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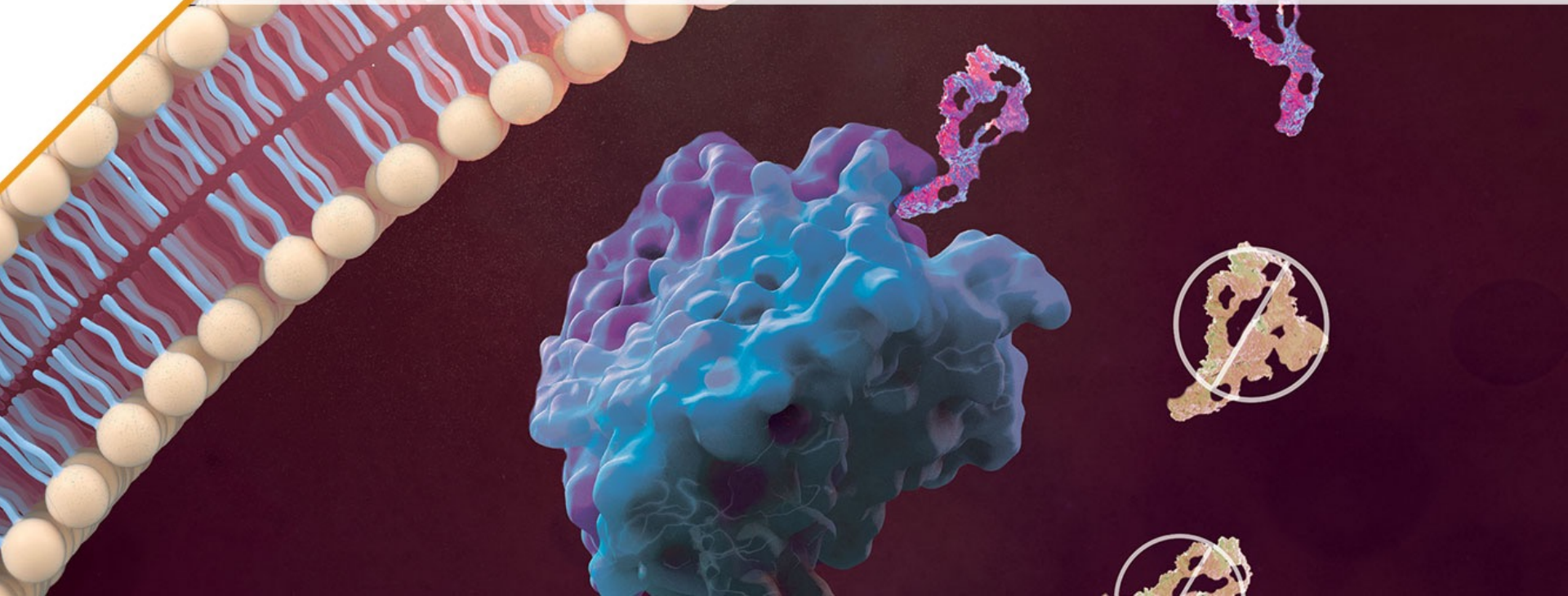
The Emerging Landscape of BTK Inhibitors for Relapsed/Refractory CLL/SLL:

Clinical Practicalities and Perspectives



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Disclosure of Conflicts of Interest

Anthony Mato, MD, MSCE, reported a financial interest/relationship or affiliation in the form of *Consulting or advisory role*: AbbVie; Acerta Pharma/AstraZeneca; Adaptive Biotechnologies; Celgene Corporation; DTRM Biopharma; Genentech; Genmab A/S; Johnson & Johnson Services; Nurix Therapeutics; Octapharma Plasma; Pharmacyclics; Sunesis Pharmaceuticals; TG Therapeutics; Verastem. *Grant/Research support*: AbbVie; Acerta Pharma/AstraZeneca; Adaptive Biotechnologies; DTRM Biopharma; Genentech; Genmab A/S; Johnson & Johnson Services; Loxo Oncology; Nurix Therapeutics; Octapharma Plasma; Pharmacyclics; Regeneron Pharmaceuticals; Sunesis Pharmaceuticals; TG Therapeutics. *Data and safety monitoring board*: AbbVie; Acerta Pharma/AstraZeneca; Adaptive Biotechnologies; Celgene Corporation; DTRM Biopharma; Genentech; Genmab A/S; Johnson & Johnson Services; Nurix Therapeutics; Octapharma Plasma; Pharmacyclics; TG Therapeutics; Sunesis Pharmaceuticals; Verastem.

Learning Objectives

Upon completion of this activity, participants should be better able to:

1. Discuss barriers to optimal CLL/SLL care associated with BTK inhibitors, such as therapeutic intolerance and resistance
2. Summarize clinical evidence and guidelines supporting the use of BTK inhibitor strategies for relapsed/refractory CLL/SLL
3. Create current and potential future treatment plans for relapsed/refractory CLL/SLL that include novel and emerging BTK inhibitors based on prognostic factors and safety and selectivity differences among BTK inhibitors

BTK Inhibitors in the Front-line Setting

A Brief Overview

Major Phase 3 Trials Support the Use of Targeted Agents in Treatment Naive and R/R CLL

Ibrutinib[1-4]	Acalabrutinib[5-7]	Zanubrutinib[8,9]	Venetoclax[10-12]
• **RESONATE-2:** superior PFS and OS vs Clb in older patients • **iLLUMINATE:** superior PFS vs GClb • **ECOG 1912:** superior PFS and OS vs FCR in younger patients • **ALLIANCE:** superior PFS vs BR in older patients	• **ELEVATE TN:** superior PFS for acalabrutinib regimens vs GClb • **ASCEND:** improved PFS vs IdelaR or BR • **ELEVATE RR:** noninferior PFS vs ibrutinib and improved safety profile	• **SEQUOIA**: superior PFS vs BR • **ALPINE:** improved safety profile vs ibrutinib	• **CLL14:** VenG superior to GClb in unfit patients • **CLL13** VenG superior to FCR/BR in fit patients • **MURANO:** VenR superior to BR

Continuous BTKi | FD BCL2i combination

BR, bendamustine + rituximab; BTKi, Bruton tyrosine kinase inhibitor; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; FCR, fludarabine + cyclophosphamide + rituximab; FD BCL2i, fixed duration B cell lymphoma-2 inhibitor; GClb, obinutuzumab + chlorambucil; IdelaR, idelalisib + rituximab; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; VenG, venetoclax + obinutuzumab; VenR, venetoclax + rituximab.

1. Shanafelt TD et al. *Blood*. 2022;140:112-120. 443. 2. Woyach JA et al. *N Engl J Med*. 2018;379:2517-2528. 3. Moreno C et al. *Lancet Oncol*. 2019;20:43-56.
4. Burger JA et al. *Leukemia*. 2020;34:787-798. 5. Sharman JP et al. *Lancet*. 2020;395:1278-1291. 6. Ghia P et al. *J Clin Oncol*. 2020;38:2849-2861.
7. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452. 8. Tam CS et al. *Lancet Oncol*. 2022;23:1031-1043. 9. Brown JR et al. *N Engl J Med*. 2023;388:319-332.
10. Al-Sawaf O et al. *J Clin Oncol*. 2021;39:4049-4060. 11. Eichhorst B et al. ASH 2021. Abstract 71. 12. Kater AP et al. *J Clin Oncol*. 2020;38:4042-4054.

Targeted Therapy: FDA Approvals and Current Status in CLL

Agent	Target		Status in CLL/SLL
Ibrutinib[1]	BTK	Covalent	Approved
Acalabrutinib[2]			Approved
Zanubrutinib[3]			Approved
Pirtobrutinib		Noncovalent	Phase 3 BRUIN CLL-321 Phase 3 BRUIN CLL-322 Phase 3 BRUIN CLL-313 Phase 3 BRUIN CLL-314
Nemtabrutinib			Phase 2 BELLWAVE-001 Phase 3 BELLWAVE-008
Venetoclax[4]	BCL-2		Approved
Idelalisib[5]	PI3K		Approved
Duvelisib[6]			Approved

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BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; FDA, Food and Drug Administration; SLL, small lymphocytic lymphoma.
1. Imbruvica (ibrutinib) Prescribing Information. 2. Calquence (acalabrutinib) Prescribing Information. 3. Brukinsa (zanubrutinib) Prescribing Information.
4. Venclexta (venetoclax) Prescribing information. 5. Zydelig (idelalisib) Prescribing information. 6. Copiktra (duvelisib) Prescribing information.

Despite These Advances, Real-World Data Suggest More Work Needs to Be Done

- European Research Initiative on CLL (ERIC)[1]
  - N = 9173 patients
  - Although practice patterns have shifted since 2014, CIT was used as frontline treatment in 60% of patients in this real-world analysis
- Flatiron Health database analysis from 280 US cancer clinics[2]
  - N = 3654 patients with CLL initiating first-line treatment between 2015 and 2020
  - Although 46% received first-line targeted therapy, 33% received CIT and 20% received anti-CD20 monotherapy

CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia.

1. Chatzikonstantinou T et al. ASH 2021. Abstract 2635. 2. Mato A et al. ASH 2021. Abstract 4086.

Covalent BTK Inhibitors in Frontline Therapy

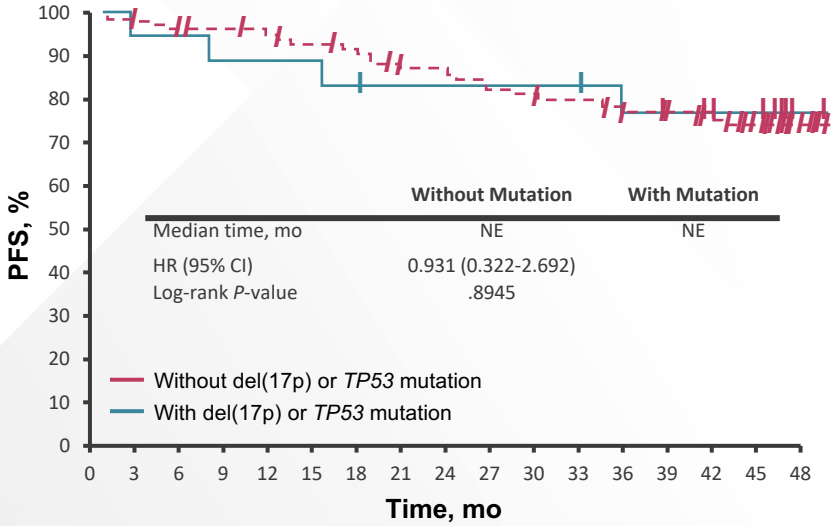
Ibrutinib	Acalabrutinib	Zanubrutinib
• As monotherapy • + rituximab • + obinutuzumab	• As monotherapy • + obinutuzumab	• As monotherapy

BTK, Bruton's tyrosine kinase.

NCCN Guidelines. CLL/SLL (Version 2.2023). https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf.

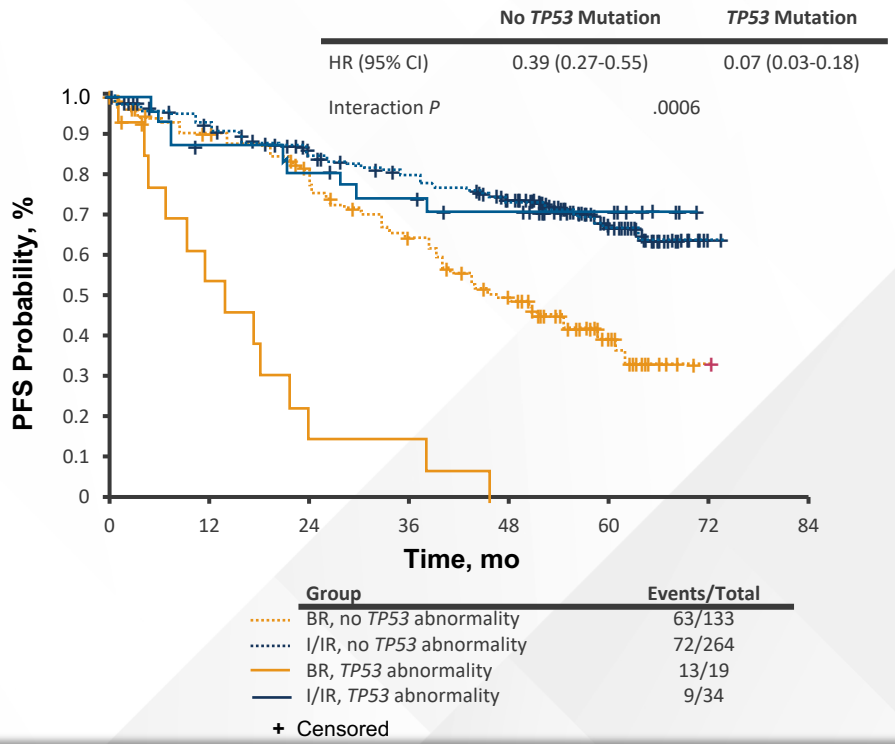
BTK Inhibitors in Very-High-Risk CLL With *TP53* Aberration

Ibrutinib in Patients With del(17p)/*TP53* Mutation[1,2]



No. at Risk																	
Without mutation	95	91	88	88	84	83	80	75	73	71	67	67	62	60	52	41	15
With mutation	18	17	17	16	16	15	14	14	14	14	14	13	12	10	7	6	2

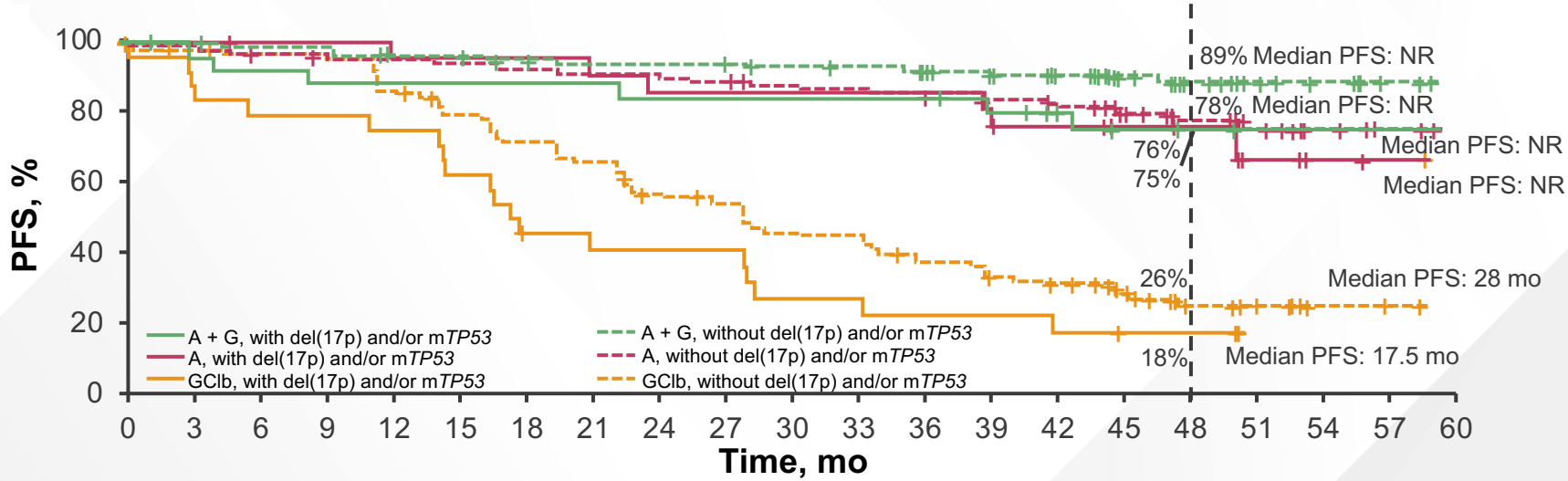
Ibrutinib ± R vs BR



BR, bendamustine + rituximab; del, deletion; HR, hazard ratio; I, ibrutinib; IR, ibrutinib + rituximab; NE, not evaluable; PFS, progression-free survival; R, rituximab; TP53, tumor protein p53.

1. Moreno C et al. *Haematologica*. 2022;107:2108-2120. 2. Woyach J et al. ASH 2021. Abstract 639.

ELEVATE-TN Study: A vs A + G vs GClb in Patients With *TP53* Aberration[1]



No. at Risk																					
A + G, with del(17p) and/or m*TP53*	25	24	23	22	22	22	22	22	21	21	21	21	21	19	16	9	8	3	1	0	0
A, with del(17p) and/or m*TP53*	23	22	21	21	20	20	20	19	18	18	18	18	18	15	15	11	9	5	2	1	0
GClb, with del(17p) and/or m*TP53*	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	3	2	0	0	0	0
A + G, without del(17p) and/or m*TP53*	154	152	148	146	142	141	138	135	135	134	132	131	129	122	116	76	51	30	11	2	0
A, without del(17p) and/or m*TP53*	156	145	142	137	136	135	133	131	131	128	124	123	118	115	108	68	52	30	14	3	0
GClb, without del(17p) and/or m*TP53*	152	142	137	134	121	110	100	91	77	73	61	60	50	43	38	19	11	6	2	1	0

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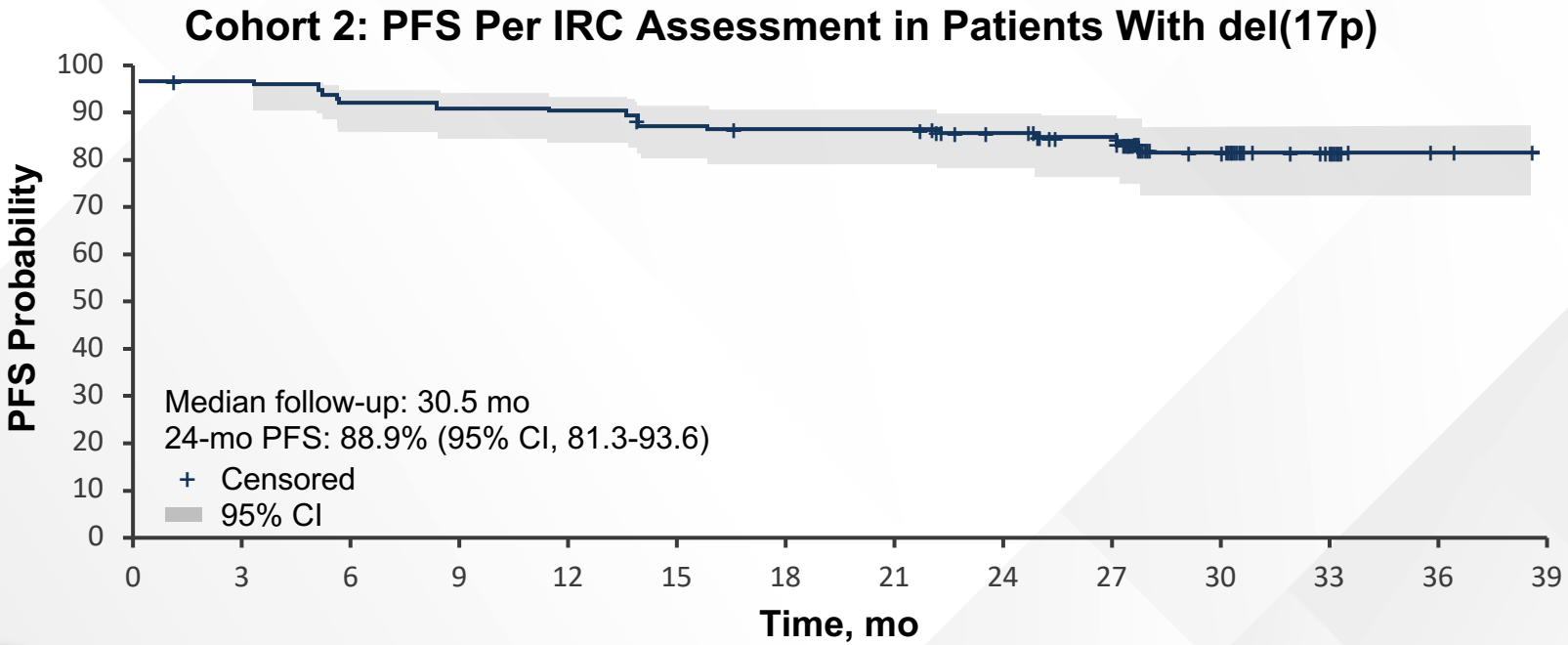
A, acalabrutinib; del, deletion; G, obinutuzumab; GClb, chlorambucil + obinutuzumab; NR, not reached; PFS, progression-free survival; TP53, tumor protein p53.
[a] Hazard ratio was based on unstratified Cox proportional hazards model. [b] *P* value was based on unstratified log-rank test.
1. Sharman JP et al. *Leukemia*. 2022;36:1171-1175.

SEQUOIA Cohort 2: Zanubrutinib in Patients With del(17p) Only

Median observation time: 30.5 months[1]



del, deletion; IRC, Institutional Review Committee; PFS, progression-free survival.

1. Tam CS et al. *Lancet Oncol*. 2022;23:1031-1043.

Retrospective Real-world Data on del(17p) CLL in First-line Ibrutinib Patients

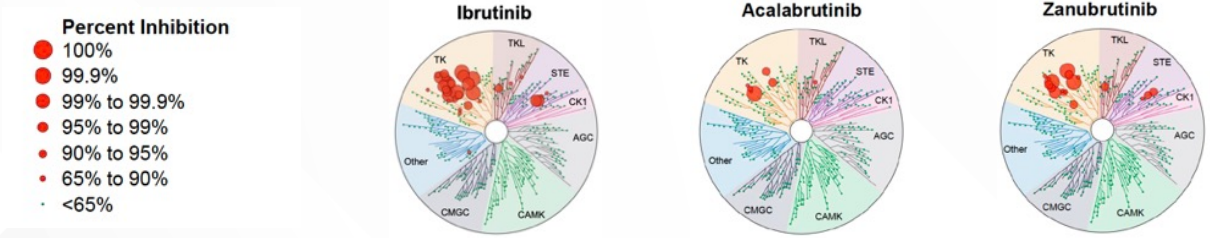
Median overall survival, time to next treatment, and time to treatment discontinuation

Outcome	Group	Number of patients	Number of events	Median months	95% CI months	Log-rank *P* value
OS	All Del(17p) present Del(17p) absent	1,069 254 815	160 64 96	NR 57.7 NR	63.2-NR 51.8-NR NR-NR	- 0.0006 -
TTNT	All Del(17p) present Del(17p) absent	1,069 254 815	259 86 173	NR 49.4 NR	49.4-NR 38.0-NR NR-NR	- 0.0330 -
TTD*	All Del(17p) present Del(17p) absent	1,069 254 815	343 95 248	38.6 32.5 42.9	33.4-42.9 24.0-39.4 38.1-48.4	- 0.3370† -

*Time to treatment discontinuation was estimated using non-parametric maximum likelihood estimator. †Calculated with the Sun log-rank test for interval censoring.
CI, confidence interval; Del(17p), 17p deletion; NR, not reached; OS, overall survival; TTNT, time to next treatment; TTD, time to treatment discontinuation.
Mato et al. *Haematologica*. 2022;107(11):2630–2640.

Adverse Events With BTK Inhibitors

Selectivity of BTK Inhibitors (Average IC_{50} nmol/L)[1]



TEC Kinases	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
BMX	0.8	46	1.4
TXK	2.0	368	2.2
ERBB2/HER2	6.4	~1000	88
EGFR	5.3	>1000	21
ITK	4.9	>1000	50
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5

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BLK, B lymphocyte kinase; BMX, bone marrow tyrosine kinase gene in chromosome X, BTK, Bruton tyrosine kinase; EGFR, epidermal growth factor receptor; ERBB2/HER2, erb-b2 receptor tyrosine kinase/human epidermal growth factor receptor 2; IC, inhibitory concentration; ITK, interleukin-2-inducible T-cell kinase; JAK3, Janus kinase 3; TEC, tyrosine kinase expressed in hepatocellular carcinoma; TXK, T and X cell expressed kinase.

1. Kaptein A et al. *Blood.* 2018;132(suppl 1):1871. *Reproduced with permission of* Kaptein A et al *in the format of electronic publication via Copyright Clearance Center.*

AE Profiles of Different BTK Inhibitors

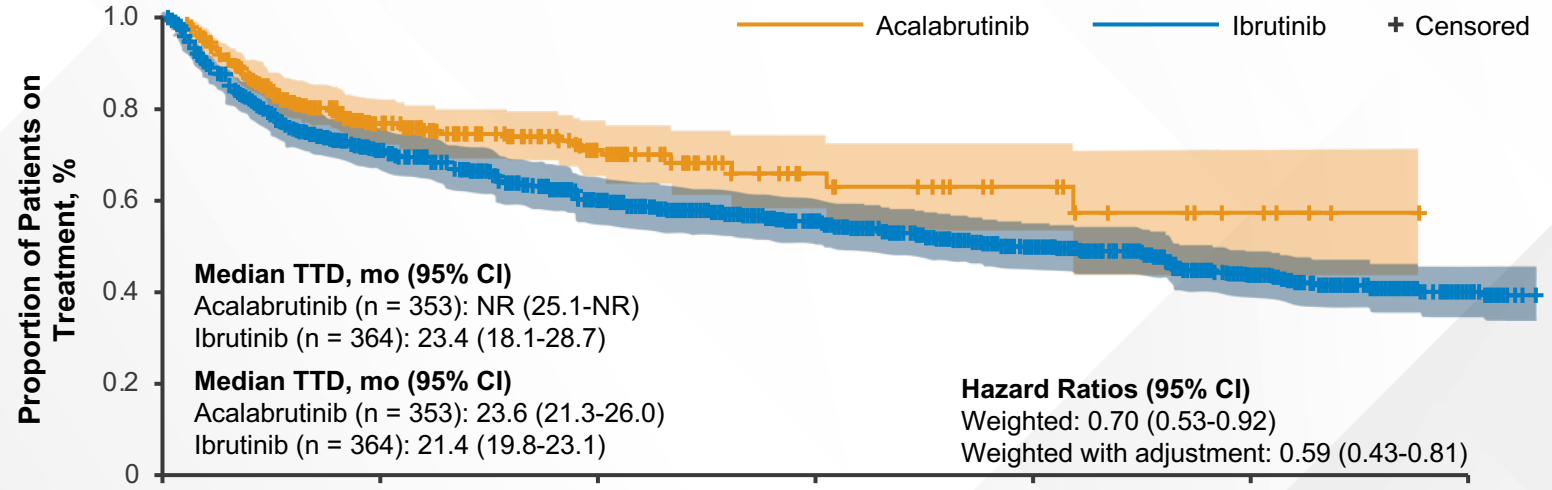
AE ≥ CTC Grade 3	Ibrutinib			Acalabrutinib	Zanubrutinib
	E1912 (I + Rituximab)[1]	RESONATE-2[2]	ALLIANCE[3]	ELEVATE-TN[4]	SEQUOIA[5]
Median observation time, months	**70**	**60**	**38**	**47**	**24**
Hypertension, %	11.4	8	29	2.8	6.3
Cardiac, %	7.7	N/A	N/A	8.4	N/A
AF, %	4.5	5	9	1.1	0.4
Neutropenia, %	28.4	13	15	11.2	11.3
Infection, %	11.4	12[a]	19	16.2	16.3

AE, adverse events; AF, atrial fibrillation; CTC, Common Terminology Criteria; I, ibrutinib.
[a] Pneumonia only.
1. Shanafelt TD et al. *Blood*. 2022;140:112-120. 2. Barr PM et al. *Blood Adv*. 2022;6:3440-3450. 3. Woyach JA et al. *N Engl J Med*. 2018;379:2517-2528.
4. Sharman JP et al. *Lancet*. 2020;395:1278-1291. 5. Tam C et al. ASH 2021. Abstract 396.

Retrospective Analysis on Time to Treatment Discontinuation of Ibrutinib or Acalabrutinib[1]

Retrospective database analysis in 2509 patients with CLL with a median observation time of 15.9 months

Time to Treatment Discontinuation for Patients With CLL/SLL Treated With Acalabrutinib or Ibrutinib After ATT Weighting



No. at Risk							
Acalabrutinib	353	157	63	22	13	5	0
Ibrutinib	364	175	66	27	11	5	1

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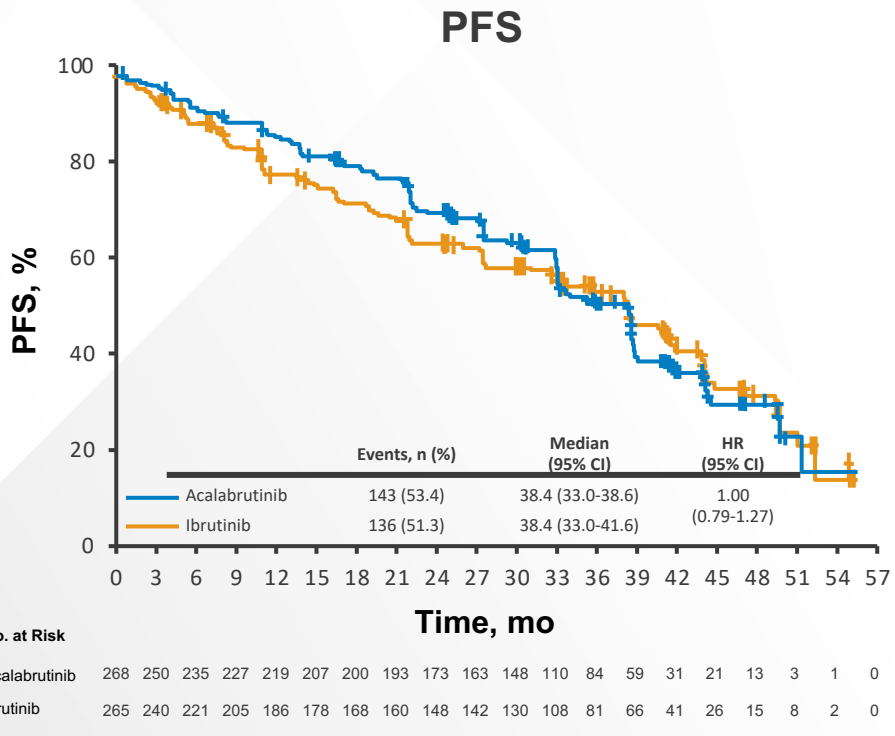
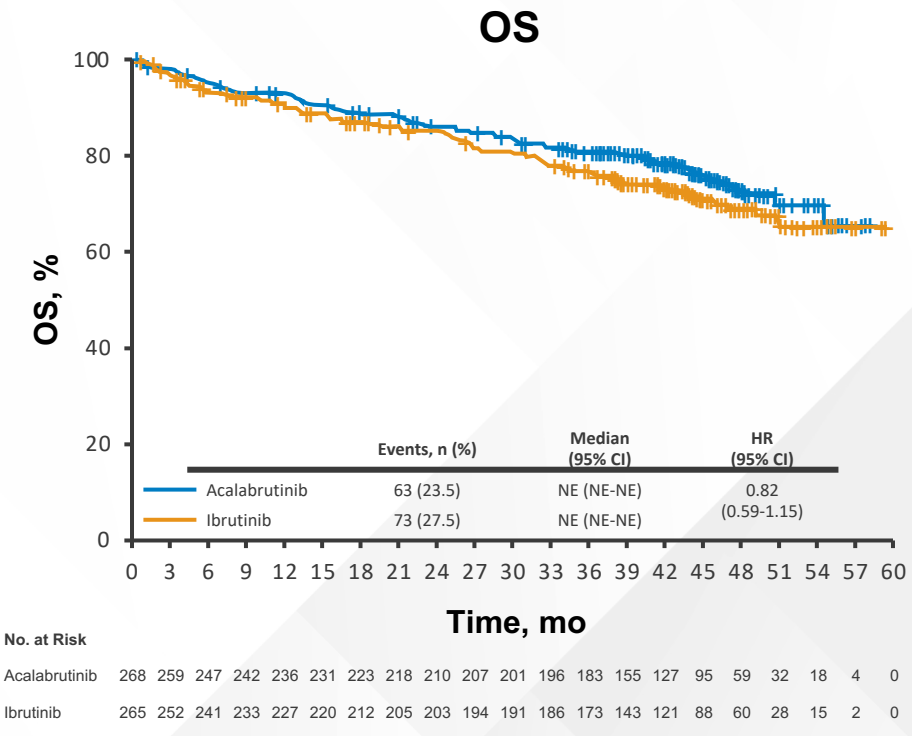
ATT, average treatment effect among the treated; CLL, chronic lymphocytic leukemia; TTD, time to treatment discontinuation; NR, not reached; SLL, small lymphocytic lymphoma.

1. Roecker L et al. ASH 2022. Abstract 1808.

BTK Inhibitors: Head-to-Head Comparisons

ELEVATE-RR (Acalabrutinib vs Ibrutinib): PFS and OS[1]



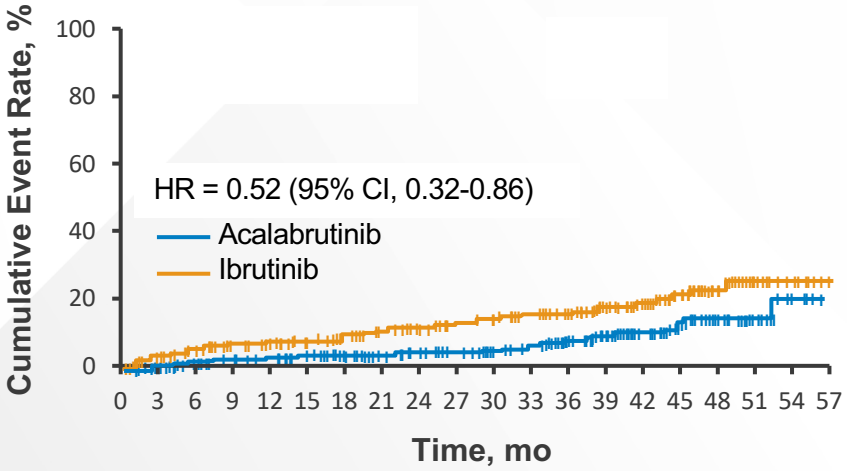


HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

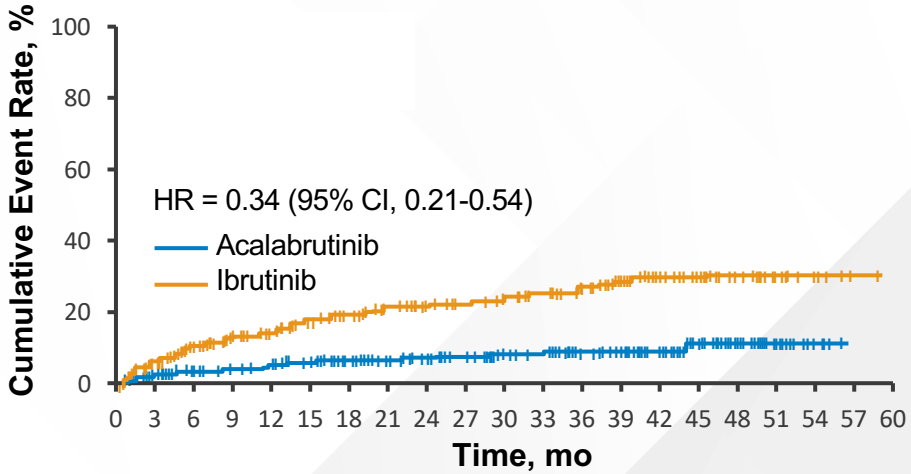
ELEVATE-RR: Cardiac AEs of Interest[1]

Atrial Fibrillation



No. at Risk																			
Acalabrutinib	268	255	240	231	228	218	206	197	188	183	172	167	142	115	89	58	35	19	8	0
Ibrutinib	263	241	224	208	199	185	176	166	156	143	136	128	117	96	73	56	26	18	8	0

Hypertension



No. at Risk																				
Acalabrutinib	266	246	229	220	216	205	193	184	176	169	157	153	136	114	89	60	34	17	5	0	0
Ibrutinib	263	230	203	183	170	153	141	130	120	111	104	98	85	69	48	40	27	15	7	1	0

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AEs, adverse events; HR, hazard ratio.

1. Byrd JC et al. *J Clin Oncol*. 2021;39:3441-3452.

ELEVATE-RR: AE Burden Score (Defined by Duration and Weighted Severity of the AE)[1]

TEAE	Patients With Event, n (%)		Grades 1-4		Grades 1-5	
			AE Burden Score, Mean (SD)		AE Burden Score, Mean (SD)	
	Acalabrutinib (n = 266)	Ibrutinib (n = 263)	Acalabrutinib	Ibrutinib	Acalabrutinib	Ibrutinib
Atrial fibrillation/flutter	25 (9)	42 **(16)**	0.03 (0.187)	**0.08 (0.316)**	0.03 (0.187)	**0.08 (0.316)**
Cardiac events	64 (24)	79 (30)	0.11 (0.355)	0.26 (1.059)	0.11 (0.354)	0.26 (1.053)
Hypertension	25 (9)	61 **(23)**	0.07 (0.336)	**0.24 (0.682)**	0.07 (0.336)	**0.24 (0.682)**
Hemorrhage	101 (38)	135 **(51)**	0.15 (0.377)	**0.26 (0.568)**	0.18 (0.667)	**0.26 (0.568)**
Major hemorrhage	12 (5)	14 (5)	0.02 (0.143)	0.01 (0.153)	0.05 (0.576)	0.01 (0.153)
Infections	208 (78)	214 (81)	0.37 (1.056)	0.36 (0.797)	0.46 (1.513)	0.41 (0.904)
Fatigue	54 (20)	44 (17)	0.088 (0.2683)	0.095 (0.4005)	0.088 (0.2683)	0.095 (0.4005)
Diarrhea	92 (35)	121 **(46)**	**0.112 (0.5370)**	0.108 (0.3245)	**0.112 (0.5370)**	0.108 (0.3245)
Headache	92 **(35)**	53 (20)	**0.084 (0.2960)**	0.076 (0.4396)	**0.084 (0.2960)**	0.076 (0.4396)
Musculoskeletal events	79 (30)	98 (37)	0.142 (0.3727)	**0.346 (1.1026)**	0.142 (0.3727)	**0.346 (1.1026)**

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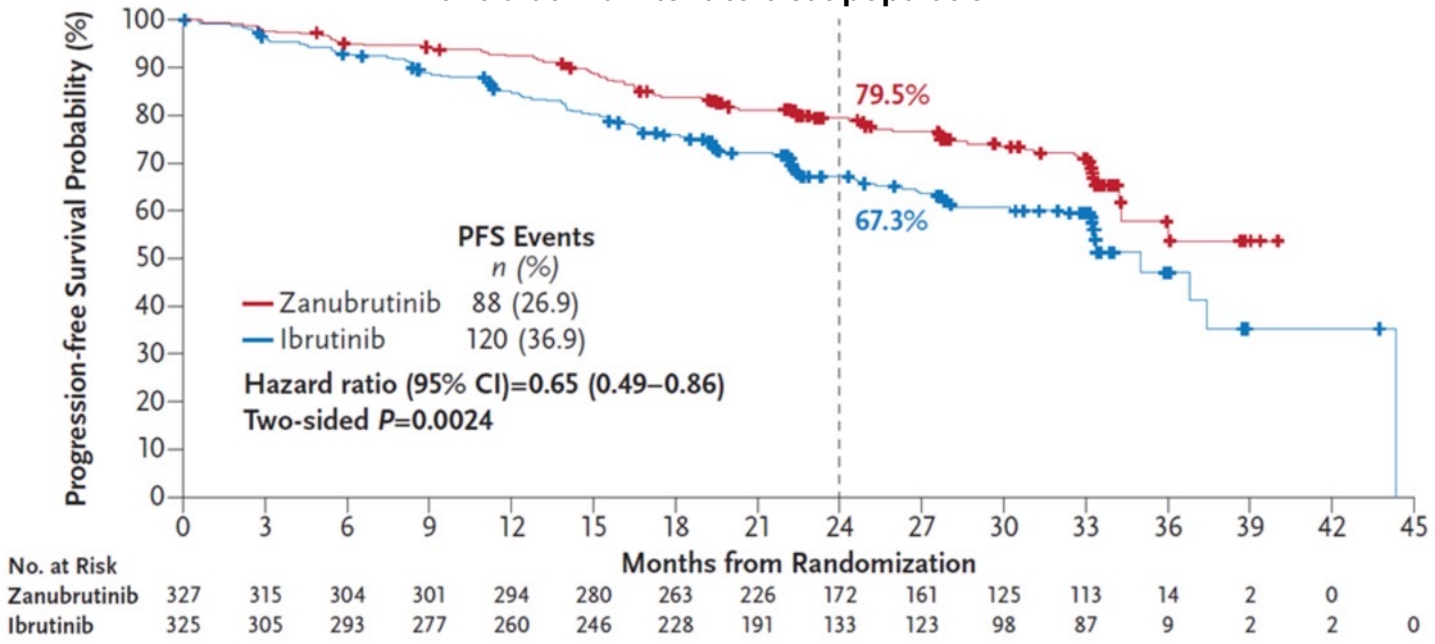
AE, adverse event; HR, hazard ratio; SD, standard deviation; TEAE, treatment emergent AE.

1. Seymour J et al. ASH 2022. Abstract 3133.

ALPINE: Improved ORR and PFS With Zanubrutinib vs Ibrutinib in R/R CLL/SLL[1]

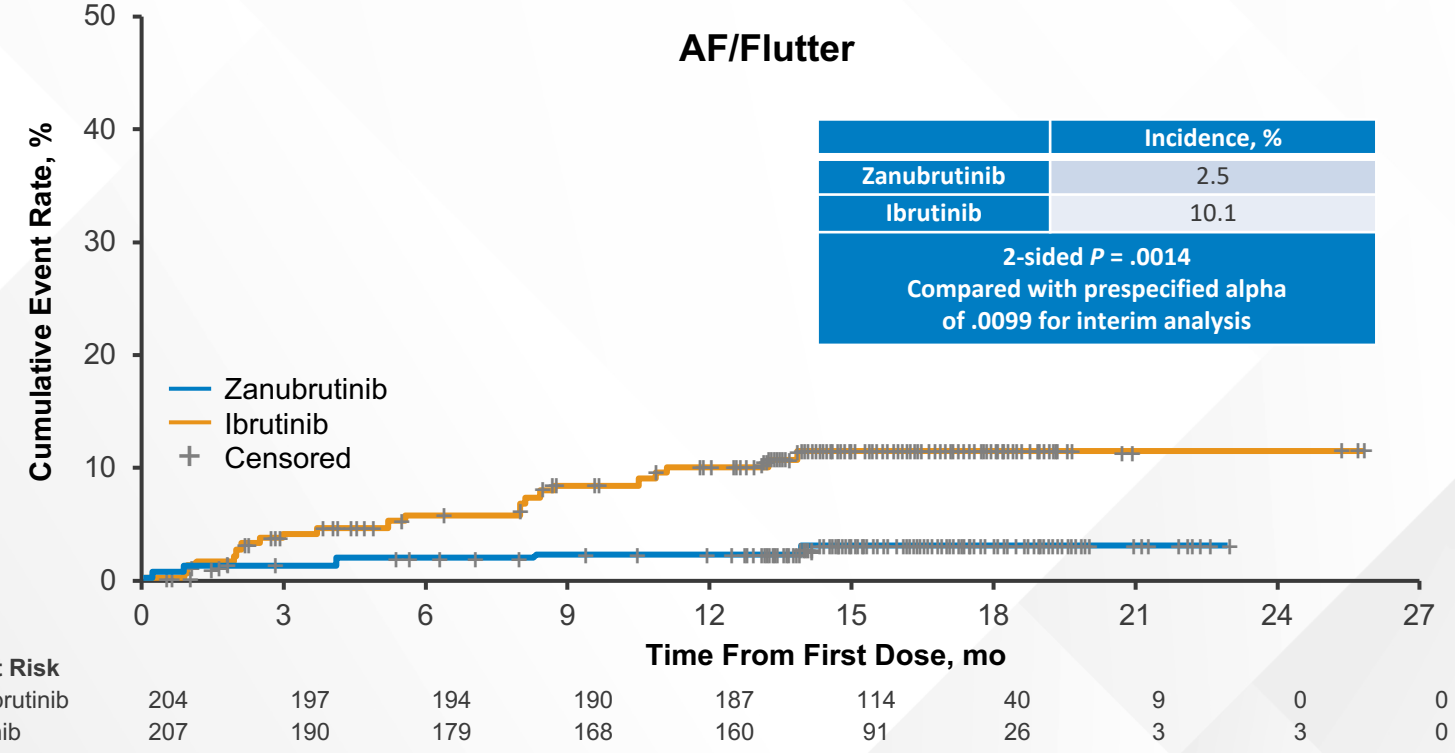
After a median follow-up of 29.6 months, improved PFS with zanubrutinib intent-to-treat population



CLL, chronic lymphocytic leukemia; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

1. Brown J et al. ASH 2022. Abstract LBA-6.

ALPINE: Safety Analysis Showed Lower Rates of AF/Flutter With Zanubrutinib[1]



AF, atrial fibrillation

1. Hillmen P et al. EHA 2021. Abstract LB1900.

ALPINE: Adverse Events of Special Interest* (Safety Population; N=648)

AESI, n (%)	Any Grade		Grade ≥3	
	Zanubrutinib (n=324)	Ibrutinib (n=324)	Zanubrutinib (n=324)	Ibrutinib (n=324)
≥1 AESI	**294 (90.7)**	**300 (92.6)**	**186 (57.4)**	**184 (56.8)**
Anemia	50 (15.4)	53 (16.4)	7 (2.2)	8 (2.5)
Atrial fibrillation and flutter	17 (5.2)	43 (13.3)	8 (2.5)	13 (4.0)
Hemorrhage	137 (42.3)	134 (41.4)	11 (3.4)	12 (3.7)
Major hemorrhage	12 (3.7)	14 (14.3)	11 (3.4)	12 (3.7)
Hypertension	76 (23.5)	74 (22.8)	49 (15.1)	44 (13.6)
Infections	231 (71.3)	237 (73.1)	86 (26.5)	91 (28.1)
Opportunistic infection	7 (2.2)	10 (3.1)	5 (1.5)	5 (1.5)
Neutropenia†	95 (29.3)	79 (24.4)	68 (21.0)	59 (18.2)
Secondary primary malignancies	40 (12.3)	43 (13.3)	22 (6.8)	17 (5.2)
Skin cancers	21 (6.5)	28 (8.6)	7 (2.2)	4 (1.2)
Thrombocytopenia	42 (13.0)	50 (15.4)	11 (3.4)	17 (5.2)
Tumor lysis syndrome	1 (0.3)	0	1 (0.3)	0

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*Specific related MedDRA preferred terms were pooled for each AESI category and summarized.
†Febrile neutropenia was reported in 4(1.2%) vs 3(0.9%) patients treated with zanubrutinib and ibrutinib, respectively.
AESI, adverse events of special interest.
Brown et al. *N Engl J Med* 2023; 388:319-332.

Sequential Management After Covalent BTKi Therapy in CLL

What are the unmet needs in the R/R setting?

Limitations of covalent BTK inhibitors?

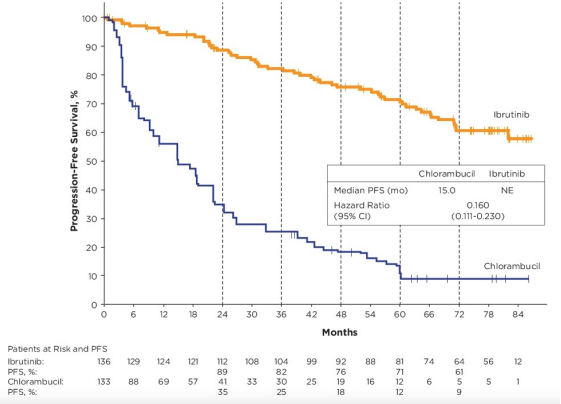
Is there a standard of care for double-refractory disease?

Up to 7 Years of Follow Up in the RESONATE-2 Study of Ibrutinib for Patients With TN CLL: Efficacy

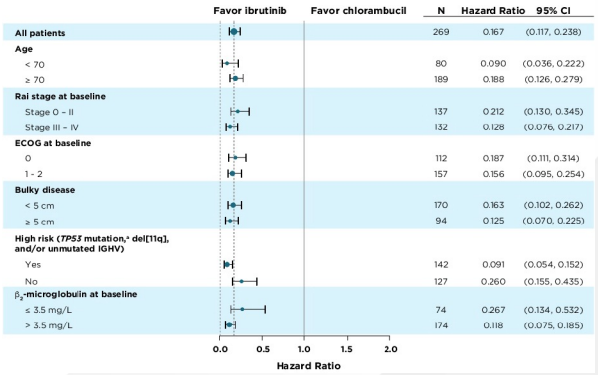
Efficacy

- Ibrutinib-treated patients had an 84% reduction in risk of progression or death
- Ibrutinib led to a 97% reduction in risk of PD or death in patients with del(11q) and 80% for those without del(11q) vs chlorambucil
- Ibrutinib led to an 89% and 80% reduction in risk of PD or death in patients with unmutated and mutated *IGHV*, respectively, vs chlorambucil

PFS: Ibrutinib vs Chlorambucil



PFS in Patient Subgroups of Interest



Overall discontinuation rate at 7 years = 53%

CLL, chronic lymphocytic leukemia; del, deletion; ECOG, Eastern Cooperative Oncology Group; IGHV, immunoglobulin heavy chain gene; NE, not evaluable; PD, progressive disease; PFS, progression-free survival; TN, treatment naïve; TP53, tumor protein p53.

Barr PB, et al. ASCO 2020. Abstract 7523.

Long-Term Results From RESONATE-2: AEs Are the Main Reason for Ibrutinib Discontinuation

53% discontinuation rate overall[1]

	First-Line Ibrutinib (N = 136)
Median duration of ibrutinib treatment, y (range)	6.2 (0.06-7.2)
Continuing ibrutinib on study, n (%)	64 (47)
Discontinued ibrutinib, n (%)	
AE	31 (23)
PD	16 (12)
Death	11 (8)
Withdrawal by patient	9 (7)
Investigator decision	4 (3)

AXIS Medical Education

AEs, adverse events; PD, progressive disease.

1. Barr PM et al. ASCO 2021. Abstract 7523.

Ibrutinib Discontinuation for Intolerance

Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis

- **41% of patients discontinued ibrutinib** at a median follow-up of 17 months
- Toxicity accounted for the **majority** of discontinuations (over half) in both F/L and R/R CLL patients
- Most common toxicities in R/R population:
  - Atrial fibrillation 12.3%
  - Infection 10.7%
  - Pneumonitis 9.9%
  - Bleeding 9%
  - Diarrhea 6.6%

Reason for ibrutinib discontinuation	Ibrutinib in front-line (n=19)	Ibrutinib in relapse (n=231)
Toxicity	63.1% (n=12)	50.2% (n=116)
CLL progression	15.8% (n=3)	20.9% (n=49)
Other/unrelated death	5.3% (n=1)	12.1% (n=28)
Physician's or patient's preference	10.5% (n=2)	6.7% (n=15)
RT DLBCL	5.3% (n=1)	4.6% (n=10)
Stem cell transplantation/CAR T-cell	0	3.3% (n=8)
Financial concerns	0	0.8% (n=2)
Secondary malignancy	0	0.8% (n=2)
RT Hodgkin lymphoma	0	0.4% (n=1)

This study identified covalent BTK inhibitor **intolerance** as a major emerging issue in the field of CLL

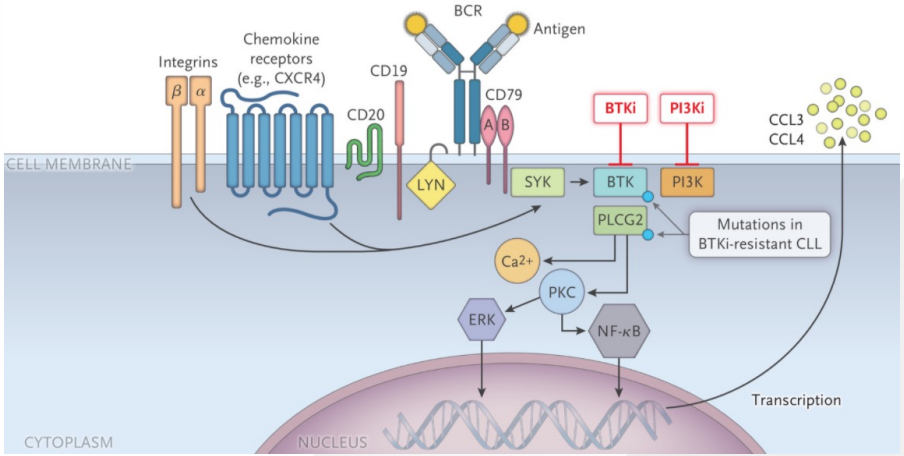
AXIS Medical Education

BTK, Bruton tyrosine kinase; CAR T-cell, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; F/L, first line; R/R, relapsed/refractory; RT, Richter transformation.

Mato et al. *Haematologica* 2018;103:874-879.

Acquired Resistance to Covalent BTKi[1-7]

- Majority of patients have identified mutations in ***BTKC481*** at the time of disease progression on ibrutinib
  - ~53-87% of patients
- Mutations also identified in PLCG2, immediately downstream of BTK
- *BTKC481* mutations are also mechanism of resistance for acalabrutinib
  - 69% of patients

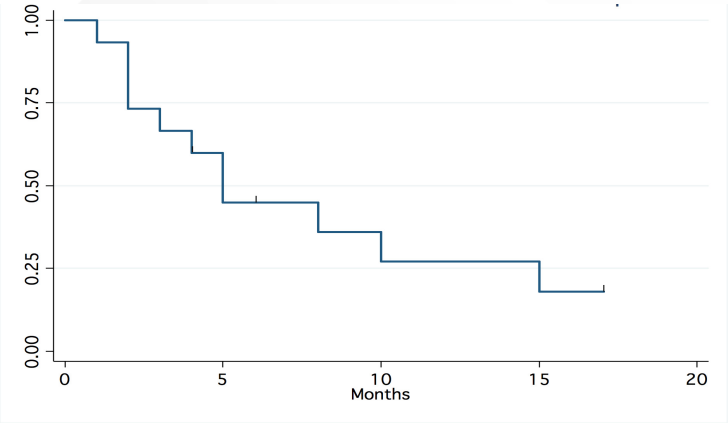


BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; PLCG2, phospholipase C gamma 2.
1. Burger JA. *N Engl J Med*. 2020;383:460-473. 2. Woyach JA et al. *N Engl J Med*. 2014;370:2286-2294. 3. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443. 4. Scarfo L et al. EHA 2020. Abstract S161. 5. Ahn IE et al. *Blood*. 2017;129:1469-1479. 6. Woyach J et al. ASH 2019. Abstract 504. 7. Burger J et al. *Nat Commun*. 2016; 7: 11589. *Reproduced with permission of Woyach* AJ et al *in the format of electronic publication via Copyright Clearance Center.*

Outcomes of Patients with CLL Sequentially Resistant to Both BCL2 and BTK Inhibition

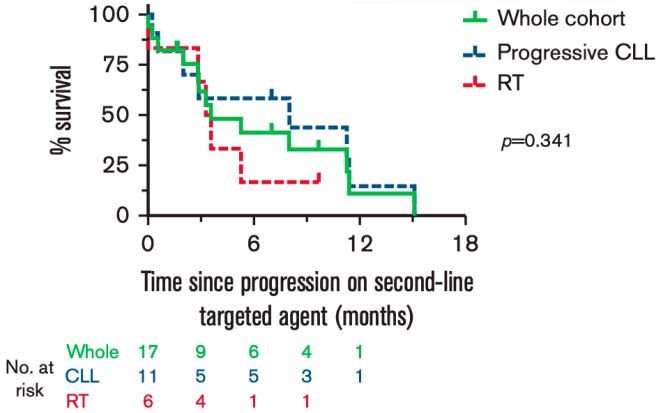
After BTKi → venetoclax: PI3Ki do not result in durable remissions and therefore is **not an acceptable SOC** in the 3rd line setting in modern era

Post Venetoclax: PFS for PI3Ki in PI3K naïve pts



Median PFS = 4 months[1]

Double Refractory Pts



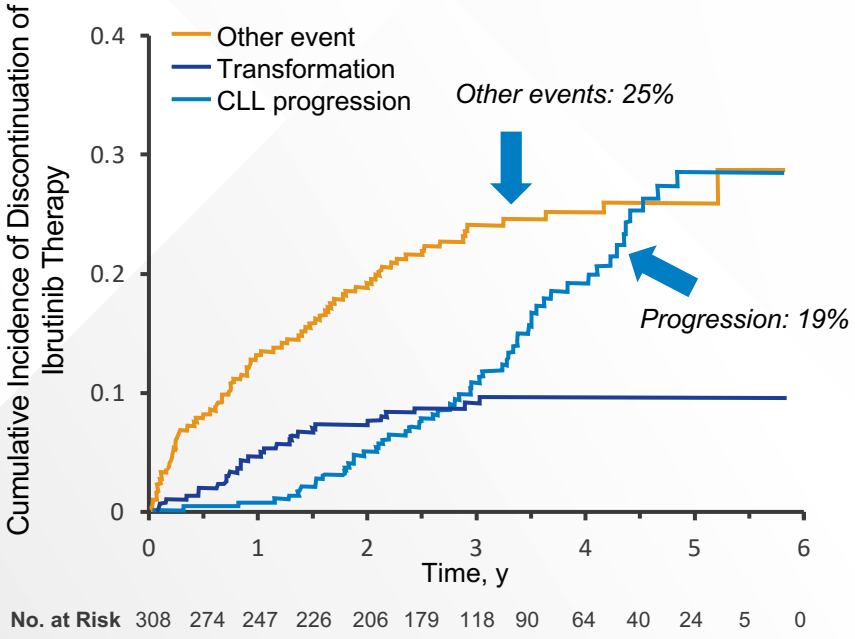
Median OS = 3.6 months[2]

BCL 2, B-cell lymphoma 2; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; i, inhibitor; OS, overall survival; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; RT, Richter transformation; SOC, standard of care.

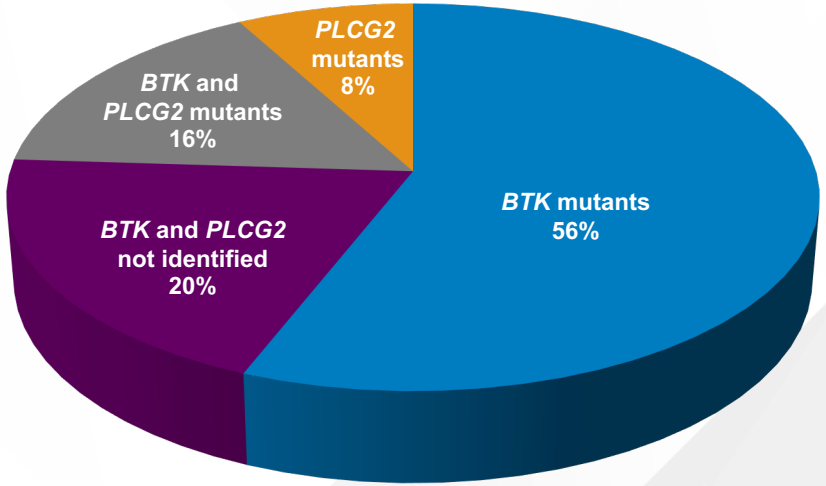
1. Mato AR et al. *Clin Cancer Res*. 2020;26:3589-3596. 2. Lew TE et al. *Blood Adv*. 2021;5:4054-4058.

Resistance and Intolerance Limit Outcomes With Covalent BTK Inhibitors in CLL

Ibrutinib Discontinuation Over Four Prospective Studies[1]



Ibrutinib-Acquired Resistance in Patients With Progressive CLL[2]



- *BTK* C481 mutations are the dominant reasons for progressive CLL after covalent BTK inhibitors[1-8]
- *BTK* C481 mutations prevent covalent BTK inhibitors from effective target inhibition[1-6]

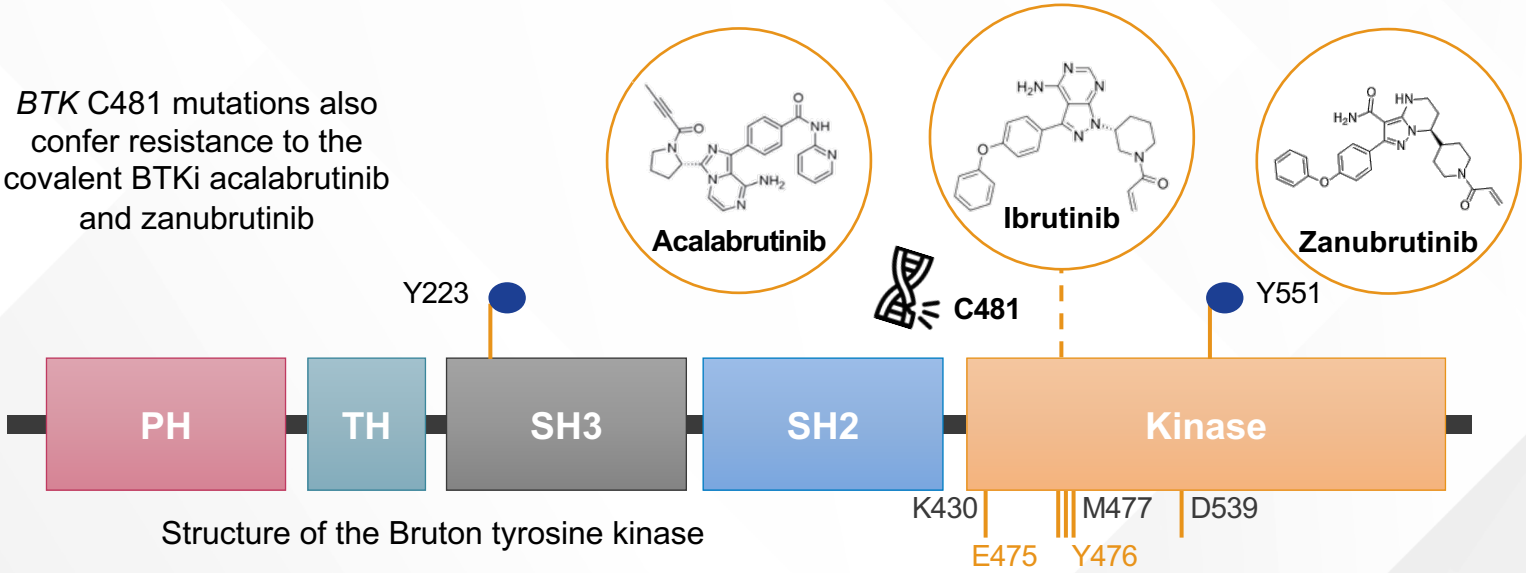
AXIS Medical Education

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PLCG2, phospholipase C gamma 2.

1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443. 2. Lampson BL, Brown JR. *Expert Rev Hematol*. 2018;11:185-194. 3. Burger JA et al. *Leukemia*. 2020;34:787-798. 4. Byrd JC et al. *N Engl J Med*. 2016;374:323-332. 5. Hershkovitz-Rokah O et al. *Br J Haematol*. 2018;181:306-319. 6. Woyach JA et al. *N Engl J Med*. 2014;370:2286-2294. 7. Woyach JA et al. *Blood*. 2019;134(suppl 1):504. 8. Xu L et al. *Blood*. 2017;129:2519-2525.

Acquired Resistance to Covalent BTK Inhibitors Is Generally Driven by Mutations in *BTK* at the C481 Site

BTK C481 mutations also confer resistance to the covalent BTKi acalabrutinib and zanubrutinib



Structure of the Bruton tyrosine kinase

In sum, *BTK* resistance contributes to disease progression and diminishes the efficacy of all covalent BTK inhibitors[1-8]

BTKi, Bruton tyrosine kinase inhibitor; PH, pleckstrin homology domain; TH, TEC homology domain; SH, SRC homology domain.

1. Woyach JA et al. *J Clin Oncol*. 2017;35:1437-1443. 2. Lampson BL, Brown JR. *Expert Rev Hematol*. 2018;11:185-194. 3. Burger JA et al. *Leukemia*. 2020;34:787-798. 4. Byrd JC et al. *N Engl J Med*. 2016;374:323-332. 5. Hershkovitz-Rokah O et al. *Br J Haematol*. 2018;181:306-319. 6. Woyach JA et al. *N Engl J Med*. 2014;370:2286-2294. 7. Woyach JA et al. *Blood*. 2019;134(suppl 1):504. 8. Xu L et al. *Blood*. 2017;129:2519-2525.

BTKi Resistance and Intolerance: What Are the Options?

Sequential Use of Acalabrutinib in Patients With Ibrutinib Intolerance Is an Effective and Safe Option[1]

AE	No. of Patients With Ibrutinib Intolerance[a]	Acalabrutinib Experience for Same Patients, n			
		Total	Lower Grade	Same Grade	Higher Grade
AF	16[b]	2	2	0	0
Diarrhea	7	5	3	2	0
Rash	7	3	3	0	0
Bleeding[c,d]	6	5	3	2	0
Arthralgia	7[e]	2	1	1	0
Total	41	24	18	6	1

AXIS Medical Education

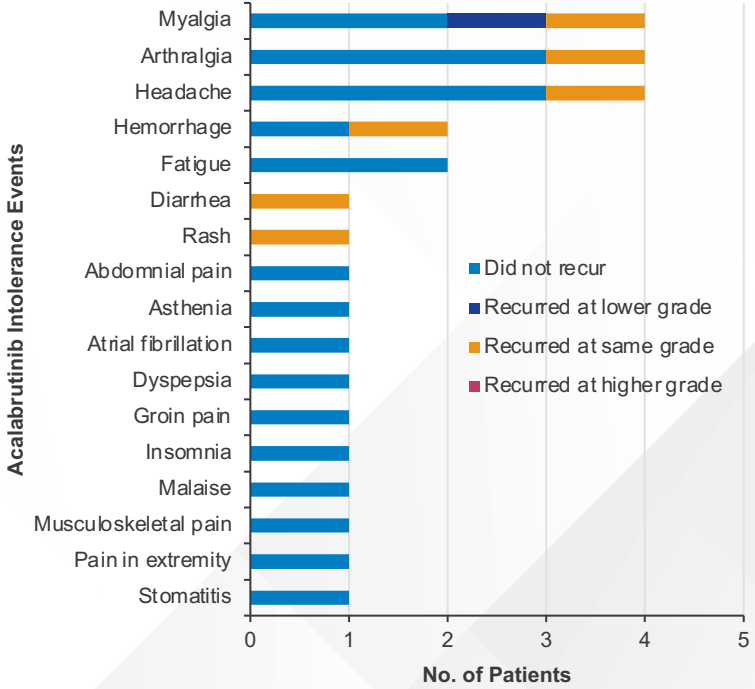
AE, adverse event; AF, atrial fibrillation.
[a] Among 60 patients meeting the study enrollment criteria, 41 patients had a medical history of ≥1 (43 events in total) of the following categories of ibrutinib-intolerance events: AF, diarrhea, rash, bleeding, or arthralgia. [b] Includes patients with atrial flutter (n = 2). [c] Events categorized as bleeding included ecchymosis, hemorrhage, epistaxis, contusion, hematuria, and subdural hematoma. [d] All but 1 patient experienced a different type of bleeding event with acalabrutinib compared with ibrutinib treatment. [e] Includes 1 patient with arthritis.
1. Rogers KA et al. *Haematologica*. 2021;106:2364-2373.

Similarly, Zanubrutinib Is Effective in the Setting of BTK Inhibitor Intolerance

- Prior evidence has shown that zanubrutinib was effective in B-cell cancer patients intolerant of ibrutinib or acalabrutinib[1]
- For example, of 87 ibrutinib-intolerant events, 72 intolerant events (83%) did not recur

ASH 2022: zanubrutinib in acalabrutinib-intolerant patients with B-cell malignancies[2]

- Disease was controlled in 13 (93%) of 14 efficacy-evaluable patients treated with zanubrutinib, and 11 (65%) did not experience any recurrence of prior intolerance events



Medical Education

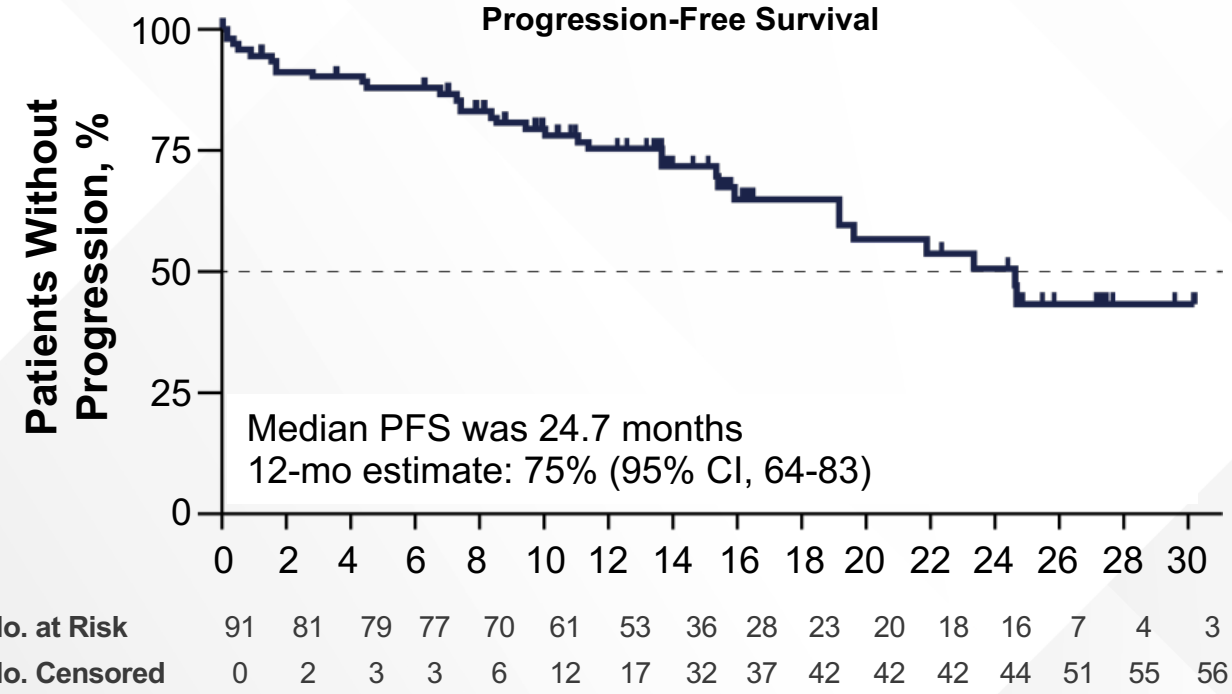
ASH, American Society of Hematology; BTK, Bruton's tyrosine kinase.
[a] No intolerance AEs recurred at a higher grade.
1. Shadman M et al. ASCO 2021. Abstract e19506. 2. Shadman M et al. ASH 2022. Abstract 1587.

What Strategies Can We Use Against BTK Inhibitor Resistance in CLL?

Supported by Current Evidence	Limited Evidence	Not Appropriate
• **Venetoclax:** efficacious, but complicated administration and not appropriate for all patients • **Noncovalent BTK inhibitors:** initial evidence suggests potent efficacy against resistance mutations and in the setting of progressive disease	• **PI3K inhibitors:** limited benefit in this population and significant toxicity burden • **Chemoimmunotherapy:** limited benefit in this population, and most current patients have already received these regimens	• **Covalent BTK inhibitor retreatment:** only effective in the context of covalent BTK intolerance, not progression

BTK, Bruton's tyrosine kinase; PI3K, phosphoinositide 3-kinases.

Venetoclax Is an Active Approach in Ibrutinib-Refractory CLL/SLL[1,2]



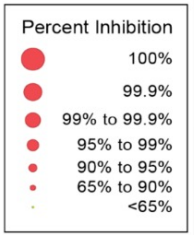
- N = 91
- Median of 4 prior therapies
- 47% with del(17p)
- ORR: 70%
- ORR of 61% (28 of 46 patients) in the del(17p) or *TP53*-mutated subset

Del, deletion; CLL, chronic lymphocytic leukemia; ORR, overall response rate; PFS, progression-free survival; SLL, small lymphocytic lymphoma, TP53, tumor protein 53.

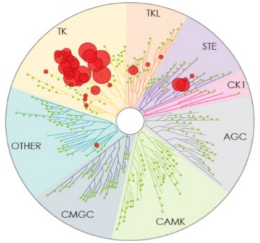
1. Kater AP et al. ASH 2020. Abstract 125. 2. Jones JA et al. *Lancet Oncol*. 2018;19:65-75.

Several BTKi Options to Consider With Differences in BTKi Specificity, MOA, and Potential for Off-target Effects

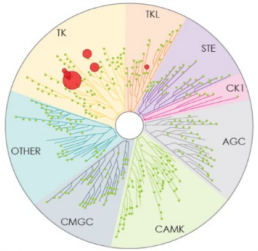
Irreversible



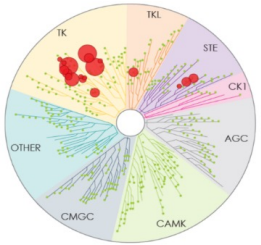
Ibrutinib



Acalabrutinib

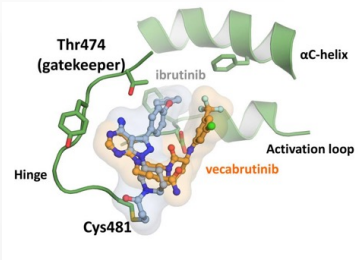


Zanubrutinib

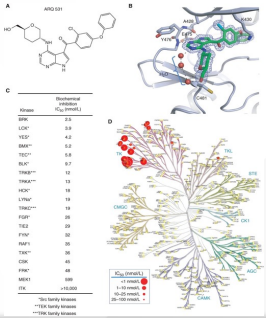


Reversible

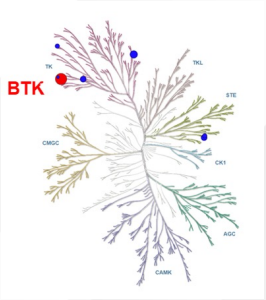
Vecabrutinib



Nemtabrutinib/ARQ-531



Pirtobrutinib/LOXO-305

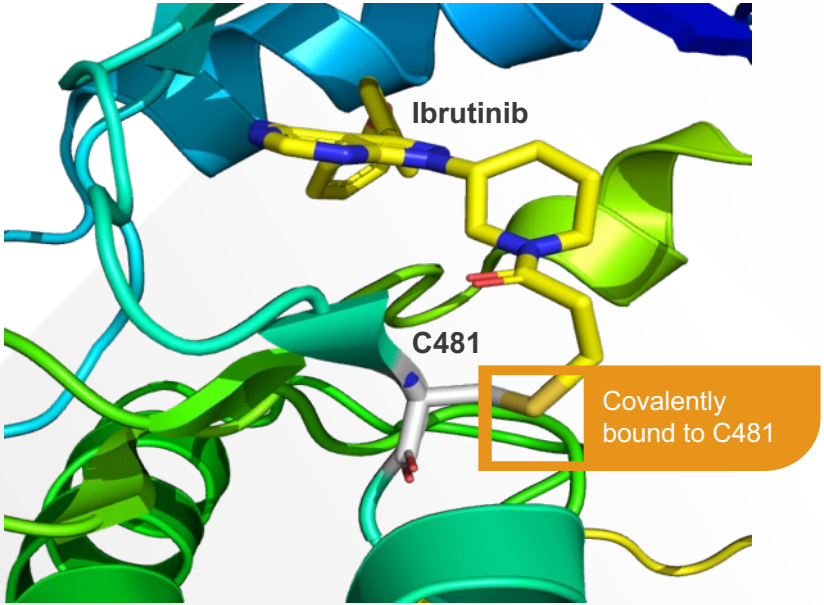


BTKi, Bruton tyrosine kinase inhibitor; MOA, mechanism of action.

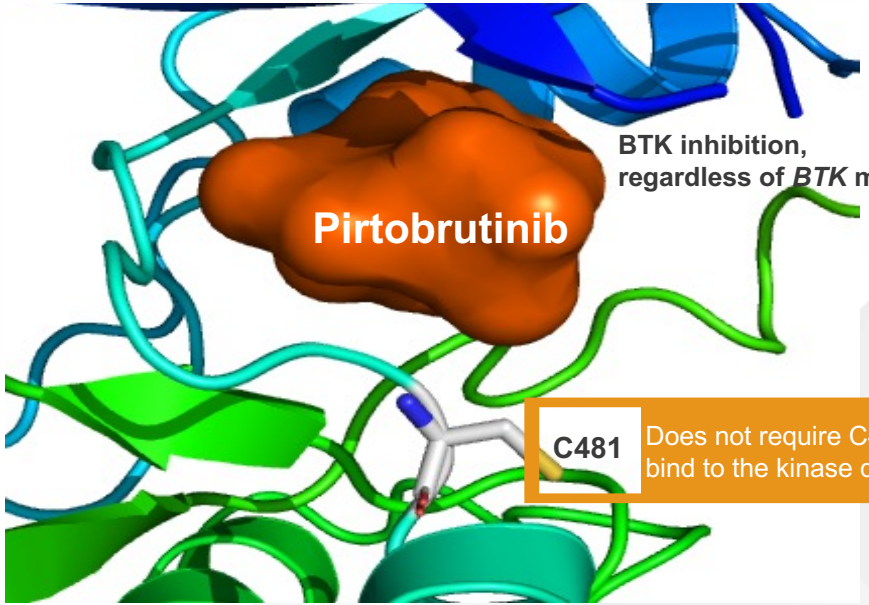
Kaptein A et al. *Blood*. 2018;132(suppl 1):1871.

How Noncovalent BTK Inhibitors Overcome Resistance

Covalent BTK Inhibitors (Ibrutinib, Acalabrutinib, and Zanubrutinib) Require WT *BTK* for Activity[1]



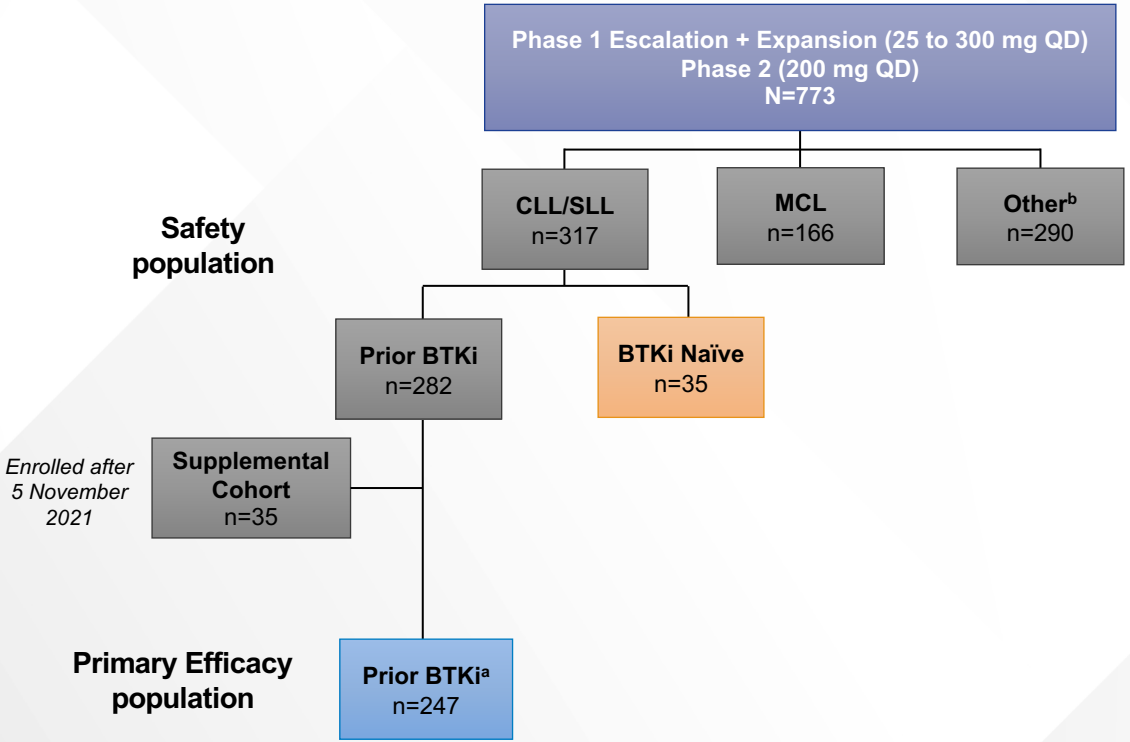
Pirtobrutinib Is a Noncovalent BTK Inhibitor That Is Potent Against Both WT and C481-Mutated *BTK*[2]



BTK, Bruton tyrosine kinase; WT, wild type.

1. Wang E et al. *N Engl J Med*. 2022;386:735-743. 2. Aslan B et al. *Blood Cancer J*. 2022;12:80.

Pirtobrutinib in Covalent BTK-Inhibitor Pre-Treated R/R CLL/SLL 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

BTK, Bruton's tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; ECOG PS, Eastern Cooperative Oncology Group Performance Status; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; DOR, duration of response; IRC, institutional review committee; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; MCL, mantle cell lymphoma; MTD, maximum tolerated dose; ORR, objective response rate; SLL, small lymphocytic lymphoma.

Mato AR et al. *Blood* (2022) 140 (Supplement 1): 2316–2320.

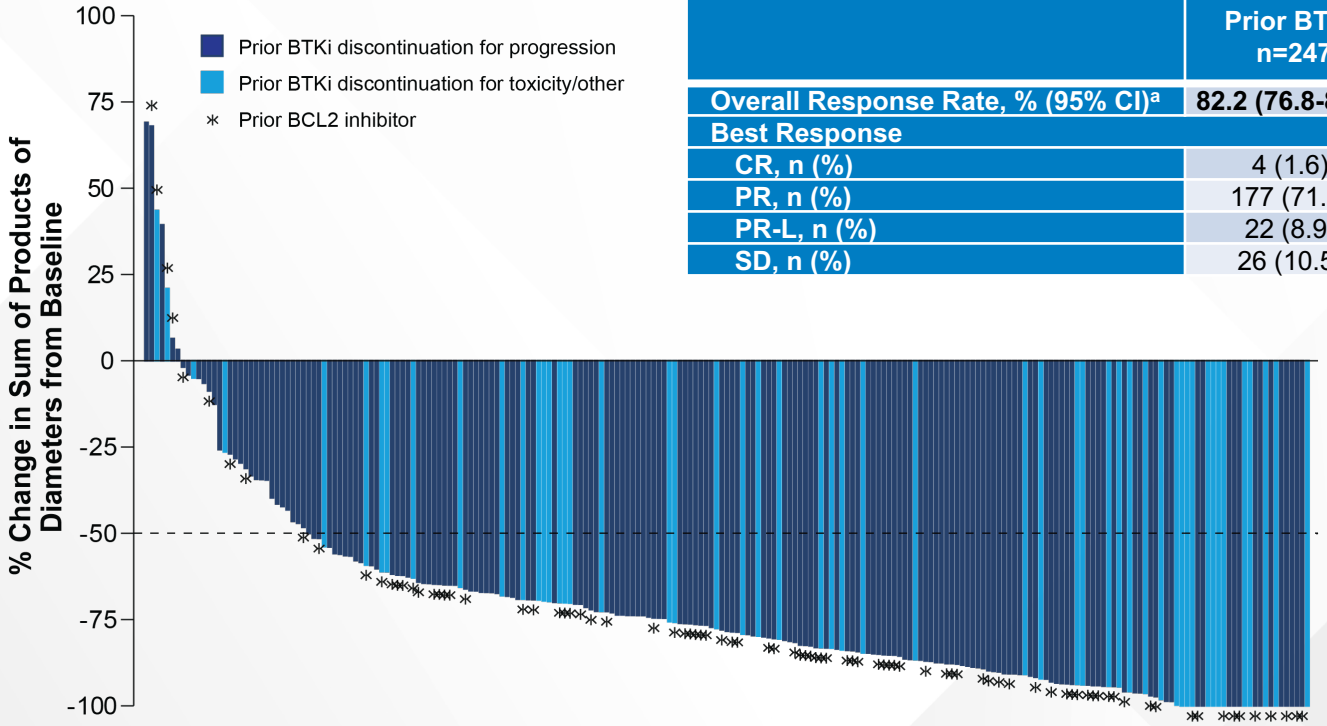
Phase 1/2 BRUIN Study: CLL/SLL Patient Characteristics

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)

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.
BCL-2, B cell lymphoma-2; BTK, Bruton tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor-T-cell therapy; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain gene; IQR, interquartile range; PI3K, phosphoinositide-3-kinase; PLCG2, phospholipase C gamma 2; SLL, small lymphocytic lymphoma; TP53, tumor protein p53.
Mato AR et al. *Blood* (2022) 140 (Supplement 1): 2316–2320.

Phase 1/2 BRUIN Study: 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)

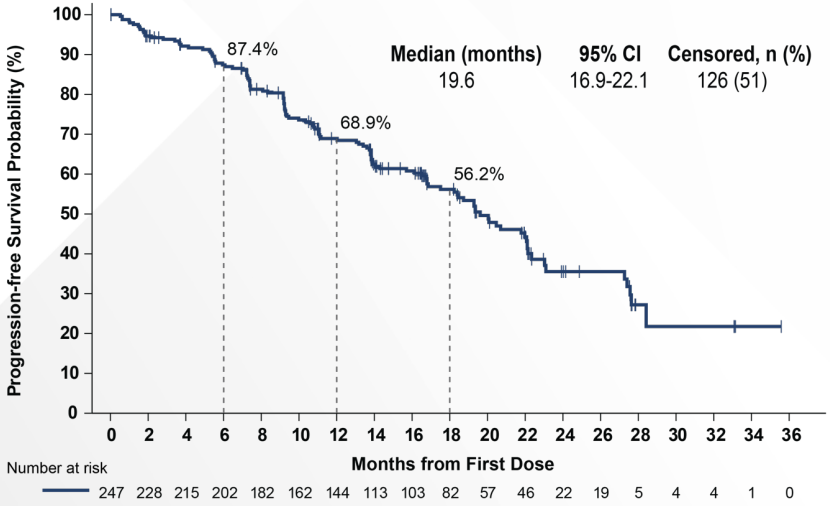
Data cutoff date of 29 July 2022. Data for 24 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.
BCL-2, B cell lymphoma-2; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; PR, partial response; PR-L, partial response with rebound lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma.
Mato AR et al. *Blood* (2022) 140 (Supplement 1): 2316–2320.

AXIS Medical Education

Phase 1/2 BRUIN Study: Progression-Free Survival in CLL/SLL Patients who Received Prior BTKi Treatment

All prior BTKi patients

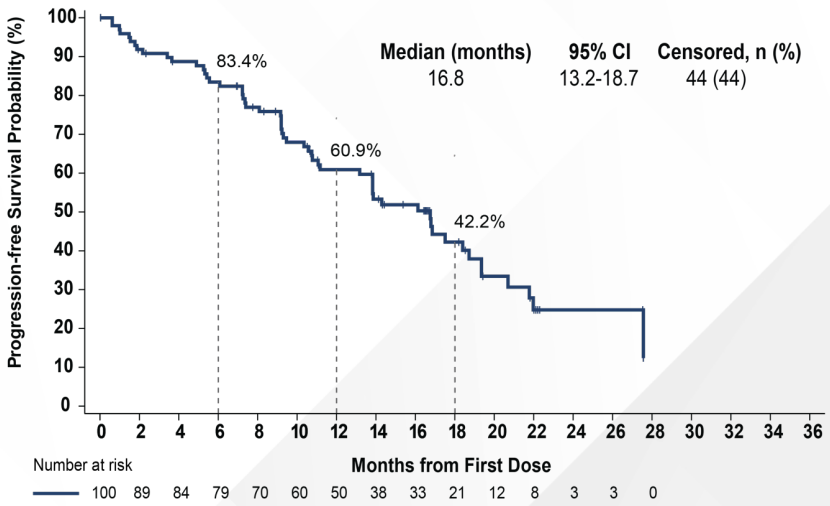
Median prior lines = 3



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

Prior BTKi and BCL2i patients

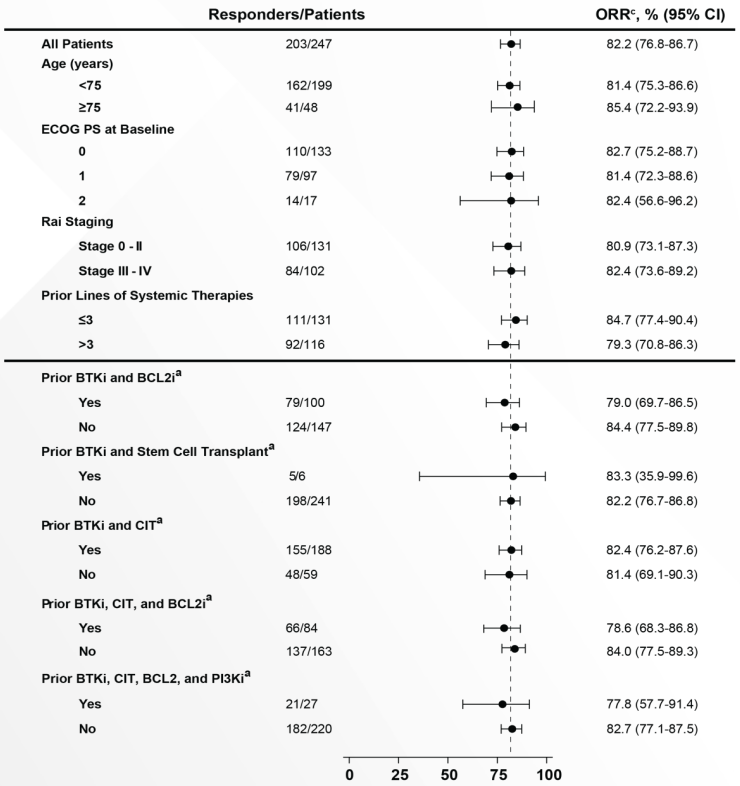
Median prior lines = 5

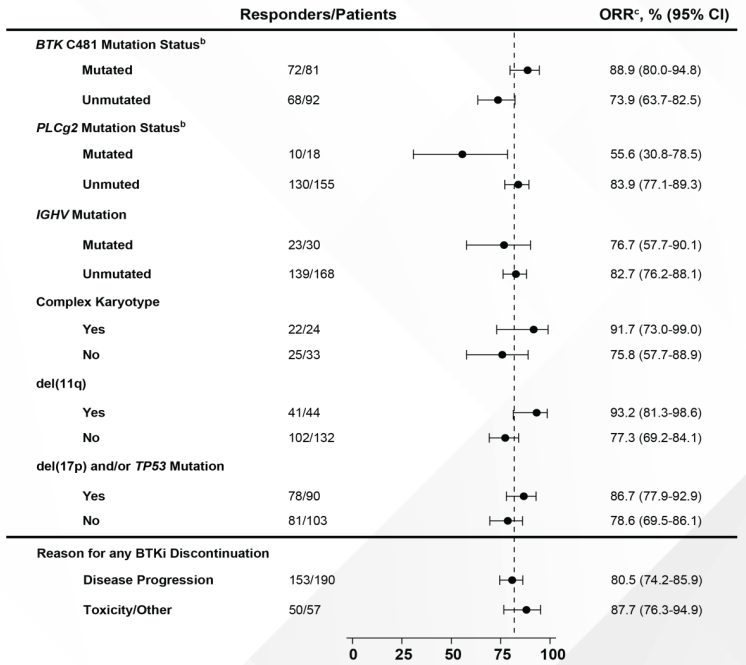


- Median follow-up of 18.2 months for patients who received prior BTKi and BCL2i

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.
BCL-2i, B cell lymphoma-2 inhibitor; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; SLL, small lymphocytic lymphoma.
Mato AR et al. *Blood* (2022) 140 (Supplement 1): 2316–2320.

Phase 1/2 BRUIN Study: Overall Response Rate in CLL/SLL Subgroups



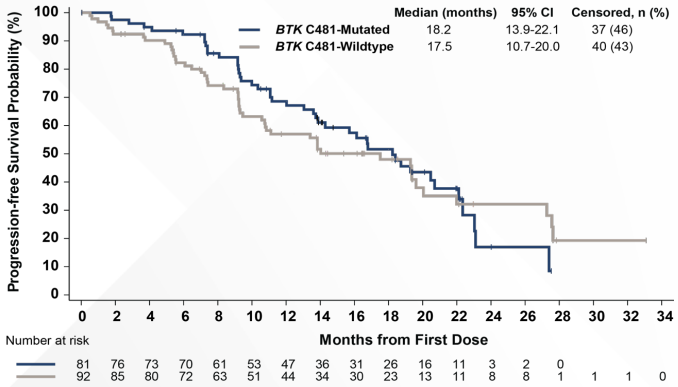


Data cutoff date of 29 July 2022. [a]Prior therapy labels indicate that patients received at least the prior therapy, rows are not mutually exclusive. [b]Patients with available mutation data who progressed on any prior BTKi. [c]Response includes partial response with lymphocytosis. Response status per iwCLL 2018 according to independent review committee assessment.
BCL-2i, B cell lymphoma-2 inhibitor; BTKi, Bruton tyrosine kinase inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del, deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain gene; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ORR, overall response rate; PI3Ki, phosphoinositide-3-kinase inhibitor; PLCG2, phospholipase C gamma 2; SLL, small lymphocytic lymphoma; TP53, tumor protein 53.
Mato AR et al. *Blood* (2022) 140 (Supplement 1): 2316–2320.

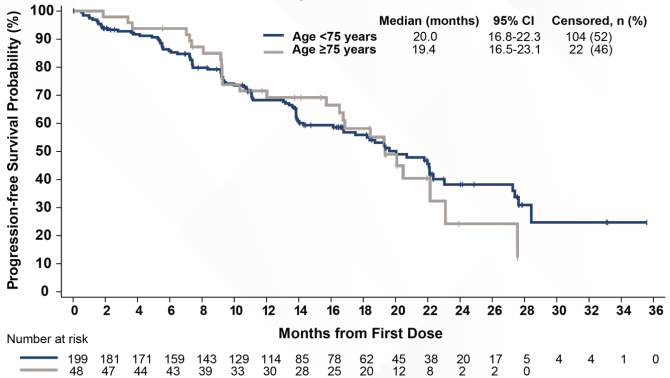
AXIS Medical Education

Phase 1/2 BRUIN Study: Progression-Free Survival in CLL/SLL Subgroups

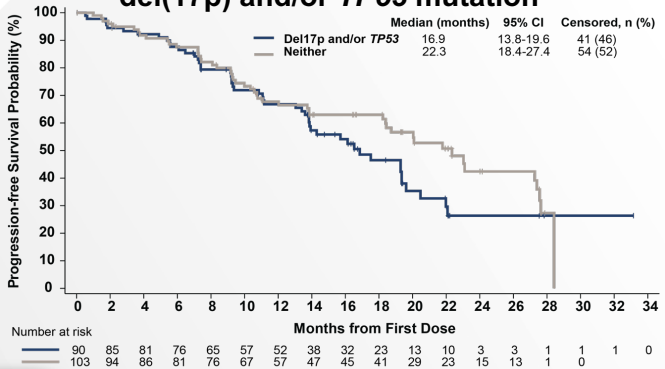
BTK C481 mutation status[a,b]



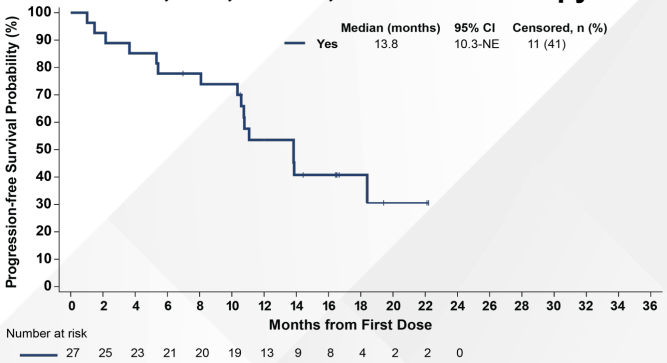
Age



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.
BCL-2i, B cell lymphoma-2 inhibitor; BTK, Bruton's tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; del, deletion; PI3Ki, phosphoinositide-3-kinase inhibitor; SLL, small lymphocytic lymphoma; TP53, tumor protein 53.

Mato AR et al. *Blood* (2022) 140 (Supplement 1): 2316–2320.

Phase 1/2 BRUIN Study: 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.
AEs, adverse events; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.
Mato AR et al. *Blood* (2022) 140 (Supplement 1): 2316–2320.

Ongoing Phase 3 Trials With Pirtobrutinib in CLL/SLL

Trial	Comparator	Setting/Population
BRUIN CLL-321 **NCT04666038**	Pirtobrutinib vs. Investigator's choice of: • Idelalisib + rituximab • Bendamustine + rituximab	BTK inhibitor pretreated CLL/SLL • Prior treatment with a covalent BTK inhibitor • Prior venetoclax is permitted
BRUIN CLL-322 **NCT04965493**	Pirtobrutinib + venetoclax + rituximab vs. venetoclax + rituximab	Previously treated CLL/SLL • Prior treatment may include a covalent BTKi • No prior venetoclax permitted
BRUIN CLL-313 **NCT05023980**	Pirtobrutinib vs. bendamustine + rituximab	Untreated Patients with CLL/SLL
BRUIN CLL-314 **NCT05254743**	Pirtobrutinib vs. ibrutinib	Patients with CLL/SLL

BTK, Bruton's tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

BELLWAVE-001: Nemtabrutinib Demonstrated Robust and Durable Clinical Responses in Pretreated CLL[1,2]

Nemtabrutinib: Reversible Inhibitor of Both WT and Ibrutinib-Resistant C481S-Mutated *BTK*

n (%) [95% CI]	CLL/SLL 65 mg QD n = 57	CLL/SLL Cohort A[a] n = 25	CLL/SLL Cohort B[b] n = 10
ORR	30 (53) [39-66]	15 (60) [39-79]	4 (40) [12-74]
CR	2 (4) [0.4-12]	0 (0) [0-14]	1 (10) [0.3-45]
PR	15 (25) [15-40]	5 (20) [7-41]	2 (20) [3-56]
PR-L	13 (23) [13-36]	10 (40) [21-61]	1 (10) [0.3-45]
SD	17 (30) [18-43]	8 (32) [15-54]	3 (30) [7-65]
PD	2 (4) [0.4-12]	0 (0) [0-14]	2 (20) [3-56]
No assessment	8 (14) [6-26]	2 (8) [1-26]	1 (10) [0.3-45]

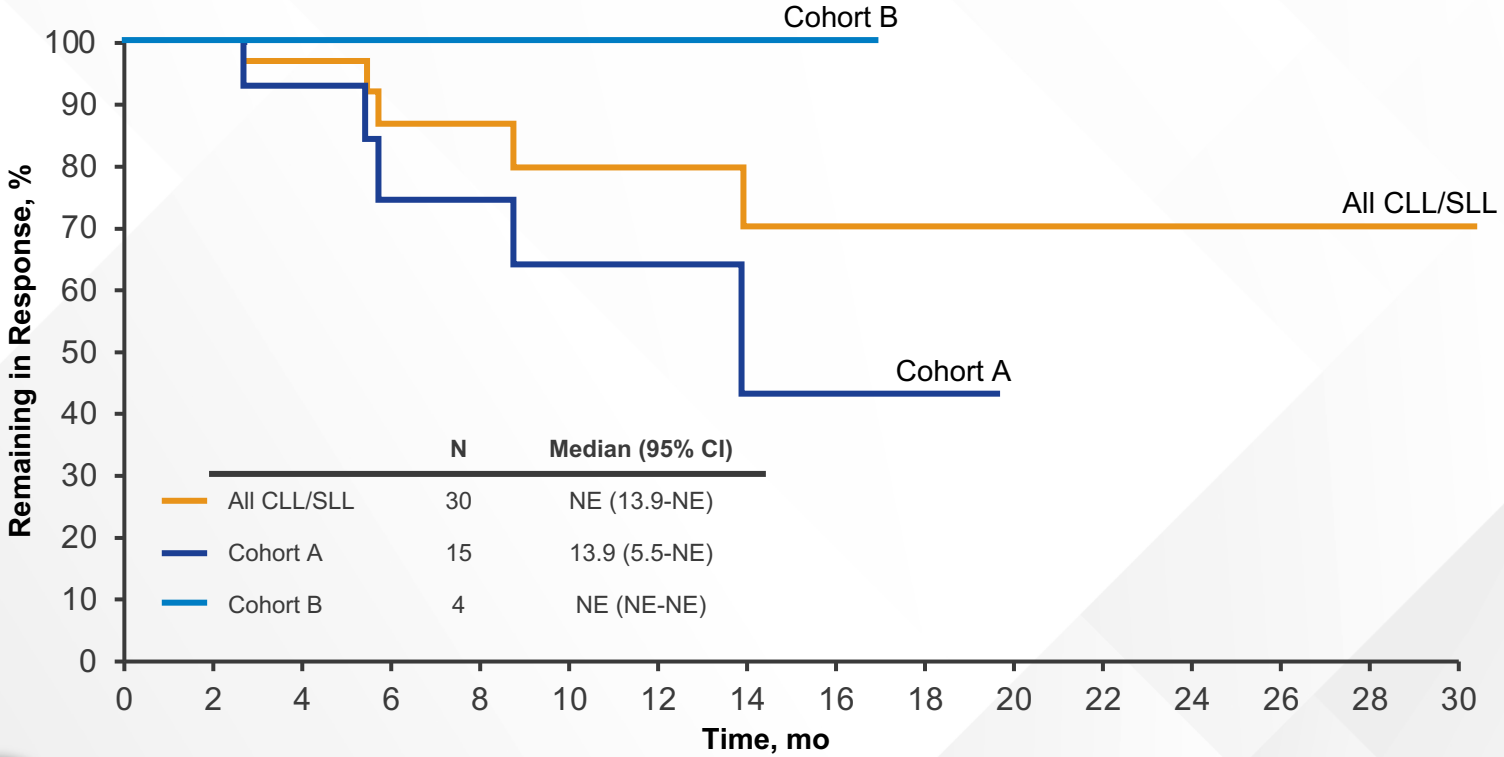
AXIS Medical Education

BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; ORR, overall response rate; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease; PD, progressive disease; QD, daily; SLL, small lymphocytic lymphoma; WT, wild type.

[a] Cohort A comprises patients with mCLL/SLL who received ≥2 prior therapies, including covalent BTKi and who have C481S mutation. [b] Cohort B comprises patients with mCLL/SLL who received ≥2 prior therapies, are intolerant to BTKi, and who have no C481S mutation.

1. Woyach J et al. EHA 2022. Abstract P682. 2. A Study of Nemtabrutinib (MK-1026) (ARQ 531) in Participants With Selected Hematologic Malignancies. Clinical Trials Identifier: NCT03162536.

BELLWAVE-001: Nemtabrutinib Demonstrated Robust and Durable Clinical Responses in Pretreated CLL[1]

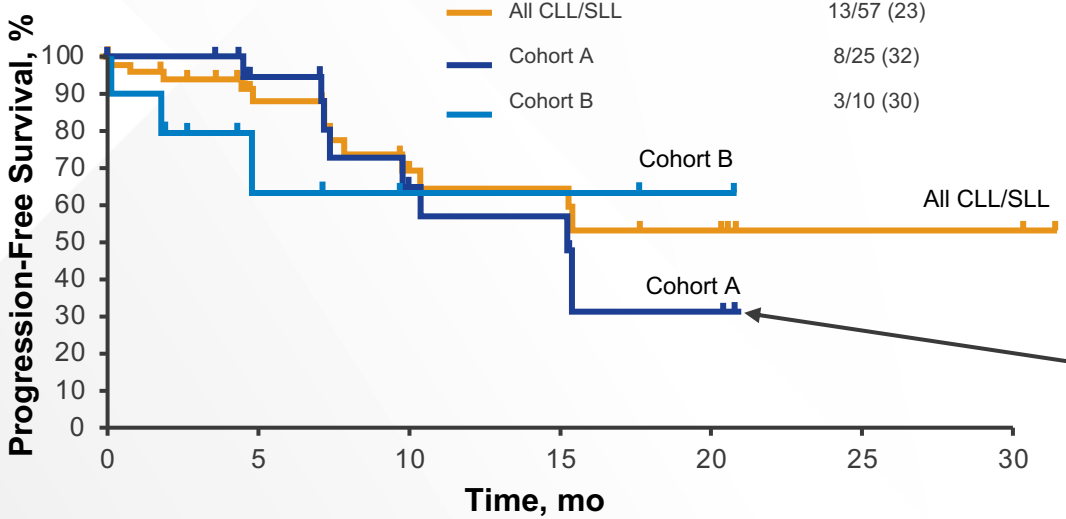


CLL, chronic lymphocytic leukemia; NE, not evaluable; SLL, small lymphocytic lymphoma.

1. Woyach J et al. EHA 2022. Abstract P682.

BELLWAVE-001: Nemtabrutinib Is Effective Against *BTK* Resistance Mutations[1]

	PFS Events, n/N, %	PFS Median (95% CI), mo
All CLL/SLL	13/57 (23)	NE (10.6-NE)
Cohort A	8/25 (32)	15.7 (7.6-NE)
Cohort B	3/10 (30)	NE (5.0-NE)



No. at Risk						
All	57	28	19	14	7	2
Cohort A	25	15	10	7	2	0
Cohort B	10	4	2	2	1	0

Cohort A: patients with R/R CLL/SLL who received ≥2 prior therapies, including covalent BTKi, and who have a C481S mutation

AXIS Medical Education

BTK, Bruton tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; NE, not evaluable; PFS, progression-free survival; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

1. Woyach J et al. EHA 2022. Abstract P682.

Updated Findings Continue to Show Efficacy of Nemtabrutinib in Pretreated CLL/SLL[1]

Patients With CLL/SLL Treated With Nemtabrutinib 65 mg Once Daily (N = 57)

	CLL/SLL With Prior BTK and BCL-2 Inhibitors	C481S-Mutated BTK	del(17p)	IGHV Unmutated
n (%)	24 (42)	36 (63)	19 (33)	30 (53)
ORR, % (95% CI)	58 (37-78)	58 (41-75)	53 (29-76)	50 (31-69)
Objective response, n (%) CR PR PR with residual lymphocytosis	14 (58) 0 6 (25) 8 (33)	21 (58) 1 (3) 11 (31) 9 (25)	10 (53) 1 (5) 2 (11) 7 (37)	15 (50) 0 8 (27) 7 (23)
Median DOR, mo 95% CI	8.5 2.7-NE	24.4 8.8-NE	11.2 5.7-NE	24.4 8.5-NE
Median PFS, mo 95% CI	10.1 7.4-15.9	26.3 10.1-NE	10.1 4.6-NE	15.9 7.4-NE

- Nemtabrutinib 65 mg continued to show promising and durable anti-tumor activity with a manageable safety profile in a highly R/R population who had prior therapy with novel agents
- ORR of 63% in C481S-mutated disease

AXIS Medical Education

BCL-2, B cell lymphoma-2; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; del, deletion; DOR, duration of response; IGHV, immunoglobulin heavy chain gene; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; SD, stable disease; PD, progressive disease; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma.

1. Woyach J et al. ASH 2022. Abstract 3114.

BELLWAVE-001: Nemtabrutinib Safety

Treatment-related Adverse Events, n (%)	All Patients at 65 mg QD N=112	
	All	Grade ≥3
Any treatment-related AEs	82 (73)	45 (40)
Treatment-related AEs ≥ 5%		
Dysgeusia	23 (21)	0 (0)
Neutrophil count decreased	22 (20)	19 (17)
Fatigue	14 (13)	2 (2)
Platelet count decreased	13 (12)	5 (4)
Nausea	13 (12)	0 (0)
Hypertension	11 (10)	4 (4)
Diarrhea	11 (10)	2 (2)
Pyrexia	9 (8)	0 (0)
Constipation	8 (7)	0 (0)
Vomiting	7 (6)	0 (0)
Arthralgia	6 (5)	0 (0)
Dizziness	6 (5)	0 (0)
Rash maculopapular	6 (5)	3 (3)

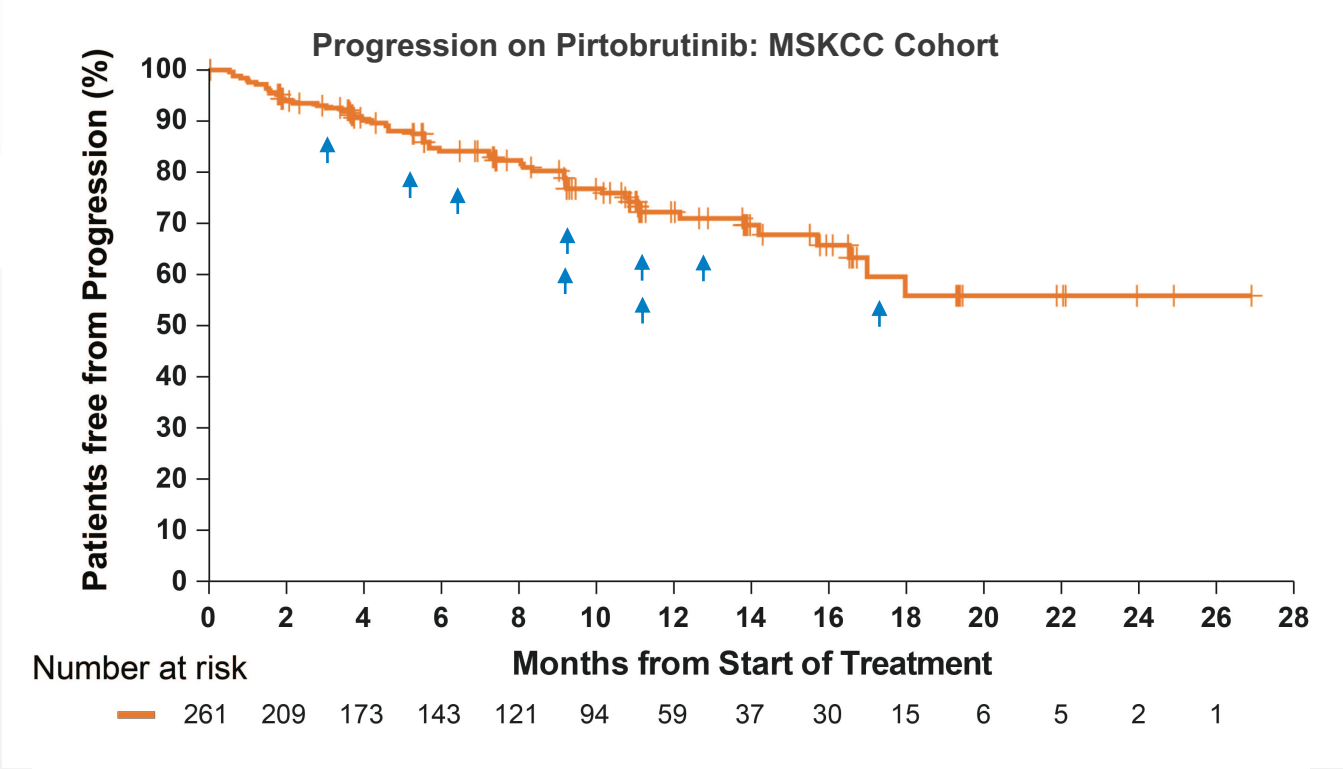
QD, daily.
Woyach J et al. ASH 2022. Abstract 3114.

Ongoing Phase 3 Trials With Nemtabrutinib in CLL/SLL

Trial	Comparator	Setting/Population
BELLWAVE-008 **NCT05624554**	nemtabrutinib vs. chemoimmunotherapy (investigator's choice of fludarabine + cyclophosphamide + rituximab [FCR] or bendamustine + rituximab [BR])	Previously untreated CLL/SLL without TP53 aberrations

CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; TP53, tumor protein 53.

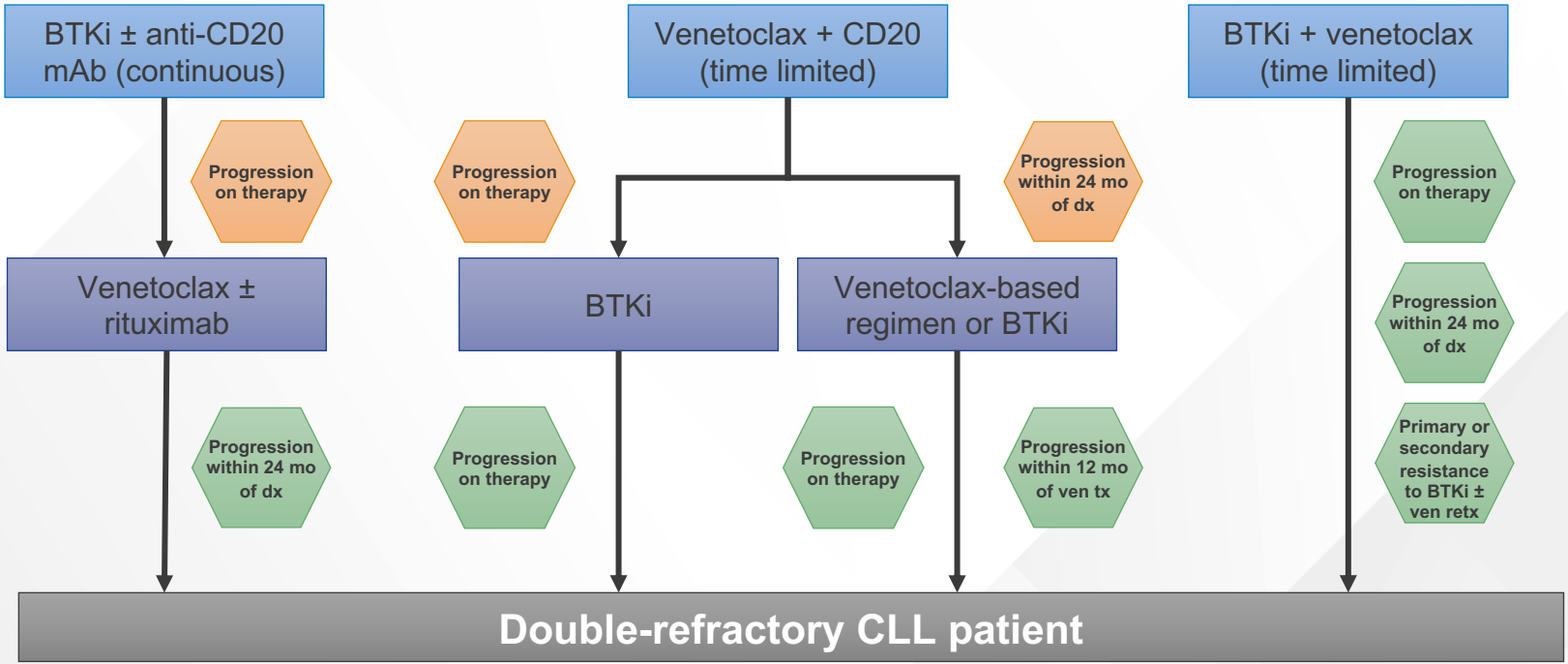
Progression of Disease on Pirtobrutinib



MSKCC, Memorial Sloan Kettering Cancer Center.
Mato A et al. ASH 2021. Abstract 391.

Addressing the Challenge of Double-Refractory CLL

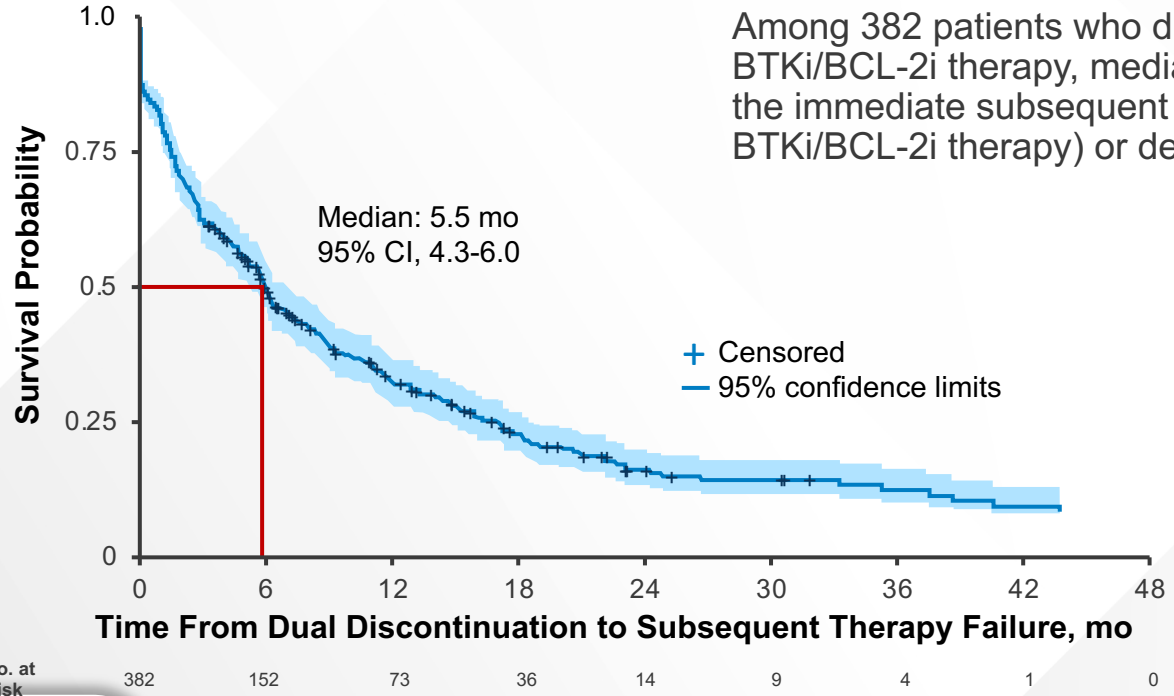
Defining Double-Refractory Disease



Dx, diagnosis; BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; mAB, monoclonal antibody; retx, retreatment; tx, treatment; ven, venetoclax.

1. Aronson JH et al. *Am J Hematol*. 2022;97(suppl 2):S19-S25.

Real-World Data Show That Double-Refractory Disease Represents a Clear Unmet Medical Need in CLL/SLL



Among 382 patients who discontinued covalent BTKi/BCL-2i therapy, median time to discontinuation of the immediate subsequent line of therapy (post–BTKi/BCL-2i therapy) or death was 5.5 months[1]

Patients previously treated with <u>both a covalent BTKi and a BCL-2i</u> experience poor outcomes with currently available post-covalent BTKi/BCL-2i therapy

BCL-2i, B cell lymphoma-2 inhibitor; BTK, Bruton's tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

1. Mato A et al. ASH 2021. Abstract 3743.

Where Do We Stand With Treatment for Double-Refractory Disease?

- There are few good options; median time to discontinuation of the immediate subsequent LOT (post–BTKi/BCL-2i therapy) or death was 5.5 months[1]
- Novel BCL-2 mutations have been described in venetoclax-resistant, ibrutinib-resistant CLL patients with BTK/PLCG2 mutations[2]
- What is being explored?
  - Venetoclax retreatment
  - Noncovalent BTKi
  - CAR-T therapy

BCL-2, B cell lymphoma-2; BTK, Bruton's tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor-T-cell therapy; CLL, chronic lymphocytic leukemia; LOT, line of treatment; PLCG2, phospholipase C gamma 2.

1. Mato A et al. ASH 2021. Abstract 3743. 2. Lucas F et al. *Blood.* 2020;135: 2192-2195.

Is Venetoclax Retreatment an Option?[1]

- Retrospective study investigating outcomes and safety data for patients with CLL treated with a venetoclax-based regimen (Ven1) in any line of therapy and then re-treated with a second venetoclax-based regimen (Ven2) in a later line of therapy
- Data sources included
  - 15 medical centers (n = 30)
  - CLL Collaborative Study of Real-World Evidence database (n = 5)
  - Patients from the MURANO trial dataset (n = 11)

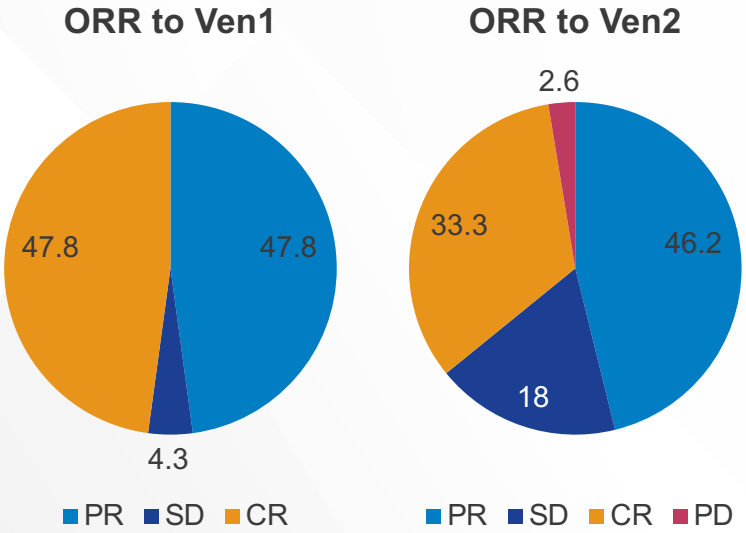
Baseline Characteristics	Results	Patients With Available Data, n
Median age at CLL diagnosis, y (range)	55.5 (24-75)	46
Median age at Ven1 start, y (range)	64 (31-75)	46
Men	73.9%	46
Race	83.3% White 9.5% Black 7.1% other	42
Ven1 administered as part of a clinical trial	56.5%	46
Ven1 as monotherapy	37%	46
Ven1 as first-line treatment	8.7%	46
Median prior lines of therapy (range)	2 (0-10)	46
Prior BTKi	40%	45
del(17p)	25%	44
TP53 mutation	15.6%	32
Complex karyotype	20.5%	39
IGHV unmutated	82.1%	39

AXIS Medical Education

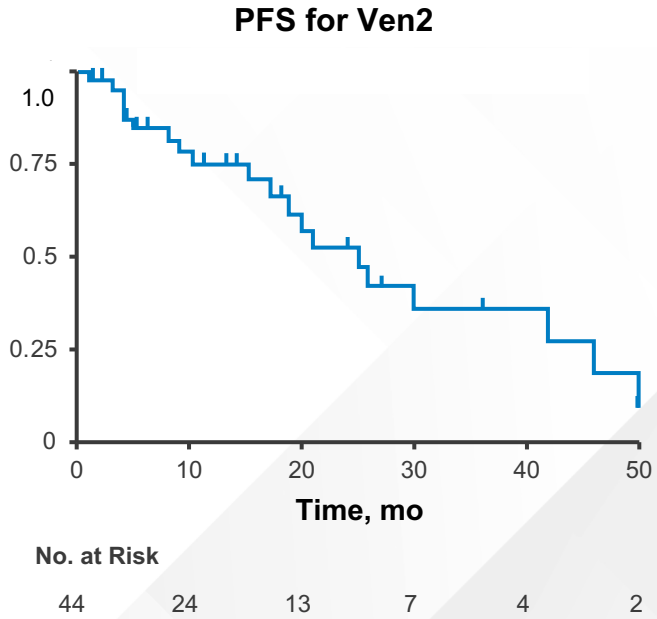
BTKi, Bruton's tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; del, deletion; IGHV, immunoglobulin heavy chain gene; TP53, tumor protein 53.

1. Thompson M et al. *Blood Adv*. 2022;6:4553-4557.

Retrospective Evidence Suggests Venetoclax Can Be Effective, Including in Double-Exposed Patients[1]



- ORR to Ven2 was 79.5
- ORR of 56.3% in BTKi-exposed patients



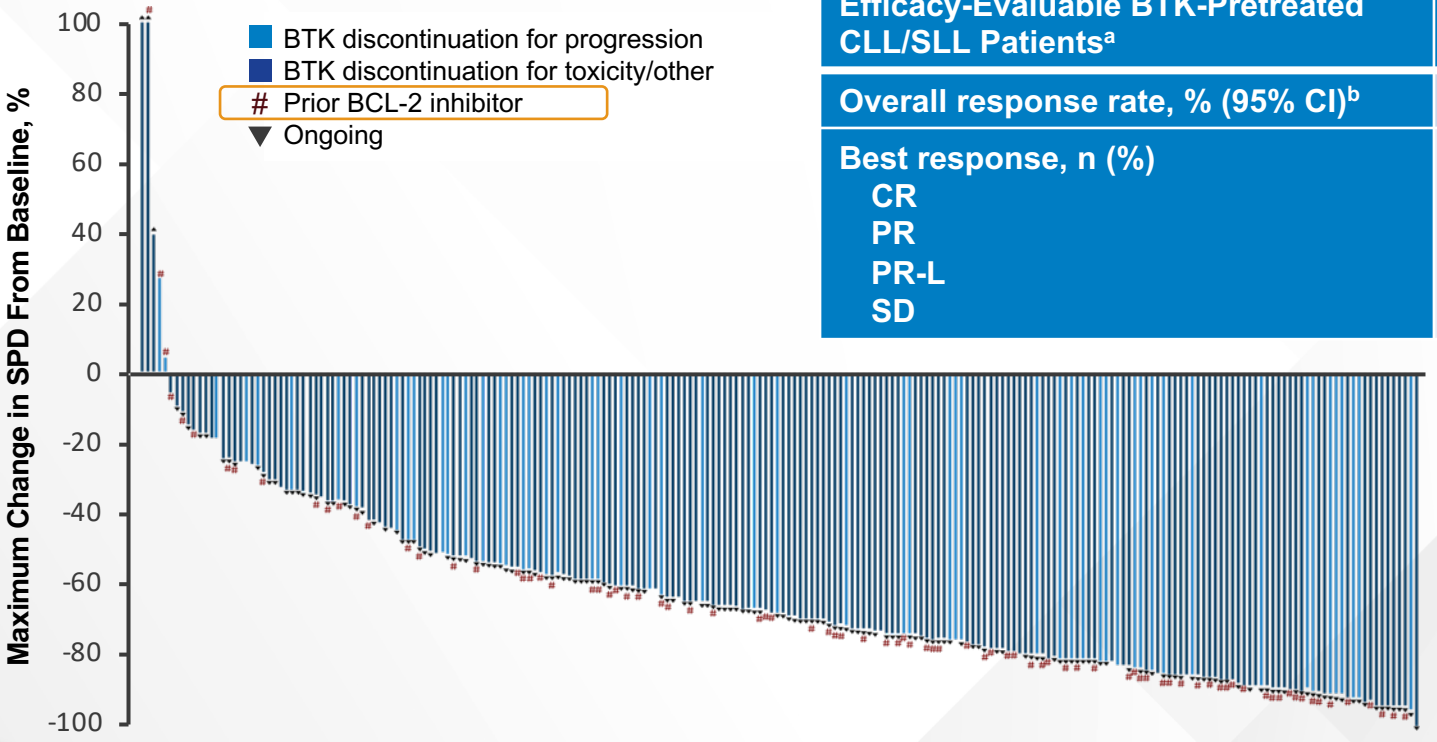
Although prospective studies are needed, the high ORR and durability of observed remissions support venetoclax retreatment, and it appears to be highly active in “double-exposed” CLL

AXIS Medical Education

BTKi, Bruton’s tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; CR, complete response; ORR, overall response rate; PFS, progression-free survival; PR, partial response; PD, progressive disease; SD, stable disease; Ven1; first treatment with a venetoclax-based regimen; Ven2; retreatment with a second venetoclax-based regimen

1. Thompson M et al. *Blood Adv*. 2022;6:4553-4557.

Pirtobrutinib (BRUIN Trial) in Patients With Prior Exposure to BCL-2 Inhibitor Therapy[1]



Efficacy-Evaluable BTK-Pretreated CLL/SLL Patients[a]	N = 252
Overall response rate, % (95% CI)[b]	68 (62-74)
Best response, n (%)	
CR	2 (1)
PR	137 (54)
PR-L	32 (13)
SD	62 (25)

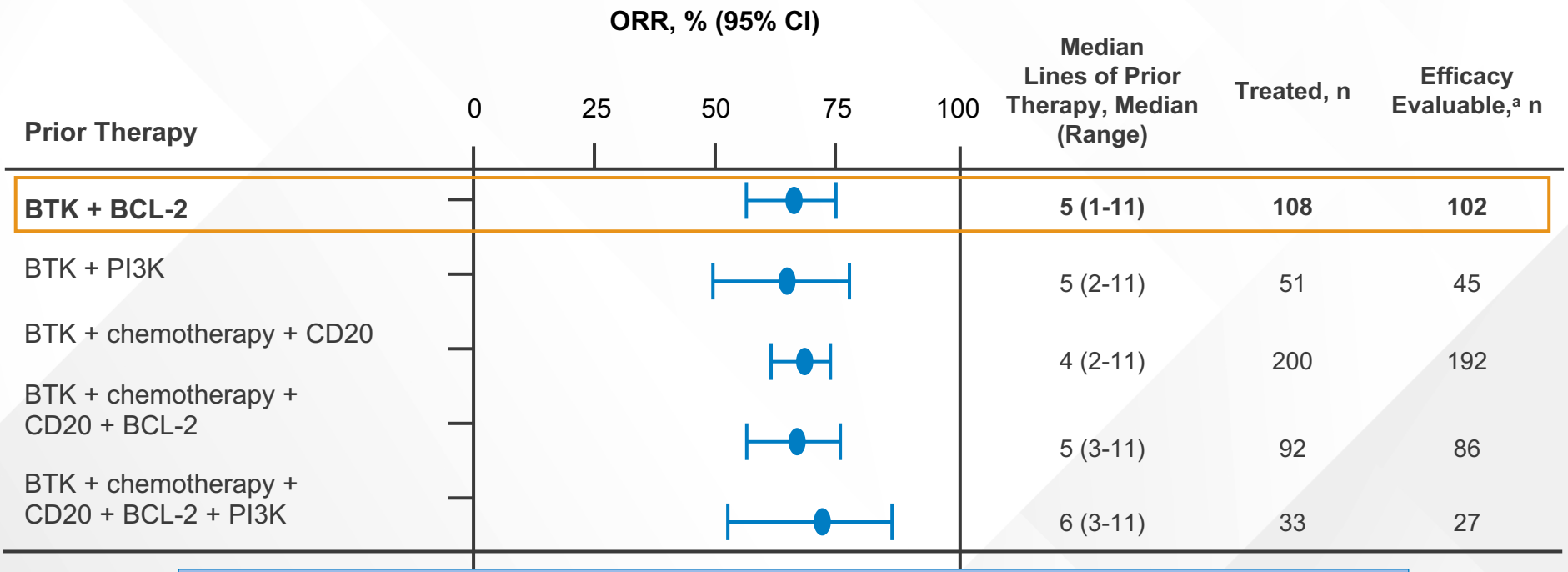
[a] Efficacy-evaluable patients are those who had ≥1 postbaseline response assessment or had discontinued treatment prior to first postbaseline response assessment. [b] ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to investigator assessment. Total percentage may be different than the sum of the individual components because of rounding.

BCL-2, B cell lymphoma-2; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; CR, complete response; ORR, overall response rate; PR, partial response; PR, partial response with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma; SPD, sum of the products of the greatest perpendicular diameters.

1. Mato A et al. EHA 2021. Abstract S147.

AXIS Medical Education

BRUIN: Pirtobrutinib Is Active in CLL/SLL Patients Progressing After BTKi Therapy and Venetoclax[1]



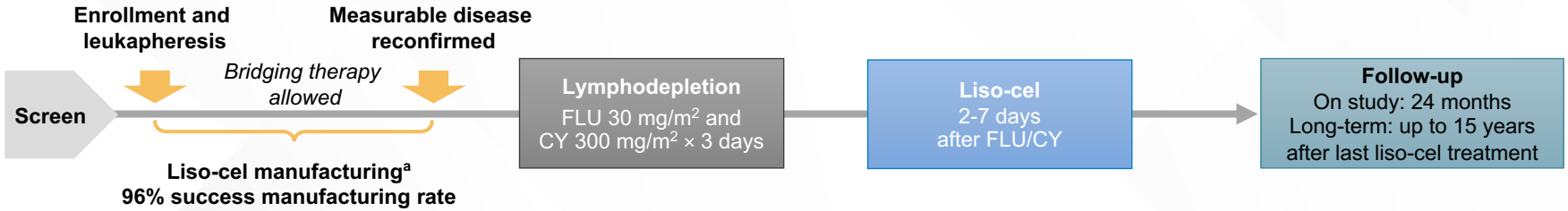
Prior Therapy	Median Lines of Prior Therapy, Median (Range)	Treated, n	Efficacy Evaluable,[a] n
BTK + BCL-2	**5 (1-11)**	**108**	**102**
BTK + PI3K	5 (2-11)	51	45
BTK + chemotherapy + CD20	4 (2-11)	200	192
BTK + chemotherapy + CD20 + BCL-2	5 (3-11)	92	86
BTK + chemotherapy + CD20 + BCL-2 + PI3K	6 (3-11)	33	27

ASH 2022: with longer follow-up, ORR of 74% in patients failing prior cBTKi and venetoclax[2]

AXIS Medical Education

[a] Efficacy-evaluable patients are those who had ≥1 evaluable postbaseline assessment or had discontinued treatment prior to first postbaseline assessment.
ASH, American Society of Hematology; BCL-2, B cell lymphoma-2; BTK, Bruton's tyrosine kinase; BTKi, Bruton tyrosine kinase inhibitor; cBTKi, covalent Bruton tyrosine kinase inhibitor; CLL, chronic lymphocytic leukemia; ORR, overall response rate; PI3K, phosphoinositide-3-kinase; SLL, small lymphocytic lymphoma.
1. Mato A et al. ASH 2021. Abstract 391. 2. Mato A et al. ASH 2022. Abstract 961.

TRANSCEND CLL 004: CAR-T Therapy Is Another Novel Option Being Explored in CLL[1]



Key Eligibility

- Relapsed/refractory CLL/SLL
- **Failed or ineligible for BTKi[b]**
- **High-risk disease[c]: failed ≥2 prior therapies**
- **Standard-risk disease: failed ≥3 prior therapies**
- ECOG PS of 0-1

Dose Escalation: mTPI-2 Design[d]

28-day DLT period

Primary objectives

- Safety
- Determine recommended dose

Exploratory objectives

- Antitumor activity
- Pharmacokinetic profile

Dose Level	Dose	Evaluable (N = 23)
1	50 × 10^6 CAR-T cells	9
2	100 × 10^6 CAR-T cells	14

ClinicalTrials.gov identifier: NCT03331198.

[a] One patient received nonconforming product. [b] Failure defined as SD or PD as best response, or PD after previous response, or discontinuation due to intolerance (unmanageable toxicity). Ineligibility defined as requirement for full-dose anticoagulation or history of arrhythmia. [c] Complex cytogenetic abnormalities, del(17p), *TP53* mutation, or unmutated IGHV. [d] Guo W et al. *Contemp Clin Trials.* 2017;58:23-33.

1. Siddiqi T et al. ASH 2019. Abstract 503; Siddiqi T et al. *Blood.* 2022;139:1794-1806.

BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor-T-cell therapy; CLL, chronic lymphocytic leukemia; CY, cyclophosphamide; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; FLU, fludarabine; liso-cel, lisocabtagene maraleucel; mTPI-2, modified toxicity probability interval-2 design.

Additional Novel Agents in CLL
Potential Applications in Double-Exposed Patients

- Novel BCL-2is
  - Lisaftoclax (APG-2575)[1]
  - BGB-11417[2]
  - LP-118 (dual BCL-2/BCL-XL inhibitor)[3]
  - PZ18753b (BCL-2/BCL-XL PROTAC)[4]
- PKCβ inhibitor – MS-553[5]
- BTK degrader – NX-2127[6]
- CD20 bispecifics – epcoritamab[7]

AXIS Medical Education

BCL-2, B cell lymphoma-2; BCL-2i, B cell lymphoma-2 inhibitor; B-cell lymphoma-extra large, BCL-XL, BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; PKCβ, protein kinase C beta.

1. Davids MS et al. ASH 2022. Abstract 964. 2. Cheah CY et al. ASH 2022. Abstract 962. 3. Ravikrishan J et al. ASH 2021. Abstract 679. 4. Rohena DD et al. ASH 2022. Abstract 206. 5. Blachly JS et al. ASH 2022. Abstract 963. 6. Mato A et al. ASH 2022. Abstract 965. 7. Kater AP et al. ASH 2022. Abstract 348.

Take-Home Messages

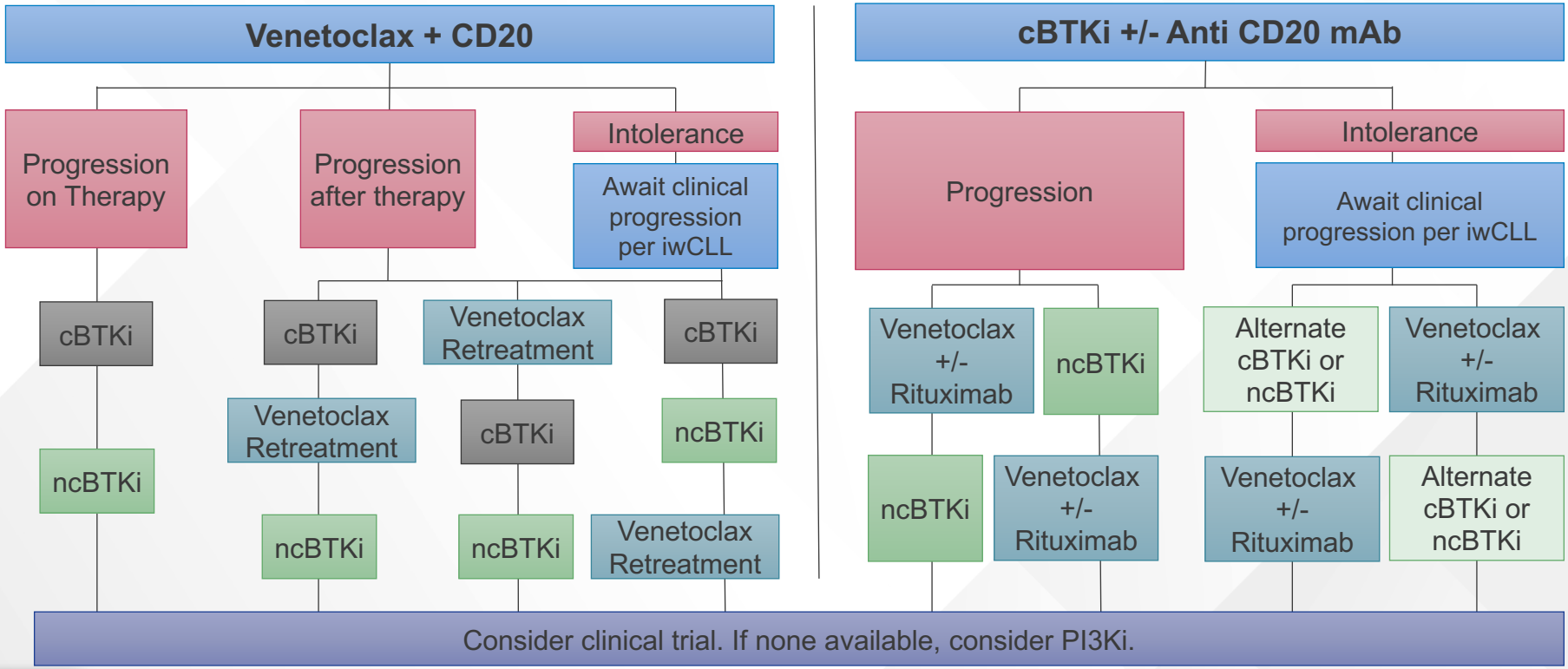
- Double-refractory CLL represents a clear unmet medical need—one that is likely to increase as more patients are treated with BTKi and venetoclax
- Retreatment with venetoclax is an intriguing approach that requires prospective validation
- New options, including noncovalent BTKi and CAR-T therapy, have shown efficacy in double-refractory settings

BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor-T-cell therapy; CLL, chronic lymphocytic leukemia.

From Bench to Practice: Treatment Algorithms Which Include ncBTKis (Should They Be Approved)

ncBTKis, non-covalent Bruton's tyrosine kinase inhibitors.

From Bench to Practice: Treatment Algorithms Which Include ncBTKis (Should They Be Approved)



cBTKi, covalent Bruton's tyrosine kinase inhibitor; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; ncBTKi; noncovalent Bruton's tyrosine kinase inhibitor; PI3Ki, phosphoinositide 3-kinase inhibitor.

Practical Application Case Learning Lab

Sequencing of Targeted Therapies 1: Intolerance

- 75-year-old IGHV mutated, trisomy 12, CLL
  - 1st line therapy: BR 2016
  - 2nd line therapy: Ibrutinib 2019
    - > Discontinued 2019 in the setting of rash/arthralgias
  - 3rd line therapy 2023

- How would you treat this patient?
  - a) Alternate covalent BTK inhibitor
  - b) Noncovalent BTK inhibitor
  - c) PI3K inhibitor
  - d) CIT retreatment
  - e) Venetoclax based therapy
  - f) Unsure

AXIS Medical Education

BR, bendamustine + rituximab; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain gene; PI3Ki, phosphoinositide 3-kinase inhibitor.

Sequencing of Targeted Therapies 1: Discussion

- 75-year-old IGHV mutated, trisomy 12, CLL
  - 1st line therapy: BR 2016
  - 2nd line therapy: Ibrutinib 2019
    - Discontinued 2019 in the setting of rash/arthralgias
  - 3rd line therapy

- Discuss role of alternate cBTKi in the setting of intolerance
- Discuss role of alternate ncBTKi in the setting of intolerance
- Discuss role of Pi3Ki in the setting of BTKi intolerance (if any)
- Discuss role of CIT retreatment in 2023
- Discuss role of venetoclax based therapy in this case
- Discuss how real-world data has contributed to c and ncBTKi use in clinical setting

BR, bendamustine + rituximab; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; cBTKi, covalent Bruton's tyrosine kinase inhibitor; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor; IGHV, immunoglobulin heavy chain gene; PI3Ki, phosphoinositide 3-kinase inhibitor.

Sequencing of Targeted Therapies 2: Progression

- 75-year-old IGHV mutated, trisomy 12, CLL
  - 1st line therapy: BR 2016
  - 2nd line therapy: Ibrutinib 2019
    - > Discontinued 2021 in the setting of clinical POD with bone marrow showing an acquired C481 mutation and del17p
  - 3rd line therapy

- How would you treat this patient?
  - a) Alternate covalent BTK inhibitor
  - b) Noncovalent BTK inhibitor
  - c) PI3K inhibitor
  - d) CIT retreatment
  - e) Venetoclax based therapy
  - f) Unsure

AXIS Medical Education

BR, bendamustine + rituximab; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain gene; PI3Ki, phosphoinositide 3-kinase inhibitor; POD, progression of disease.

Sequencing of Targeted Therapies 2: Discussion

- 75-year-old IGHV mutated, trisomy 12, CLL
  - 1st line therapy: BR 2016
  - 2nd line therapy: Ibrutinib 2019
    - > Discontinued 2021 in the setting of clinical POD with bone marrow showing an acquired C481 mutation and del17p
  - 3rd line therapy

- Discuss role of alternate covalent and noncovalent BTKi in the setting of clinical progression
- Discuss role of venetoclax based therapy in this case
- Discuss sequencing of ncBTKi and venetoclax in the R/R setting

AXIS Medical Education

BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain gene; ncBTKi, noncovalent Bruton's tyrosine kinase inhibitor; POD, progression of disease; R/R, relapsed/refractory.

Sequencing of Targeted Therapies 3

- 75-year-old IGHV mutated, trisomy 12, CLL
  - 1st line therapy: BR 2016
  - 2nd line therapy: Ibrutinib 2019
    - > Discontinued 2021 in the setting of BTKi associated intolerance (atrial fibrillation)
  - 3rd line therapy: Ven-R (24 months fixed duration)
  - 2023 = POD and need for CLL directed therapy

- How would you treat this patient?
  - a) Alternate covalent BTK inhibitor
  - b) Noncovalent BTK inhibitor
  - c) Venetoclax based re-treatment
  - d) PI3K inhibitor
  - e) Unsure

BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain gene; PI3K, phosphoinositide 3-kinase; POD, progression of disease; Ven-R, venetoclax + rituximab.

Sequencing of Targeted Therapies 3: Discussion

- 75-year-old IGHV mutated, trisomy 12, CLL
  - 1st line therapy: BR 2016
  - 2nd line therapy: Ibrutinib 2019
    - > Discontinued 2021 in the setting of BTKi associated intolerance (atrial fibrillation)
  - 3rd line therapy: Patient treated with Ven-R (24 months fixed duration)
  - 2023 = POD and need for CLL directed therapy

- Discuss role of alternate covalent and noncovalent BTKi in this setting
- Discuss role of venetoclax based re-treatment (vs ncBTKi)
- If this patient were age 55, what criteria would you use to refer for allo SCT or CAR-T (if available)?
- Discuss sequencing of ncBTKi and venetoclax in the R/R setting

BR, bendamustine + rituximab; BTKi, Bruton's tyrosine kinase inhibitor; CAR-T, chimeric antigen receptor T-cell therapy; CLL, chronic lymphocytic leukemia; IGHV, immunoglobulin heavy chain gene; POD, progression of disease; R/R, relapsed/refractory; SCT, stem cell transplant; Ven-R, venetoclax + rituximab.

AXIS Medical Education

The Emerging Landscape of BTK Inhibitors for Relapsed/Refractory CLL/SLL:

Clinical Practicalities and Perspectives