Chronic Lymphocytic Leukemia Update

Boyu Hu, MD

January 26th, 2024

Annual Hematology and Breast Cancer Update for Oregon Health Sciences University

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

Disclosures

- **Consulting:** Novartis, Bristol Meyers Squibb, Eli Lilly, GenMab, ADC Therapeutics, ImmPACT Bio, Seattle Genetics, Regeneron, Caribou Biosciences

- **Research Funding:** Genentech, Celgene, CRISPR Therapeutics, Morphosys AG, Caribou Biosciences, Repare Therapeutics, Artiva Biotherapeutics, Newave, AstraZeneca, ImmPACT Bio

- **Grant Funding:** Lymphoma Research Foundation

Extended Follow Ups of Prior Trials

Extended Follow-up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-free Survival of Zanubrutinib Versus Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL)

Jennifer R. Brown, MD, PhD[1]; Barbara Eichhorst, MD[2]; Nicole Lamanna, MD[3]; Susan M. O'Brien, MD[4]; Constantine S. Tam, MBBS, MD[5,6]; Lugui Qiu, MD[7]; Maciej Kaźmierczak, MD, PhD[8]; Wojciech Jurczak, MD, PhD[9]; Keshu Zhou, MD, PhD[10]; Martin Simkovic, MD, PhD[11,12]; Jiri Mayer, MD[13]; Amanda Gillespie-Twardy, MD[14]; Alessandra Ferrajoli, MD[15]; Peter S. Ganly, BMBCh, MD[16]; Robert Weinkove, MBBS, PhD[17,18]; Sebastian Grosicki, MD, PhD[19]; Andrzej Mital, MD, PhD[20]; Tadeusz Robak, MD, PhD[21]; Anders Osterborg, MD, PhD[22,23]; Habte A. Yimer, MD[24]; Megan (Der Yu) Wang, PharmD[25]; Tommi Salmi, MD[26]; Liping Wang[27];Jessica Li, MS[27]; Kenneth Wu, PhD[25]; Aileen Cohen, MD, PhD[25]; Mazyar Shadman, MD, MPH[28,29]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA; [2]Department of Internal Medicine, University of Cologne, Center for Integrated Oncology Aachen, Bonn, Cologne, Duesseldorf, Cologne, Germany; [3]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA; [4]Chao Family Comprehensive Cancer Center, University of California, Irvine, CA, USA; [5]The Alfred Hospital, Melbourne, Victoria, Australia; [6]Monash University, Melbourne, Victoria, Australia; [7]State Key Laboratory of Experimental Hematology, National 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; [8]Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poznan, Poland; [9]MSC National Research Institute of Oncology, Krakow, Poland; [10]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China; [11]4th Department of Internal Medicine – Haematology, University Hospital Hradec Kralove, Czech Republic; [12]Faculty of Medicine in Hradec Kralove, Charles University, Czech Republic [13]Department of Internal Medicine-Hematology and Oncology, Masaryk University and University Hospital, Brno, Czech Republic; [14]Blue Ridge Cancer Care, Roanoke, VA, USA; [15]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [16]Department of Haematology, Christchurch Hospital, Christchurch, New Zealand; [17]Te Rerenga Ora Blood and Cancer Centre, Te Whatu Ora Health New Zealand Capital Coast & Hutt Valley, Wellington, New Zealand; [18]Cancer Immunotherapy Programme, Malaghan Institute of Medical Research, Wellington, New Zealand; [19]Medical University of Silesia, Katowice, Poland; [20]Department of Hematology and Transplantology, Medical University of Gdańsk, Gdańsk, Poland; [21]Medical University of Lodz, Lodz, Poland; [22]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [23]Department of Hematology, Karolinska University Hospital, Stockholm, Sweden; [24]Texas Oncology-Tyler/US Oncology Research, Tyler, TX, USA; [25]BeiGene USA, Inc., San Mateo, CA, USA; [26]BeiGene International GmbH, Basel, Switzerland; [27]BeiGene (Beijing) Co., Ltd., Beijing, China; [28]Fred Hutchinson Cancer Center, Seattle, WA, USA; [29]Department of Medicine, University of Washington, Seattle, WA, USA

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

Zanubrutinib Is a Differentiated BTKi With High Potency, Bioavailability, and Selectivity

- Zanubrutinib is highly selective for BTK and has potent inhibitory activity against BTK[1]
- Zanubrutinib has no active metabolite; ibrutinib and acalabrutinib each have an active metabolite (PCI-45227 and M27, respectively) with activity on kinases other than BTK[1]
- Zanubrutinib has continuous exposure coverage above its IC_{50} compared with ibrutinib[2] and acalabrutinib[3]
  - Higher drug-concentration/IC_{50} ratios would be expected to lead to more sustained and complete BTK inhibition to improve efficacy

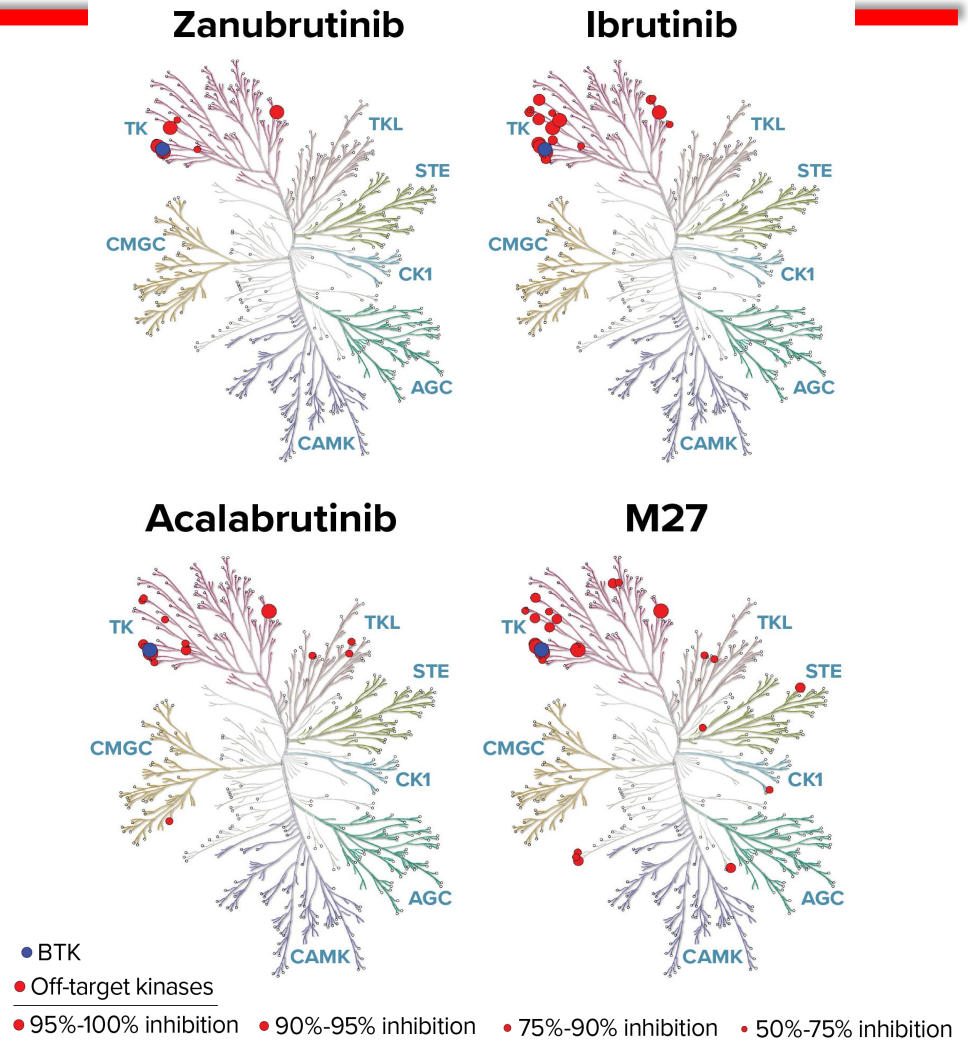


Figure adapted from Shadman et al. *Lancet Haematol.* 2023.

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

ALPINE Study Design (NCT03734016)

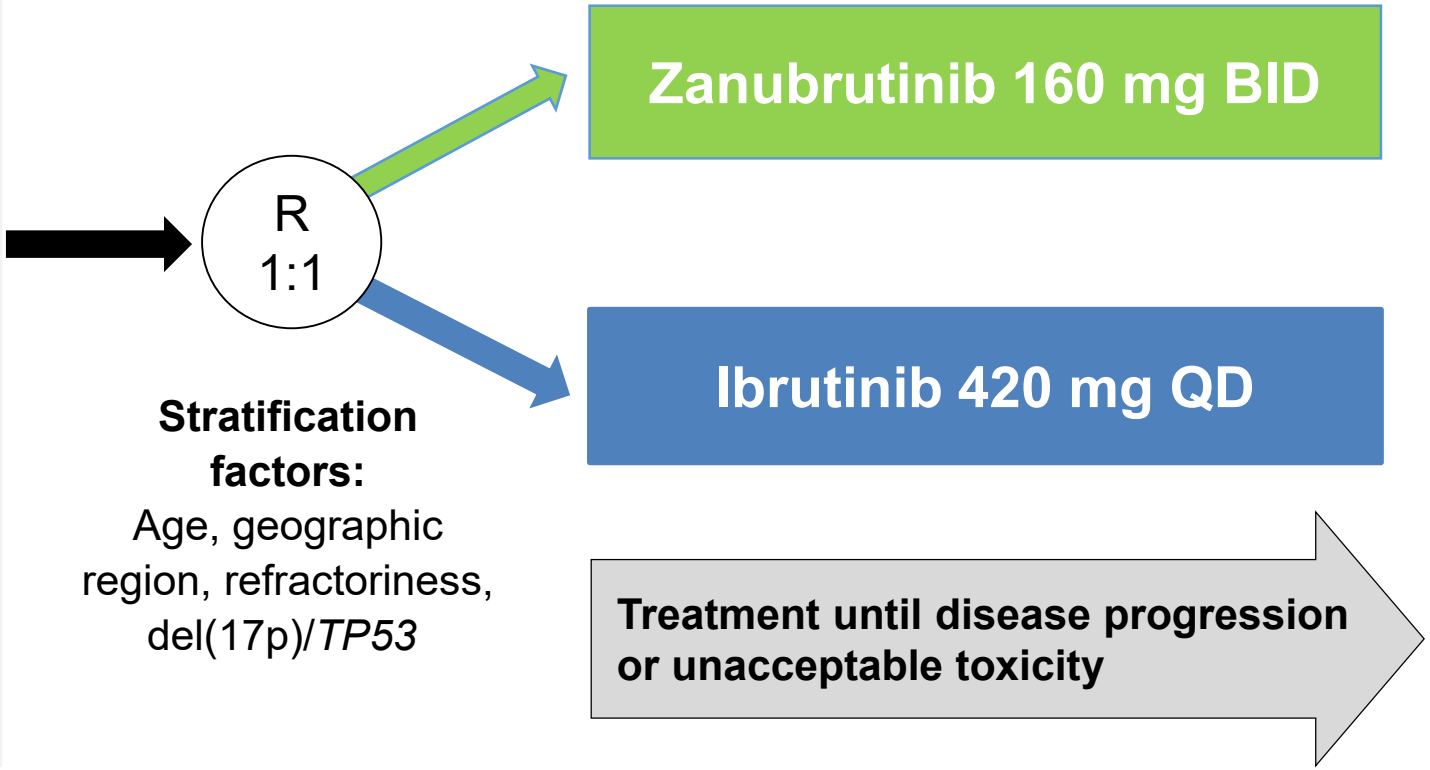
R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

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

Key Exclusion Criteria

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



Brown JR, Eichhorst B, Hillmen P, et al. *N Engl J Med*. 2023;388:319-332.

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)
IGHV mutational status, n (%) Mutated Unmutated	 80 (24.5) 240 (73.4)	 70 (21.5) 241 (74.2)
Complex karyotype[a]	**56 (17.1)**	**70 (21.5)**
Bulky disease (≥5 cm), n (%)	**145 (44.3)**	**149 (45.8)**

[a]Complex karyotype is defined as having ≥3 abnormalities.

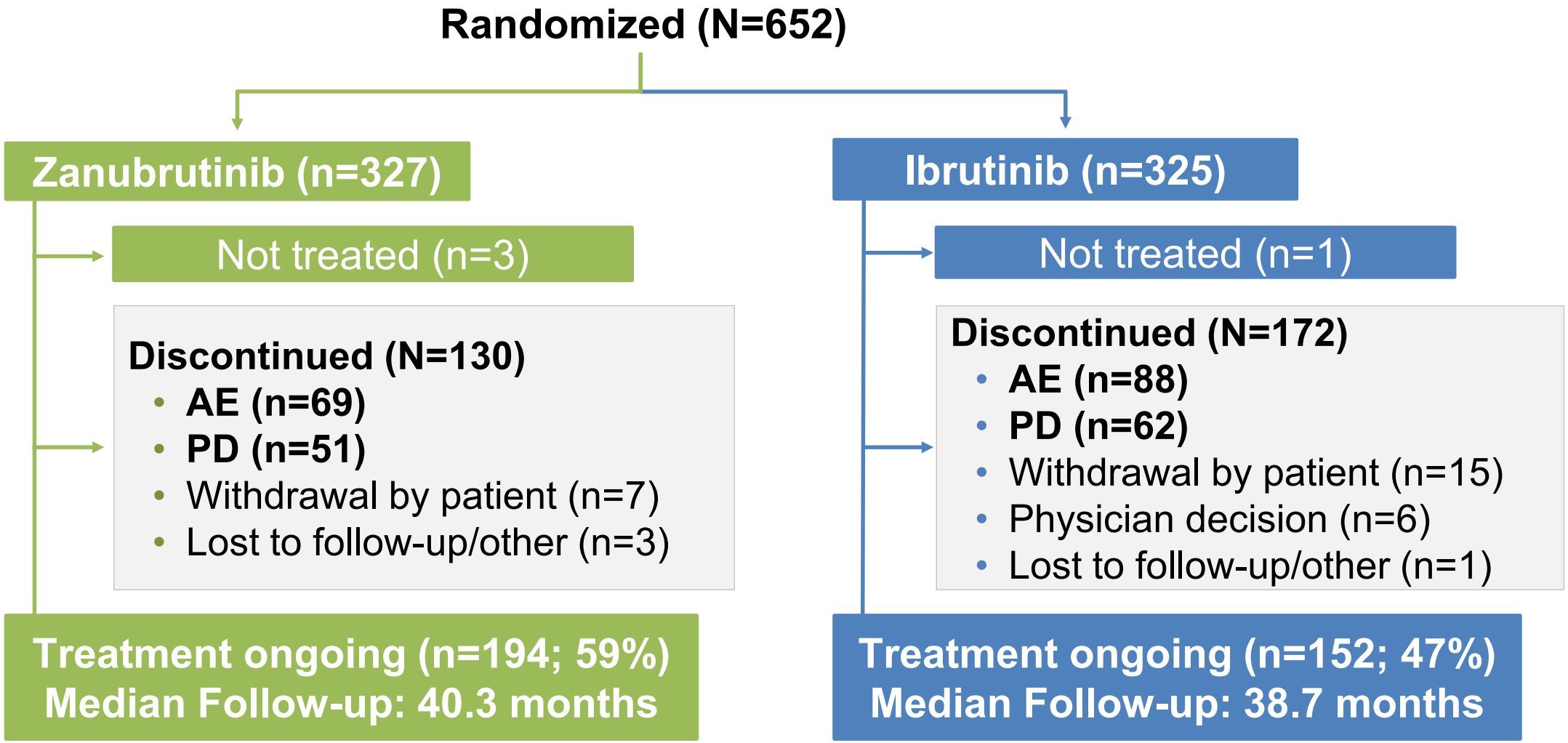
Data cutoff: 15 Sep 2023

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

Brown JR, Eichhorst B, Hillmen P, et al. *N Engl J Med*. 2023;388:319-332.

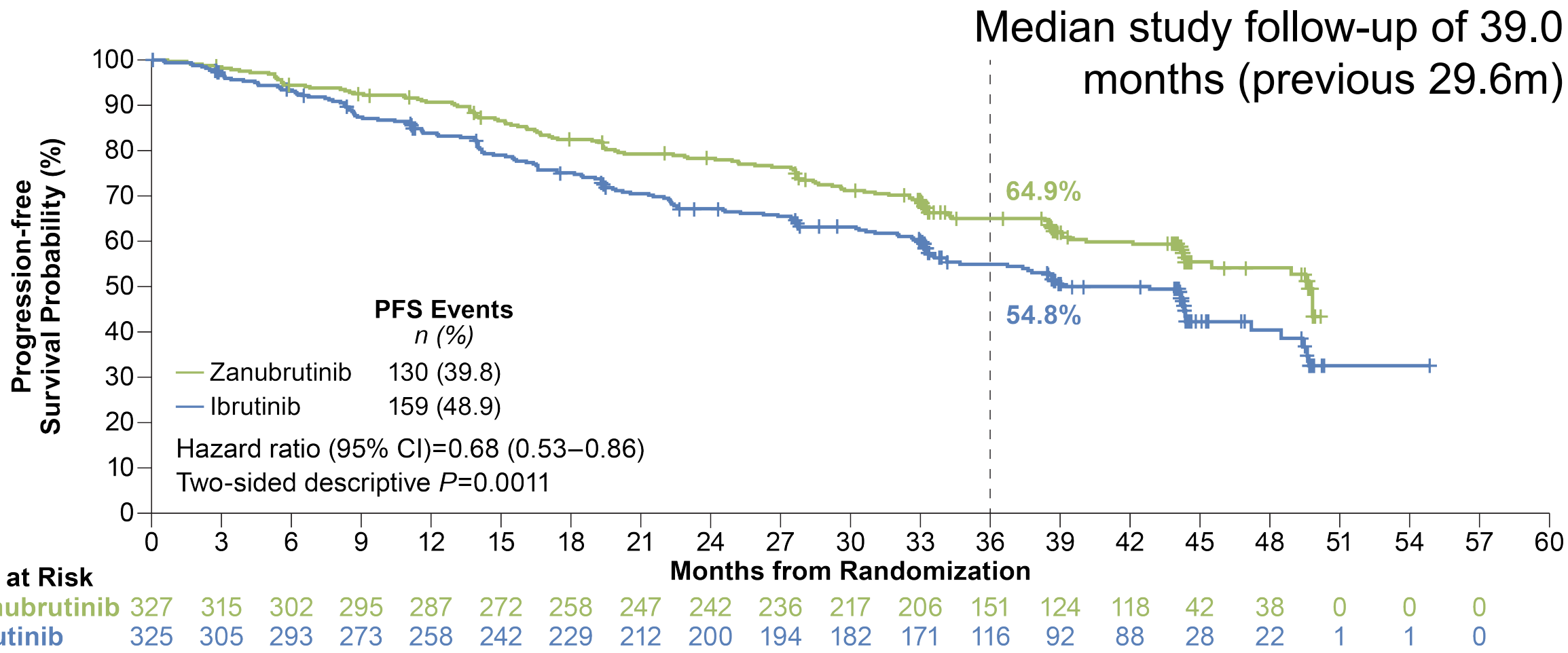
HEALTH UNIVERSITY OF UTAH

Patient Disposition at Extended Follow-up



Data cutoff: 15 Sep 2023

Zanubrutinib Sustains PFS Benefit Over Ibrutinib At Extended Follow-up

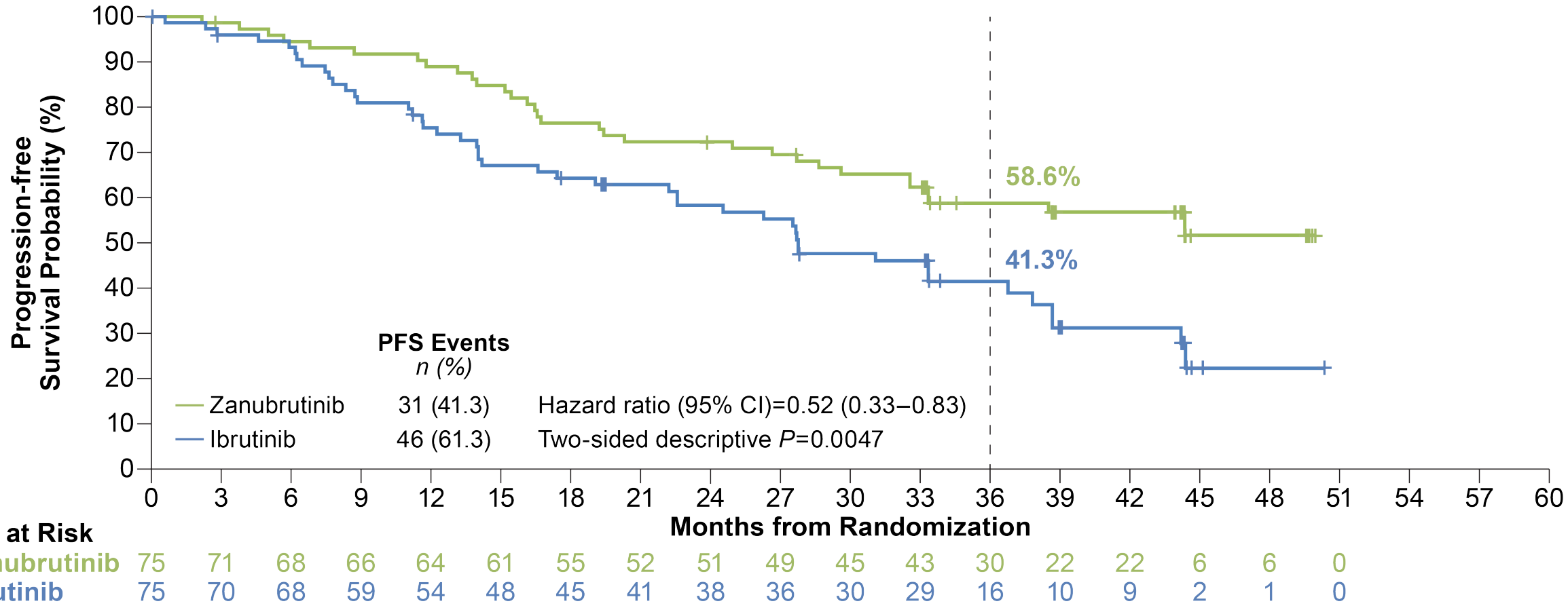


HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

Data cutoff: 15 Sep 2023

U HEALTH UNIVERSITY OF UTAH

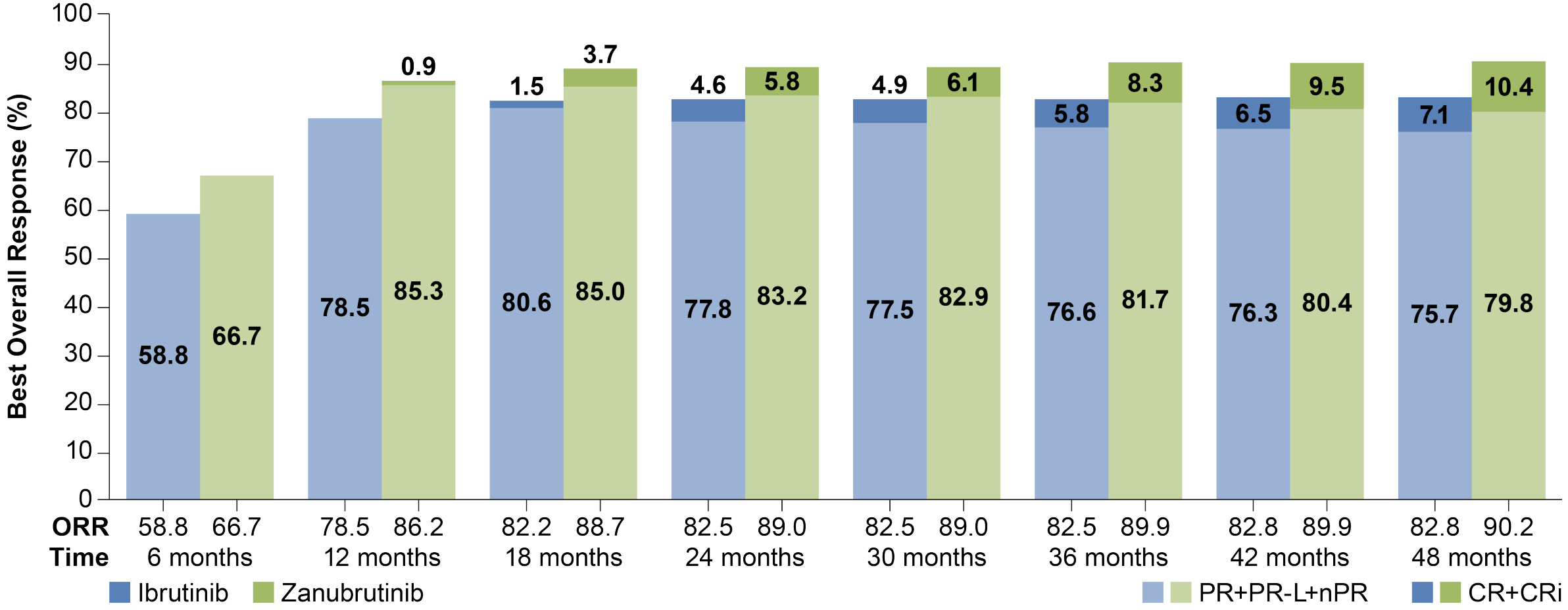
Improved PFS Was Demonstrated With Zanubrutinib in Patients With del(17p)/*TP53*^{mut}



Data cutoff: 15 Sep 2023

Complete Responses Deepen Over Time in Both Arms

A higher proportion of patients achieved CR/CRi with zanubrutinib than ibrutinib

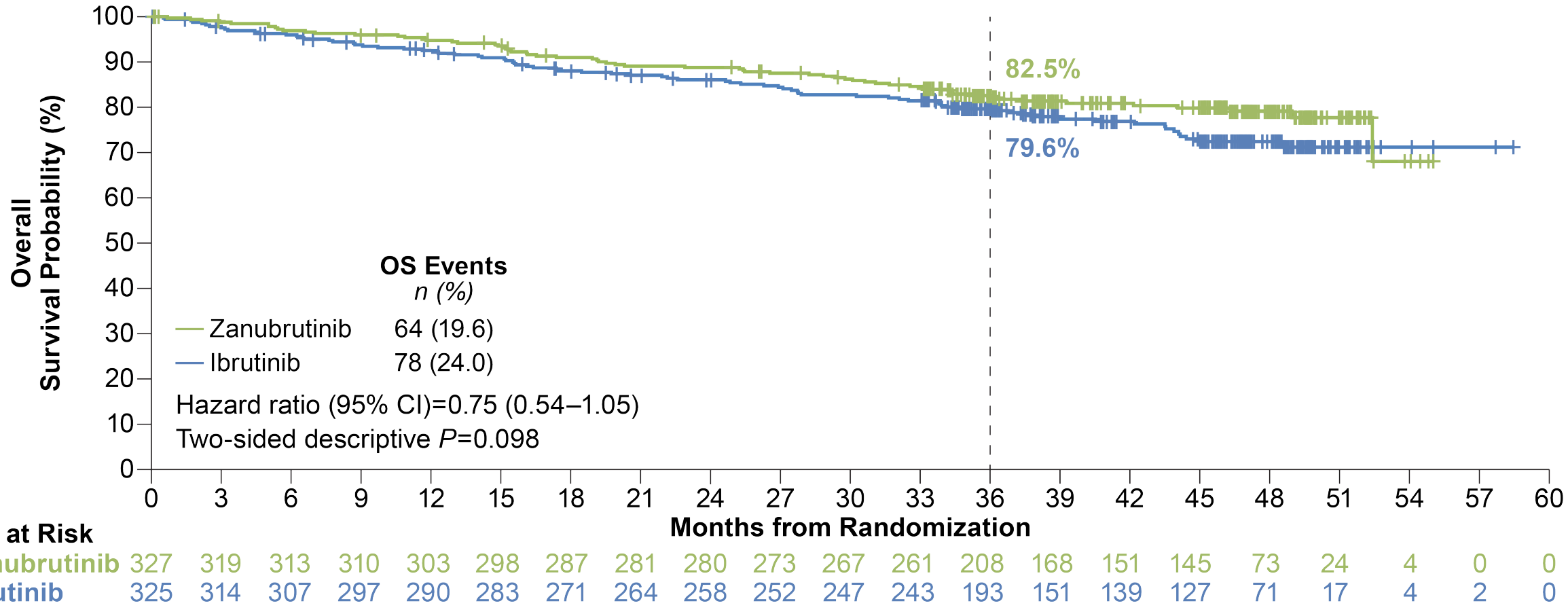


HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

Data cutoff: 15 Sep 2023

U HEALTH UNIVERSITY OF UTAH

Overall Survival at Longer Follow-up



No. at Risk

Zanubrutinib	327	319	313	310	303	298	287	281	280	273	267	261	208	168	151	145	73	24	4	0	0
Ibrutinib	325	314	307	297	290	283	271	264	258	252	247	243	193	151	139	127	71	17	4	2	0

Data cutoff: 15 Sep 2023

Overall Safety/Tolerability Summary

Zanubrutinib safety profile remained favorable vs ibrutinib

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, months	**38.3 (0.4, 54.9)**	**35.0 (0.1, 58.4)**
Any grade adverse event	**320 (98.8)**	**323 (99.7)**
Grade 3 to 5	**235 (72.5)**	**251 (77.5)**
Grade 5	41 (12.7)	40 (12.3)
Serious adverse event	**165 (50.9)**	**191 (59.0)**
Adverse events leading to		
Dose reduction	**47 (14.5)**	**59 (18.2)**
Dose interruption	196 (60.5)	201 (62.0)
Treatment discontinuation	**64 (19.8)**	**85 (26.2)**
Hospitalization	**150 (46.3)**	**180 (55.6)**

Data cutoff: 15 Sep 2023

Adverse Events of Special Interest[a] Occurring in ≥2 Patients

	Zanubrutinib (n=324)		Ibrutinib (n=324)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infection	264 (81.5)	115 (35.5)	260 (80.2)	111 (34.3)
Opportunistic Infections	8 (2.5)	6 (1.9)	13 (4.0)	5 (1.5)
COVID-19 Related[b]	**145 (44.8)**	**56 (17.3)**	**105 (32.4)**	**38 (11.7)**
Bleeding	142 (43.8)	12 (3.7)	144 (44.4)	13 (4.0)
Major Hemorrhage	13 (4.0)	12 (3.7)	16 (4.9)	13 (4.0)
Hypertension	**86 (26.5)**	**53 (16.4)**	**80 (24.7)**	**47 (14.5)**
Atrial fibrillation/flutter	**22 (6.8)**	**10 (3.1)**	**53 (16.4)**	**16 (4.9)**
Anemia	53 (16.4)	7 (2.2)	59 (18.2)	11 (3.4)
Neutropenia	**100 (30.9)**	**72 (22.2)**	**94 (29.0)**	**72 (22.2)**
Thrombocytopenia	43 (13.3)	12 (3.7)	53 (16.4)	19 (5.9)
Second primary malignancies	46 (14.2)	26 (8.0)	52 (16.0)	19 (5.9)

[a]Pooled MedDRA preferred terms.

[b]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

Data cutoff: 15 Sep 2023

U HEALTH UNIVERSITY OF UTAH

Zanubrutinib Continues to Demonstrate a More Favorable Cardiac Safety Profile Than Ibrutinib

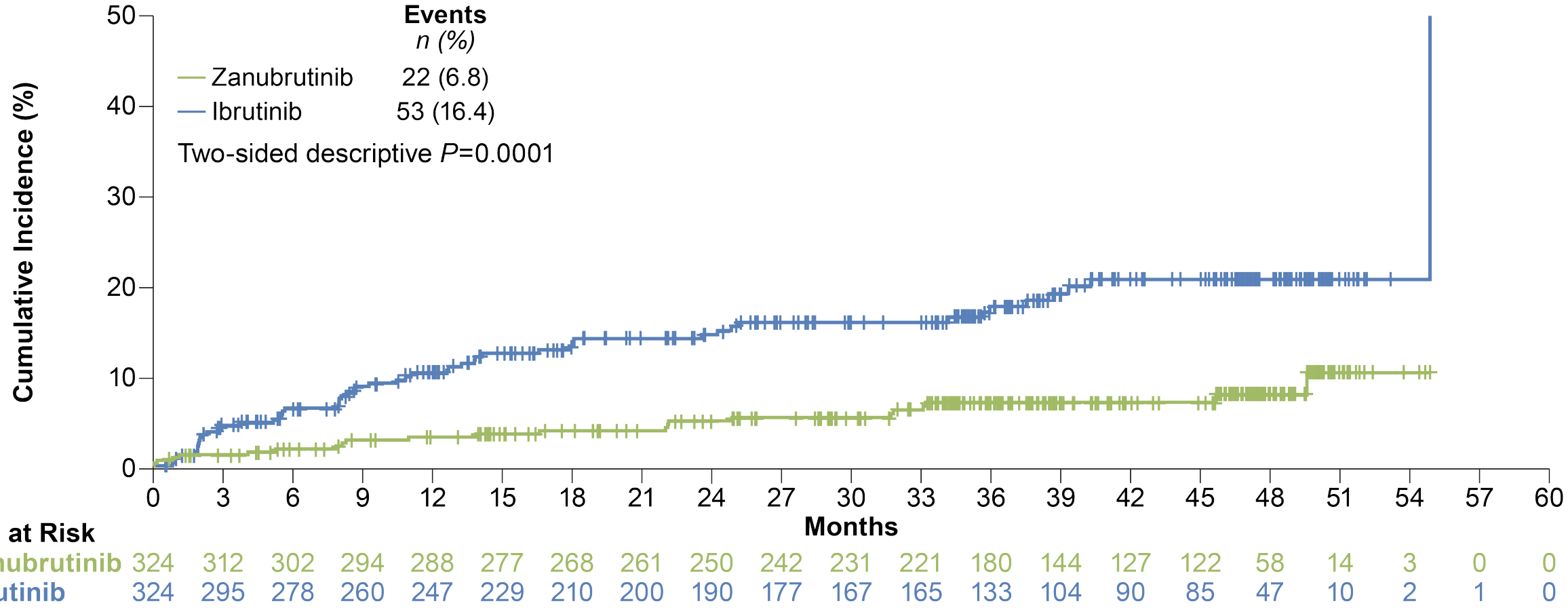
- Serious cardiac adverse events were lower with zanubrutinib vs ibrutinib
  - Atrial fibrillation/flutter (3 vs 13)
  - Ventricular fibrillation (0 vs 2)
  - MI[a]/acute coronary syndrome (3 vs 3)
- **Fatal cardiac events[b]:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**80 (24.7)**	**112 (34.6)**
Serious cardiac adverse events	**11 (3.4)**	**31 (9.6)**
Cardiac adverse events leading to treatment discontinuation	**3 (0.9)**	**15 (4.6)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation/flutter	1 (0.3)	6 (1.9)
Cardiac failure	1 (0.3)	2 (0.6)
Cardiac arrest	0	2 (0.6)[b]
Cardiac failure acute	0	1 (0.3)[b]
Congestive cardiomyopathy	0	1 (0.3)[b]
Myocardial infarction	0	1 (0.3)[b]
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

[a]Including acute MI.
[b]Fatal cardiac event (n=6); 1 death (myocardial infarction with ibrutinib) was not listed due to discontinuation due to diarrhea 14 days prior to the fatal event.
Abbreviations: MI, myocardial infarction.

Data cutoff: 15 Sep 2023

Significantly Fewer Atrial Fibrillation/Flutter Events With Zanubrutinib Than Ibrutinib

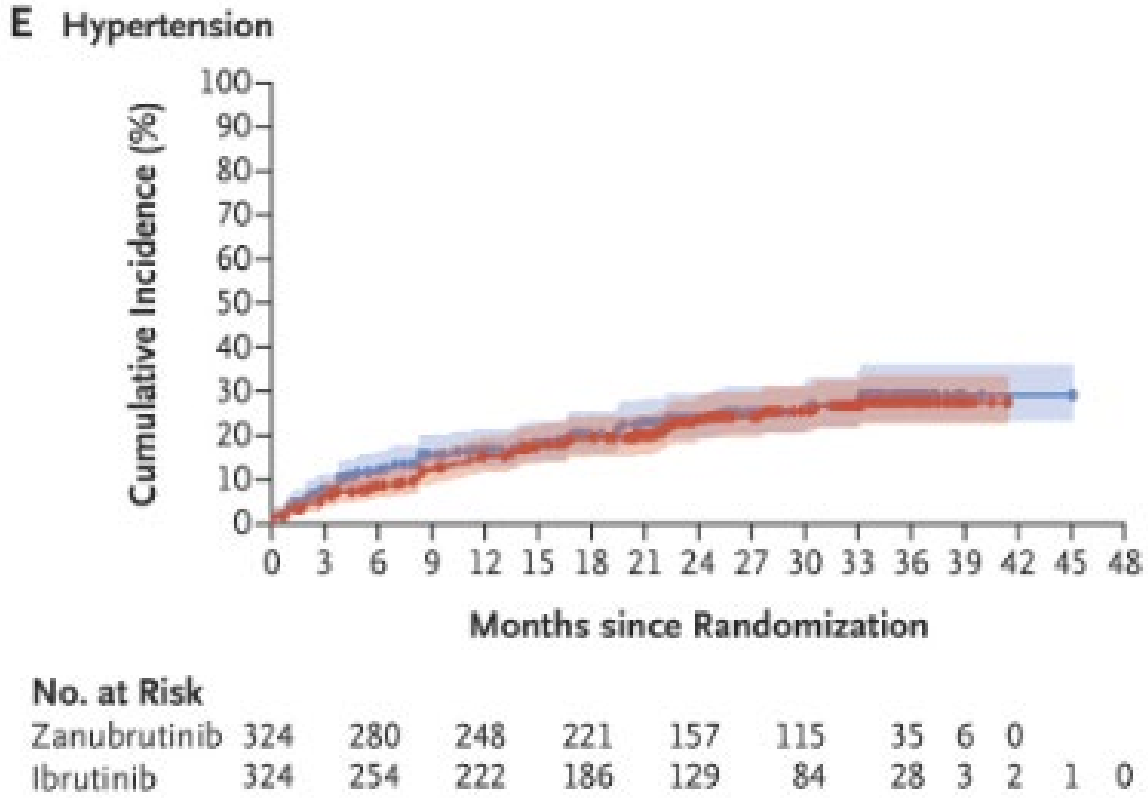


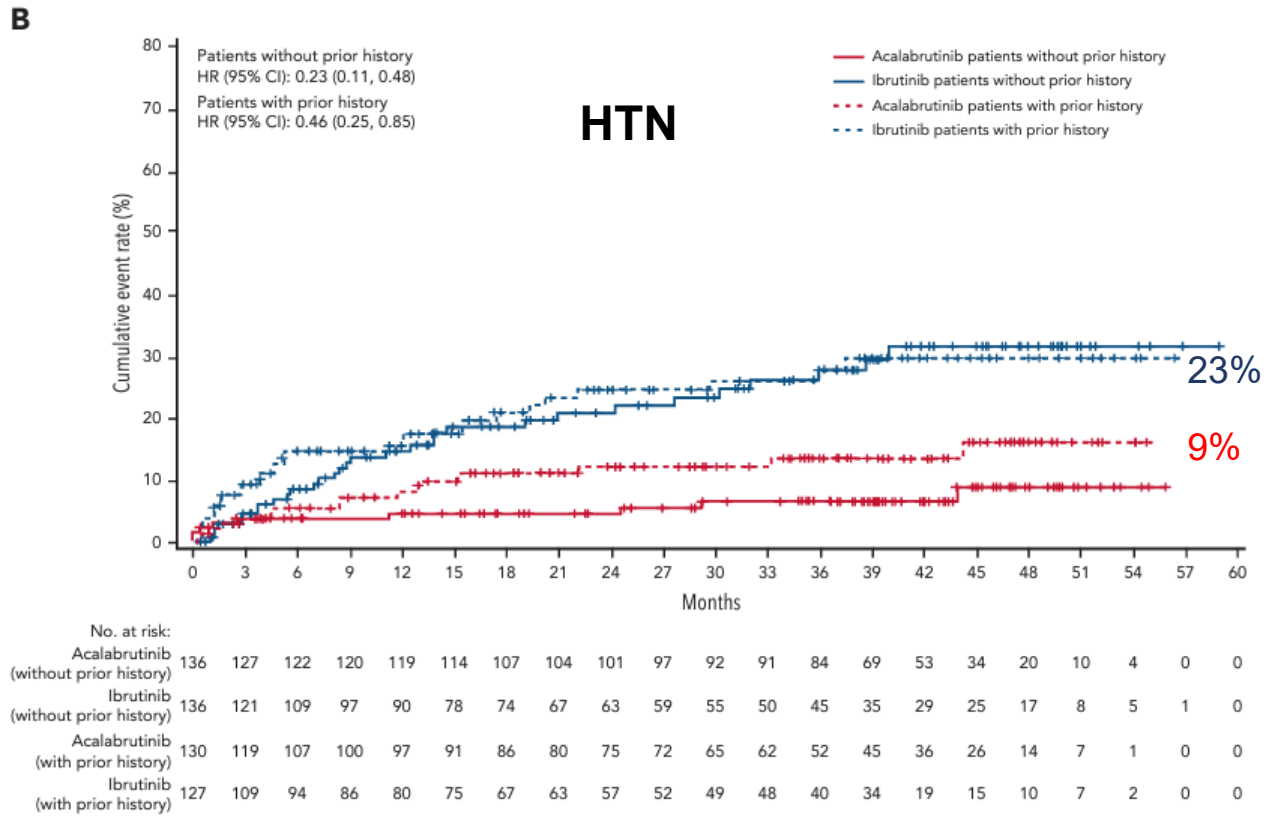
Median study follow-up 39.0 months

Data cutoff: 15 Sep 2023

Comparison to ELEVATE-RR (Acalabrutinib vs. Ibrutinib)

Median follow up 40.9 months





- Acala with increased HA and cough; Ibrutinib with worse diarrhea
- No differences in cytopenias

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

Seymour et al. Blood (2023) 142;8: 687-699.

HEALTH UNIVERSITY OF UTAH

Presentation #636

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-naive Chronic Lymphocytic Leukemia: 6-Year Follow-up of ELEVATE-TN

Jeff P. Sharman,[1] Miklos Egyed,[2] Wojciech Jurczak,[3] Alan Skarbnik,[4] Krish Patel,[5] Ian W. Flinn,[6] Manali Kamdar,[7] Talha Munir,[8] Renata Walewska,[9] Marie Hughes,[10] Laura Maria Fogliatto,[11] Yair Herishanu,[12] Versha Banerji,[13] George Follows,[14] Patricia Walker,[15] Karin Karlsson,[16] Paolo Ghia,[17] Ann Janssens,[18] Florence Cymbalista,[19] John C. Byrd,[20] Emmanuelle Ferrant,[21] Alessandra Ferrajoli,[22] William G. Wierda,[22] Veerendra Munugalavadla,[23] Catherine Wangui Wachira,[24] Chuan-Chuan Wun,[23] Jennifer A. Woyach[20]

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

Introduction

- Acalabrutinib is a second-generation, potent, highly selective BTKi approved for the treatment of CLL/SLL and previously treated MCL[1-3]
- Results from the phase 3 ELEVATE-TN study at a median follow-up of 28.3, 46.9, and 58.2 months reported superior efficacy of A±O compared with O+Clb, with an acceptable tolerability profile in patients with TN CLL[3-5]
- We report efficacy and safety results of a 74.5-month (~6-year) update of ELEVATE-TN

ELEVATE-TN Study Design

TN CLL (N=535)

Key inclusion criteria

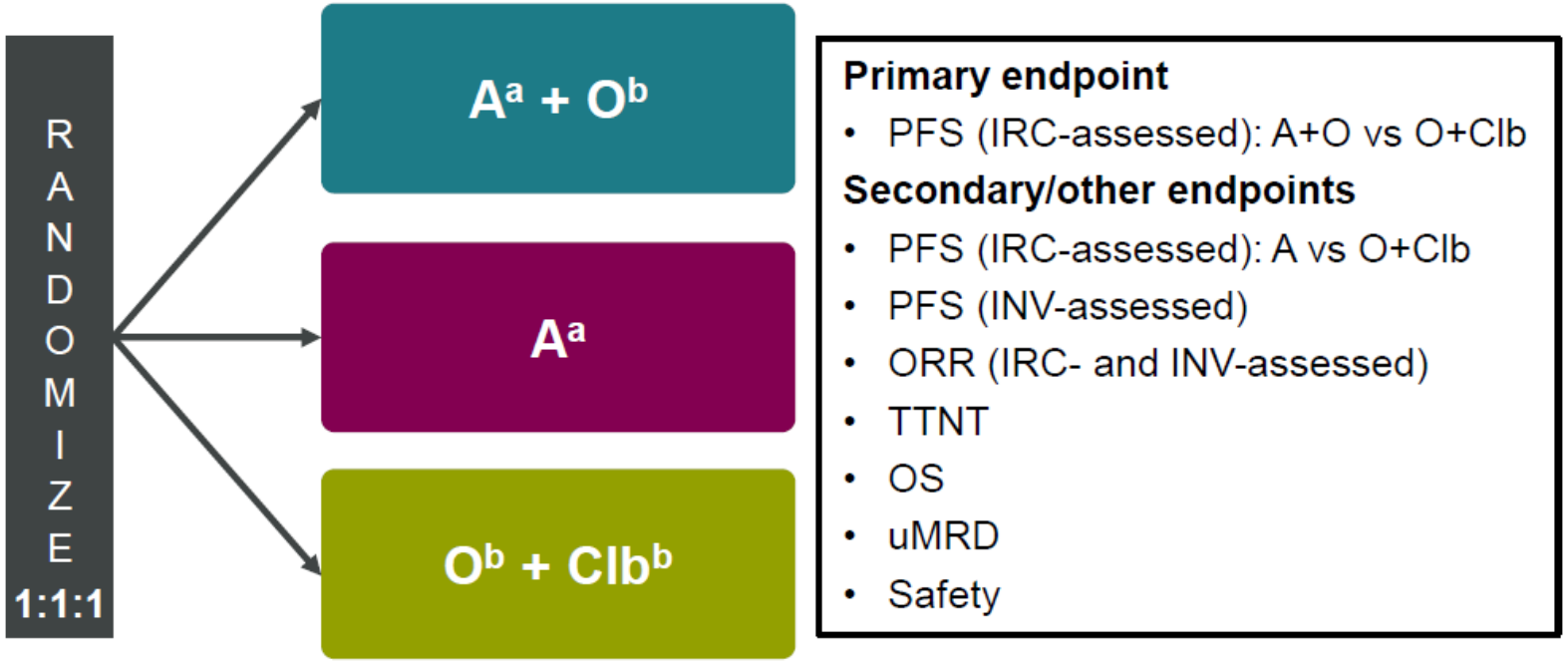
- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria[6]
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- del(17p), yes vs no
- ECOG PS 0–1 vs 2
- Geographic region



Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

***Crossover** from O+Clb to A was allowed after IRC-confirmed progression*

Note: After interim analysis, PFS assessments were by investigator only.[3]
All analyses are ad-hoc and *P*-values are descriptive.

NCT02475681. Data cutoff: March 3, 2023. Patients were enrolled between September 2015 and February 2017.
[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID.
[b]Treatments were fixed duration and administered for 6 cycles.

Demographics and baseline characteristics

Characteristic	A+O (n=179)	A (n=179)	O+Clb (n=177)
Age, median (range), y	70 (41–88)	70 (44–87)	71 (46–91)
Male sex	111 (62.0)	111 (62.0)	106 (59.9)
ECOG PS score			
0–1	169 (94.4)	165 (92.2)	167 (94.4)
2	10 (5.6)	14 (7.8)	10 (5.6)
Bulky disease ≥5 cm	46 (25.7)	68 (38.0)	54 (30.5)
Rai stage			
III	47 (26.3)	51 (28.5)	40 (22.6)
IV	38 (21.2)	37 (20.7)	38 (21.5)
Cytogenetic subgroup			
del(17p)	17 (9.5)	16 (8.9)	17 (9.6)
del(17p) and/or mutated *TP53*	25 (13.9)	23 (12.8)	25 (14.1)
Complex karyotype[a]	28 (15.6)	31 (17.3)	32 (18.1)
Mutated *TP53*	21 (11.7)	19 (10.6)	21 (11.9)
Unmutated IGHV	103 (57.5)	118 (65.9)	116 (65.5)

Data are n (%) unless otherwise specified.
[a]Patients with ≥3 abnormalities with at least one structural abnormality excluding inversion of chromosome 9.

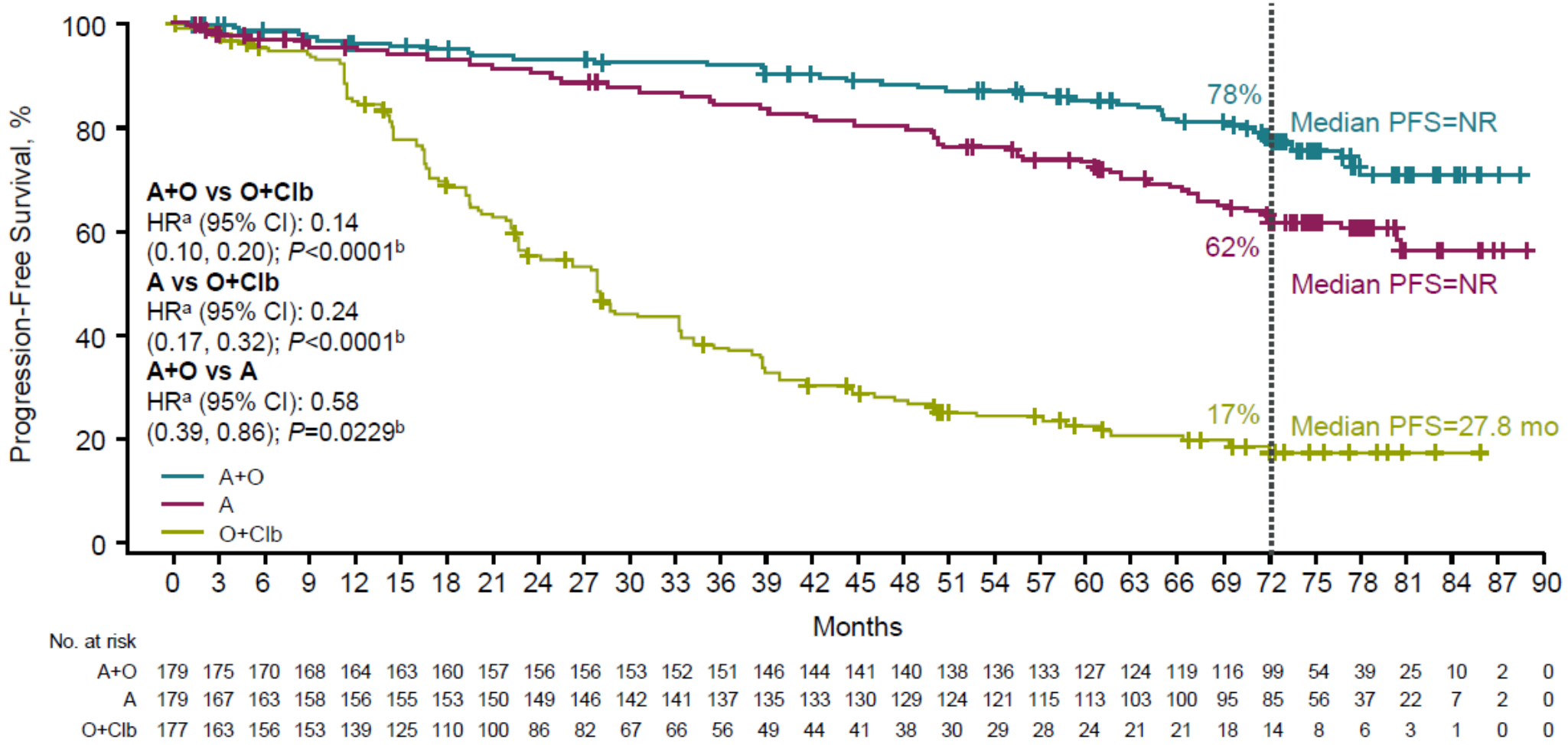
Patient disposition

Characteristic	A+O (n=179)	A (n=179)	O+Clb (n=177)
Median study follow-up, mo (range)	74.6 (1.7, 89.0)	74.5 (0.1, 88.8)	73.3 (0.0, 88.8)
Treated with ≥1 dose of study drug	179 (100.0)	178 (99.4)	169 (95.5)
Randomized but not treated	0	1 (0.6)	8 (4.5)
Treatment status[a]			
Ongoing	96 (53.6)	84 (46.9)	0
Completed regimen	–	–	136 (76.8)
Discontinued regimen	83 (46.4)	95 (53.1)	41 (23.2)
Death	5 (2.8)	16 (8.9)	3 (1.7)
AE	38 (21.2)	32 (17.9)	25 (14.1)
Acalabrutinib-related AE	9 (5.0)	13 (7.3)	–
Lost to follow-up	2 (1.1)	1 (0.6)	1 (0.6)
CLL progressive disease	10 (5.6)	25 (14.0)	4 (2.3)
Withdrawal of consent	5 (2.8)	3 (1.7)	6 (3.4)
Investigator's discretion	13 (7.3)	13 (7.3)	0
Other	10 (5.6)	5 (2.8)	2 (1.1)

Crossover to A monotherapy	O+Clb (n=177)
Crossed over	79 (44.6)
Discontinued A monotherapy	32 (40.5)
AE	10 (12.7)
CLL progressive disease	13 (16.5)
Death	3 (3.8)
Withdrawal of consent	1 (1.3)
Investigator's discretion	1 (1.3)
Other	4 (5.1)

Data are n (%) unless otherwise specified.
[a]Treatment status refers to the period on treatment. For A-containing arms, patients are treated to progression or unacceptable toxicity; treatment period is 6 months fixed duration for O+Clb.

Median PFS was significantly higher for A-containing arms vs O+Clb

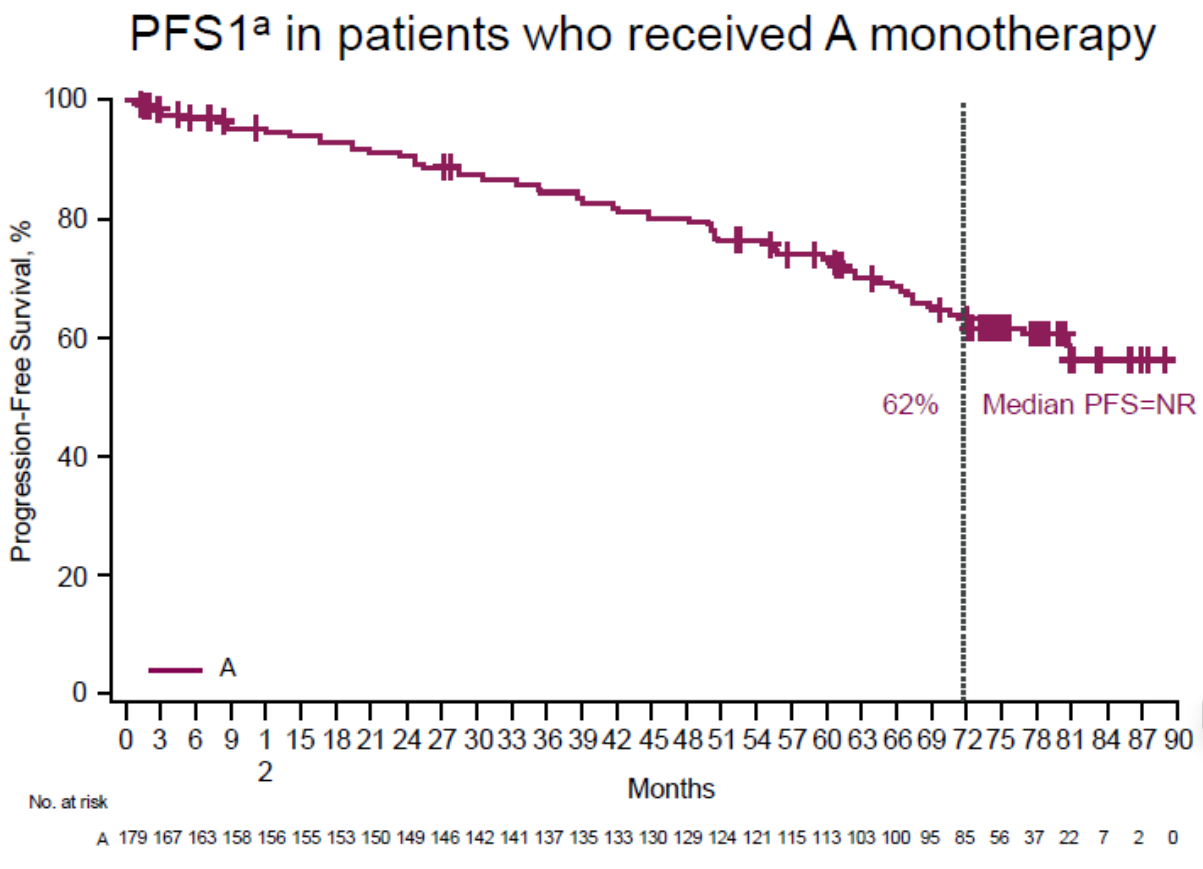


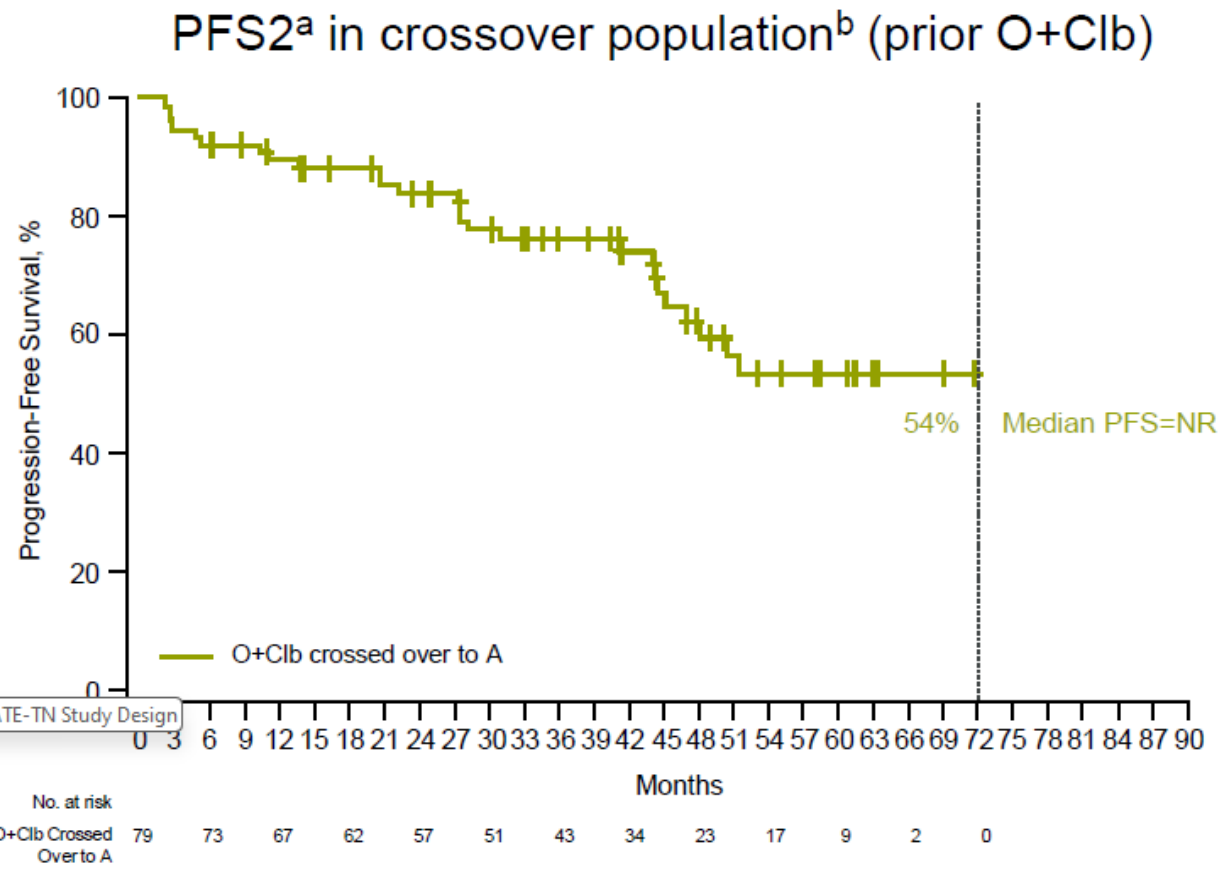
- Median PFS was significantly higher for A+O vs A

[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

ELEVATE-TN 6 Year Update

PFS for acalabrutinib monotherapy in frontline and crossover patients (PFS2)

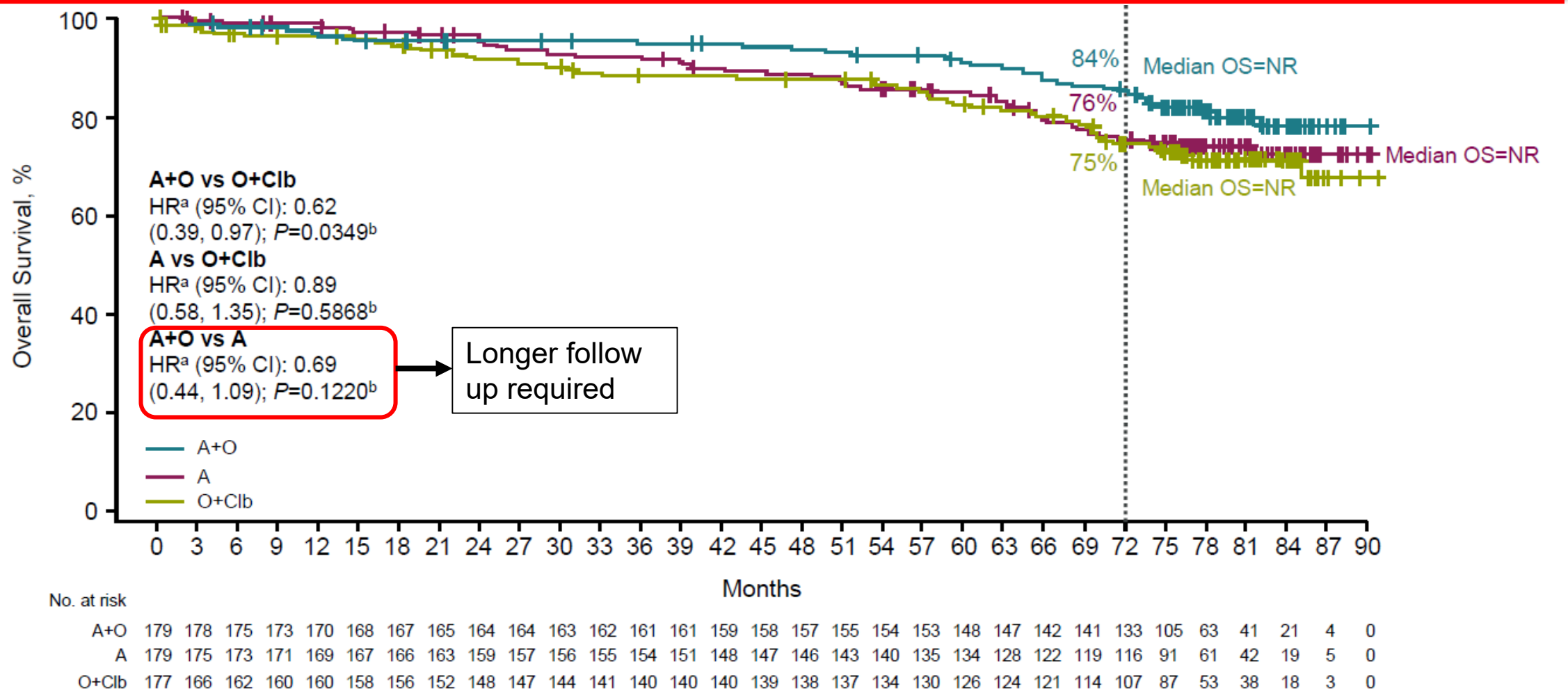




ELEVATE-TN Study Design

[a]PFS1, time to first disease progression or death; PFS2, time to second disease progression or death.
[b]At investigator discretion, crossover from O+Clb to A monotherapy was allowed for patients who had confirmed disease progression.

Overall Survival



No. at risk

A+O	179	178	175	173	170	168	167	165	164	164	163	162	161	161	159	158	157	155	154	153	148	147	142	141	133	105	63	41	21	4	0
A	179	175	173	171	169	167	166	163	159	157	156	155	154	151	148	147	146	143	140	135	134	128	122	119	116	91	61	42	19	5	0
O+Clb	177	166	162	160	160	158	156	152	148	147	144	141	140	140	140	139	138	137	134	130	126	124	121	114	107	87	53	38	18	3	0

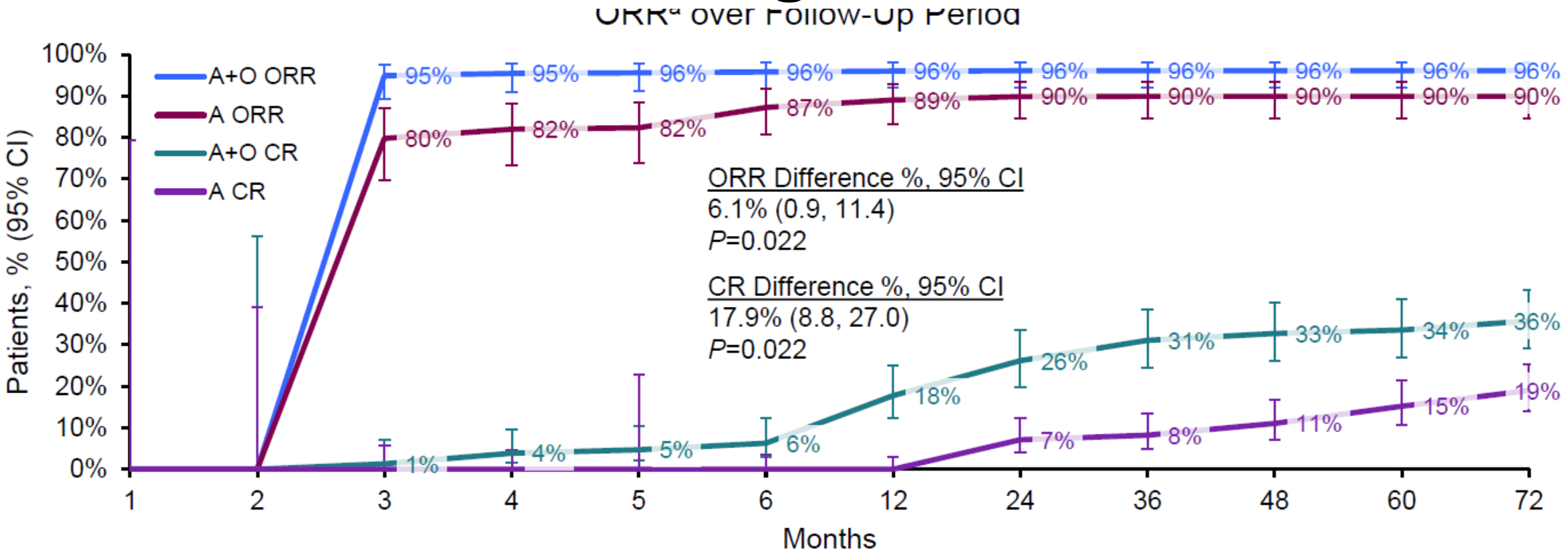
[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

ELEVATE-TN 6 Year Update

Death Reason	Incidence of Death During Main Study Period		
	A+O (n=179)	A (n=179)	O+Clb[a] (n=177)
Total deaths	33 (18.4)	43 (24.0)	45 (25.4)
CLL progressive disease	5 (2.8)	4 (2.2)	4 (2.3)
Richter transformation	0	1 (0.6)	1 (0.6)
Other	3 (1.7)	9 (5.0)	13 (7.3)
Unknown	5 (2.8)	5 (2.8)	5 (2.8)
AE Preferred term[b]	20 (11.2)	24 (13.4)	22 (12.4)
COVID-19	3 (1.7)	5 (2.8)	1 (0.6)
Sepsis	2 (1.1)	1 (0.6)	3 (1.7)
Pneumonia	2 (1.1)	0	1 (0.6)
Cerebrovascular accident	2 (1.1)	0	0

Data are n (%).
[a]Includes all deaths during main study period and crossover period.
[b]In ≥2 patients in any treatment group.

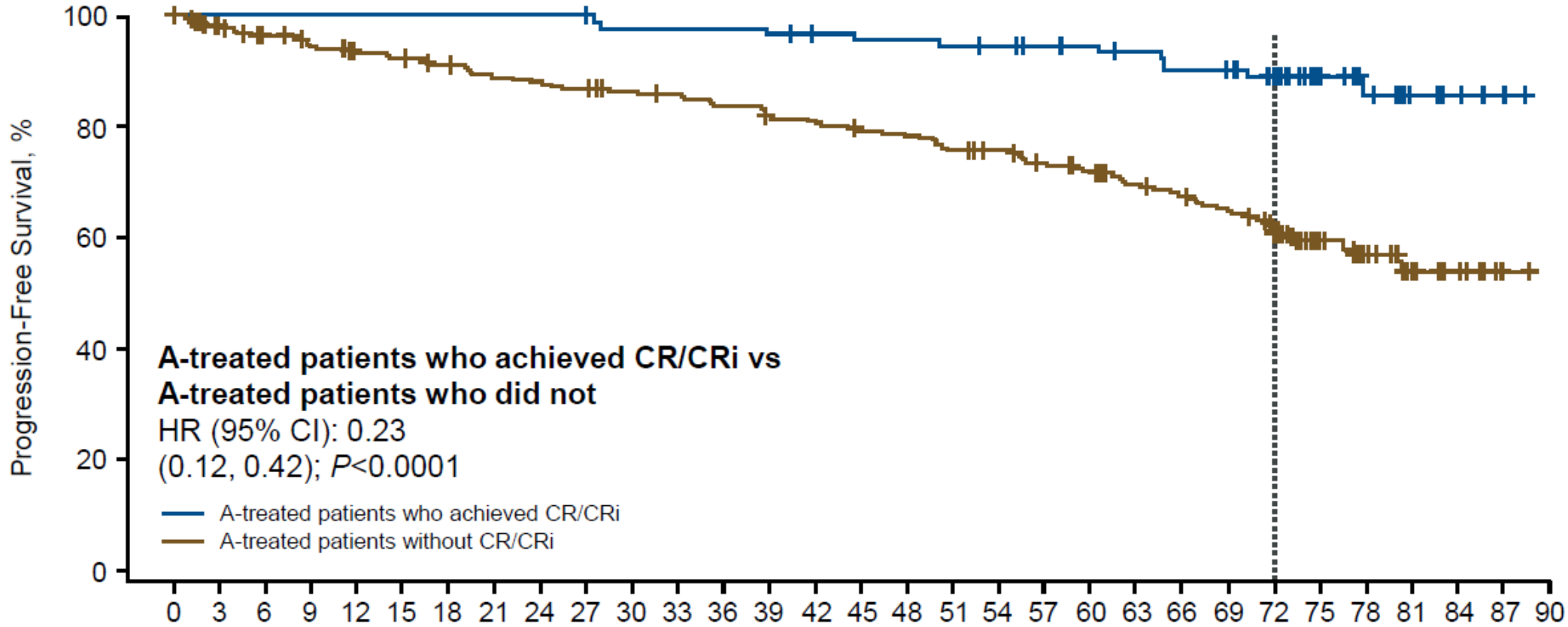
ORR consistently improved over time in acalabrutinib-containing arms



- ORR and CR/CRi rates were significantly higher with A+O and A vs O+Clb ($P \leq 0.0499$ for both arms of the analyses)
- ORR and CR/CRi rates were significantly higher with A+O vs A ($P=0.022$ for both comparisons)

[a]ORR is defined as achieving CR, CRi, nPR, or PR per the investigator per iwCLL 2008 criteria[6] at or before initiation of subsequent anticancer therapy. ORR does not include PRL.

Acalabrutinib-treated patients who achieved CR/CRi had longer PFS



No. at risk																													
A-treated patients who achieved CR/CRi	100	100	100	100	100	100	100	100	100	100	97	97	97	96	94	93	93	92	91	89	86	84	81	80	70	36	26	14	4	2	0
A-treated patients without CR/CRi	258	242	233	226	220	218	213	207	205	202	198	196	191	185	183	178	176	170	166	159	154	143	138	131	114	74	50	33	13	2	0

Events of clinical interest

ECI Category ECI Subcategory	A+O (n=178)		A (n=179)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac events	49 (27.5)	22 (12.4)	42 (23.5)	21 (11.7)
Atrial fibrillation	13 (7.3)	3 (1.7)	16 (8.9)	3 (1.7)
Bleeding	95 (53.4)	12 (6.7)	81 (45.3)	8 (4.5)
Major bleeding	16 (9.0)	12 (6.7)	10 (5.6)	8 (4.5)
Hypertension[a]	20 (11.2)	8 (4.5)	20 (11.2)	9 (5.0)
Infections	147 (82.6)	63 (35.4)	144 (80.4)	50 (27.9)
SPMs	36 (20.2)	18 (10.1)	35 (19.6)	9 (5.0)
SPMs excluding non-melanoma skin	24 (13.5)	13 (7.3)	22 (12.3)	7 (3.9)

Data are n (%).
[a]Hypertension events were based on Standardized MedDRA query (SMQ) Hypertension (narrow).

Most common any-grade AEs

	A+O (n=178)		A (n=179)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Diarrhea	78 (43.8)	11 (6.2)	76 (42.5)	1 (0.6)
Headache	72 (40.4)	2 (1.1)	70 (39.1)	2 (1.1)
Arthralgia	64 (36.0)	4 (2.2)	49 (27.4)	2 (1.1)
Neutropenia	61 (34.3)	55 (30.9)	23 (12.8)	21 (11.7)
Fatigue	55 (30.9)	4 (2.2)	43 (24.0)	2 (1.1)
Cough	50 (28.1)	1 (0.6)	45 (25.1)	1 (0.6)
COVID-19	44 (24.7)	16 (9.0)	38 (21.2)	13 (7.3)
Thrombocytopenia	26 (14.6)	15 (8.4)	16 (8.9)	6 (3.4)
Pneumonia	25 (14.0)	13 (7.3)	27 (15.1)	11 (6.1)
Hypertension	17 (9.6)	8 (4.5)	19 (10.6)	9 (5.0)
Syncope[b]	12 (6.7)	9 (5.1)	5 (2.8)	4 (2.2)

Data are n (%).
[a]Any-grade AEs in ≥30% of acalabrutinib-treated patients or grade ≥3 in ≥5% of acalabrutinib-treated patients.
[b]Cardiac-related syncope events were reported separately.

Conclusions

- Extended follow up of ALPINE to median 39m continued to show ~10% benefit of zanubrutinib over ibrutinib.
  - Increased CR rates
  - Decreased toxicities, especially Afib and sudden cardiac deaths, but not HTN
- Extended 6-year follow up of ELEVATE-TN continue to show improvement in PFS for A-arms vs. O-Chl arm (HR 0.14 for O-A; HR 0.24 for A).
  - O-A superior to A for PFS (78% vs. 62%)
  - Small trend towards superior OS in O-A arm, but don't think this will pan out with longer follow up.
  - Increased toxicities with O-A: all grade bleeding, neutropenia, thrombocytopenia; grade ≥3 infections, SPMs and diarrhea.

Combination Targeted Therapies for Frontline CLL

Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI Flair

Peter Hillmen, David Cairns, Adrian Bloor, David Allsup, Kate Cwynarski, Andrew Pettitt, Shankara Paneesha, Christopher Fox, Toby Eyre, Francesco Forconi, Nagah Elmusharaf, Ben Kennedy, John Gribben, Nicholas Pemberton, Oonagh Sheehy, Gavin Preston, Anna Schuh, Dena Howard, Anna Hockaday, Sharon Jackson, Natasha Greatorex, Sean Girvan, Sue Bell, Julia M Brown, Nichola Webster, Surita Dalal, Ruth de Tute, Andrew Rawstron, Piers EM Patten, Talha Munir
on behalf of the NCRI CLL Subgroup.

Abstract No: 631, Oral Presentation, ASH Annual Meeting
Sunday, December 10th 2023

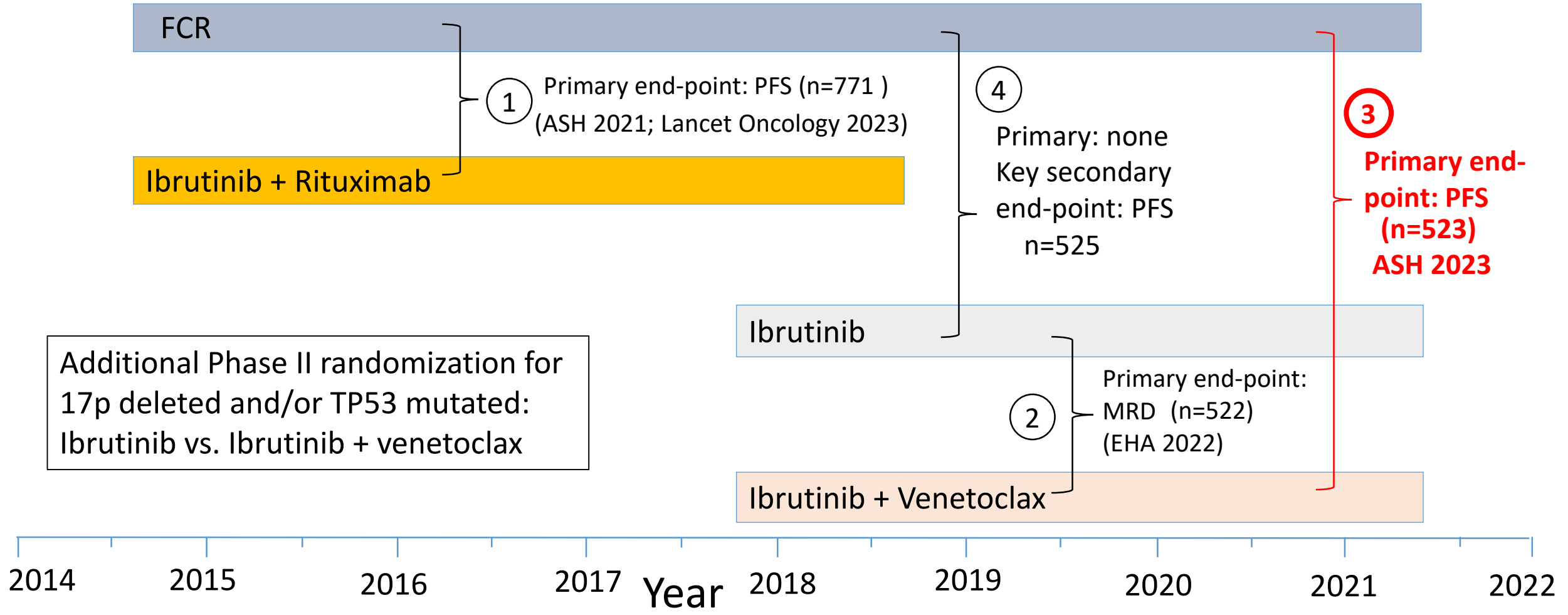
National Cancer Research Institute

CANCER RESEARCH UK

ctru University of Leeds

LEEDS CLINICAL TRIALS UNIT

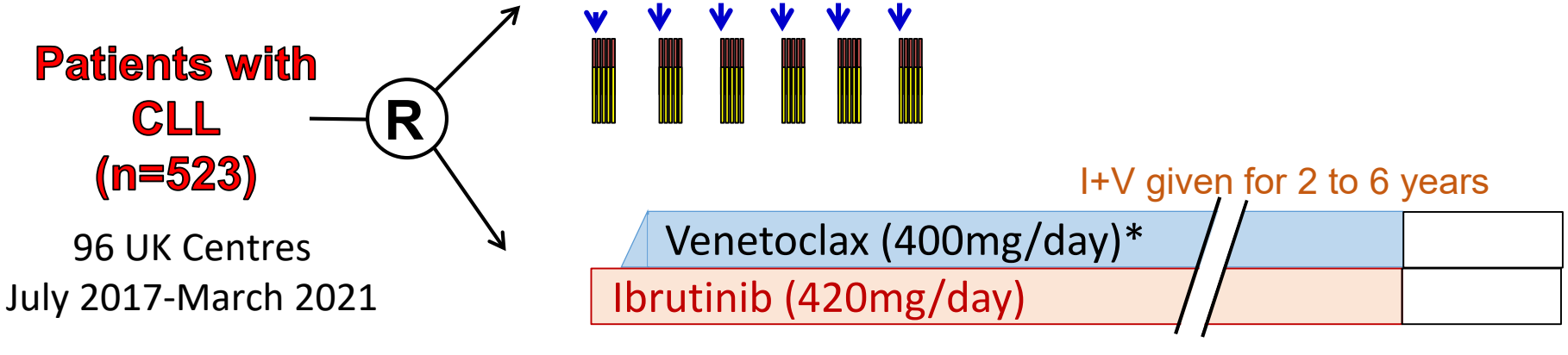
Adaptive design of Flair



HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

Flair+V: Trial design



Primary end-point:
To assess whether I+V is superior to FCR in terms of PFS

Key secondary end-points:
Overall survival
Response incl. MRD
Safety and toxicity

Key Inclusion Criteria:

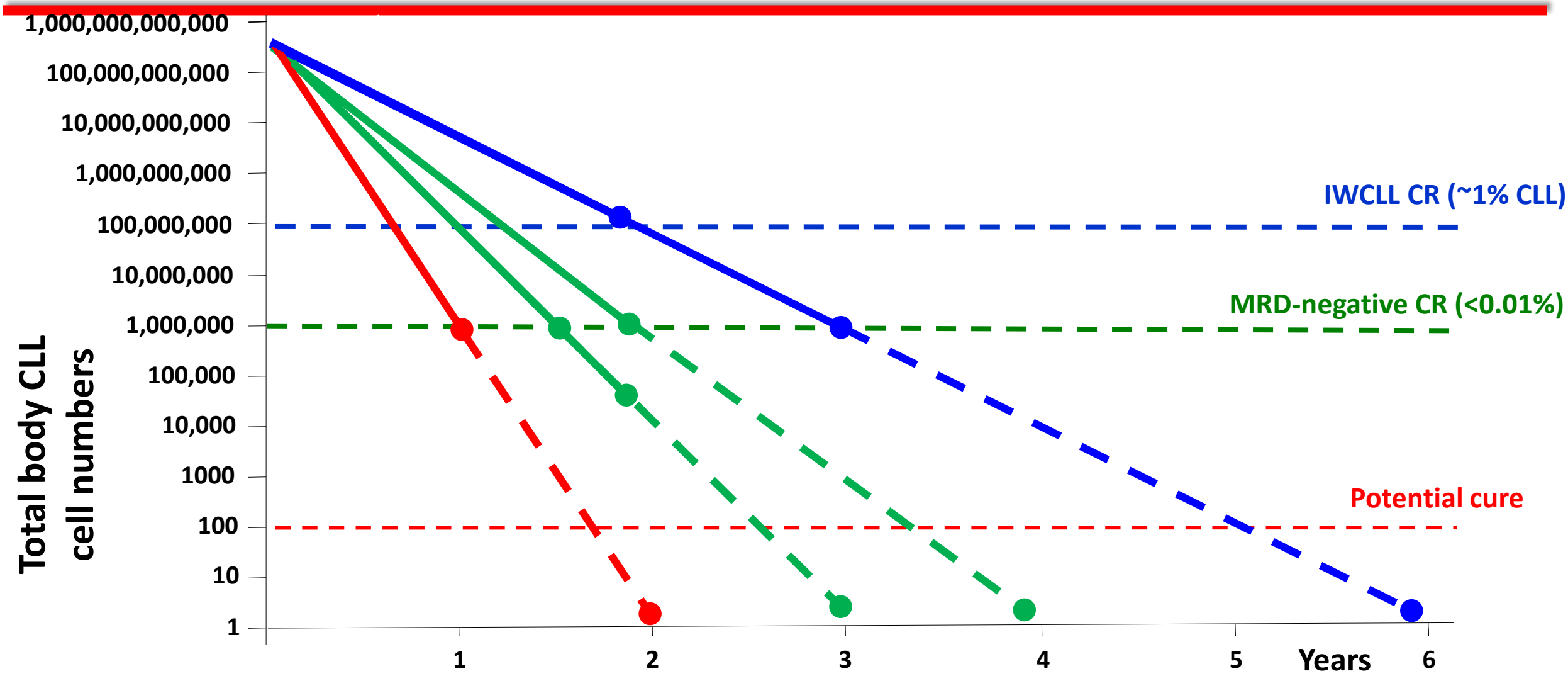
- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:
Prior therapy for CLL; History of Richter's transformation; >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent) Symptomatic cardiac failure or angina

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

MRD-guided duration of I+V in FLAIR

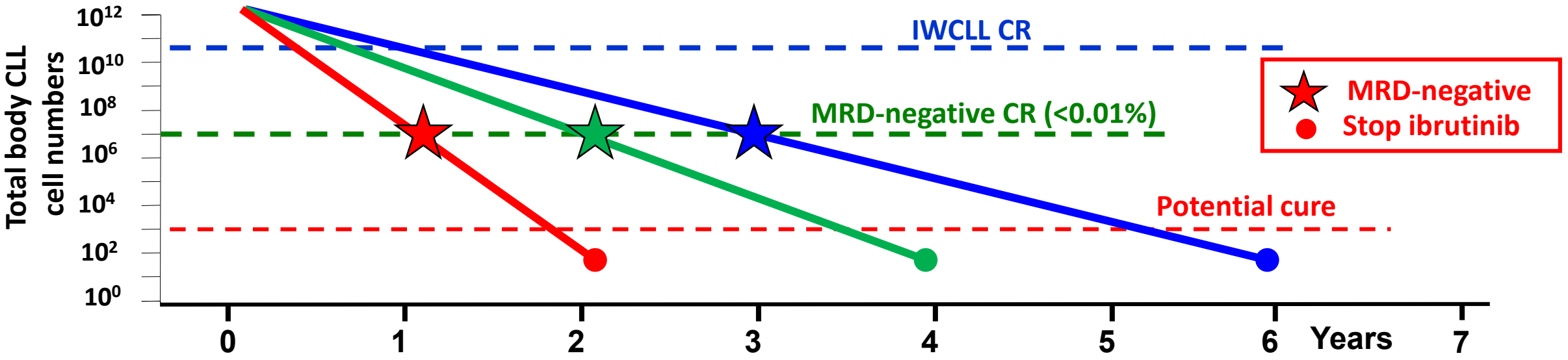


HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

Stopping rules for ibrutinib + venetoclax in

Flair



HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

FCR vs I+V: Baseline Characteristics

		FCR (n=263)	Ibrutinib +venetoclax (n=260)	Total (n=523)
Age	Median (yr)	62	62	62
	>65 years	82 (31.2%)	81 (31.2%)	163 (31.2%)
Gender	Male	187 (71.1%)	186 (71.5%)	373 (71.3%)
Binet stage	Prog A or B	152 (57.8%)	151 (58.1%)	303 (57.9%)
	C	111 (42.2%)	109 (41.9%)	220 (42.1%)
Duration of CLL prior to randomisation	Median (mo)	33.7	37.9	35.8
B symptoms	Yes	121 (46.5%)	128 (49.2%)	249 (47.9%)

FCR vs I+V: Prognostic markers

		FCR (n=263)	Ibrutinib+venetoclax (n=260)	Total (n=523)*
IGHV	Mutated (excl subset 2)	79 (30%)	92 (35.8%)	171 (32.7%)
	Unmutated (excl subset 2)	139 (52.8%)	124 (47.7%)	*261* (49.9%)
	Ig Stereotype Subset 2	13 (4.9%)	13 (5%)	26 (5%)
	Not available	32 (12.2%)	31 (11.9%)	63 (12%)
FISH Hierarchy	17p deletion*	0 (0%)	1 (0.4%)	1 (0.2%)
	11q deletion	50 (19%)	45 (17.3%)	95 (18.2%)
	Trisomy 12	29 (11%)	57 (21.9%)	86 (16.4%)
	Normal	69 (26.2%)	52 (20%)	121 (23.1%)
	13q deletion	100 (38%)	87 (33.5%)	187 (35.8%)
	Failed/incomplete	15 (5.7%)	18 (6.9%)	33 (6.3%)

* Patients with >20% 17p deleted cells were excluded.

Flair

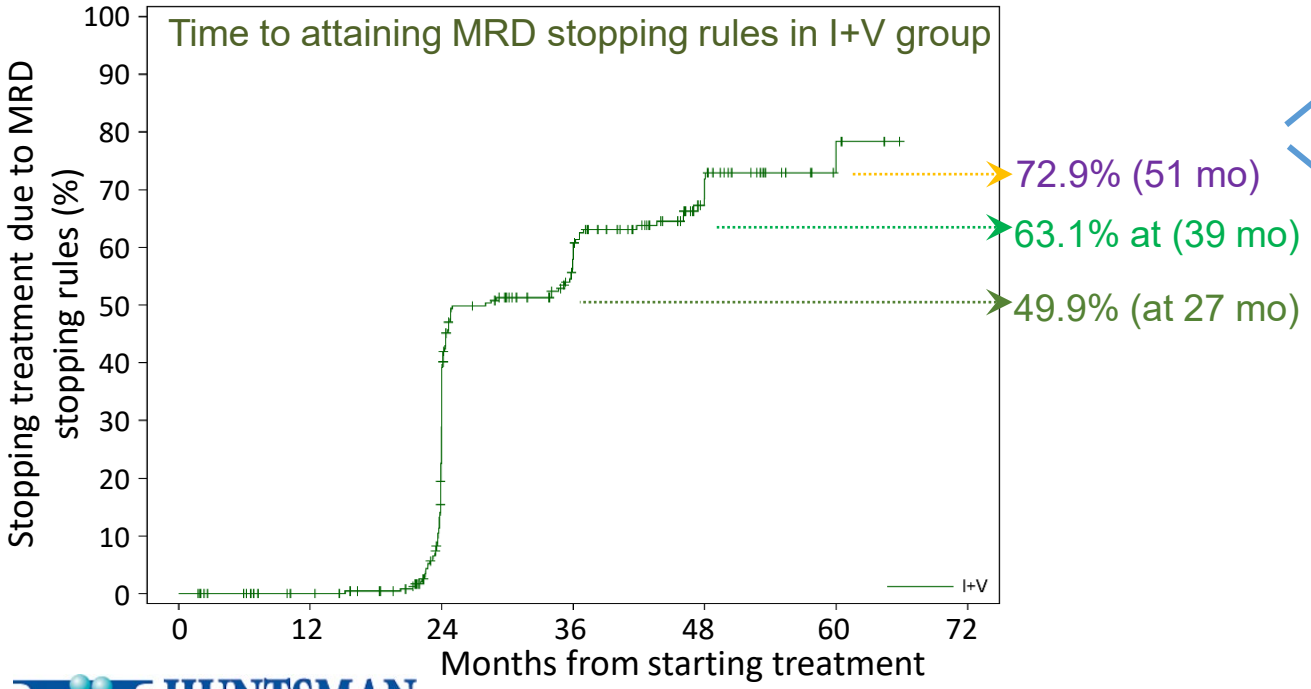
iwCLL response and MRD stopping rules

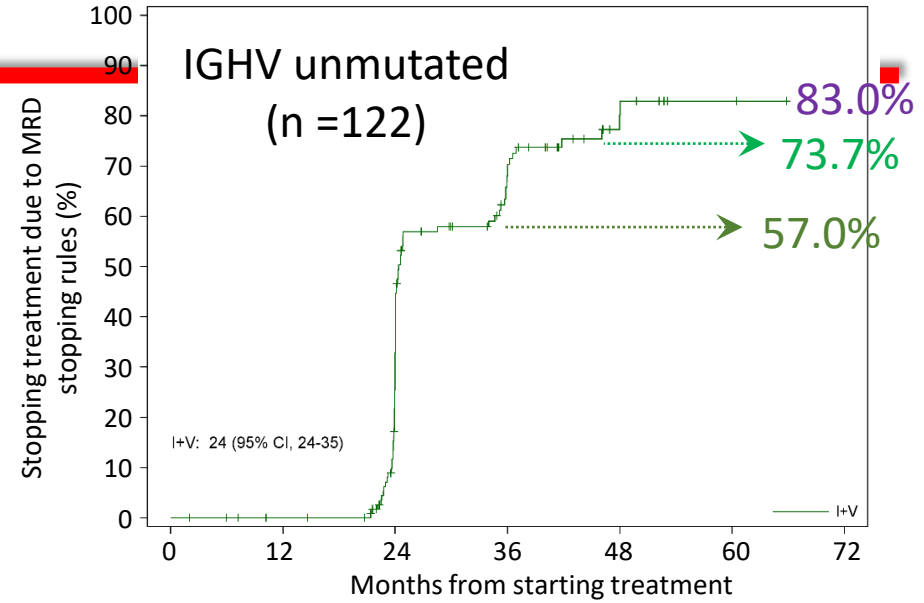
iwCLL Responses

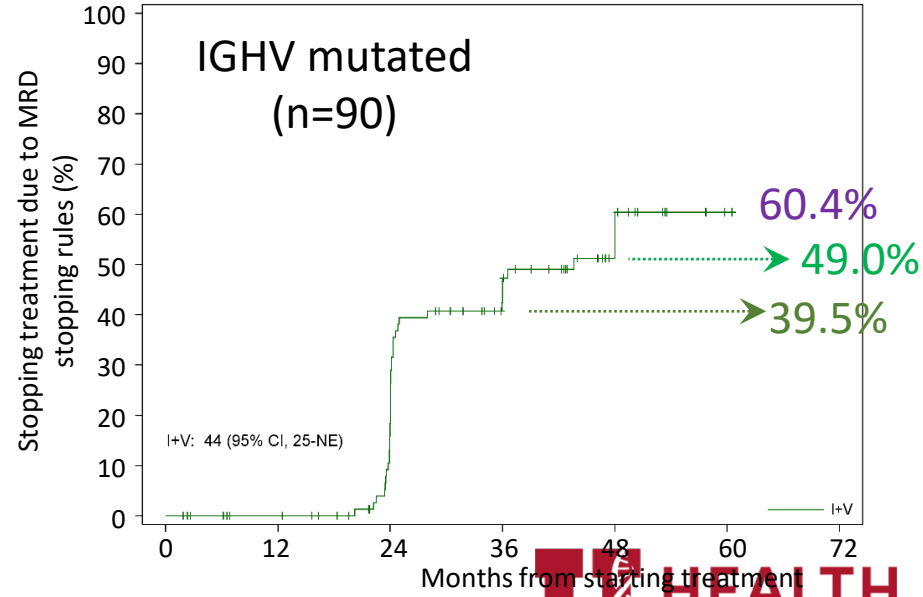
	Complete Response/CRi		Overall Response		BM uMRD
	9 months	Anytime	9 months	Anytime	Anytime
FCR	**49%**	**71.5%**	**76.4%**	**83.7%**	**40.3%**
I+V	**59.2%**	**92.3%**	**86.5%**	**95.4%**	**61.9%**

Odds ratio: 1.51
P<0.05

Odds ratio: 2.0
P<0.005



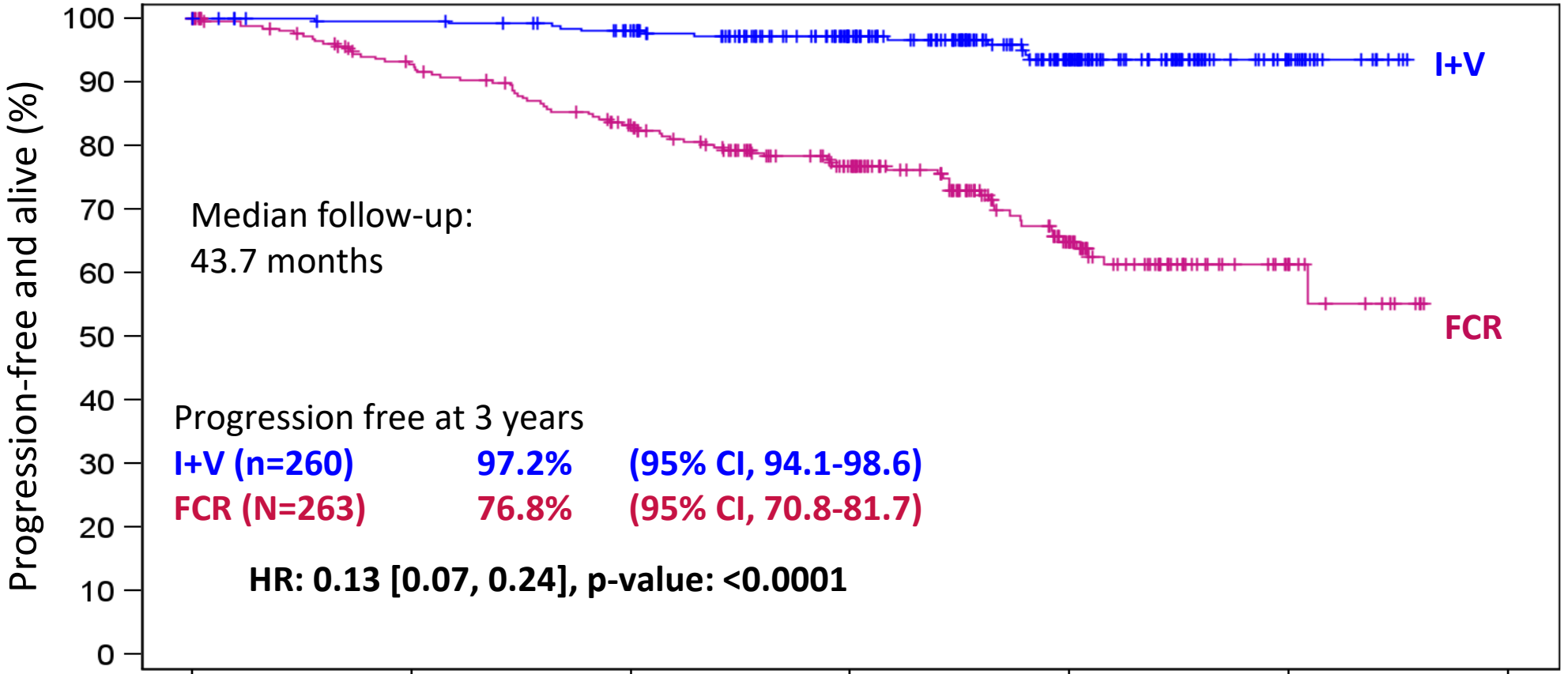




HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

Flair Primary end-point: PFS for FCR versus I+V



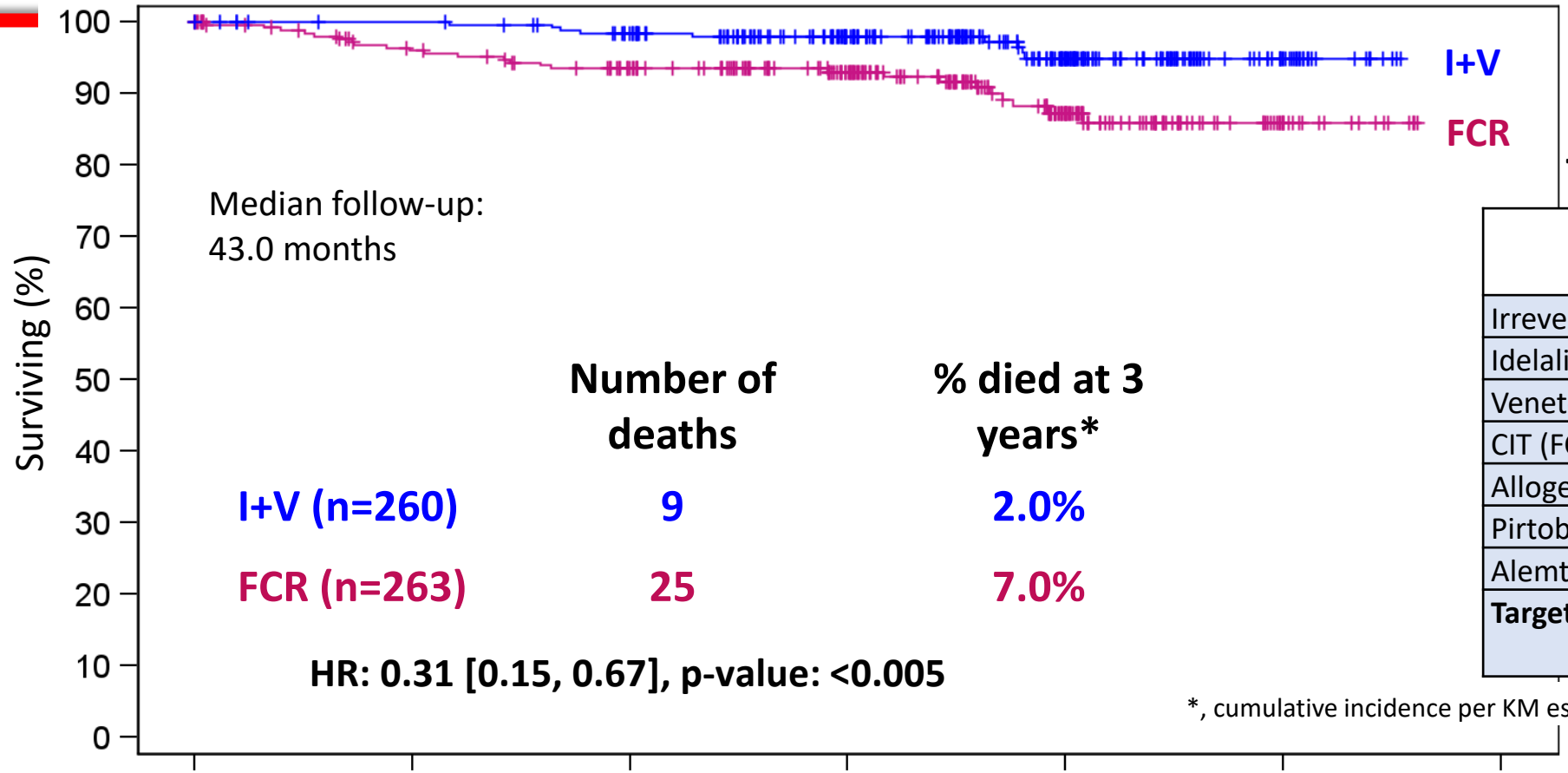
No. at risk						
I+V	260	253	239	183	99	21	0
FCR	263	227	194	145	68	12	0

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

Flair

Overall Survival in FCR versus I+V



Treatment after progression

	FCR (n=42)	I+V (n=5)
Irreversible BTKi	23	2
Idelalisib + R	1	0
Venetoclax + R	11	0
CIT (FCR/BR/ChlR)	6	1
Allogeneic SCT	1	0
Pirtobrutinib	0	1
Alemtuzumab	0	1
Targeted therapy for CLL	**35/42 (83%)**	**3/5 (60%)**

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

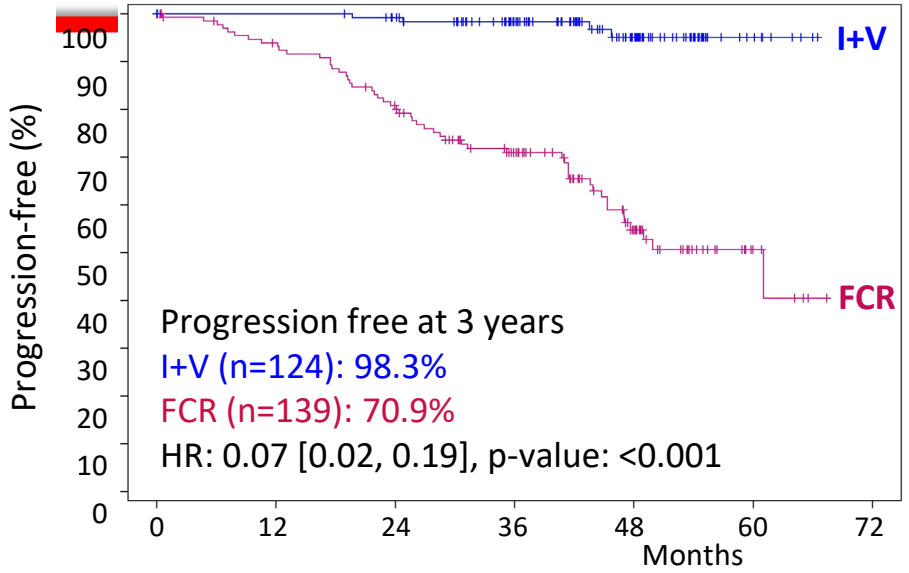
HEALTH UNIVERSITY OF UTAH

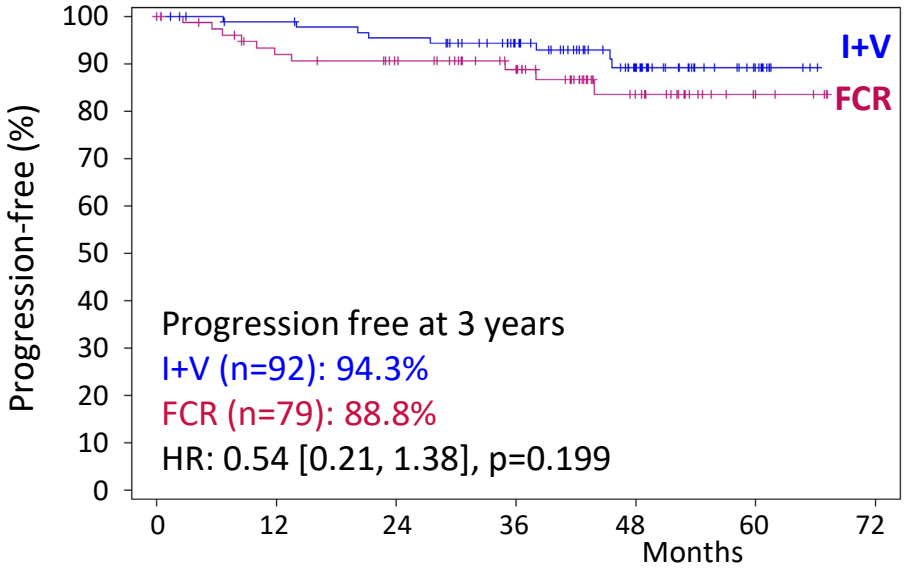
Outcome by IGHV mutation status

IGHV unmutated (excl. Subset 2)

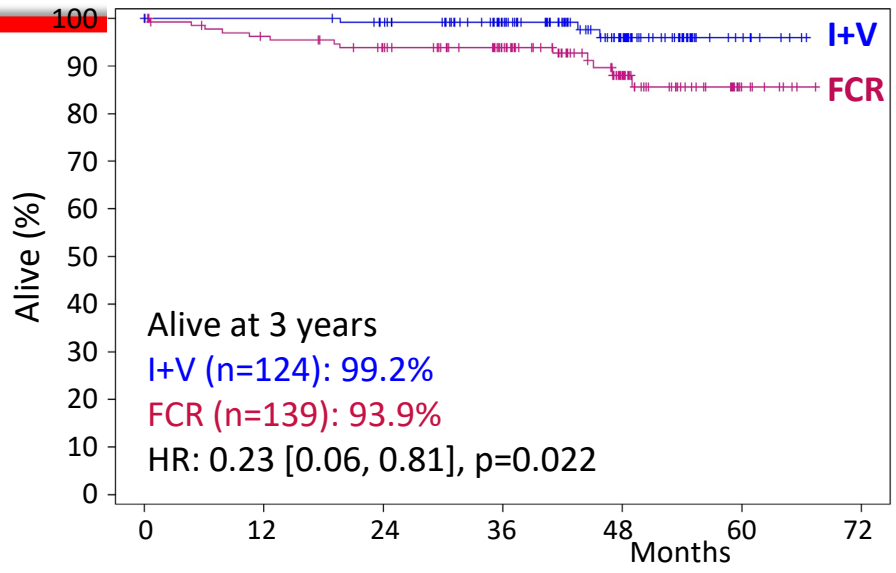
IGHV mutated (excl. Subset 2)

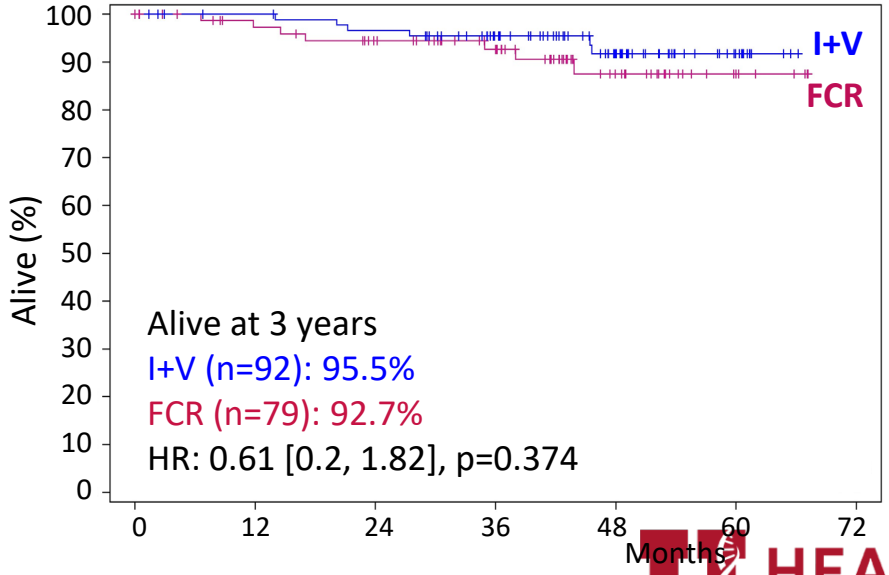
Progression Free Survival





Overall Survival





HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

Serious Adverse Events & malignancies

SAEs, by MedDRA System organ class

	Number of participants reporting ≥1 SAE	
	FCR (n=239)	I+V (n=252)
Infections and infestations	45 (18.8%)	56 (22.2%)
Blood and lymphatic system disorders	**74 (31%)**	**13 (5.2%)**
Cardiac disorders	**1 (0.4%)**	**27 (10.7%)**
Gastrointestinal disorders	19 (7.9%)	9 (3.6%)
General disorders and administration site conditions	**12 (5%)**	**4 (1.6%)**
Neoplasms benign, malignant and unspecified (including cysts and polyps)	5 (2.1%)	6 (2.4%)
Metabolism and nutrition disorders	**0 (0%)**	**10 (4%)**
Respiratory, thoracic and mediastinal disorders	6 (2.5%)	4 (1.6%)
Musculoskeletal and connective tissue disorders	3 (1.3%)	6 (2.4%)
Skin and subcutaneous tissue disorders	5 (2.1%)	4 (1.6%)
Nervous system disorders	2 (0.8%)	5 (2%)
Eye disorders	**0 (0%)**	**6 (2.4%)**

Secondary malignancies (SM)

	FCR	I+V
Incidence rate of cancers per 100 person-years (95% CIs)	**5.4** (5.11, 5.68)	**2.6** (2.40, 2.79)

	FCR	I+V
BCC/SCC	16	13
MDS/AML	8	1
Lymphoma	5	3
Prostate/urological	5	1
Lung	3	0
GI	3	1
Breast	1	1
Melanoma	1	1
Myeloma	1	0
Endocrine	0	1
Other	5	2
Total patients*	**39**	**17**

*, some patients had more than one SM

UNIVERSITY OF UTAH

Flair Safety and Toxicity: Deaths

- 31 deaths have occurred in the safety population. 23 from FCR participants and 8 from I+V.
- 7 deaths have been assessed as related to treatment (6 FCR; 1 I+V)
- 13 deaths were related to SAEs or SUSARs (8 FCR; 5 I+V)
- 2 of the 3 cardiac deaths in the I+V arm occurred after treatment was completed (35 days and 411 days later)

	FCR	I+V
Infection	7	1
Sudden/Cardiac	2	3
COVID-19	2	2
Richter's transformation	2	1
Non-haem malignancy	2	1
Allogeneic SCT – infection	1	0
Allogeneic SCT – GvHD	1	0
Disease progression	1	0
Hemorrhage	1	0
Lymphoma	1	0
Treatment related MDS/BMF	3	0
Total:	**23**	**8**

FLAIR Conclusions

- Majority of patients treated with IV combination will achieve uMRD (10^{-4}) by 24 months.
  - ~20-25% improvement in uMRD rates if treated to 4-5 years
  - Unmutated *IGHV* patients more readily achieved uMRD than mutated (83% vs. 60.4%)
- Unanswered questions
  - Is it really necessary to treat twice as long beyond initial detection of uMRD
    - Especially when the standard is moving towards ≤10^{-6} MRD detection
  - Is combination really better than sequential?
  - Could use of second generation BTKi in combo with venetoclax improve outcomes and safety?
    - Randomized phase IIIs: MAJIC, Beigene

Frontline IV combination not ready for prime time in the US yet.

Awaiting future confirmatory trials.

Richter's Transformation

Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy for Richter's Transformation: An International Multicenter Retrospective Study

Adam S Kittai, MD, *David A. Bond, MD, Ying Huang, MS, MA, Seema A Bhat, MD, Emily Blyth, B.Med(Hons), FRACP, FRCPA, PhD, John C. Byrd, MD, Julio C Chavez, MD, Matthew S. Davids, MD, MMSc, Jamie P Dela Cruz, Mark R Dowling, MBBS, PhD, Caitlyn Duffy, Carrie I Ho, MD, Caron A Jacobson, MD, MMSc, Samantha M. Jaglowski, MD, MPH, Nitin Jain, MD, Kevin H Lin, MD, Christine McCarthy, BS, Erin M Parry, MD, PhD, Manoj Rai, MD, Kerry A Rogers, MD, Aditi Saha, MBBS, Levanto Schachter, DO, MS, Hamish Scott, MD, Jayastu Senapati, MD, MBBS, DM, Mazyar Shadman, MD, MPH, Tanya Siddiqi, MD, Deborah M. Stephens, DO, Vinay Vanguru, MBBS, FRACP, FRCPA, William G. Wierda, MD, PhD, Omer Zulfa, MD, Jennifer A. Woyach, MD and Philip A. Thompson, MBBS*

The James

THE OHIO STATE UNIVERSITY
COMPREHENSIVE CANCER CENTER

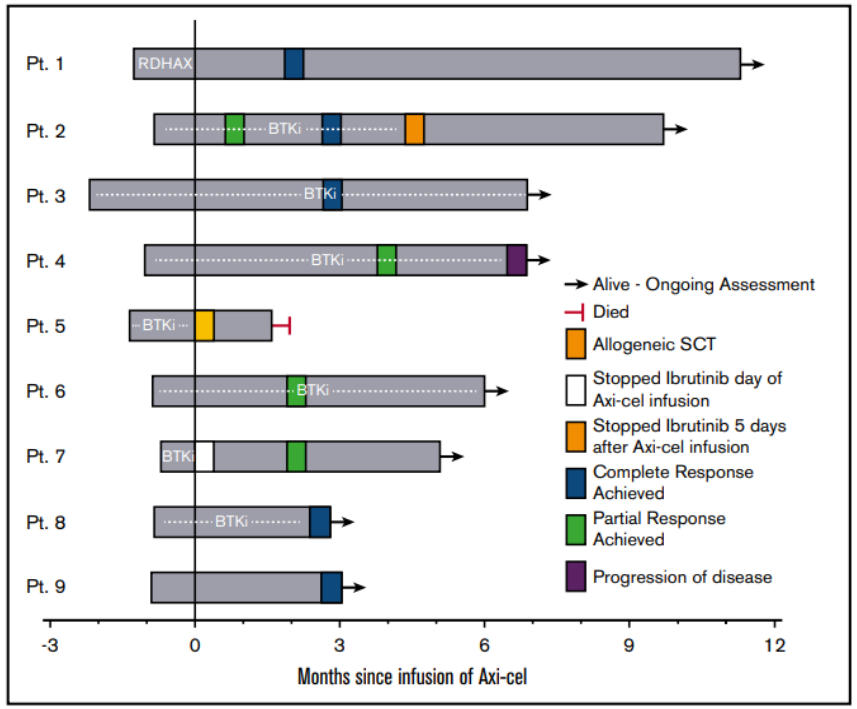
Introduction – RT is a disease of unmet need

- Richter's transformation (RT) is defined as the transformation of CLL into an aggressive lymphoma, typically Large B-cell Lymphoma (LBCL).[1]
- No standard of care treatment options, as survival is measured in months.
- Outcomes of patients with RT that has developed on small molecule inhibitors with no prior chemotherapy remains poor.[2]
  - Median overall survival 8.2 months
- Therefore, RT represents a true area of unmet need.

[1]Tsimberidou et al JCO 2006, [2]Kittai et al ASH Oral 2023

Background – Anti-CD19 CART for RT

- Anti-CD19 CAR T-cell therapy (CD19 CART) has revolutionized the way we treat LBCL.
- RT was mostly excluded from clinical trials with CD19 CART.
- We published our experience treating patients with RT with axicabtagene ciloleucel showing impressive response rates.[1]



Given unclear durability, and limited number of patients in this study we performed a large international retrospective study to determine efficacy and safety of CAR19 for RT.

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

[1]Kittai et al Blood Advances 2020

HEALTH UNIVERSITY OF UTAH

Methods

- International multicenter retrospective study of patients with RT who received FDA approved CD19 CART
  - Including axi-cel, tisa-cel, liso-cel, and brexu-cel
- 12 academic centers in the US and Australia
- RT defined as patients with LBCL with preceding or concurrently diagnosed CLL
- PFS and OS measured from date of CD19 CART
- Cox regression model used to associate prognostic factors with OS

Baseline CLL Characteristics

CLL Treatment History	N=69
Prior Chemo for CLL, N (%)	39 (56.5)
Prior BTKi for CLL, N (%)	44 (63.8)
Prior Ven for CLL, N (%)	23 (33.3)
Prior Allo-SCT for CLL, N (%)	3 (4.4)
Prior CART for CLL, N (%)	1 (1.4)
Median # of CLL TRMT prior to RT	2 (0-10)
De novo RT (0 TRMT for CLL), N (%)	12 (17.4)

Median years from CLL dx to RT – 6 (0-28)

CLL Molecular Data	N=69
IGHV, N (%)	
Mutated	8 (13.3)
Unmutated	52 (86.7)
Unknown	9
del(17p), N (%)	23 (41.8)
Unknown	14
del(11q), N (%)	13 (23.6)
Unknown	14
Tri 12, N (%)	9 (16.4)
Unknown	14
Del(13q), N (%)	21 (38.2)
Unknown	14
TP53 mut, N (%)	20 (50.0)
Unknown	29
NOTCH1 mut, N (%)	6 (18.8)
Unknown	37
Complex KT (≥3 abn), N (%)	22 (51.2)
Unknown	26

Baseline RT Characteristics

RT Characteristics and TRMT	N=69
Age at RT Dx, median (range)	63 (26-80)
Clonal relationship to CLL, N (%)	
Related	23 (100)
Unknown	46
Complex KT (≥3 abn) at RT, N (%)	19 (65.5)
Unknown	40
del17p (RT), N (%)	12 (41.4)
Unknown	40
TP53 mut (RT), N (%)	14 (58.3)
Unknown	45
NOTCH1 mut (RT), N (%)	4 (21.1)
Unknown	50
MYC translocation, N (%)	8 (20.0)
Unknown	29
Median Ki-67 (%)	80 (40-100)
Unknown	9
Prior BTKi alone or in combo for RT	46 (66.7)
Prior Ven alone or in combo for RT	35 (50.7)
Prior BTKi or Ven for RT or CLL, N (%)	58 (84%)

RT Characteristics collected at CAR19

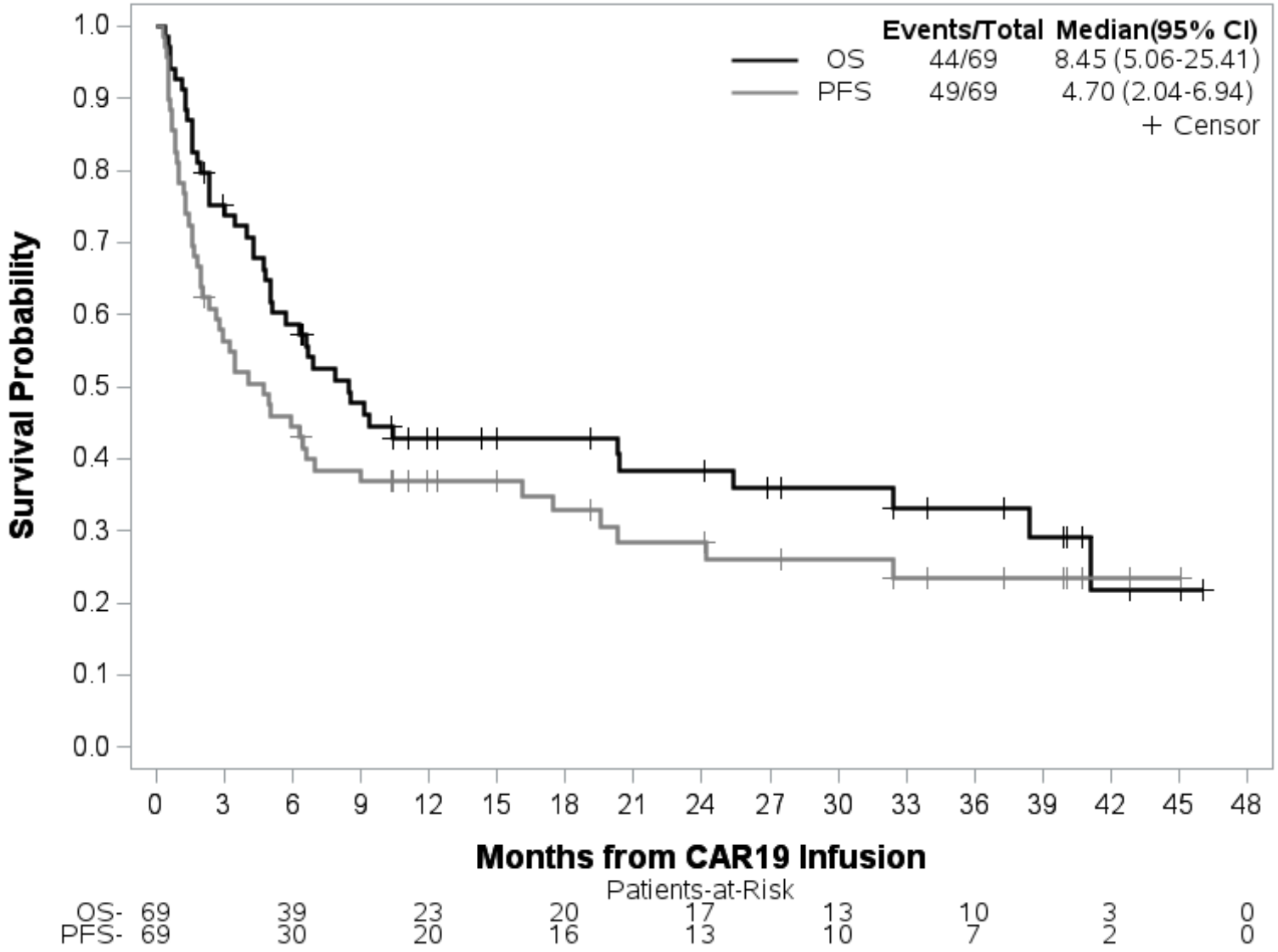
RT at CART Baseline Characteristics and TRMT	N=69
Median age at CART infusion	64 (27-80)
Median months from RT dx to CART	7.3 (0.4-65.6)
Median # TRMT for RT prior to CART	2 (0-7)
Median Total # of prior TRMT	4 (1-15)
Received bridging, N (%)	59 (85.5)
CAR-T product given, N (%)	
Axi-cel[1]	45 (65.2)
Liso-cel	7 (10.1)
Tisa-cel	17 (24.6)
Median days from Apheresis to CART infusion	34 (24-100)
Concurrent BTKi therapy, N (%)	31 (44.9)
Median LDH prior to CART	258 (96-2878)
Median largest LN (cm) prior to CART	3.5 (0.7-16)
Unknown	9
Median highest SUV on PET prior to CART	14.8 (3-50.6)
Unknown	7

Progression free and Overall survival

Median follow-up in months (range) – 24.13 (2.14-46.02)

	N=69
PFS from CART Infusion	
Number of events	49
Median in months (95% CI)	4.70 (2.04-6.94)
OS from CART Infusion	
Number of events	44
Median in months (95% CI)	8.45 (5.06-25.41)

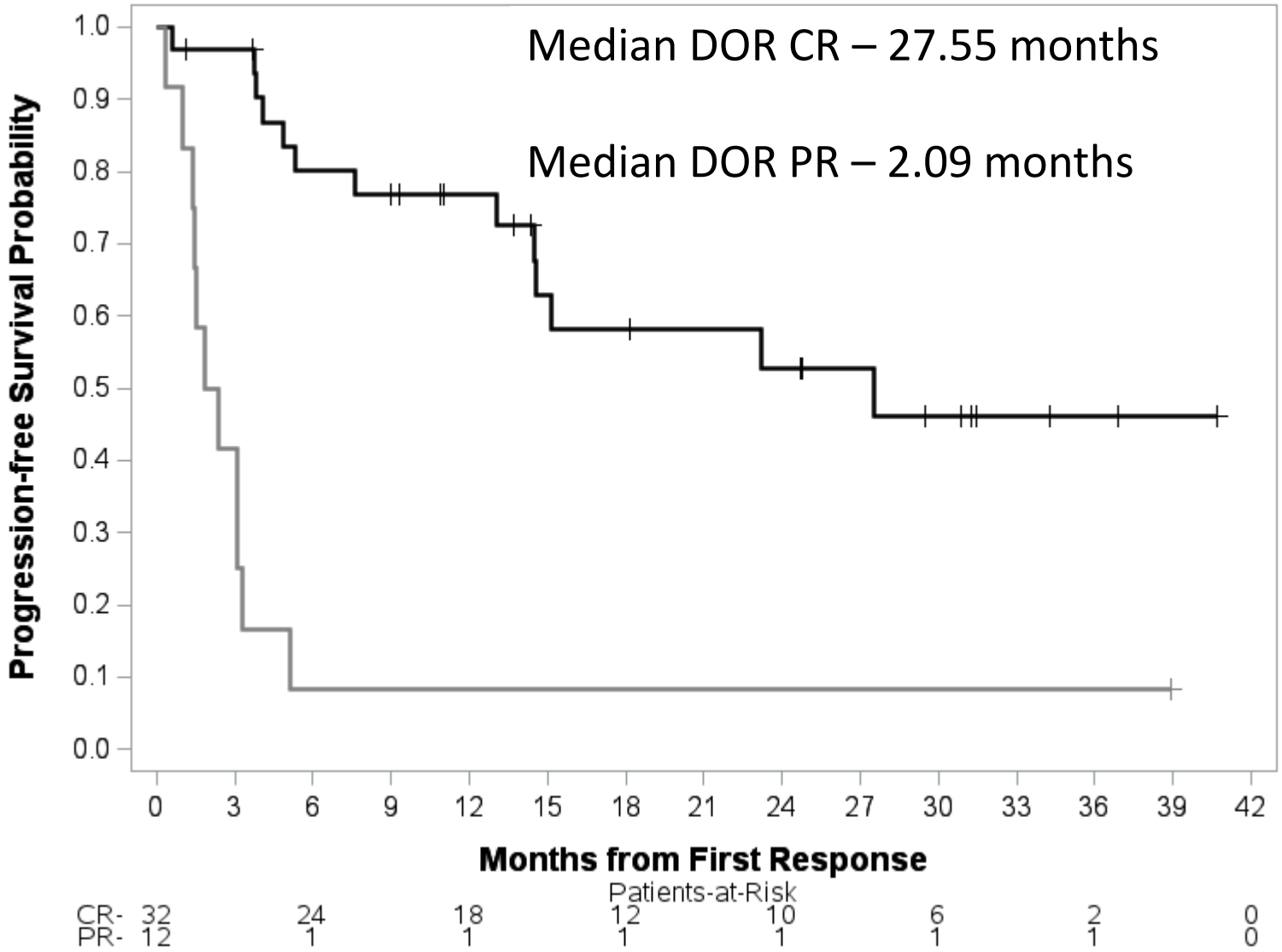
OS from RT Diagnosis	
Number of events	**44**
Median in months (95% CI)	**29.4 (15.7-33.5)**
Median follow-up (range)	**36.1 (8.2-82.9)**



HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

Duration of response by CR or PR

Best response to CART, N (%)	
CR	32 (46.4)
PR	12 (17.4)
SD	1 (1.5)
PD	21 (30.4)
Died prior to assessment	3 (4.4)



HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

UNIVERSITY OF UTAH

Safety Outcomes

	N=69
Cause of Death (N=44), N (%)	
Disease	32 (72.7)
Non-disease	12 (27.3)
Non-relapse Mortality from CART Infusion, % (95% CI)	
Number of events	12
3-month estimate	7.3% (2.7-15.0)
6-month estimate	10.3% (4.5-18.9)
12-month estimate	13.4% (6.5-22.8)

CAR-T Outcomes	N=69
Grade 3-4 neutropenia, N (%)	60 (87.0)
Grade 3-4 thrombocytopenia, N (%)	49 (71.0)
Febrile neutropenia, N (%)	46 (66.7)
CRS max grade, N (%)	
0	8 (11.6)
1	24 (34.8)
2	26 (37.7)
3	9 (13.0)
4	2 (2.9)
ICANS max grade, N (%)	
0	23 (33.8)
1	12 (17.7)
2	8 (11.8)
3	17 (25.0)
4	8 (11.8)
Unknown	1
Grade 3-4 infection, N (%)	14 (20.3)

Recent ASH report of NRM in Axi-Cel treated patients

- ~4.5% in 12 months
- 14.5% overall

Spiegel et al. ASH 2023 Abstract #1032

MVA for OS – Independent prognostic factors

	Univariable Models		Multivariable Model	
	HR (95% CI)	p-value	HR (95% CI)	p-value
# prior lines of therapy for RT prior to CART	1.33 (1.05-1.70)	0.02	1.58 (1.23-2.03)	0.0004
Total prior lines of therapy	1.18 (1.04-1.35)	0.01		
Ki-67, 10% higher	1.29 (1.03-1.60)	0.03	1.49 (1.20-1.87)	0.0004
LDH, 2-fold increase	1.84 (1.36-2.49)	<.0001	1.91 (1.35-2.69)	0.0002

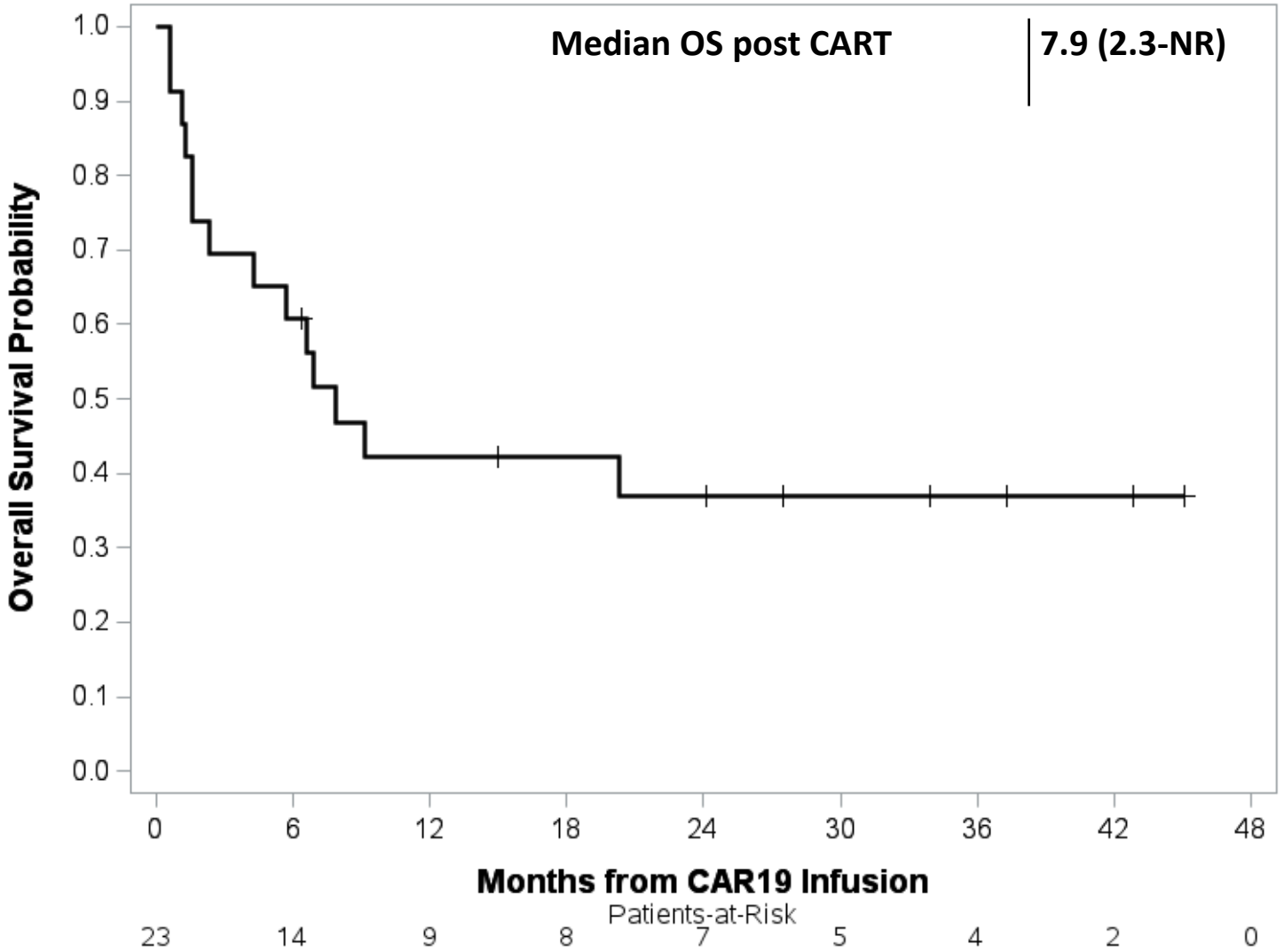
Summary of patients with Clonally-Related disease

	N=23
Age at CLL Diagnosis, median (range)	56 (37-69)
# of CLL therapies prior to RT, median (range)	2 (0-10)
De novo RT, N (%)	4 (17.4)
Years from CLL diagnosis to RT, median (range)	7 (1-18)
Age at CART infusion, median (range)	66 (42-80)
Months from RT diagnosis to CART, median (range)	5.5 (1.7-65.6)
# therapies for RT prior to CART, median (range)	2 (1-7)
Total number of prior therapies, median (range)	4 (2-15)

Best response to CAR-T (Lugano 2014), N (%)	
CR	**11 (47.8)**
PR	**2 (8.7)**
SD	**0 (0)**
PD	**9 (39.1)**
Died prior to assessment	**1 (4.4)**

OS plot for Clonally Related

Median follow-up in months - 33.9 (6.4-45.1)



HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

HEALTH UNIVERSITY OF UTAH

Conclusions

- This is the largest cohort of pts with RT to receive CD19 CART.
- Heavily pretreated group - 84% exposed to either BTKi or BCL2i, with 4 total prior lines of TRMT.
- Median OS from CAR19 was 8.5 months in this study.
- Median DOR from CAR19 for those patients that attained a CR was 27.55 months.
- Higher number of prior therapies is associated with worse OS.
  - Earlier use of CD19 CART in the RT disease course may be warranted.
- Prospective clinical trials ongoing.

Resistance Mutations in CLL

Genomic Evolution and Resistance during Pirtobrutinib Therapy in Covalent BTK-Inhibitor (cBTKi) Pre-treated Chronic Lymphocytic Leukemia Patients: Updated Analysis from the BRUIN Study

Jennifer R. Brown[1], Sai Prasad Desikan[2], Bastien Nguyen[3], Helen Won[3], Shady I. Tantawy[2], Samuel C. McNeely[4], Narasimha Marella[3], Kevin Ebata[3], Jennifer A. Woyach[5], Krish Patel[6], Constantine S. Tam[7], Toby A. Eyre[8], Chan Y. Cheah[9,10], Nirav N. Shah[11], Paolo Ghia[12], Wojciech Jurczak[13], Minna Balbas[3], Binoj Nair[3], Paolo Abada[3], Chunxiao Wang[4], Denise Wang[3], Lindsey E. Roeker[14], Varsha Gandhi[2], William G. Wierda[2]

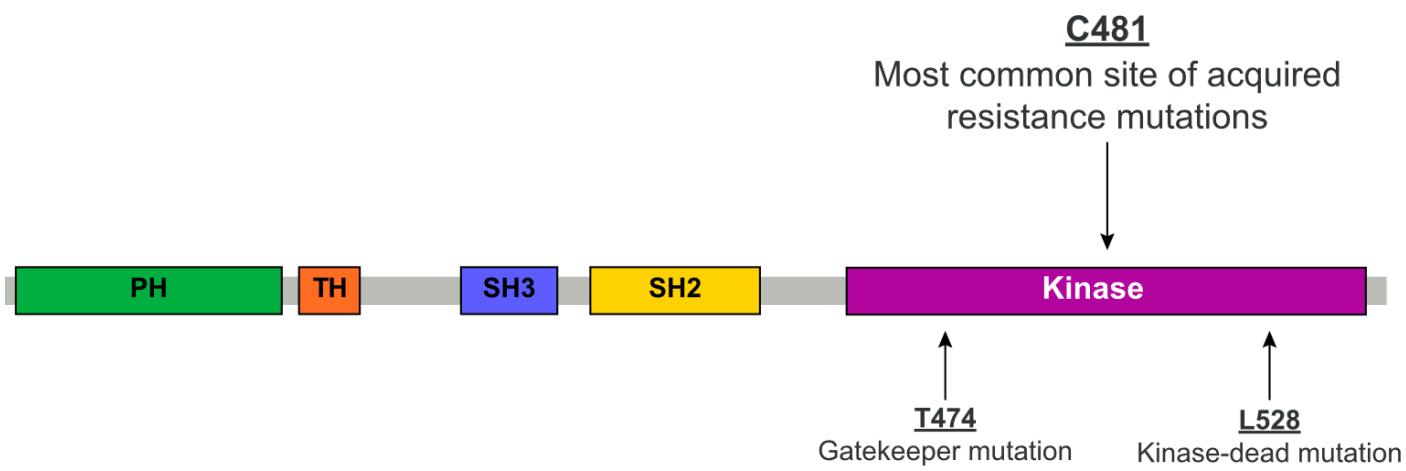
[1]Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA, USA; [2]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Loxo@Lilly, Indianapolis, IN, USA; [4]Eli Lilly and Company, Indianapolis, IN, USA; [5]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA; [6]Swedish Cancer Institute, Seattle, WA, USA; [7]Alfred Health and Monash University, Melbourne, Victoria, AUS; [8]Oxford University Hospitals NHS Foundation Trust, Oxford, UK; [9]Linear Clinical Research, Nedlands, AUS; [10]Sir Charles Gairdner Hospital, Nedlands, AUS; [11]Medical College of Wisconsin, Milwaukee, WI, USA; [12]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Italy; [13] Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland; [14]Memorial Sloan Kettering Cancer Center, New York, NY, USA

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

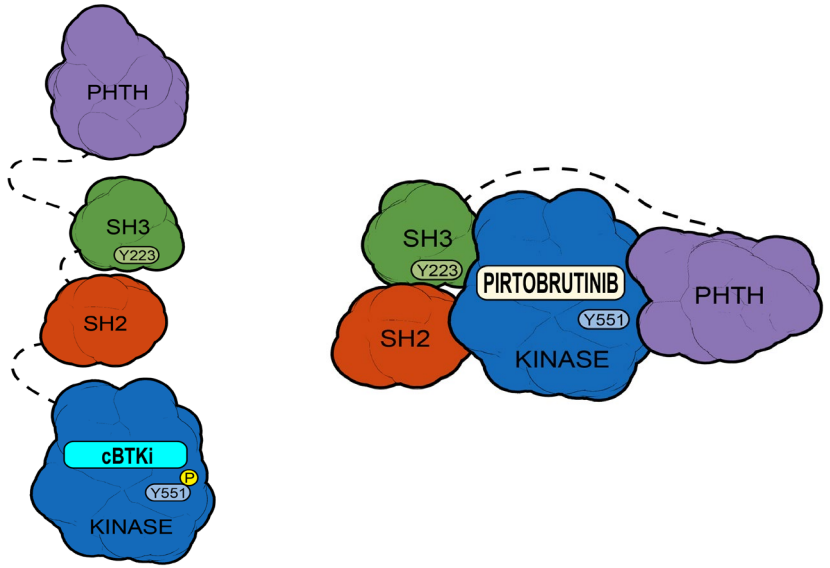
HEALTH UNIVERSITY OF UTAH

Pirtobrutinib Non-covalent Binding Inhibits both WT and C481-mutated *BTK*

BTK sites with known cBTKi resistance mutations



Pirtobrutinib may stabilize BTK in a closed inactive conformation[9]



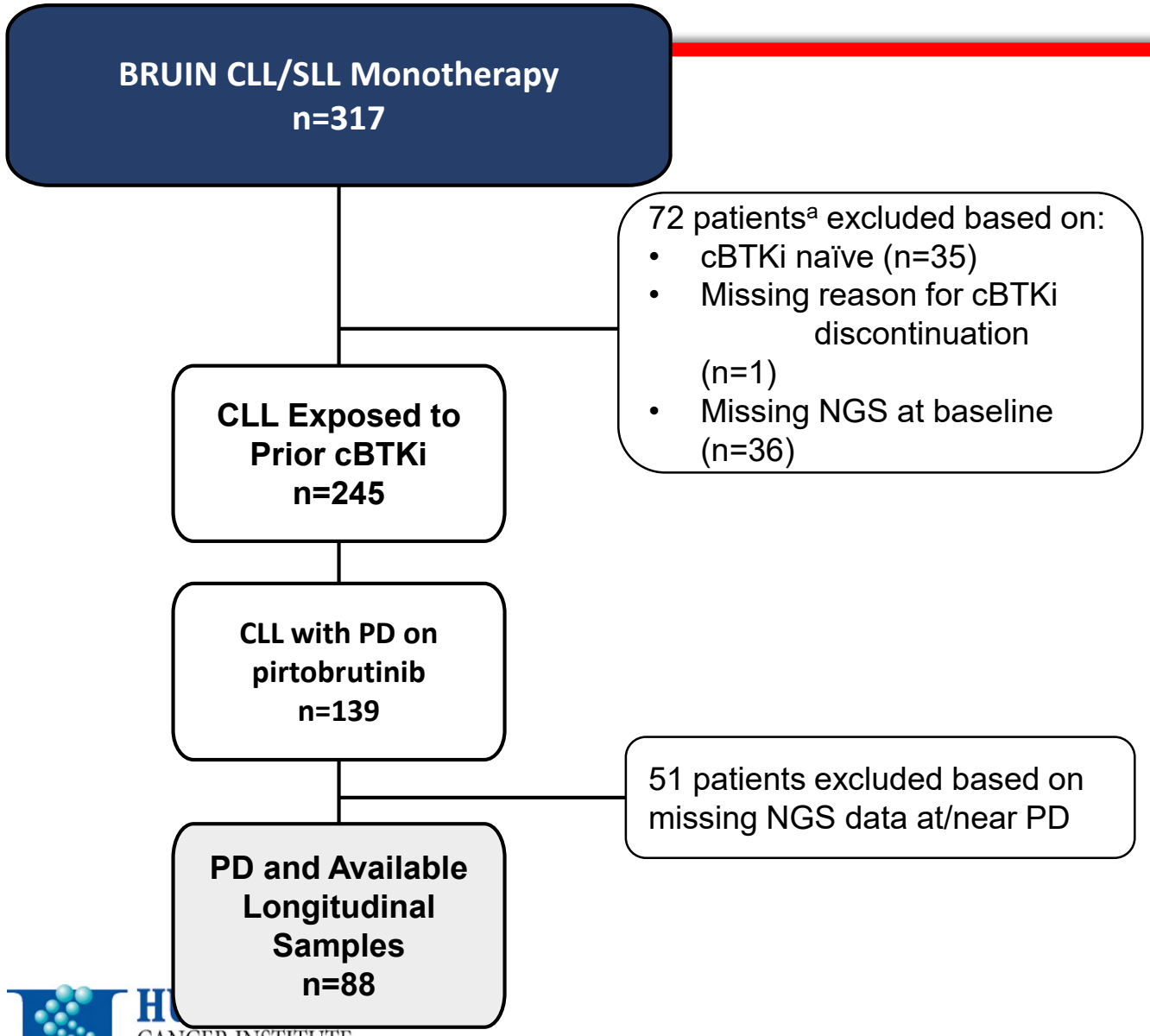
- The majority of patients discontinue covalent BTK inhibitors (cBTKi) due to intolerance or progression[1,2,3]
- BTK C481 substitutions are the most common resistance mechanism to cBTKi[4,5,6]
- Acquired mutations have been identified in a limited number of patients treated with pirtobrutinib[7,8]

Inactive conformation of BTK by pirtobrutinib:

- blocks access to upstream kinases and phosphorylation of Y551
- inhibits both WT and C481-mutant BTK with equal low nM potency[7,9]
- may inhibit kinase-independent BTK signaling[9]

[1]Woyach et al. *J Clin Oncol*. 2017. [2]Barr et al. *Blood Adv*. 2022. [3]Byrd et al. ASH Annual Meeting. 2022. [4]Estupinan et al. Leukemia. 2021. [5]Handunnetti et al. ASH Annual Meeting. 2019. [6]Blombery et al. Blood Advances. 2022. [7]Wang et al. NEJM. 2022 [8]Naeem et al. Blood Advances. 2023. [9]Gomez et al. Blood.2023.

Study Design & Methods



- Next-generation sequencing (NGS) of paired baseline and progression PBMC samples from 88 cBTKi pre-treated CLL patients who progressed on pirtobrutinib
- Targeted NGS (5% VAF limit of detection [LoD]) gene list (all exons, 74 genes):
  - ***BTK***, ***PLCG2***, ***TP53***, *ABL1, APC, ARID1A, ATM, BAP1, BCL2, BCL6, BRAF, BRD4, CARD11, CCND1, CCND3, CD79A, CD79B, CDK4, CDKN2A, CDKN2B, CREBBP, EP300, EPHA7, ERBB3, EZH2, FAS, FGFR1, FLT1, FOXP1, GNA13, GRIN2A, GSK3B, HRAS, IKZF1, IRF4, JAK1, JAK2, KDR, KIT, KLHL6, KMT2C, KMT2D, KRAS, MAP2K1, MED12, MEF2B, MTOR, MYC, MYD88, NFKBIA, NOTCH1, NOTCH2, NRAS, NTRK1, PDGFRA, PIK3CA, PIK3CG, PIK3R1, PIK3R2, PRDM1, PRKDC, PTEN, RAF1, RB1, ROS1, SF3B1, SMARCA4, SOCS1, STAT3, SYK, TET2, TNFAIP3, TNFRSF14, XPO1*
- 79 baseline PBMC samples were re-sequenced using a more sensitive assay (LoD ~ 0.5% VAF) to assess the presence of pre-existing *BTK* mutations

HUNTSMAN CANCER INSTITUTE
UNIVERSITY OF UTAH

Data cutoff date of 05 May 2023 (NCT03740529). [a]Patients with SLL were excluded from the analysis with these criteria.

Baseline Characteristics & Response

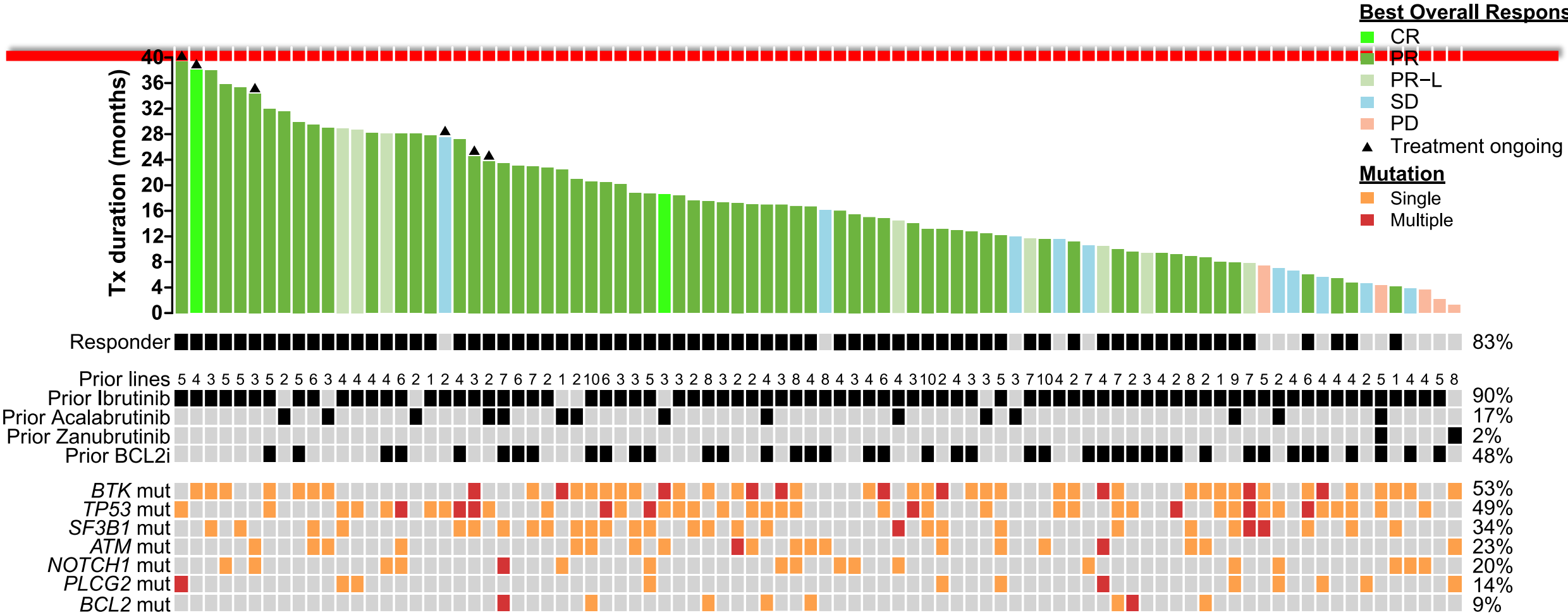
Characteristics	Overall n=245	Patients with PD and Longitudinal Samples n=88
Median Age, years (range)	69 (36-88)	69 (36-86)
Female, n (%)	78 (32)	32 (36)
ECOG, n (%)		
0	126 (51)	43 (49)
1	103 (42)	41 (47)
2	16 (7)	4 (5)
Median time on treatment, Months (range)	19 (0.20-49)	16 (1.2-39)
Median number of prior lines of systemic therapy, n (range)	4 (1-11)	4 (1-10)
Median number of prior cBTKi, n (range)	1 (1-5)	1 (1-4)
Reason for prior cBTKi discontinuation[a], n (%)		
Disease progression	181 (74)	75 (85)
Toxicity/ Other	64 (26)	13 (15)

Patients with documented PD may be allowed to continue study treatment if the patient is tolerating study drug and, in the opinion of the Investigator, the patient is deriving clinical benefit from continuing study treatment. [a]In the event more than one reason was noted for discontinuation, disease progression took priority.

Characteristics	Overall n=245	Patients with PD and Longitudinal Samples n=88
Prior therapy, n (%)		
cBTK inhibitor		
Ibrutinib	218 (89)	79 (90)
Acalabrutinib	40 (16)	15 (17)
Zanubrutinib	7 (3)	2 (2)
Chemotherapy	199 (81)	75 (85)
CD20 antibody	217 (89)	79 (90)
BCL2 inhibitor	113 (46)	42 (48)
PI3K inhibitor	61 (25)	21 (24)
CAR-T	15 (6)	8 (9)
Pirtobrutinib Efficacy	**Overall n=245**	**Patients with PD and Longitudinal Samples n=88**
Overall Response Rate[b], % (95%CI)	82 (76-86)	83 (73-90)
Best Response, n (%)		
CR	5 (2)	2 (2)
PR	176 (72)	63 (72)
PR-L	19 (8)	8 (9)
SD	26 (11)	10 (11)
PD	8 (3)	5 (6)
NE	11 (4)	0 (0)

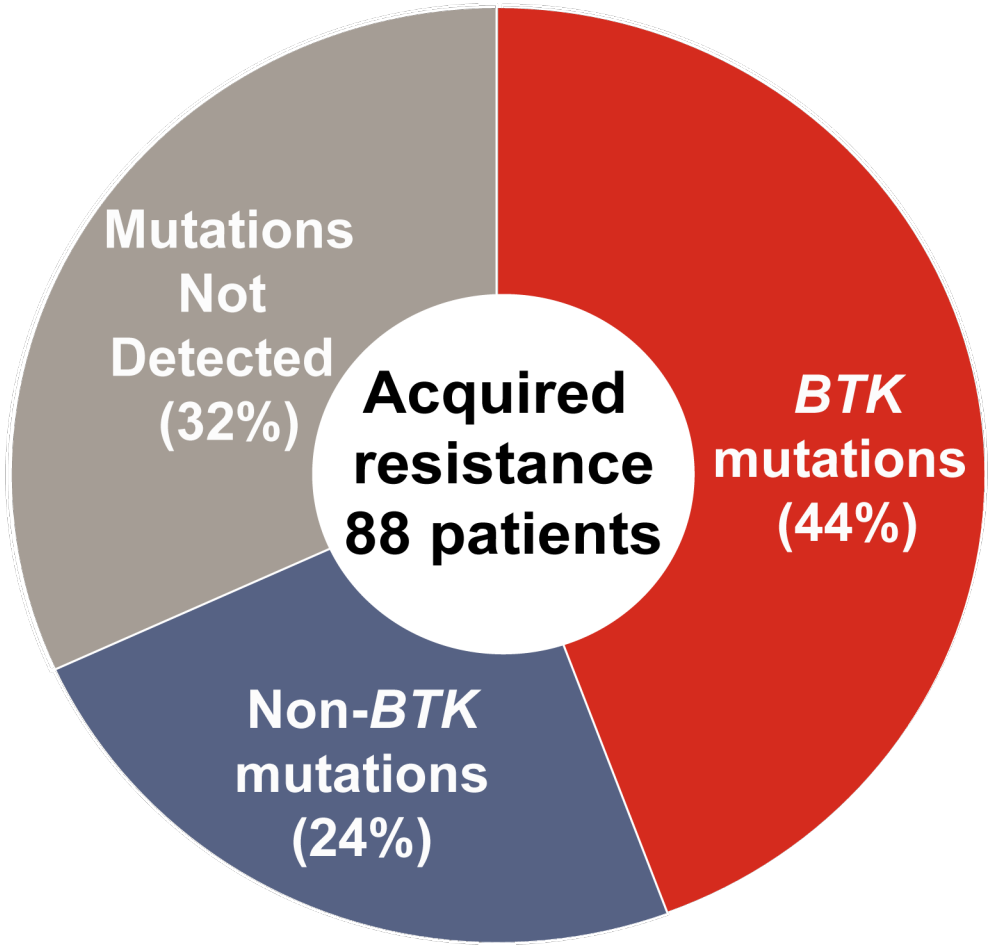
[b]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.

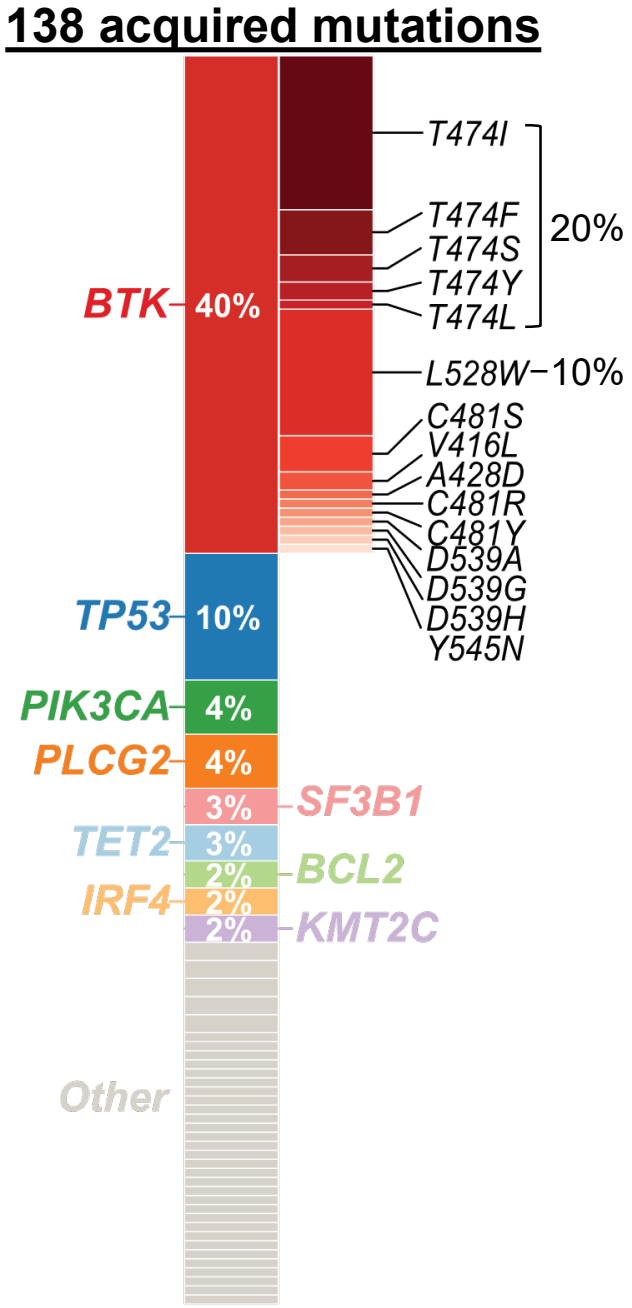
Baseline Genomics in Patients with PD on Pirtobrutinib (n=88)



- The most common mutations detected at baseline were *BTK* (53%), *TP53* (49%), *SF3B1* (34%), *ATM* (23%), *NOTCH1* (20%), *PLCG2* (14%), *BCL2* (9%)
- Pirtobrutinib demonstrated efficacy, with an ORR of 83% (73/88)
  - Baseline genomic features did not predict response to pirtobrutinib treatment

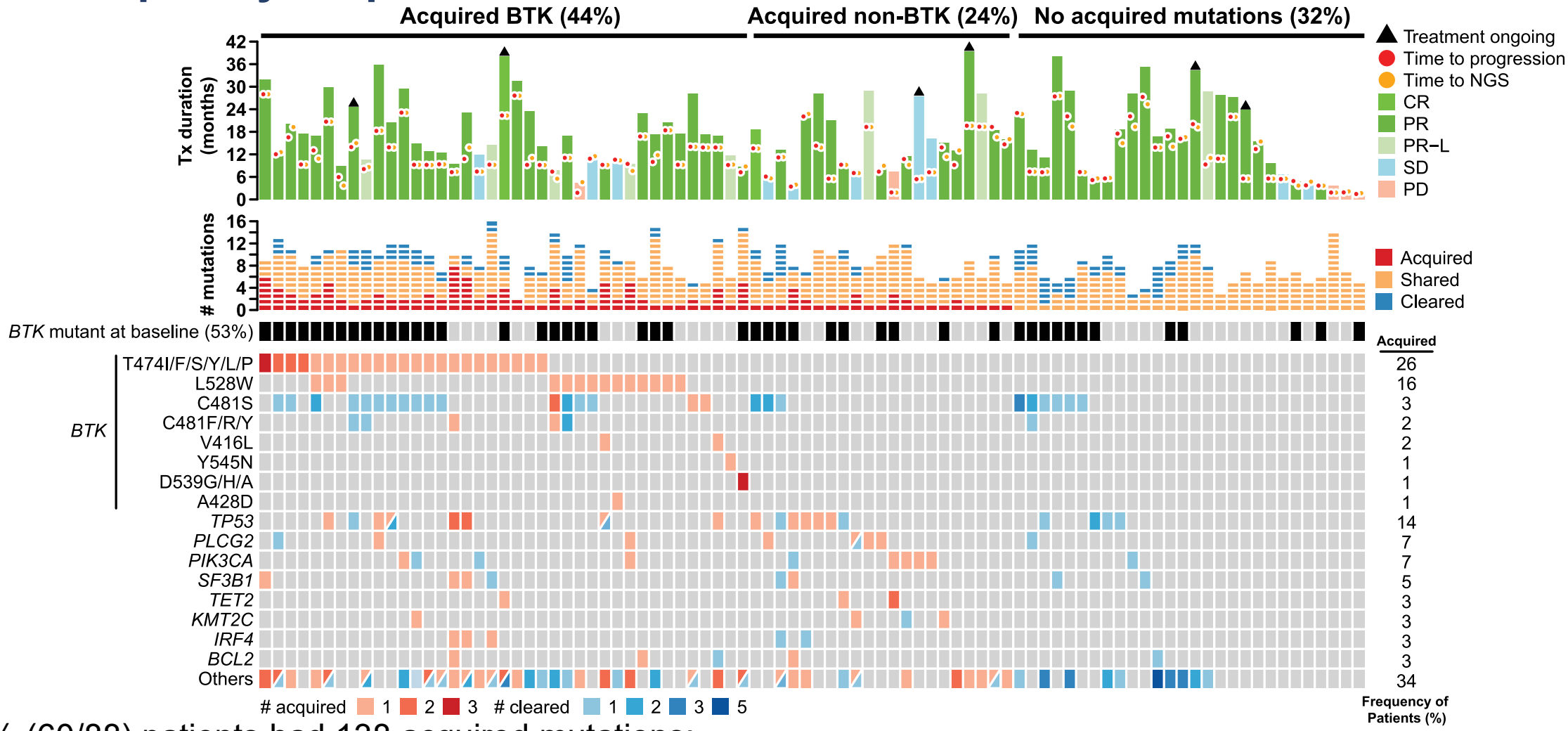
Acquired Mutations were Detected at PD in 68% of Patients





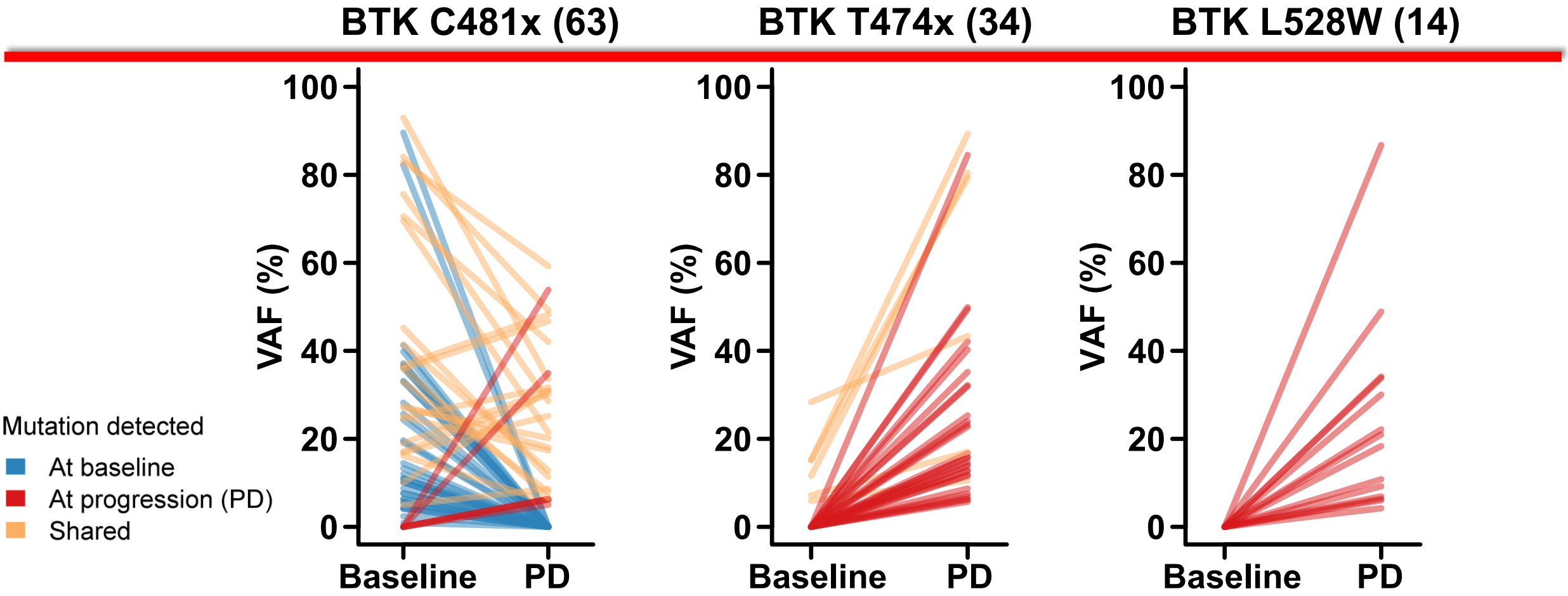
- 68% (60/88) acquired mutations at PD
  - 44% (39/88) had at least one acquired *BTK* mutation at PD
    - 64% (25/39) who acquired a *BTK* mutation had a *BTK* mutation at baseline
- 56% (49/88) did not acquire a *BTK* mutation
  - The most frequently acquired non-*BTK* mutation was *TP53*
- 32% (28/88) had no acquired mutations detected at PD

Most Frequently Acquired Mutations on Pirtobrutinib Treatment



- 68% (60/88) patients had 138 acquired mutations:
  - 28% had a single acquired mutation and 40% had multiple acquired mutations (up to 8)
  - 30% had a single acquired BTK mutation and 14% had multiple acquired BTK mutations
  - 14% had TP53, 7% had PLCG2, 7% had PIK3CA, 3% BCL2 (all had prior venetoclax)
- 51% (24/47) had clearance of BTK mutations

The Majority of *BTK* Acquired Mutations were T474x and L528W

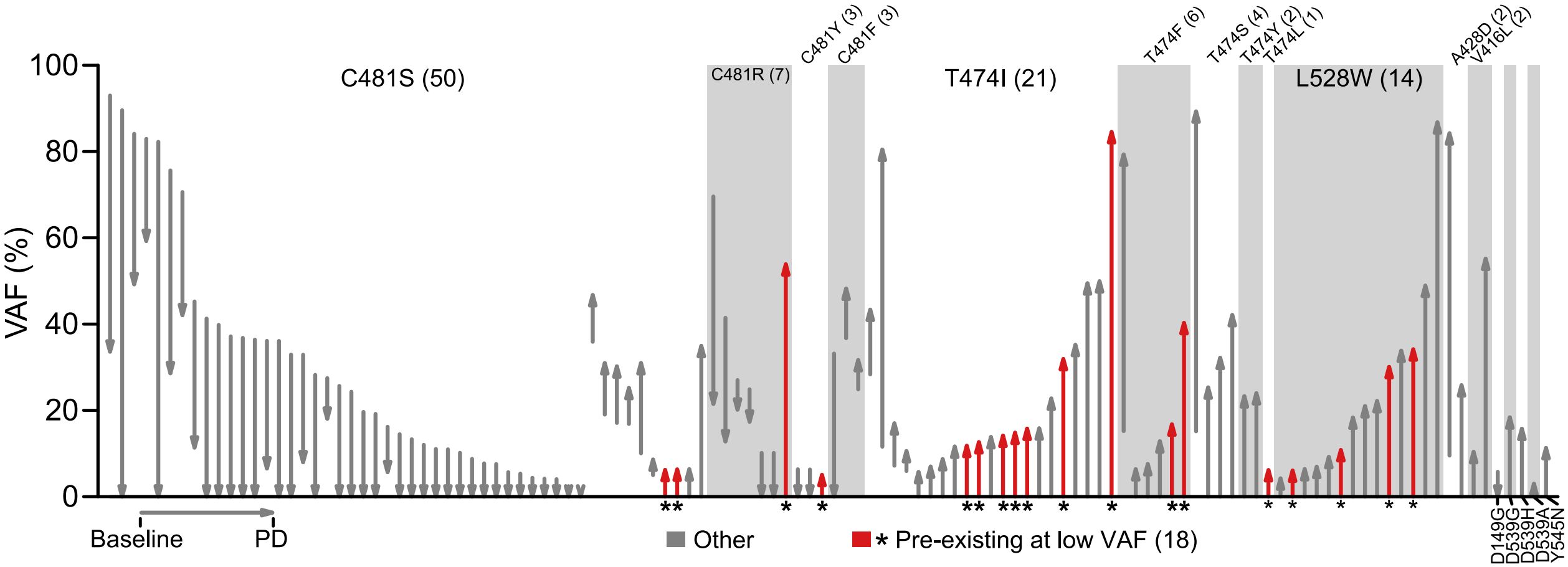


- Decrease/clearance of C481x[a] clones observed at progression in 84% (36/43) patients (clearance = 23/43, 53%)
- *BTK* C481S/Y/R, T474x[a], L528W, other kinase mutations arose at/near progression (55 mutations in 39 patients, VAF range 3-86%)
- ORR was similar across groups regardless of the acquired *BTK* mutation (T474x, 22/23, 96%; L528W; 11/14, 79%)

[a]any amino acid substitutions.

UNIVERSITY OF UTAH

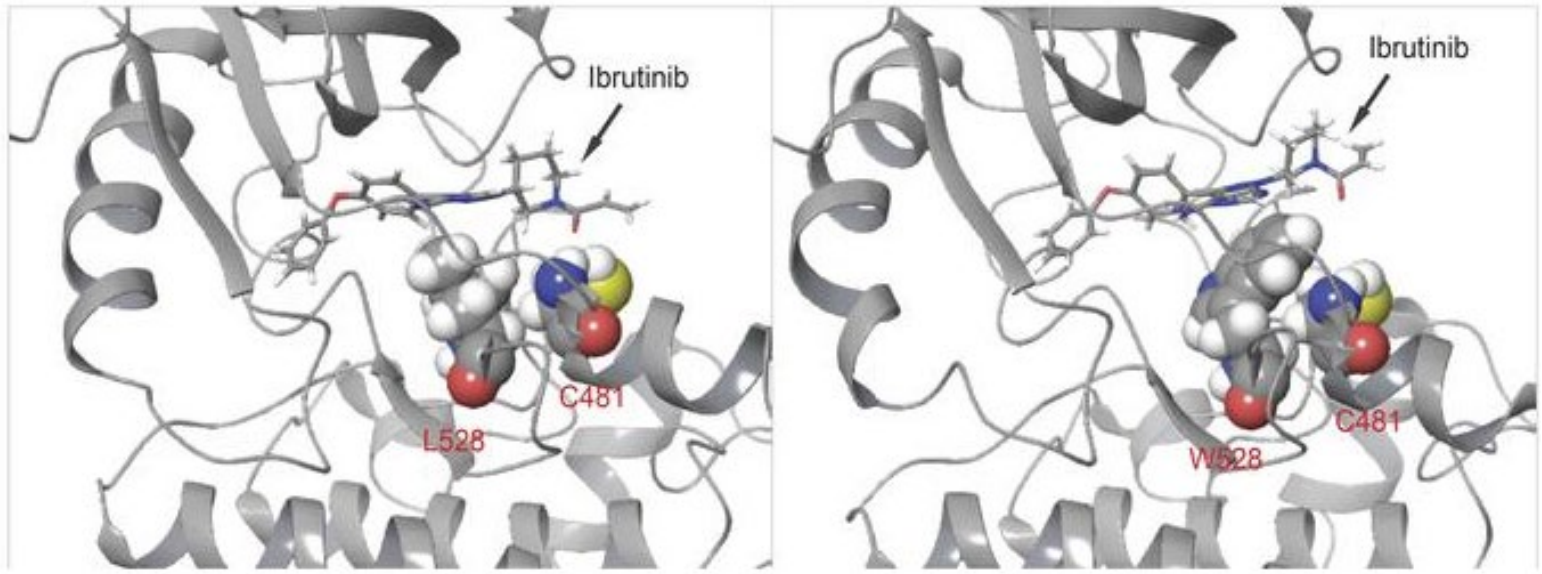
37% of *BTK* Acquired Mutations Pre-exist at Low VAF at Baseline



- Among 49[a] mutations, 18 (37%) acquired BTK mutations [T474I (7), L528W (4), T474F (2), C481S (2), C481Y, C481R, T474] were pre-existing at low VAF at baseline (VAF range; 0.2 - 5.6%)
- ORR was similar among patients with pre-existing T474x (13/14, 93%), L528W (3/4, 75%)

[a]49 BTK acquired mutations in 79/88 patients with available baseline PBMCs re-sequenced using a more sensitive assay (LoD ~ 0.5%). Baseline *BTK* mutations detected by either standard and/or sensitive assay.

cBTKi Rechallenge Probably not Possible



Net change in binding free energy: W528 VS L528: 7.8+/-0.1 (kcal/mol)

HUNTSMAN CANCER INSTITUTE UNIVERSITY OF UTAH

Wang et al. JCI Insight (2019) 3;12: e127566

HEALTH UNIVERSITY OF UTAH

Questions

- Thank you