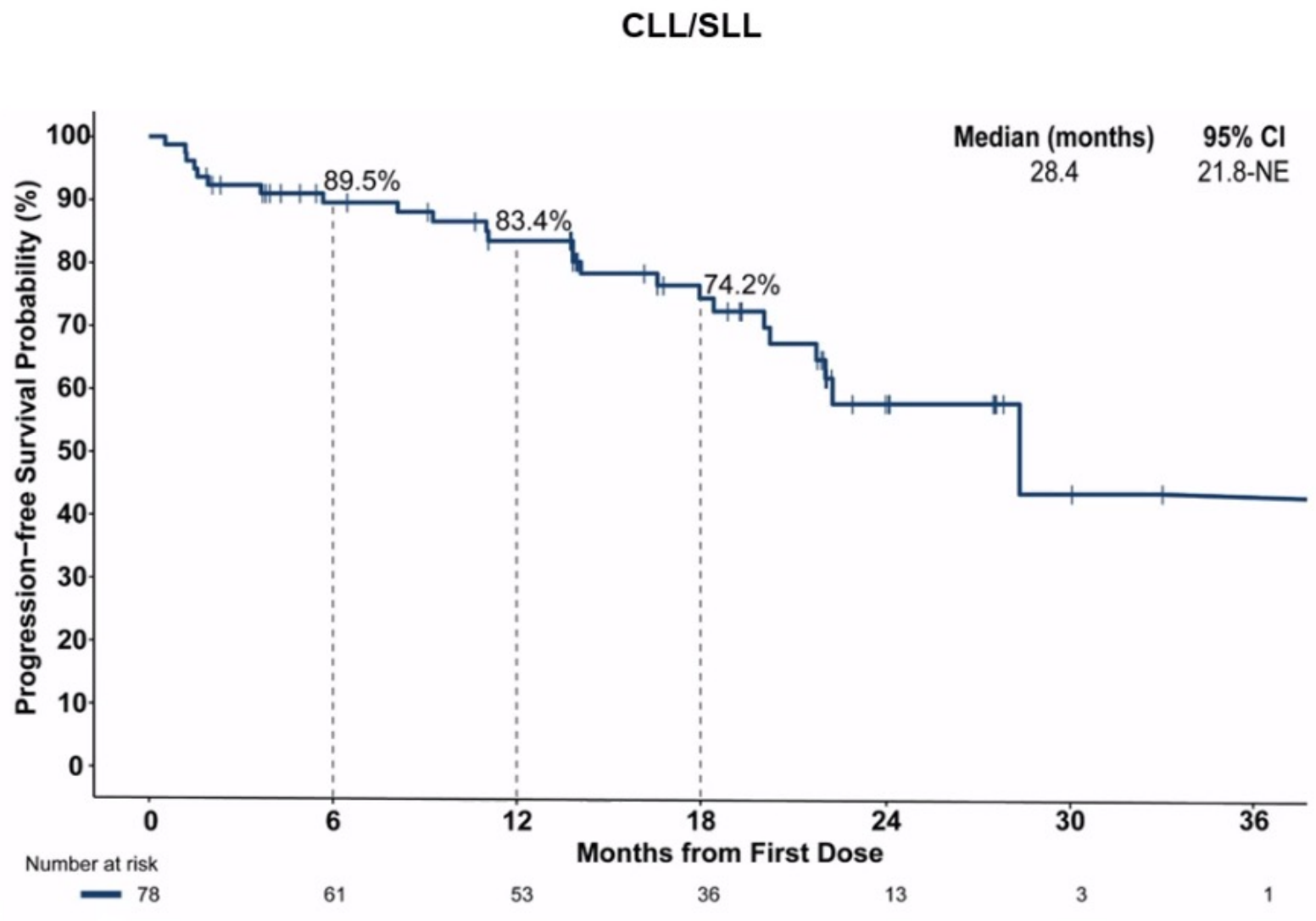
1797

Safety and Tolerability of Pirtobrutinib Monotherapy in Patients with B-cell Malignancies Who Were Previously Intolerant to a Covalent BTK Inhibitor: Results from the Phase 1/2 BRUIN Study

Nirav N. Shah[1], Michael Wang[2], Jennifer R. Brown[3], Krish Patel[4], Jennifer Woyach[5], William G. Wierda[6], Chaitra S. Ujjani[7], Toby A. Eyre[8], Pier Luigi Zinzani[9], Alvaro J. Alencar[10], Thomas Gastinne[11], Paolo Ghia[12], Nicole Lamanna[13], Marc S. Hoffmann[14], Manish R. Patel[15], Ian Flinn[16], James N. Gerson[17], Shuo Ma[18], Catherine C. Coombs[19], Chan Y. Cheah[20], Ewa Lech-Maranda[21], Bita Fakhri[22], Won Seog Kim[23], Minal A. Barve[24], Jonathon B. Cohen[25], Wojciech Jurczak[26], Talha Munir[27], Meghan C. Thompson[28], Lindsey E. Roeker[28], Katherine Bao[29], Nicholas A. Cangemi[29], Jennifer F. Kherani[29], Richard A. Walgren[29], Hongmei Han[29], Amy S. Ruppert[30], Anthony R. Mato[28]

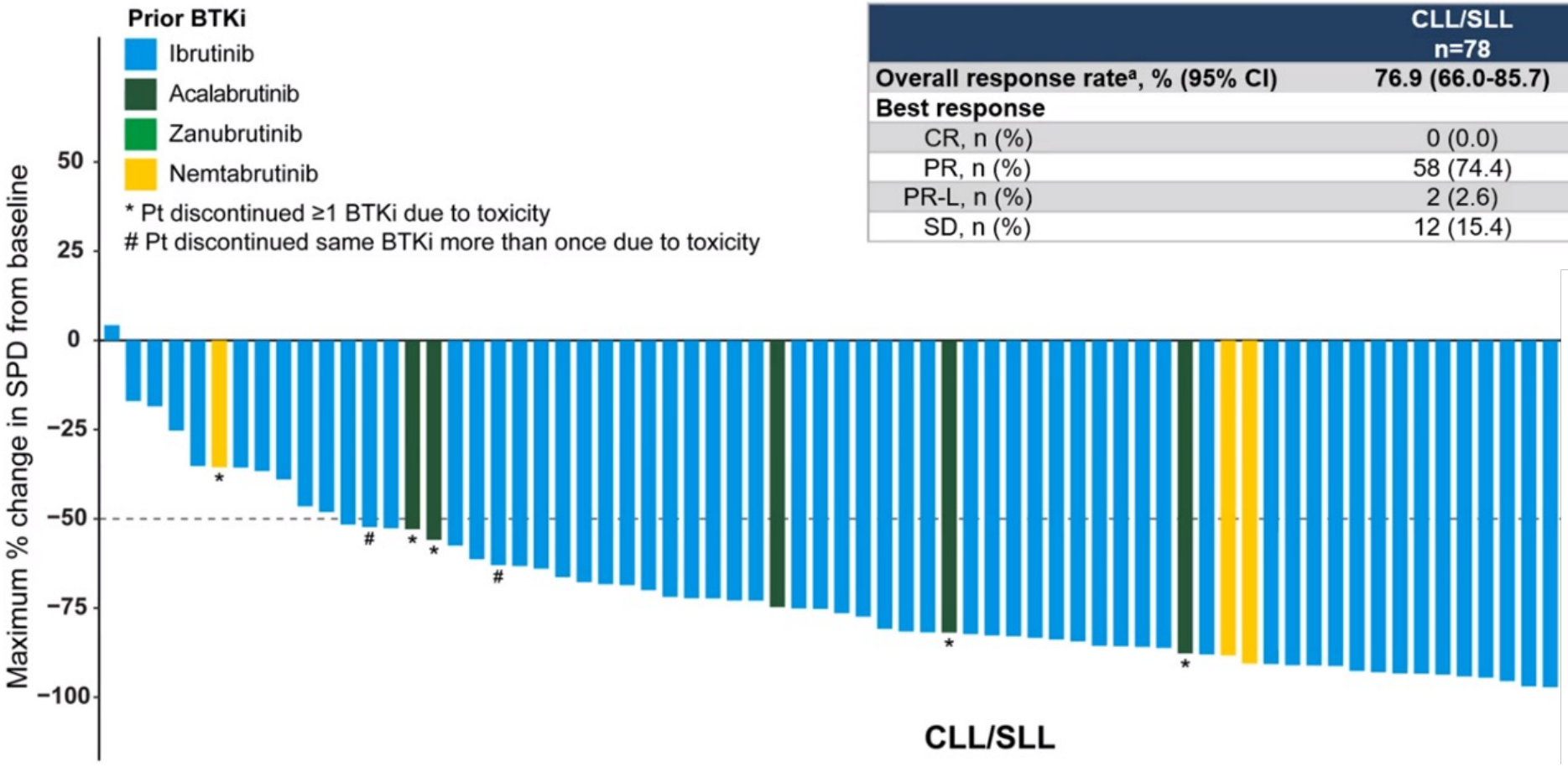
[1]Medical College of Wisconsin, Milwaukee, WI, USA; [2]MD Anderson Cancer Center, Houston, TX, USA; [3]Chronic Lymphocytic Leukemia Center, Division of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; [4]Swedish Cancer Institute, Center for Blood Disorders and Cellular Therapy, Seattle, WA, USA; [5]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [6]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [8]Oxford University Hospitals NHS Foundation Trust, Churchill Cancer Center, Oxford, UK; [9]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [10]University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA; [11]Haematology Department, University Hospital, Nantes, France; [12]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy; [13]New York-Presbyterian Columbia University Medical Center, New York, NY, USA; [14]Hematologic Malignancies and Cellular Therapeutics, University of Kansas Medical Center, Kansas City, KS, USA; [15]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL, USA; [16]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [17]Lymphoma Program, Abramson Cancer Center, Philadelphia, PA, USA; [18]Robert H. Lurie Comprehensive Cancer Center, Division of Hematology-Oncology, Northwestern University Feinberg School of Medicine, Chicago, IL, USA; [19]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA; [20]Linear Clinical Research and Sir Charles Gairdner Hospital, Perth, Australia; [21]Institute of Hematology and Transfusion Medicine, Warsaw, Poland; [22]Division of Hematology and Oncology, University of California, San Francisco, CA, USA; [23]Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [24]Mary Crowley Cancer Research Center, Dallas, TX, USA; [25]Winship Cancer Institute, Emory University, Atlanta, GA, USA; [26]Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [27]Department of Haematology, St. James's University Hospital, Leeds, UK; [28]Memorial Sloan Kettering Cancer Center, New York

Pirtobrutinib (LOXO-305) efficacy in BTKi pre-treated patients



Shah NN et al, ASH 2022

Pirtobrutinib (LOXO-305) efficacy in BTKi pre-treated patients



	CLL/SLL n=78
Overall response rate[a], % (95% CI)	**76.9 (66.0-85.7)**
Best response	
CR, n (%)	0 (0.0)
PR, n (%)	58 (74.4)
PR-L, n (%)	2 (2.6)
SD, n (%)	12 (15.4)

Shah NN et al, ASH 2022

Pirtobrutinib (LOXO-305) safety profile in BTKi pre-treated patients

	Treatment-related AEs, %			
	Any Grade		Grade ≥3	
AE	**All Doses and Patients (N=773)**	**BTKi-Intolerant (n=127)**	**All Doses and Patients (N=773)**	**BTKi-Intolerant (n=127)**
Fatigue	9.3%	9.4%	0.8%	1.6%
Diarrhea	9.3%	12.6%	0.4%	0.8%
Neutropenia	14.7%	21.3%	11.5%	17.3%
Contusion	12.8%	22.0%	0.0%	0.0%
Cough	2.3%	4.7%	0.0%	0.0%
Covid-19	1.3%	0.0%	0.0%	0.0%
Nausea	4.7%	4.7%	0.1%	0.0%
Dyspnea	3.0%	5.5%	0.1%	0.0%
Anemia	5.2%	6.3%	2.1%	2.4%
AEs of Special Interest[a]	**All Doses and Patients (N=773)**	**BTKi-Intolerant (n=127)**	**All Doses and Patients (N=773)**	**BTKi-Intolerant (n=127)**
Bruising[b]	15.1%	26.8%	0.0%	0.0%
Rash[c]	6.0%	8.7%	0.4%	0.8%
Arthralgia	3.5%	4.7%	0.0%	0.0%
Hemorrhage/hematoma[d]	4.0%	4.7%	0.6%	0.8%
Hypertension	3.4%	3.1%	0.6%	0.0%
Atrial fibrillation/flutter[e,f]	0.8%	0.8%	0.1%	0.0%

Shah NN et al, ASH 2022

FDA grants accelerated approval to pirtobrutinib for relapsed or refractory mantle cell lymphoma

On January 27, 2023, the Food and Drug Administration (FDA) granted accelerated approval to pirtobrutinib [redacted] for relapsed or refractory mantle cell lymphoma (MCL) after at least two lines of systemic therapy, including a BTK inhibitor.

Where will pirto fit in?

- 3rd line? Sooner?
  - Ongoing study: ven + R +/- pirtobrutinib (fixed duration)

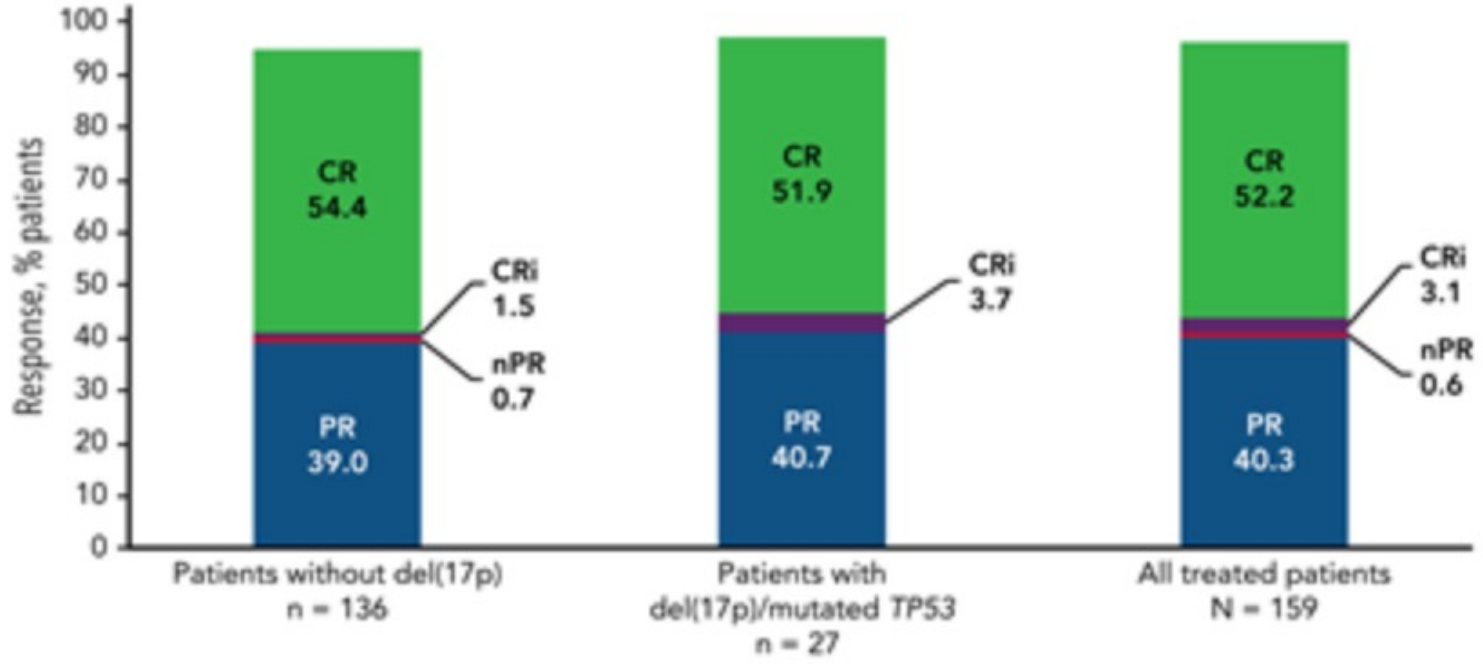
What else is coming?

- Covalent BTKi + BCL2i (Fixed duration? MRD-driven?)
- BTK degraders
- CART?
- Bi-speciifcs?

CAPTIVATE

Fixed Duration Cohort

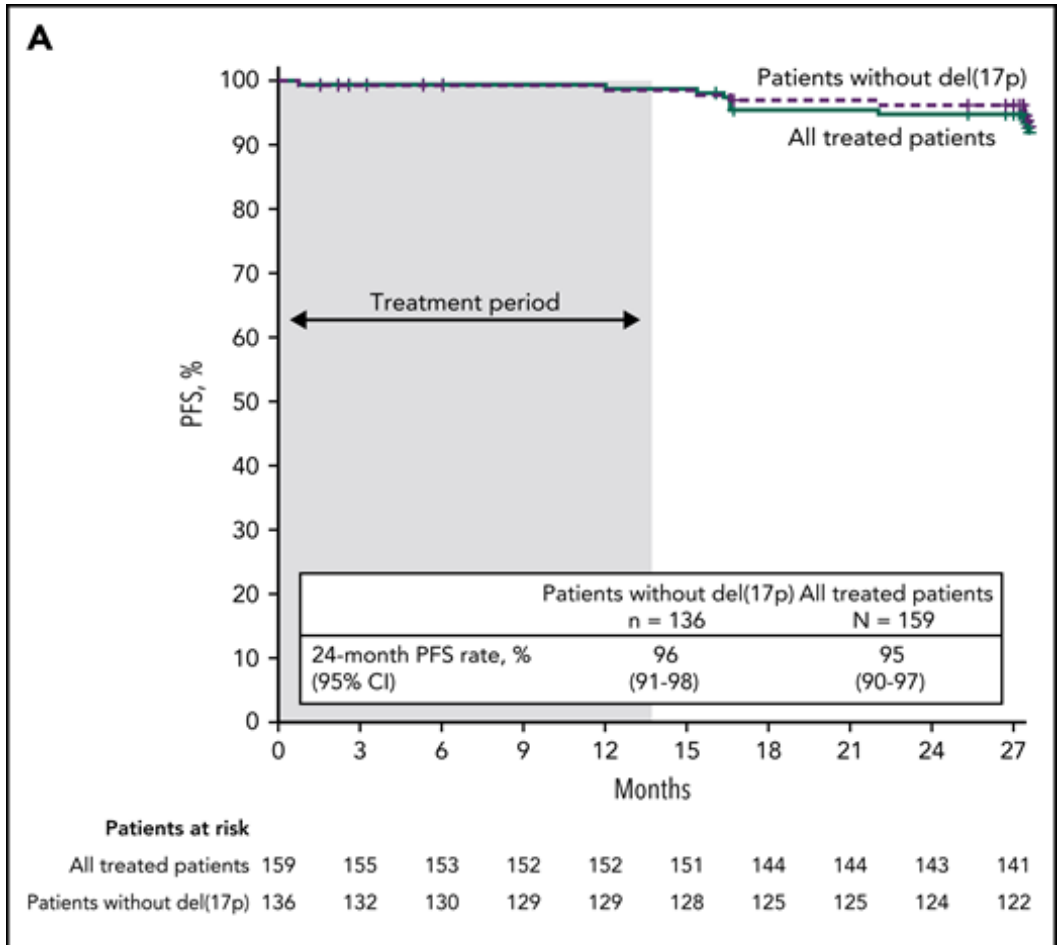
	Patients without del(17p) n = 136	Patients with del(17p)/mutated *TP53* n = 27	All treated patients N = 159
Best response, % (95% CI)			
CR/CRi	56 (48-64)	56 (37-74)	55 (48-63)
ORR	96 (92-99)	96 (89-100)	96 (93-99)
Duration of CR ≥12 cycles, n/N (%)	66/76 (87)	13/15 (87)	78/88 (89)*

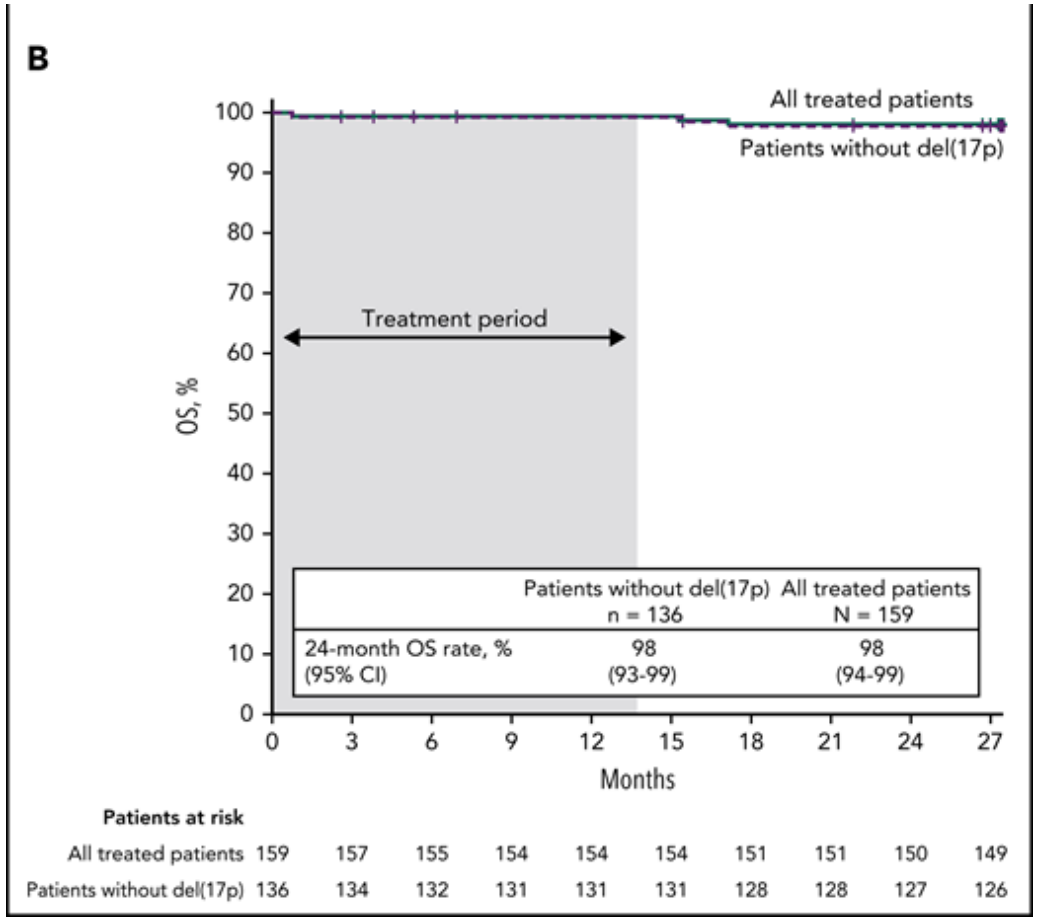


Tam CS et al, Blood, 2022

CAPTIVATE

Fixed Duration Cohort





Tam CS et al, Blood, 2022

CAPTIVATE

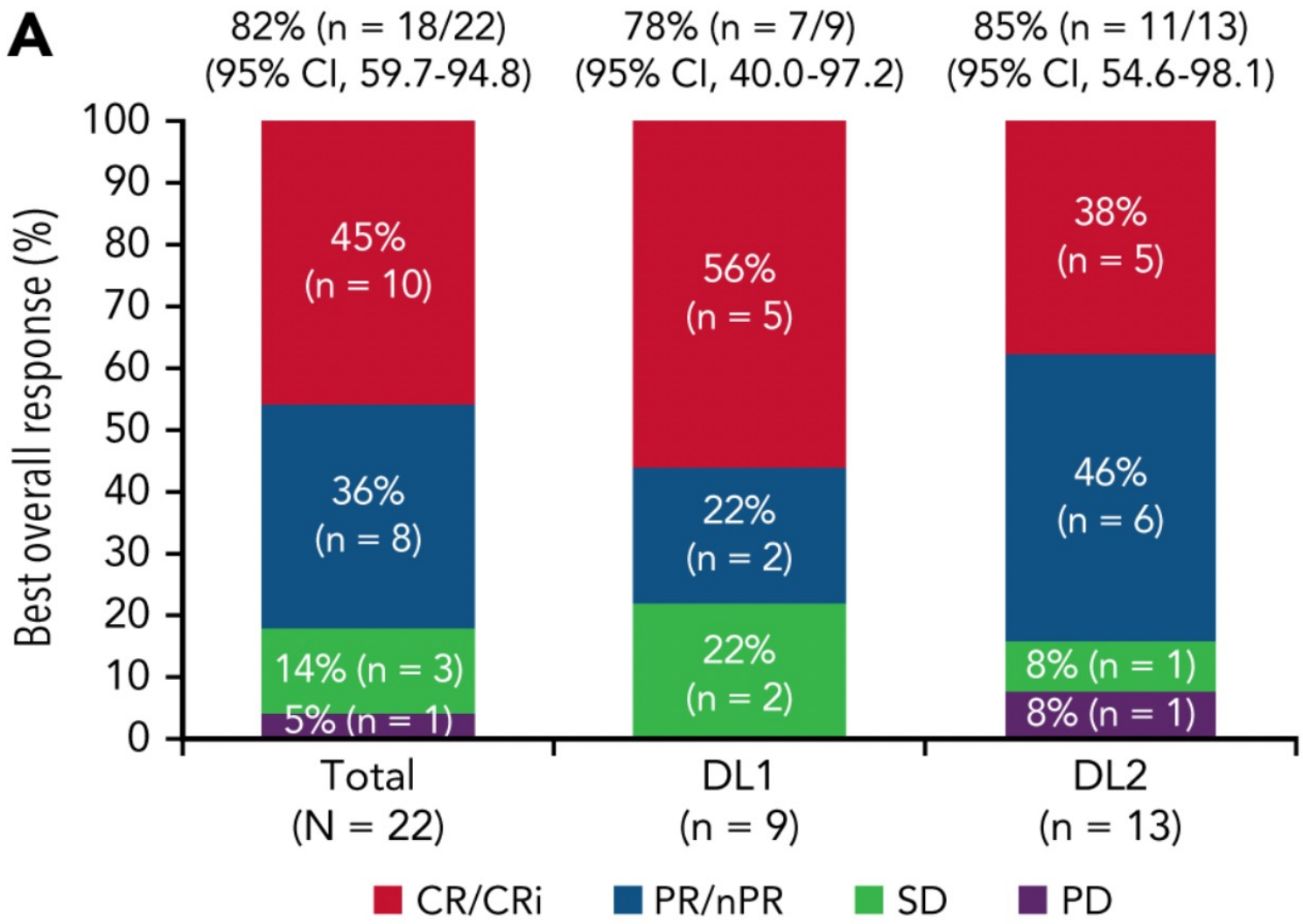
Fixed Duration Cohort

Treatment-emergent AEs

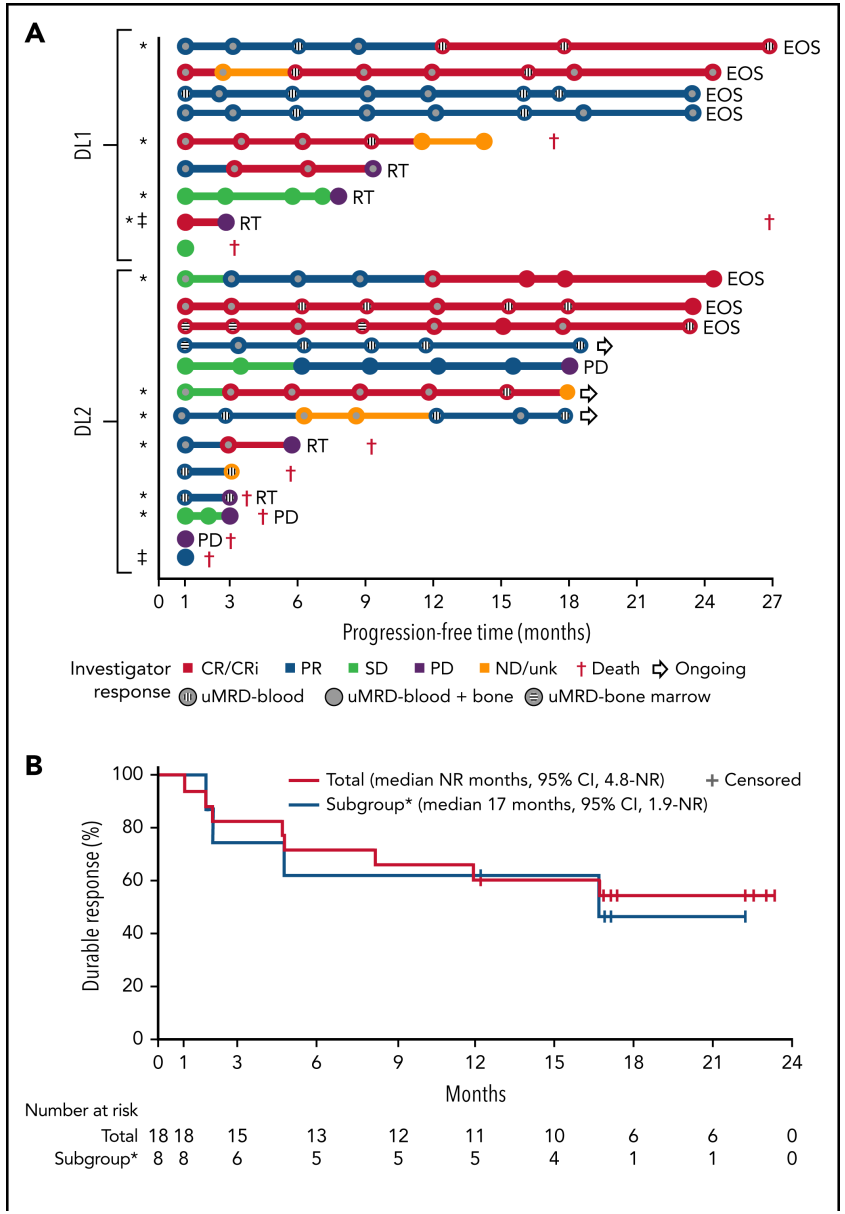
AEs	All treated patients (n = 159), n (%)	
	Any grade	Grade 3/4
Most common AEs*		
Diarrhea	99 (62)	5 (3)
Nausea	68 (43)	2 (1)
Neutropenia	66 (42)	52 (33)
Arthralgia	53 (33)	2 (1)
Hypertension	25 (16)	9 (6)
Neutrophil count decreased	16 (10)	8 (5)
Other AEs of clinical interest		
Atrial fibrillation	7 (4)	2 (1)
Major hemorrhage†	3 (2)	2 (1)

Tam CS et al, Blood, 2022

Phase 1 TRANSCEND CLL 004 study (liso-cel)



Siddiqi T et al, Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL, Blood, 2022, Figure 3.



Siddiqi T et al, Phase 1 TRANSCEND CLL 004 study of lisocabtagene maraleucel in patients with relapsed/refractory CLL or SLL, Blood, 2022, Figure 3.

Bi-Specific Data Limited to Date

- Higher risk of CRS?
- Epco in CLL: 100% CRS (but all grade 1-2), no TLS, no ICANS
  - 3/5 pts with PR (n=7; Kater AP et al, ASH 21)
- Epco in Richter's: 90% CRS (all gr 1-2), no ICANS, 1 case of TLS.
  - ORR 60%, CR 50% (n=10; Kater AP et al, ASH 22)

Summary

- We now have both zanu and acala for treatment of CLL.
  - Differences in study designs make comparisons between the 2 hard
- Movement is towards combination therapies with limited duration
- Pirtobrutinib likely to be available soon for after covalent BTKi and BCL2i
  - Not 100% clear what will be next after pirto —> BTK degraders? CAR? Bi-specific? Something else?

Questions?

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