Therapeutic Road map of the last 7 years: a dynamic period with the escalation of BTKi

Matthew S. Davids, MD, MMSc
Clinical Research Director | Division of Lymphoma
Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
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LEUCEMIA LINFATICA CRONICA:
L'INNOVATIVITÀ TERAPEUTICA ED OLTRE...

28-29 MARZO 2023 BOLOGNA ROYAL HOTEL CARLTON

Relationships with financial interests

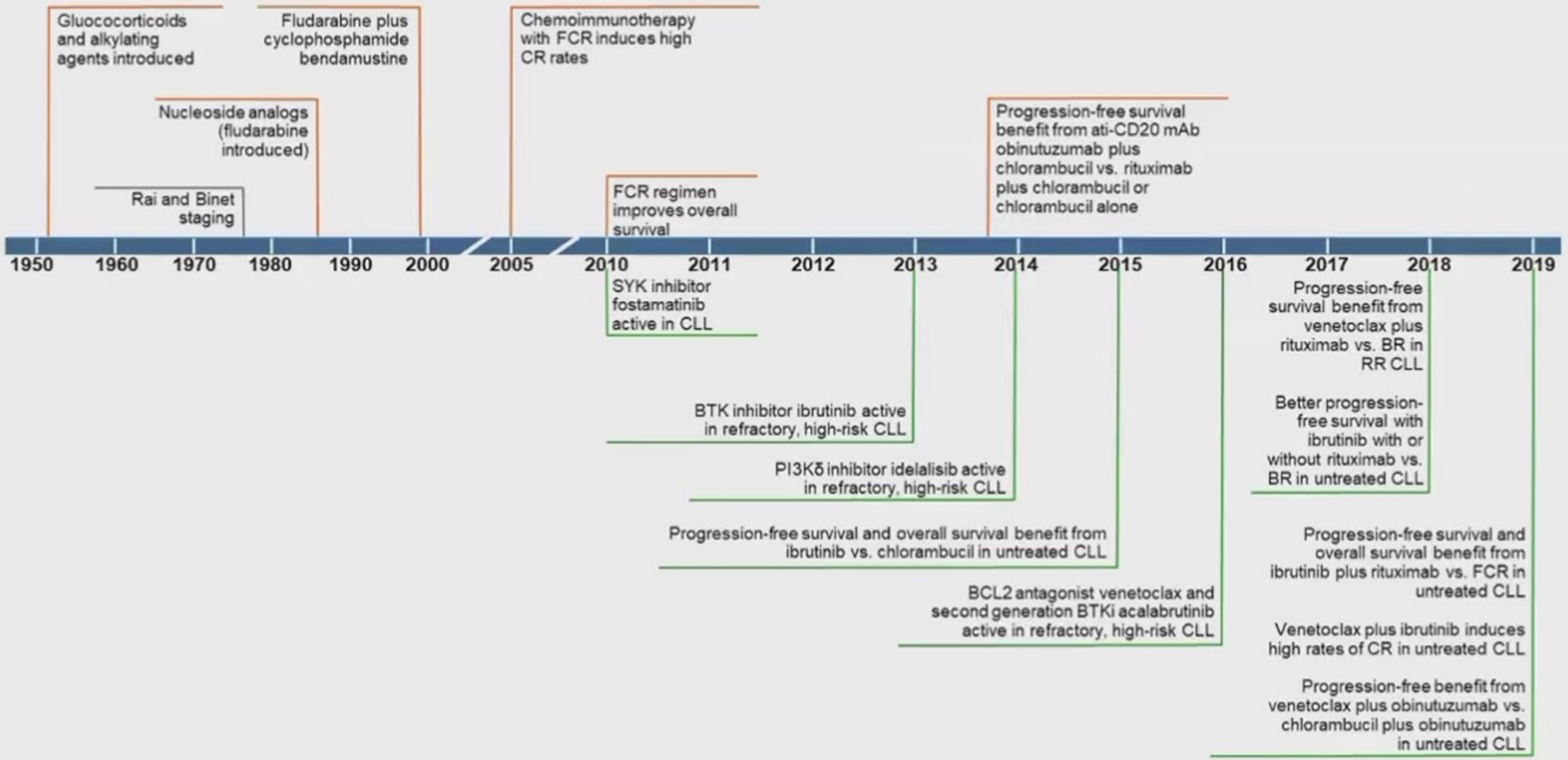
Consulting/SAB: AbbVie, Adaptive Biotechnologies, Ascentage Pharma, AstraZeneca, BeiGene, Bristol-Myers Squibb, Eli Lilly, Genentech, Genmab, Janssen, Merck, Mingsight Pharmaceuticals, Ono Pharmaceuticals, Secura Bio, Takeda, and TG Therapeutics

Research Support: AbbVie, Ascentage Pharma, AstraZeneca, Genentech, Novartis, Secura Bio, and TG Therapeutics

Honoraria for CME Activities: Aptitude Health, AXIS Medical Education, BioAscend, Curio Science, Medscape Education, PeerView Institute for Medical Education, Physician's Education Resource, PlatformQ Health Education, Plexus Communications, and Research to Practice

Royalties: Up-to-Date

Timeline of CLL Clinical Investigation



Burger JA. *N Engl J Med*. 2020;383(5):460-473.

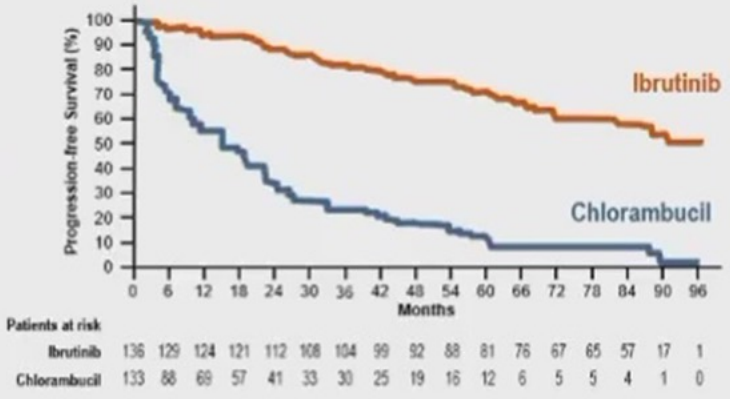
2016-2019
The Golden Age of Continuous BTKi

With up to 8-Year Follow-Up, First-Line Ibrutinib Treatment Provides Durable Benefit for Most Patients With CLL

RESONATE-2

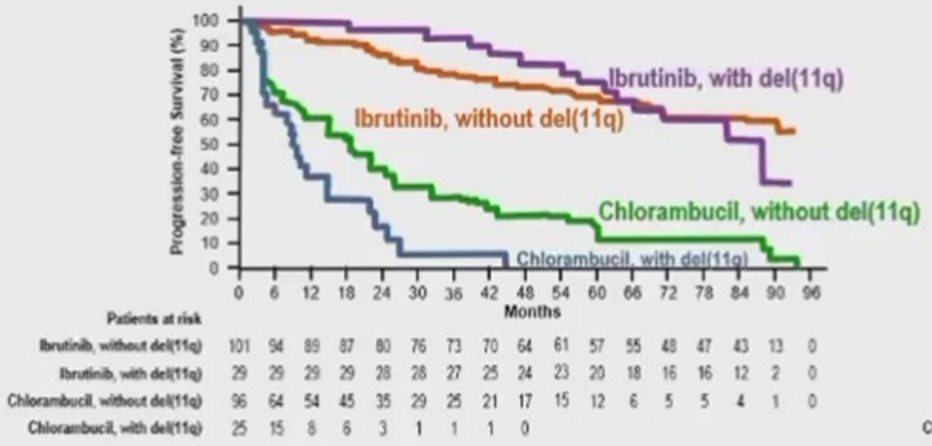
PFS (all)

	Chlorambucil	Ibrutinib
Median PFS, mo	15.0	NE
HR (95% CI)	**0.154** (0.108–0.220)	



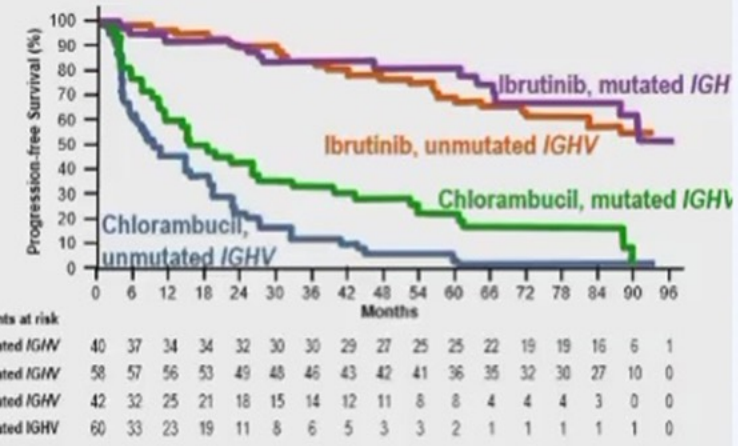
PFS by 11q

	With del(11q)		Without del(11q)	
	Ibr	Chl	Ibr	Chl
7-year PFS	52%	0	61%	12%
Median PFS, mo	88	9.0	NR	18.4
HR (95% CI)	**0.033** (0.010–0.107)		**0.193 (0.128–0.289)**	



PFS by *IGHV*

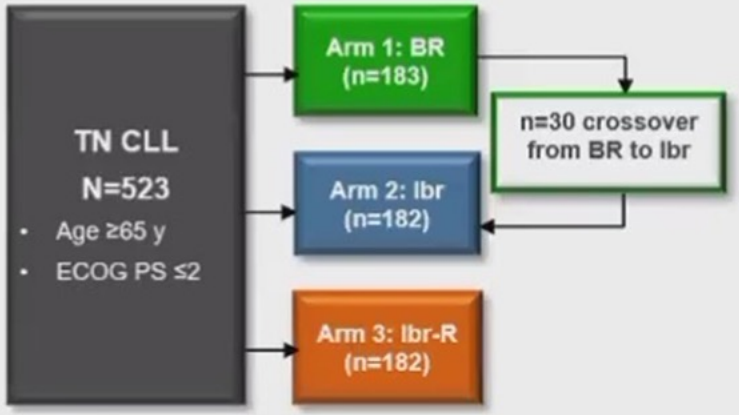
	Unmutated *IGHV*		Mutated *IGHV*	
	Ibr	Chl	Ibr	Chl
7-year PFS	58%	2%	68%	17%
Median PFS, mo	NR	9.33	NR	16.7
HR (95% CI)	**0.112** (0.065–0.192)		**0.174** (0.089–0.342)	



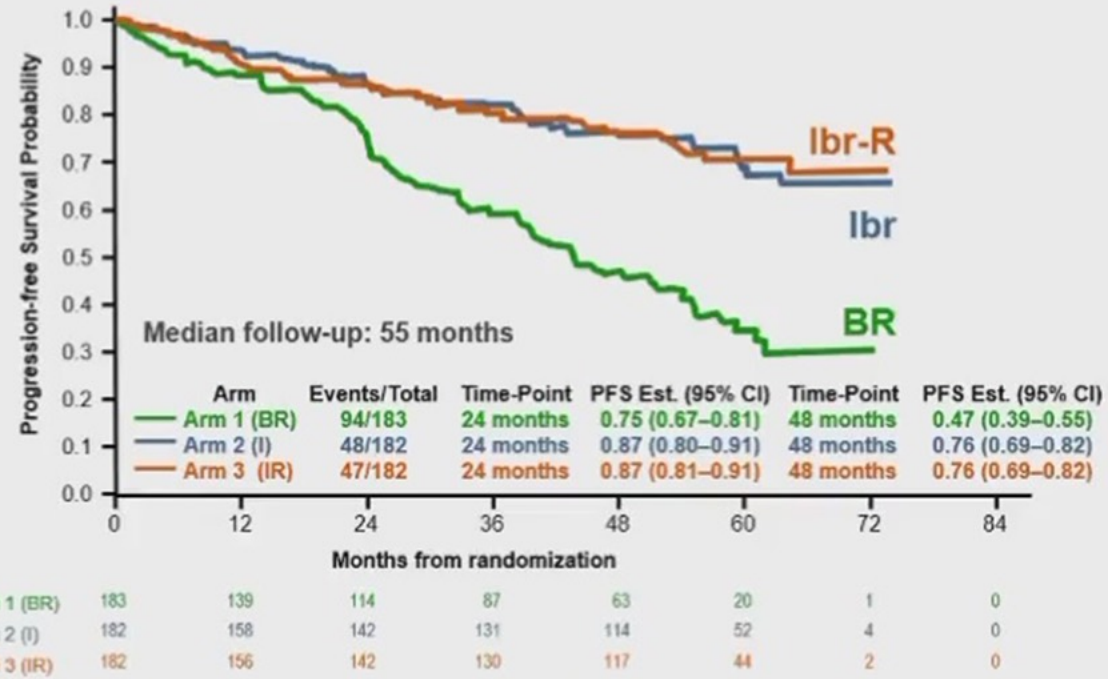
Barr, et al., *Blood Adv.* 2022;6 (11): 3440–3450.

Older Patients With TN CLL Also Benefit From Ibrutinib

Phase 3 ALLIANCE A041202



Primary Endpoint: PFS
Secondary Endpoints: OS, TTP, DOR, proportion achieving MRD negativity, biopsy-proven CR, toxicity



Baseline Characteristic	Ibr-R	Ibr	BR
Median age, y (range)	71 (65-86)	71 (65-89)	70 (65-86)
HR disease by modified Rai stage, %	54	54	54
del(17p), %	6	5	8
del(11q), %	21	19	18
IGHV-unmut, %	61	63	58
Complex karyotype, %	36	24	27

Safety, cont.	Ibr-R	Ibr	BR
Grade ≥3 nonhematologic AEs, n (%)	74	74	63
Hypertension	34	29	14
Infection	20	21	15
Bleeding	3	2	0
Febrile neutropenia	1	2	7
Atrial fibrillation	6	9	3
Unexplained or unwitnessed death, %	2	4	1

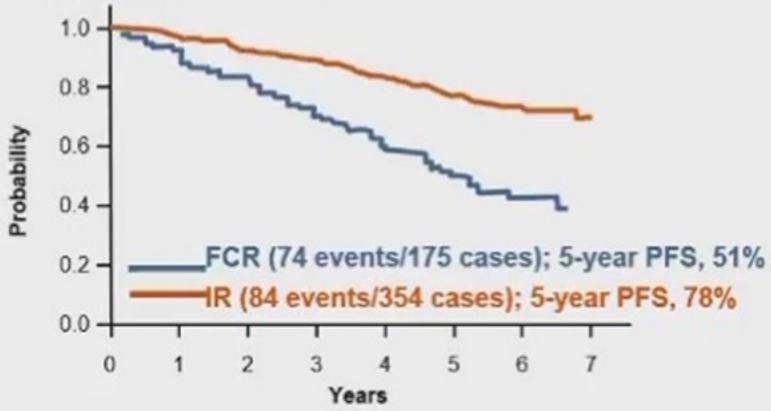
Woyach JA, et al. *N Engl J Med*. 2018;379(26):2517-2528, Woyach et al ASH 2021.

Phase 3 Data of IR vs FCR: PFS and Possibly Also OS Benefit of Continuous Ibrutinib-Based Therapy

ECOG 1912 (US)[1]

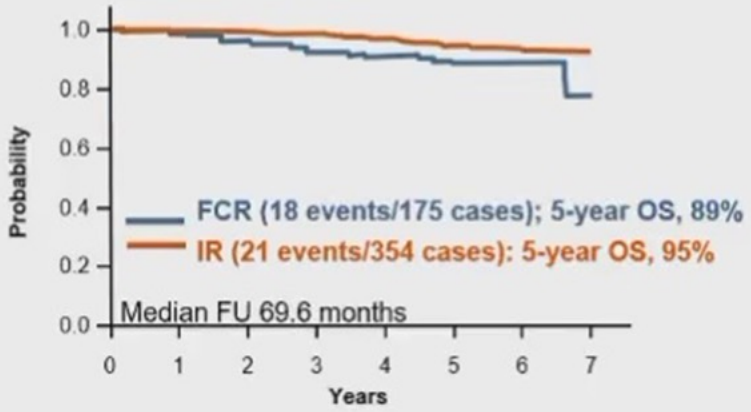
PFS

HR, 0.37 (95% CI, 0.27–0.51); *P* < 0.0001



OS

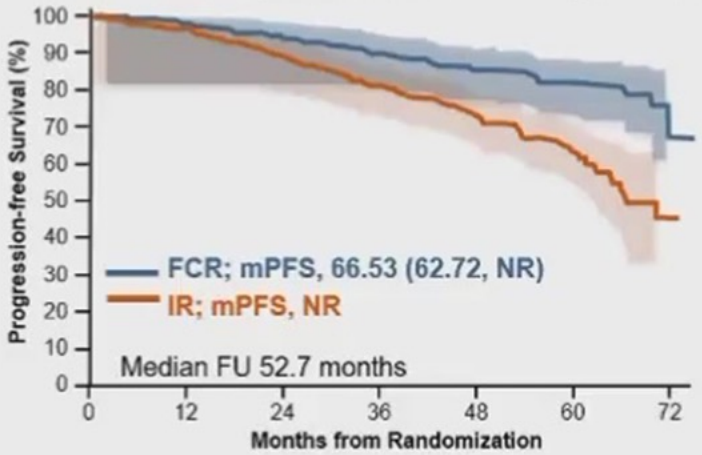
HR, 0.47 (95% CI, 0.25–0.89); *P* = 0.018



FLAIR (UK)[2]

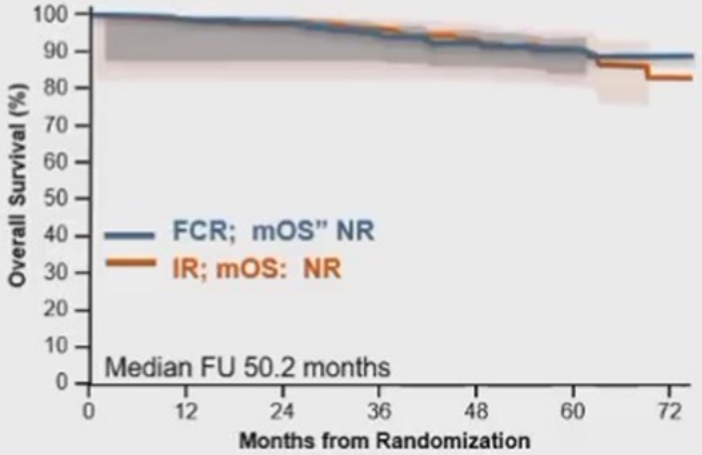
PFS

HR, 0.44 (95% CI, 0.32-0.60); *P* < 0.001



OS

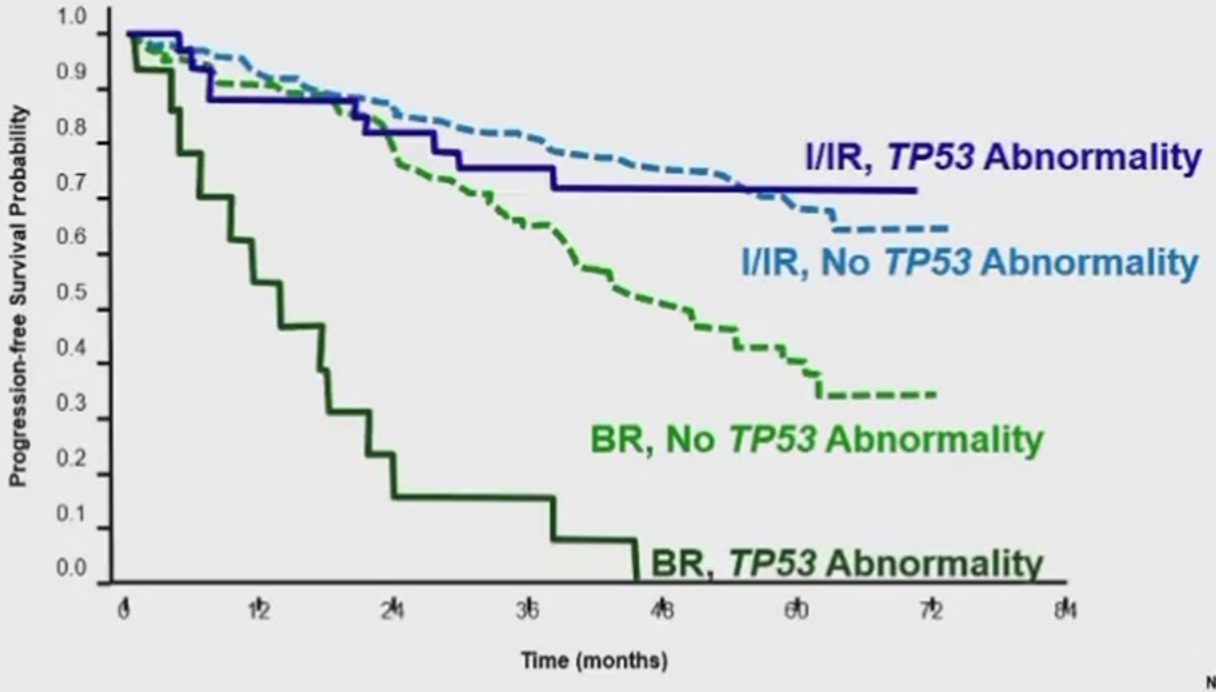
HR, 1.01 (95% CI, 0.61-1.68); *P* = 0.9560



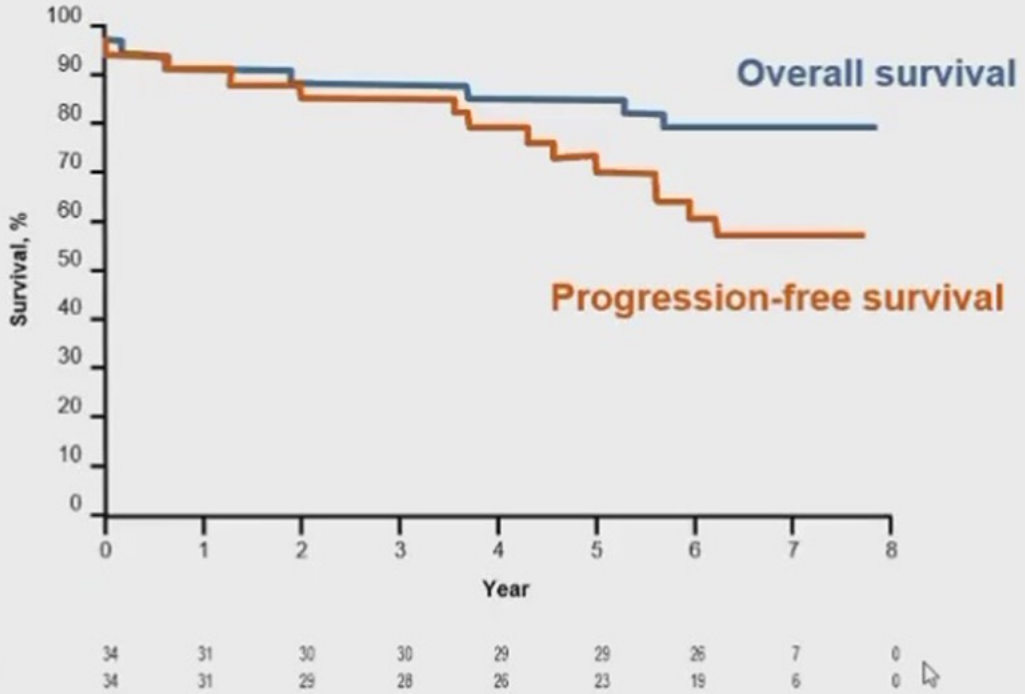
Shanafelt TD, et al. *Blood*. 2022;140(2):112-120. Hillmen, et al. *Blood*. 2021;138 (Supplement 1): 642.

Ibrutinib Can Provide Durable Response Even for *TP53* Aberrant CLL

ALLIANCE[1]
PFS with or without *TP53*

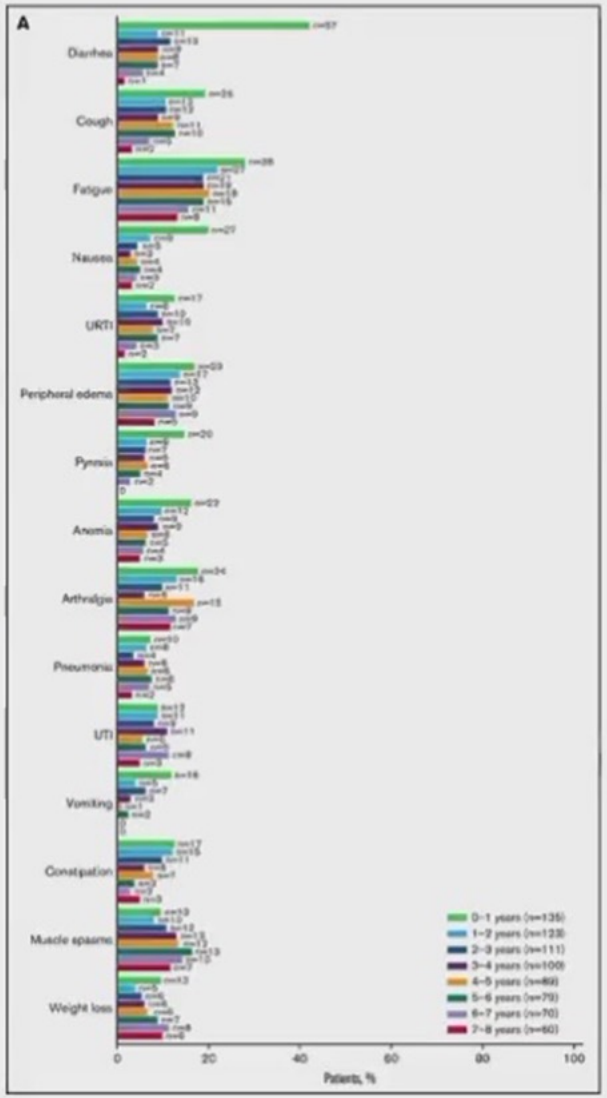


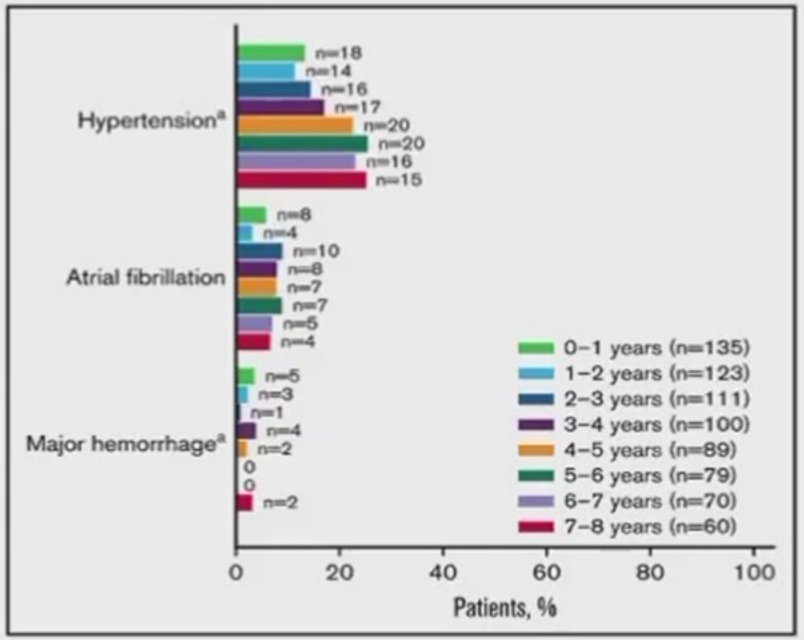
NHLBI[2]
Overall and Progression-free Survival



1. Woyach JA, et al. *Blood*. 2021; 138 (Supplement 1): 639. 2. Ahn IE, et al. *N Engl J Med*. 2020;383(5):498-500

But discontinuation rates with ibrutinib are high, and are due mostly to AEs

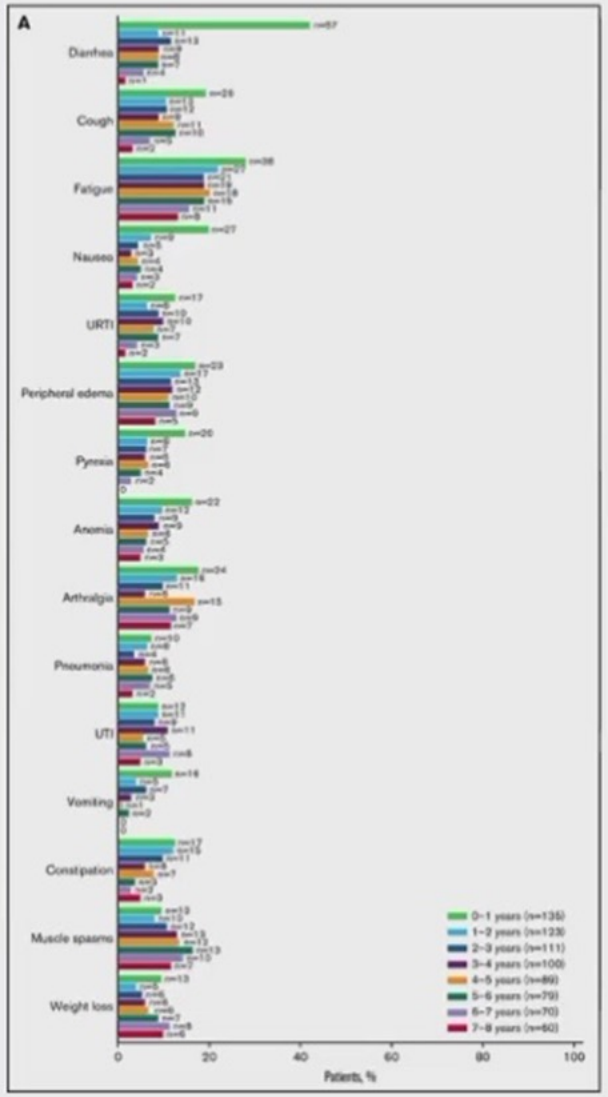




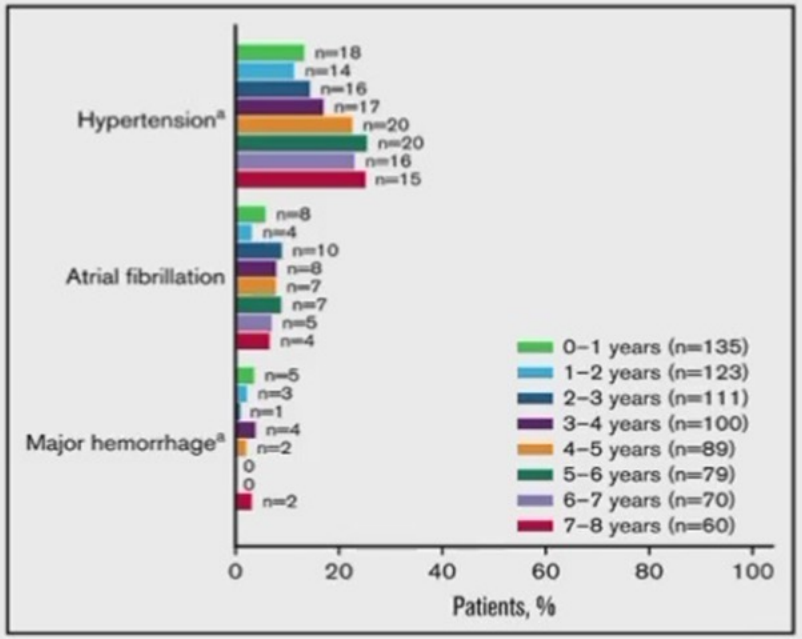
- 42% of patients still on ibrutinib at 8 years
- Most common reason for discontinuation was AEs (24%)

Barr et al., *Blood Advances*, 2022

But discontinuation rates with ibrutinib are high, and are due mostly to AEs



Barr et al., *Blood Advances*, 2022



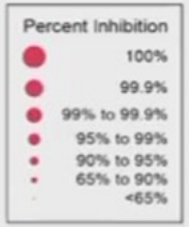
- 42% of patients still on ibrutinib at 8 years
- Most common reason for discontinuation was AEs (24%)

- Discontinuation due to AEs may be even more common in the real-world setting (41% discontinuation at median of 17 mo.)

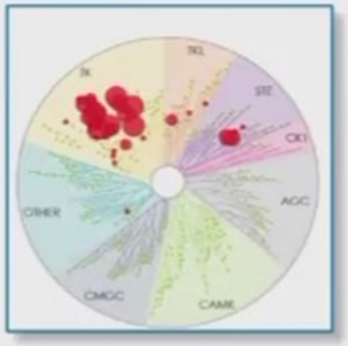
Mato et al., *Haematologica*, 2018

BTK Inhibitors Exhibit Differences in Kinase Selectivity

Covalent BTKi



Ibrutinib



Acalabrutinib

Zanubrutinib

Kaptein A, de Bruin G, Emmelot-van Hoek M, et al. *Blood*. 2018;132(Suppl 1):1871.

Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in TN CLL

4-Year Follow-Up of ELEVATE-TN

RANDOMIZED 1:1:1

Acalabrutinib + Obinutuzumab (A+O)
Acala 100 mg PO BID until PD or unacceptable toxicity
6 cycles

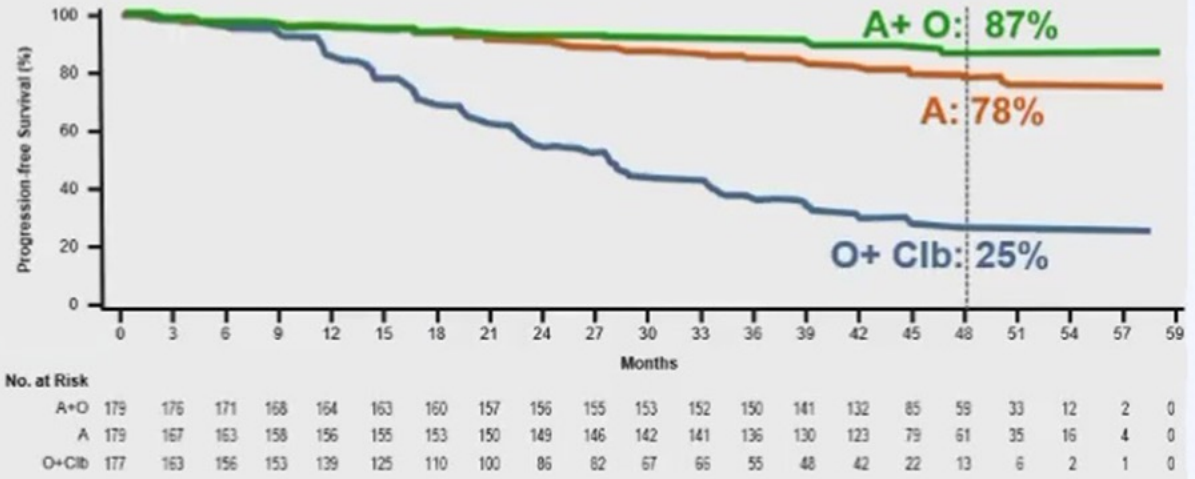
Acalabrutinib Monotherapy (A)
Acala 100 mg PO BID until PD or unacceptable toxicity
Crossover from O+Clb to A allowed after IRC-confirmed PD

Obinutuzumab + Chlorambucil (O+Clb)
6 cycles

Primary endpoint: IRC-assessed PFS (A+O vs O+Clb)
Secondary endpoints: IRC-assessed PFS (A vs O+Clb), INV-assessed PFS, ORR, TTNT, OS, uMRD, safety

Key Eligibility Criteria
- Age ≥65 years or >18 to <65 years with comorbidities (defined as CrCl 30-69 mL/min and CIRS-G >6)
- Untreated CLL requiring treatment per iwCLL 2008 criteria
- ECOG PS ≤2
- No significant cardiovascular disease

INV-Assessed PFS Overall



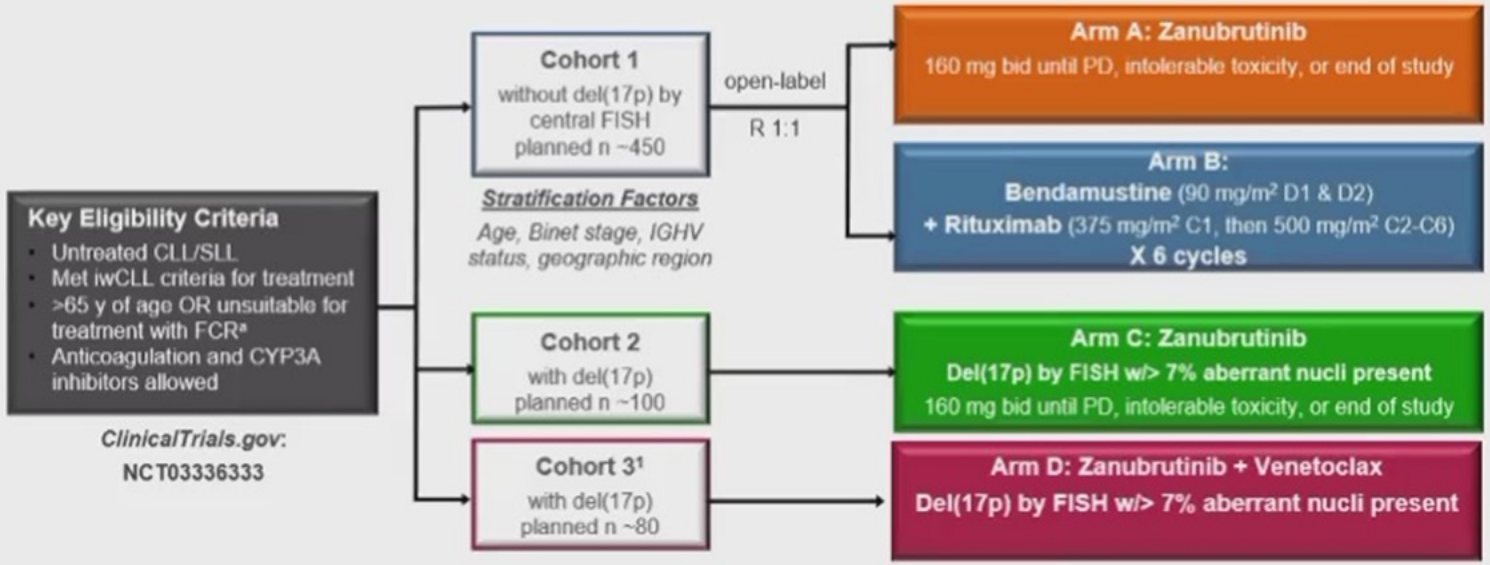
No. at Risk

A+O	179	176	171	168	164	163	160	157	156	155	153	152	150	141	132	85	59	33	12	2	0
A	179	167	163	158	156	155	153	150	149	146	142	141	136	130	123	79	61	35	16	4	0
O+Clb	177	163	156	153	139	125	110	100	86	82	67	66	55	48	42	22	13	6	2	1	0

	HR (95% CI)	*P*
A+O vs O+Clb	0.10 (0.07, 0.17)	< 0.0001
A vs O+Clb	0.19 (0.13, 0.28)	< 0.0001
A+O vs A	0.56 (0.32, 0.95)	< 0.0001

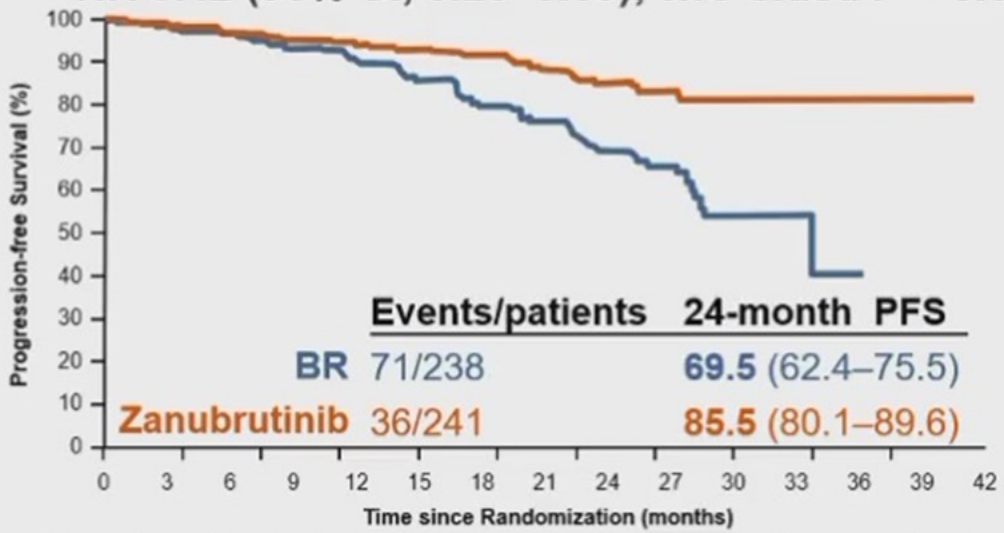
Sharman JP, et al. *Leukemia*. 2022;36(4):1171-1175.

Zanubrutinib: *Phase 3 SEQUOIA Study*

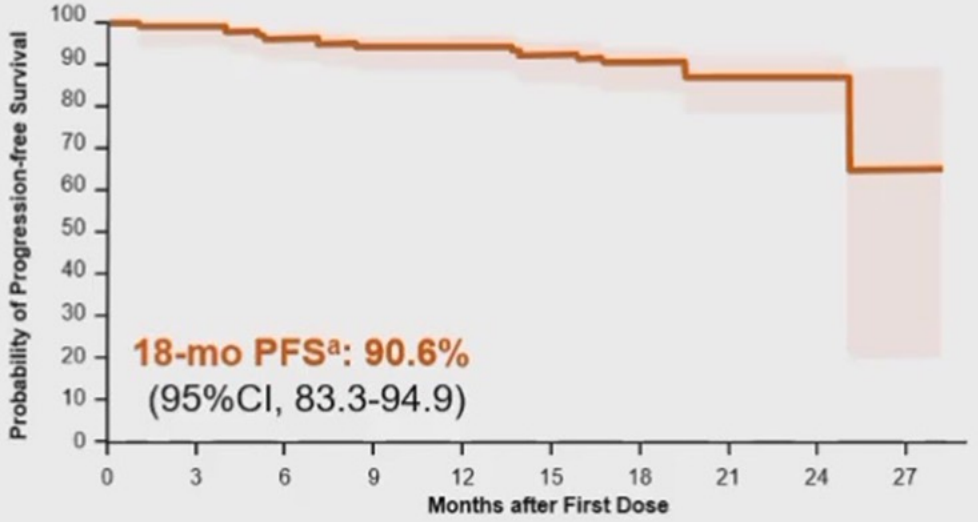


Zanu vs BR PFS in non-del(17p)[1]

HR 0.42 (95% CI, 0.28–0.63); two-sided *P* < 0.0001

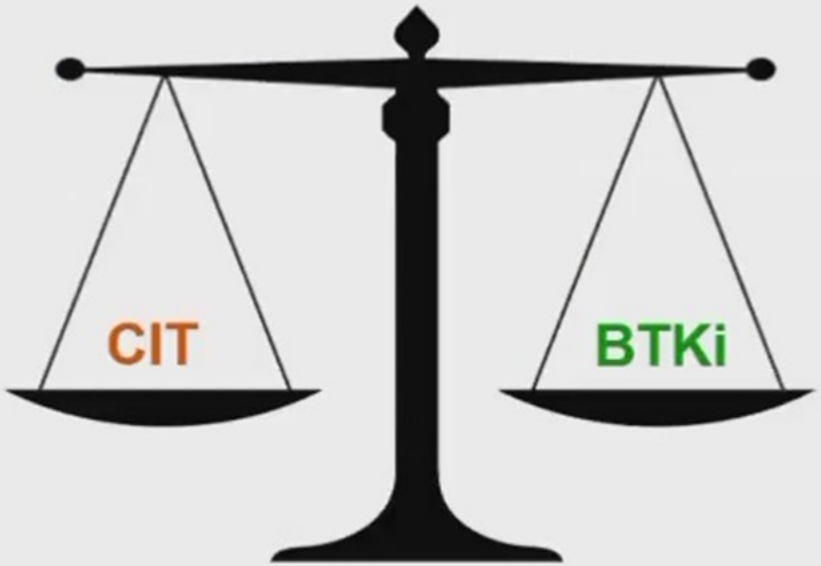


Zanu PFS in del(17p)[2]



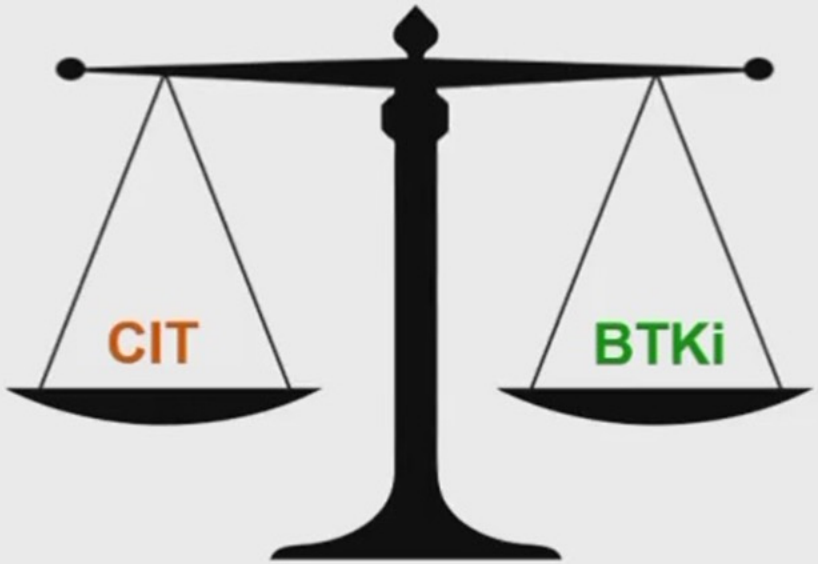
1. Tam, et al. *Lancet Oncology*. 2022;23(8):1031-1043; 2. Brown JR, et al. *Blood*. 2020; 136 (Supplement 1): 11–12

Frontline BTKi vs CIT: Factors to Consider



- 6 months time-limited therapy
- No significant cardiac or bleeding risks
- Less concern for long-term adherence
- Cost-saving
- *Risks of secondary myeloid neoplasms, clonal evolution*

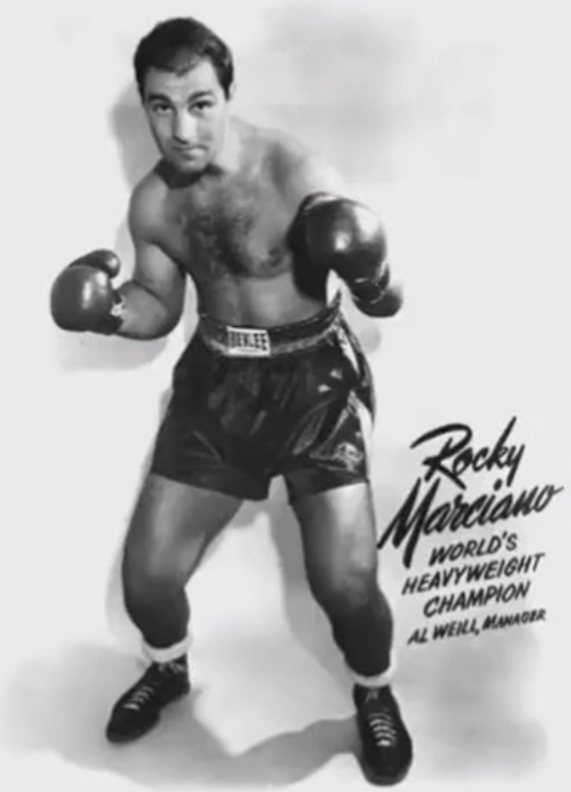
Frontline BTKi vs CIT: Factors to Consider



- 6 months time-limited therapy
- No significant cardiac or bleeding risks
- Less concern for long-term adherence
- Cost-saving
- *Risks of secondary myeloid neoplasms, clonal evolution*

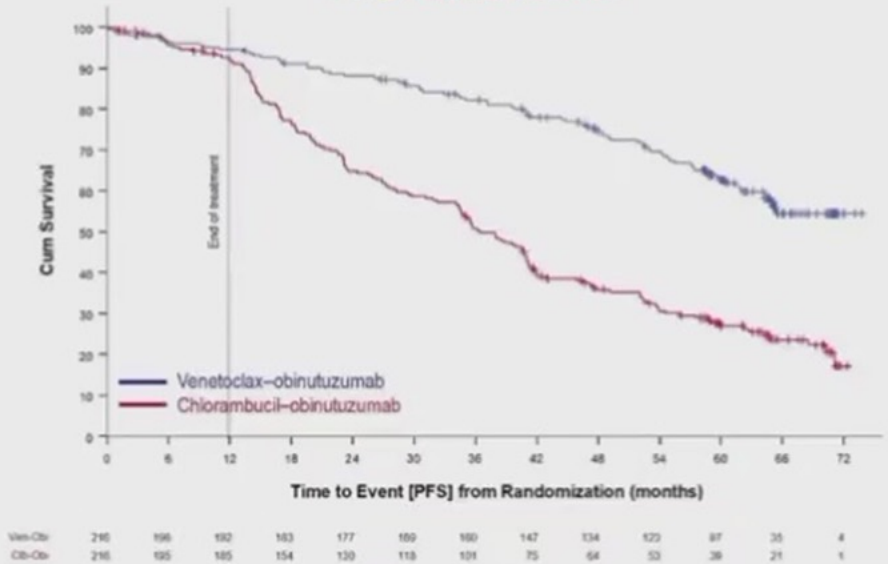
- Convenience (no infusions)
- Lower rates of cytopenias and infections
- Clearly more effective for IGHV unmutated
- Even works well for *TP53* aberrant!
- *Resistance mutations have been described*

2019-2022
The Rise of Time-Limited Novel Agent-Only Therapy
The Readout of the Head-to-Head BTKi Studies



5-year follow-up of Ven-Obin in CLL14 in frontline CLL

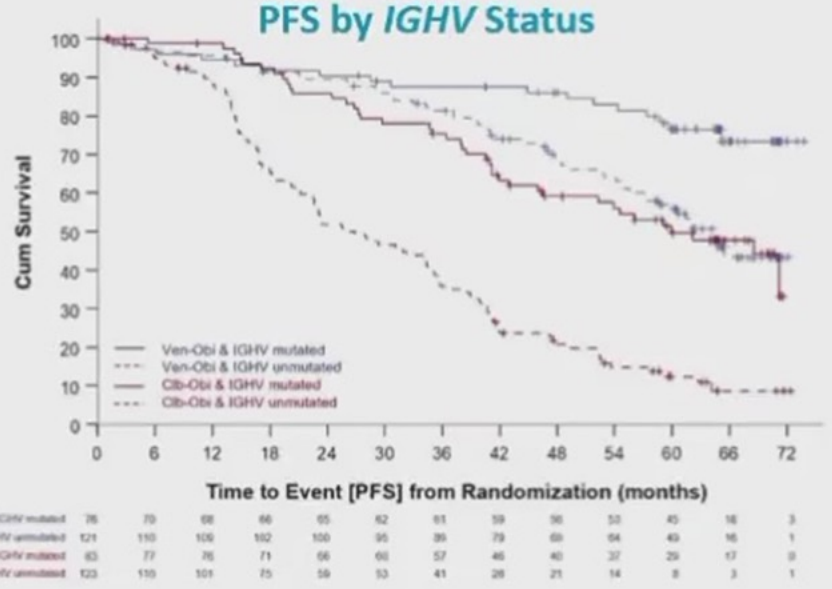
PFS: All Patients



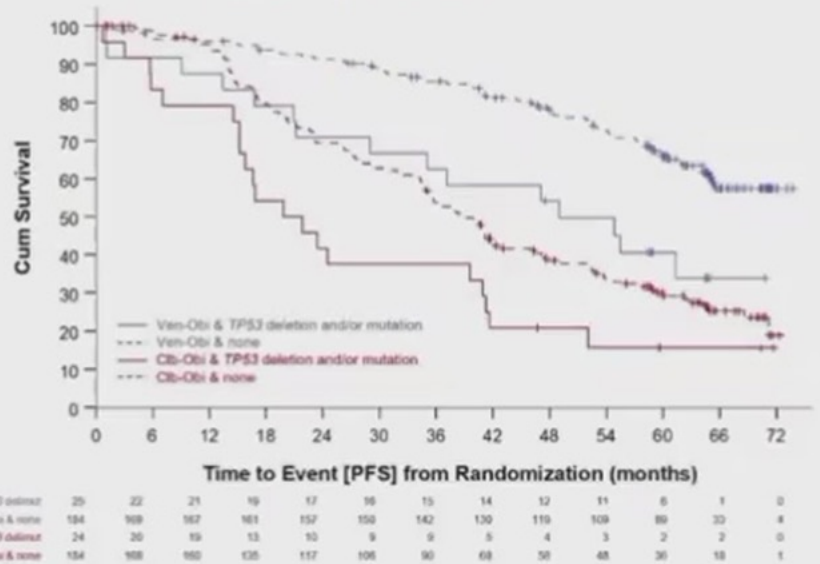
PFS by Subgroup		Ven-Obi (n=216)	Clb-Obi (n=216)
All patients	Median, months	NR	36.4
	5-year rate, %	62.6	27.0
	HR (95% CI); P value	0.35 (0.26-0.46); <0.0001	
Median, months			
TP53 del/mut	No	NR (n=184)	38.9 (n=184)
	Yes	49.0 (n=25)	19.8 (n=24)
IGHV status	Mut	NR (n=76)	59.9 (n=83)
	Unmut	64.2 (n=121)	26.9 (n=123)

Median observation time: 65.4 months

PFS by *IGHV* Status

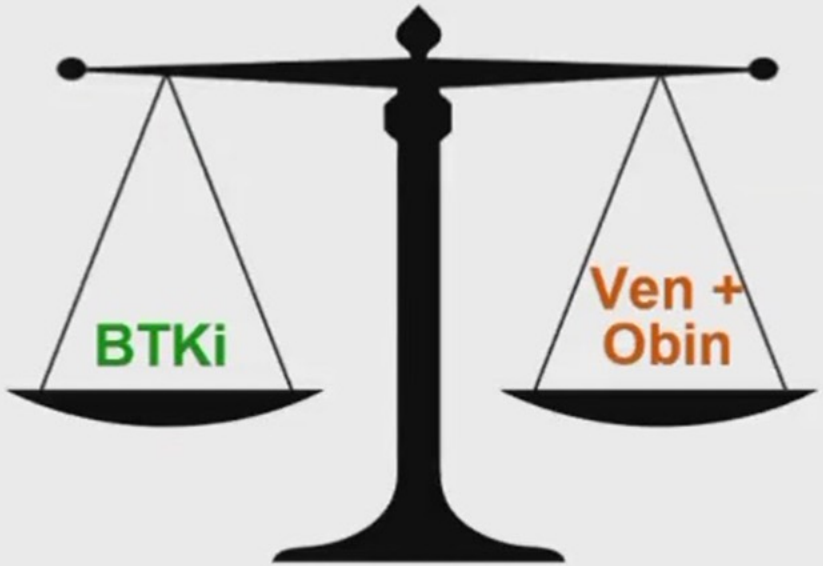


PFS by *TP53* Status



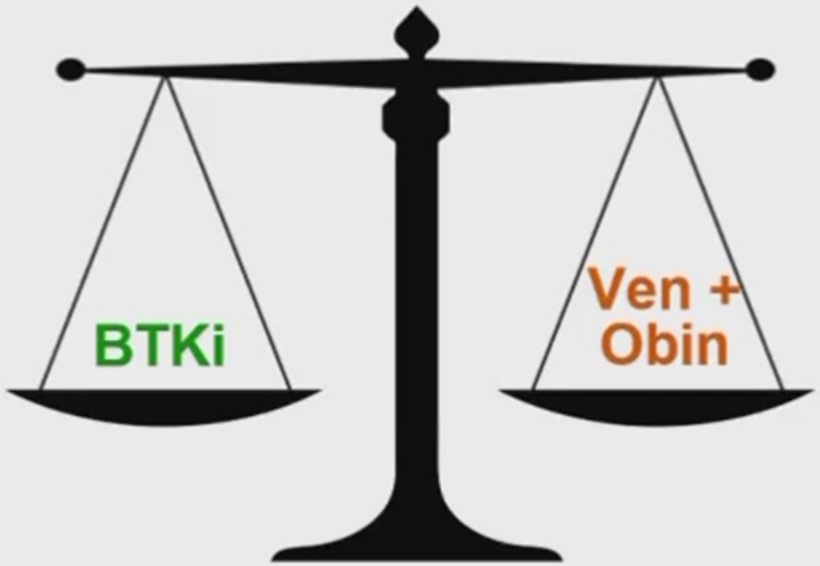
Al-Sawaf O, et al. EHA 2022. Abstract S148.

Frontline BTKi vs Ven + Obin: Factors to Consider



- Convenience (no infusions, TLS monitoring)
- Longer-term efficacy data
- Phase 3 data compared to FCR and BR
- More data for efficacy of ven at time of BTKi progression (ibrutinib)

Frontline BTKi vs Ven + Obin: Factors to Consider



- Convenience (no infusions, TLS monitoring)
- Longer-term efficacy data
- Phase 3 data compared to FCR and BR
- More data for efficacy of ven at time of BTKi progression (ibrutinib)

- 1-year time-limited therapy
- No known cardiac or bleeding risks
- Less concern for long-term adherence
- Potential for re-treatment
- Cost-saving

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in Patients With R/R CLL – Study Design and Patient Characteristics[1,2]

N=533

Enrolled from[2]:
- Europe (75%)
- US (22%)
- New Zealand and Australia (3%)

Stratification by
- Presence of del(17p)
- ECOG PS (2 vs ≤1)
- Number of prior therapies (1-3 vs ≥4)

Primary endpoint:
PFS by IRC
- Noninferiority[a]; tested after 250 events

Secondary endpoints[b]
- Incidence of atrial fibrillation
- Incidence of grade ≥3 infections
- Incidence of Richter's transformation
- OS

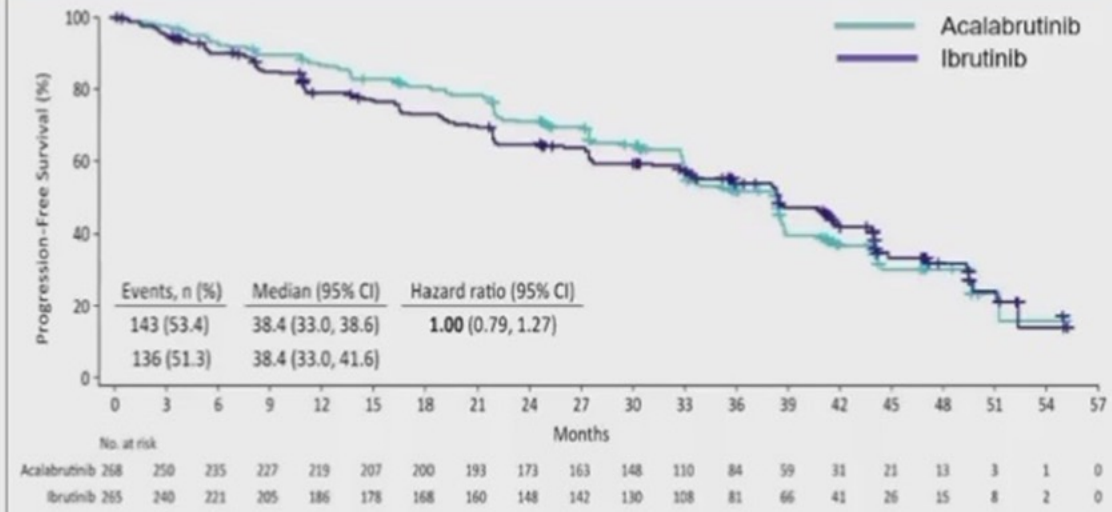
Patient Characteristics[2]	Acalabrutinib (n=268)	Ibrutinib (n=265)
Median age (range), years	66 (41-89)	65 (28-88)
≥75 years, n (%)	44 (16.4)	43 (16.2)
ECOG PS 0-1, n (%)	247 (92.2)	243 (91.7)
Median prior lines of therapy (range), n	2 (1-9)	2 (1-12)
≥4 prior lines, n (%)	33 (12.3)	28 (10.6)
del(17p), n (%)	121 (45.1)	120 (45.3)
TP53mut, n (%)	100 (37.3)	112 (42.3)
del(11q), n (%)	167 (62.3)	175 (66.0)
Unmutated IGHV, n (%)	220 (82.1)	237 (89.4)
Complex karyotype, n (%)	124 (46.3)	125 (47.2)
Bulky disease (≥5 cm), n (%)	128 (47.8)	136 (51.3)

[a] Noninferiority achieved if the upper bound of the 95% CI of HR is less than the prespecified NI margin of 1.429.
[b] If noninferior PFS achieved, the secondary endpoints will be tested in a manner that maintains the type I error rate at ≤5%.

1. Hillmen P, et al. EHA 2021. Abstract S145. **2.** Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in Patients With R/R CLL – Efficacy and Post Hoc Safety Analysis[1,2]

Primary Endpoint: Noninferiority on IRC-Assessed PFS (Median Follow-Up: 40.9 Months)



Median follow-up	Treatment ongoing	Most common reasons for discontinuation	Median treatment exposure (range)
40.9 months	46 (Acala) and 41 (Ibr)	PD (31 Acala vs 26 Ibr), AEs (15 Acala vs 22 Ibr)	38.3 mo (0.3-55.9) Acala vs 35.5 mo (0.2-57.7) Ibr

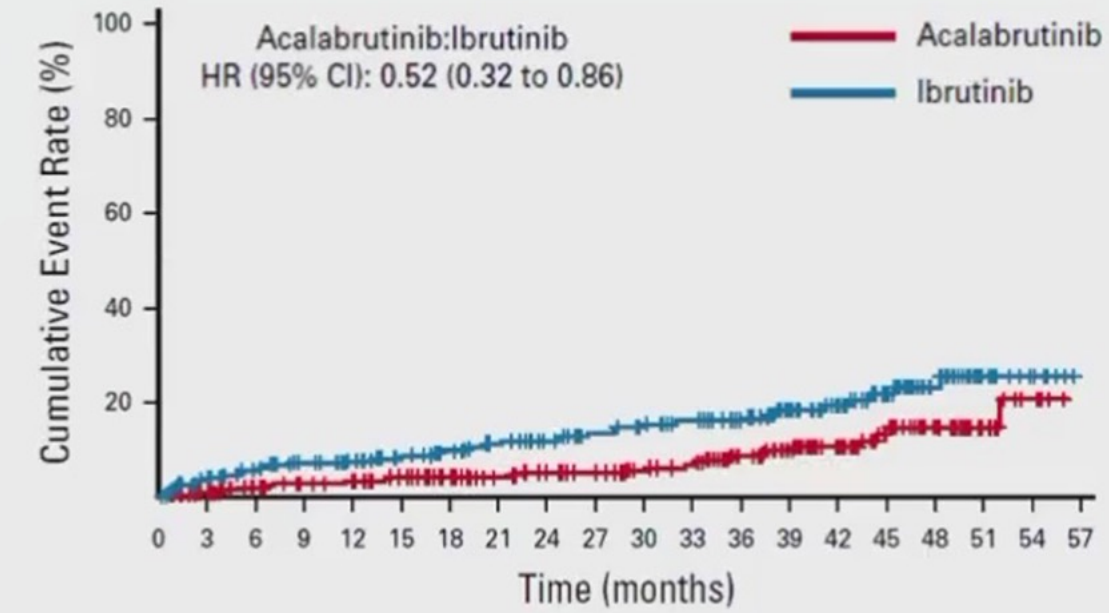
AEs	Any grade		Grade ≥3	
	Acala[a]	Ibr[b]	Acala[a]	Ibr[b]
Events of clinical interest, %				
Cardiac events	24	30	9	10
Atrial fibrillation/flutter	9	16*	5	4
Hypertension[c]	9	23*	4	9*
Bleeding events[d]	38	51*	4	5
Major bleeding events[e]	5[f]	5[g]	4	5
Infections[h]	78	81	31	30
Selected common AEs[i], %				
Diarrhea	35	46*	1	5*
Headache	35*	20	2*	0
Cough	29*	21	1	<1
Fatigue	20	17	3*	0
Arthralgia	16	23*	0	1
Back pain	8	13*	0	1
Muscle spasms	6	13*	0	1
Dyspepsia	4	12*	0	0

[a] n=266. [b] n=263. [c] Includes hypertension, blood pressure increased, and blood pressure systolic increased. [d] Bleeding events occurring in ≥10% of patients in either treatment arm include contusion and epistaxis. [e] Any hemorrhagic event that was serious, grade ≥3, or a CNS hemorrhage (any grade). [f] Of 12 patients with major hemorrhage events in the Acala arm, CNS-related hemorrhage events were reported in 4 patients. [g] Of 14 patients with major hemorrhage events in the Ibr arm, CNS-related hemorrhage events were reported in 1 patient who had 2 events. [h] Infections occurring in ≥10% of patients in either treatment arm include upper respiratory tract infection, pneumonia, bronchitis, nasopharyngitis, and urinary tract infection. [i] AEs occurring in ≥10% of patients in either treatment arm that are not already captured in the ECIs presented.

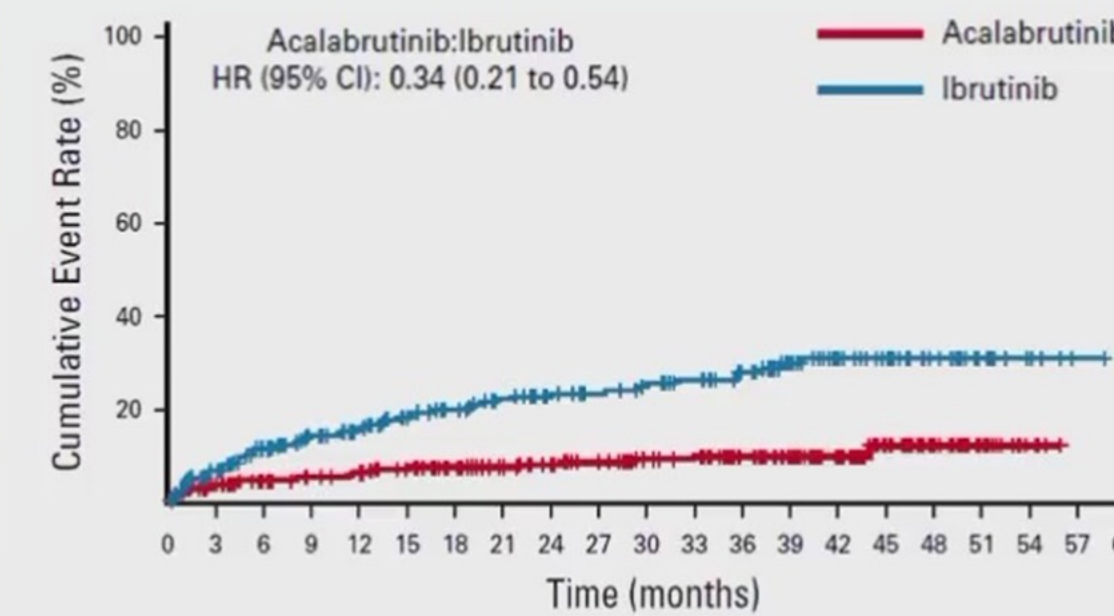
1. Hillmen P, et al. EHA 2021. Abstract S145. **2.** Seymour JF, et al. ASH 2021. Abstract 3721.

ELEVATE-RR: Phase 3 Study of Acalabrutinib vs Ibrutinib in Patients With R/R CLL – Additional Safety Analysis

Cumulative Incidence of Atrial Fibrillation/Flutter



Cumulative Incidence of Hypertension



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

ALPINE: Phase 3 Study of Zanubrutinib vs Ibrutinib in Patients With R/R CLL/SLL – Study Design and Patient Characteristics

Key Eligibility Criteria

- Patients with R/R CLL/SLL with ≥1 prior treatment
- Measurable lymphadenopathy
- No prior BTKi or warfarin/other vitamin K antagonists permitted

N=652 randomized

Enrolled from[2]:

- Europe (60%)
- US (17%)
- China (14%)
- New Zealand and Australia (9%)

Stratification by:

- Age
- Geographic region
- Refractory status
- Del(17p)/*TP53* mutation status

Primary endpoint

- ORR (CR+PR) noninferiority and INV-assessed superiority

Secondary endpoints

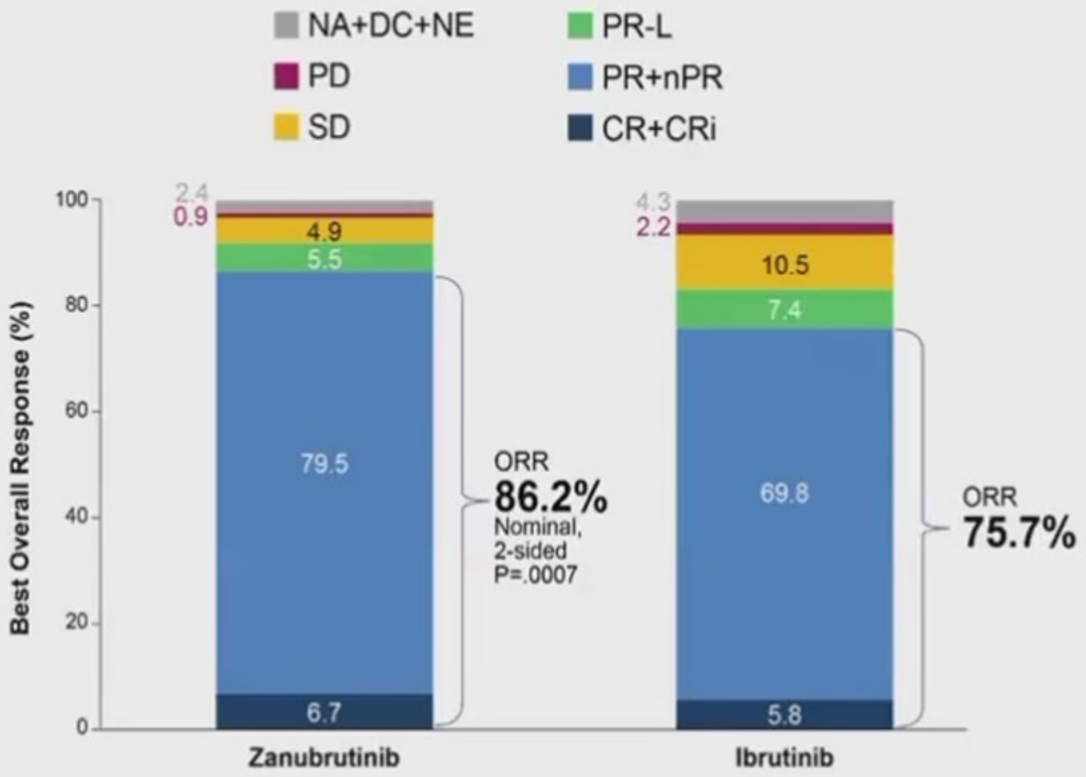
- Any grade Afib
- DOR
- PFS
- OS
- TTF
- PR-L or higher
- PROs
- Safety

Patient Characteristics	Zanubrutinib (n=327)	Ibrutinib (n=325)
Median age (range), years	67 (35-90)	68 (35-89)
≥65 years, n (%)	201 (61.5)	200 (61.5)
ECOG PS ≥1, n (%)	198 (60.6)	203 (62.5)
Median prior lines of therapy (range), n	1 (1-6)	1 (1-12)
>3 prior lines, n (%)	24 (7.3)	30 (9.2)
del(17p) and *TP53*mut, n (%)	75 (22.9)	75 (23.1)
del(17p)±*TP53*mut	45 (13.8)	50 (15.4)
*TP53*mut without del(17p)	30 (9.2)	25 (7.7)
del(11q), n (%)	91 (27.8)	88 (27.1)
Unmutated IGHV, n (%)	239 (73.1)	239 (73.5)
Complex karyotype, n (%)	56 (17.1)	70 (21.5)
Bulky disease (≥5 cm), n (%)	145 (44.3)	149 (45.8)

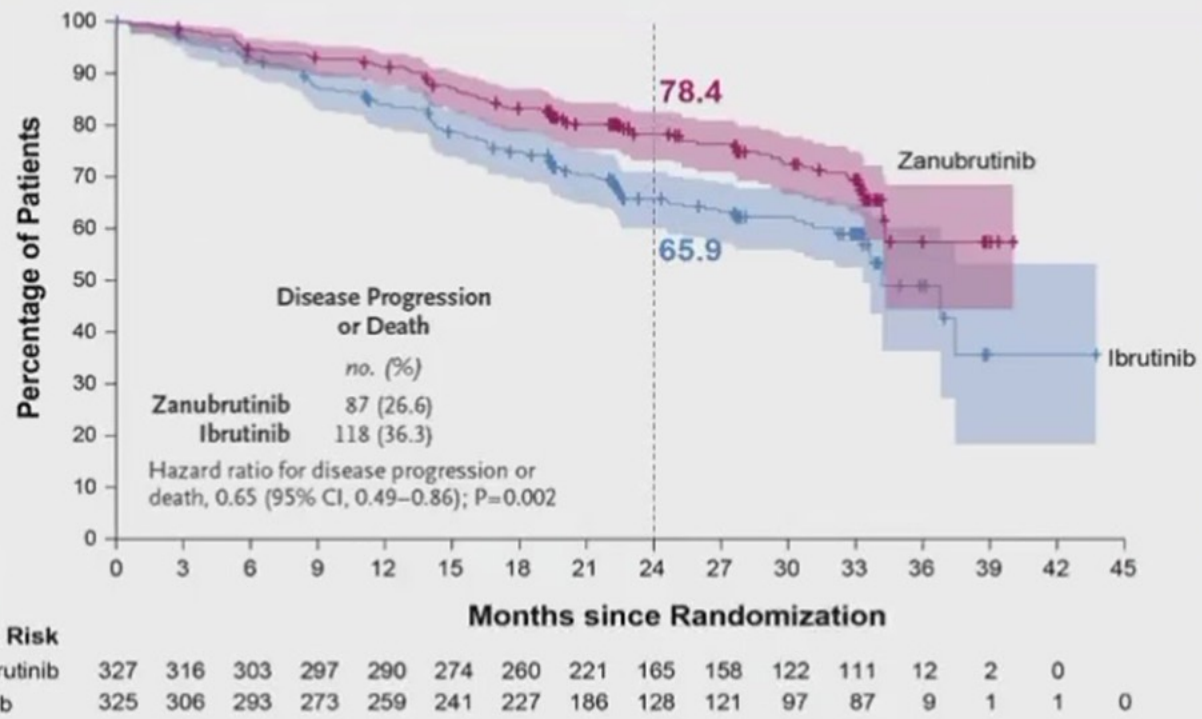
Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

ALPINE: Phase 3 Study of Zanubrutinib vs Ibrutinib in Patients With R/R CLL/SLL – Final Analysis of Efficacy

Best Overall Response



INV-Assessed PFS (Median Follow-Up: 29.6 Months)



No. at Risk

Zanubrutinib	327	316	303	297	290	274	260	221	165	158	122	111	12	2	0	
Ibrutinib	325	306	293	273	259	241	227	186	128	121	97	87	9	1	1	0

Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

ALPINE: Phase 3 Study of Zanubrutinib vs Ibrutinib in Patients With R/R CLL/SLL – Safety

Safety Population Summary[a]	Zanubrutinib (n=324)	Ibrutinib (n=324)
Median treatment duration, mo (range)	28.4 (0.4-41.6)	24.3 (0.1-45.1)
Any grade TEAE, n (%)	318 (98.1)	321 (99.1)
Grade ≥3	218 (67.3)	228 (70.4)

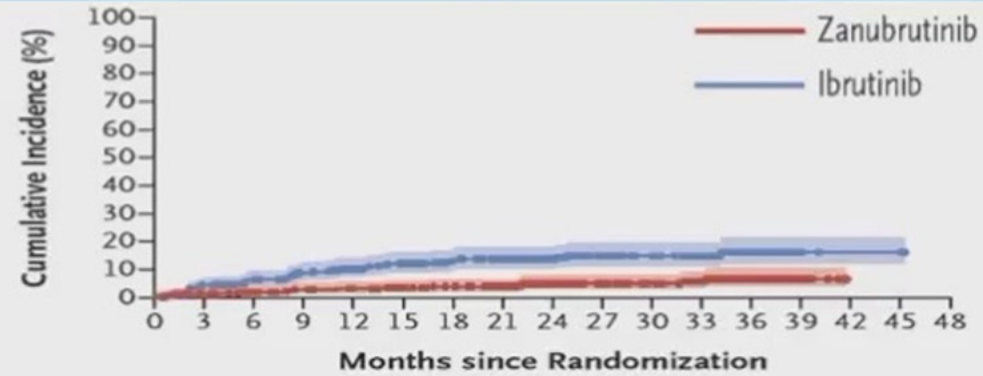
	Any grade		Grade ≥3	
	Zanubrutinib (n=324)	Ibrutinib (n=324)	Zanubrutinib (n=324)	Ibrutinib (n=324)
AEs of special interest, n (%)	294 (90.7)	300 (92.6)	186 (57.4)	184 (56.8)
Anemia	50 (15.4)	53 (16.4)	7 (2.2)	8 (2.5)
Atrial fibrillation/flutter	17 (5.2)	43 (13.3)	8 (2.5)	13 (4.0)
Hemorrhage	137 (42.3)	134 (41.4)	11 (3.4)	12 (3.7)
Major hemorrhage	12 (3.7)	14 (4.3)	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)
Neutropenia[b]	95 (29.3)	79 (24.4)	68 (21.0)	59 (18.2)
SPMs	40 (12.3)	43 (13.3)	22 (6.8)	17 (5.2)
Thrombocytopenia	42 (13.0)	50 (15.4)	11 (3.4)	17 (5.2)
Tumor lysis syndrome	1 (0.3)	0	1 (0.3)	0

Safety Population Summary[a]	Zanubrutinib (n=324)	Ibrutinib (n=324)
Grade ≥3 TEAEs reported in >2% of patients in either arm		
Neutropenia	52 (16.0)	45 (13.9)
Hypertension	48 (14.8)	36 (11.1)
COVID-19–related pneumonia	23 (7.1)	13 (4.0)
COVID-19	22 (6.8)	16 (4.9)
Pneumonia	19 (5.9)	26 (8.0)
Decreased neutrophil count	17 (5.2)	14 (4.3)
Syncope	9 (2.8)	4 (1.2)
Thrombocytopenia	9 (2.8)	12 (3.7)
Anemia	7 (2.2)	8 (2.5)
Atrial fibrillation	6 (1.9)	12 (3.7)
Increased blood pressure	4 (1.2)	10 (3.1)
Serious AEs		
All serious AEs	136 (42.0)	162 (50.0)
Leading to dose reduction	40 (12.3)	55 (17.0)
Leading to dose interruption	162 (50.0)	184 (56.8)
Leading to treatment d/c	50 (15.4)	72 (22.2)
Leading to death	33 (10.2)	36 (11.1)

Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

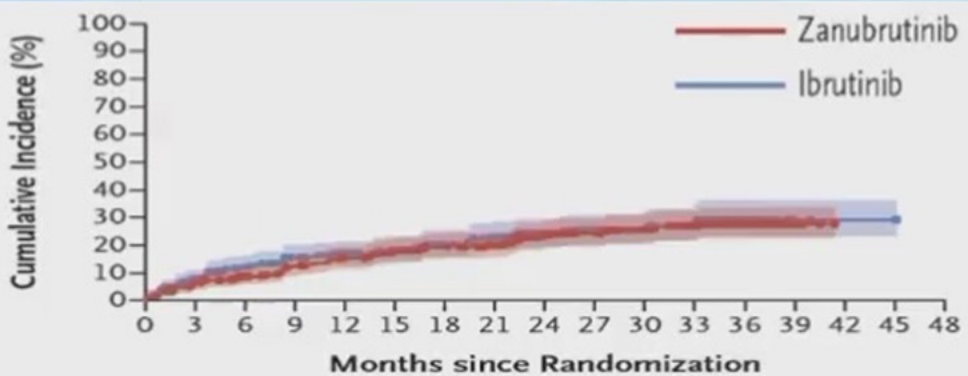
ALPINE: Phase 3 Study of Zanubrutinib vs Ibrutinib in Patients With R/R CLL/SLL – Additional Safety Analysis

Cumulative Incidence of Atrial Fibrillation/Flutter



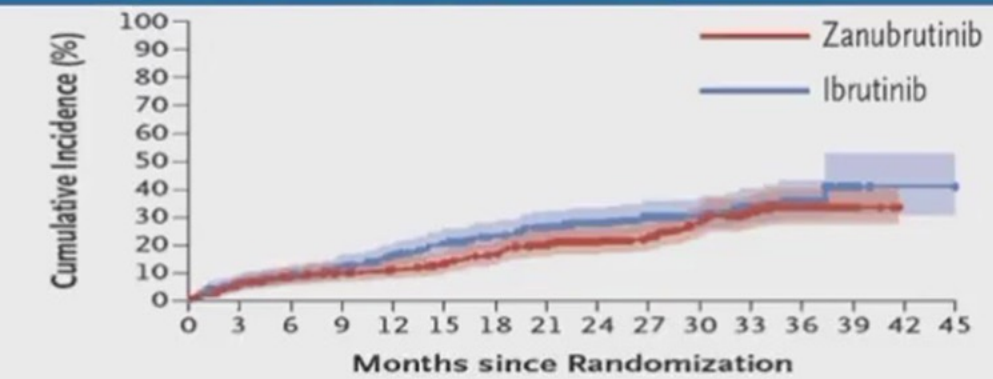
No. at Risk											
Zanubrutinib	324	302	288	268	199	148	51	10	0		
Ibrutinib	324	278	247	211	153	108	40	3	2	1	0

Cumulative Incidence of Hypertension



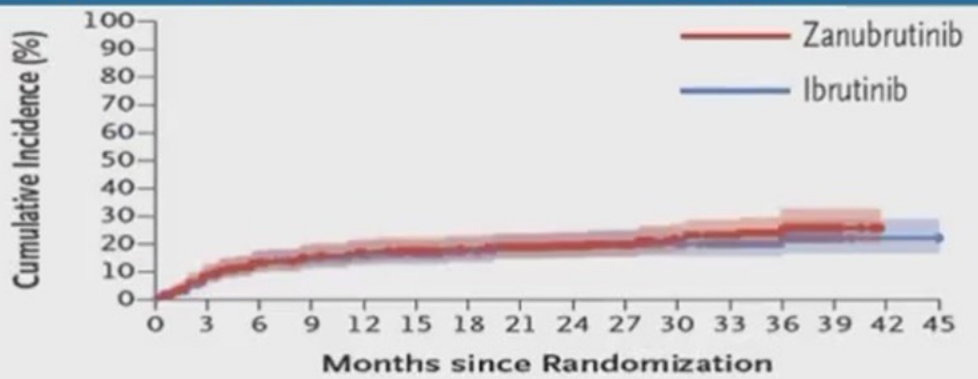
No. at Risk											
Zanubrutinib	324	280	248	221	157	115	35	6	0		
Ibrutinib	324	254	222	186	129	84	28	3	2	1	0

Cumulative Incidence of Grade ≥3 Infection



No. at Risk										
Zanubrutinib	324	289	272	247	180	125	40	7	0	
Ibrutinib	324	272	234	198	136	95	33	3	1	0

Cumulative Incidence of Grade ≥3 Neutropenia



No. at Risk										
Zanubrutinib	324	264	245	229	175	128	40	8	0	
Ibrutinib	324	253	225	199	143	101	37	3	1	0

Brown JR, et al. *N Engl J Med*. 2023;388(4):319-332.

A New Era of BTKi/BCL-2i (+/- CD20) Combination Therapy? 2023+

Summary of Mechanistic Synergies and Rationale for Combination BTKi/BCL-2i Therapy

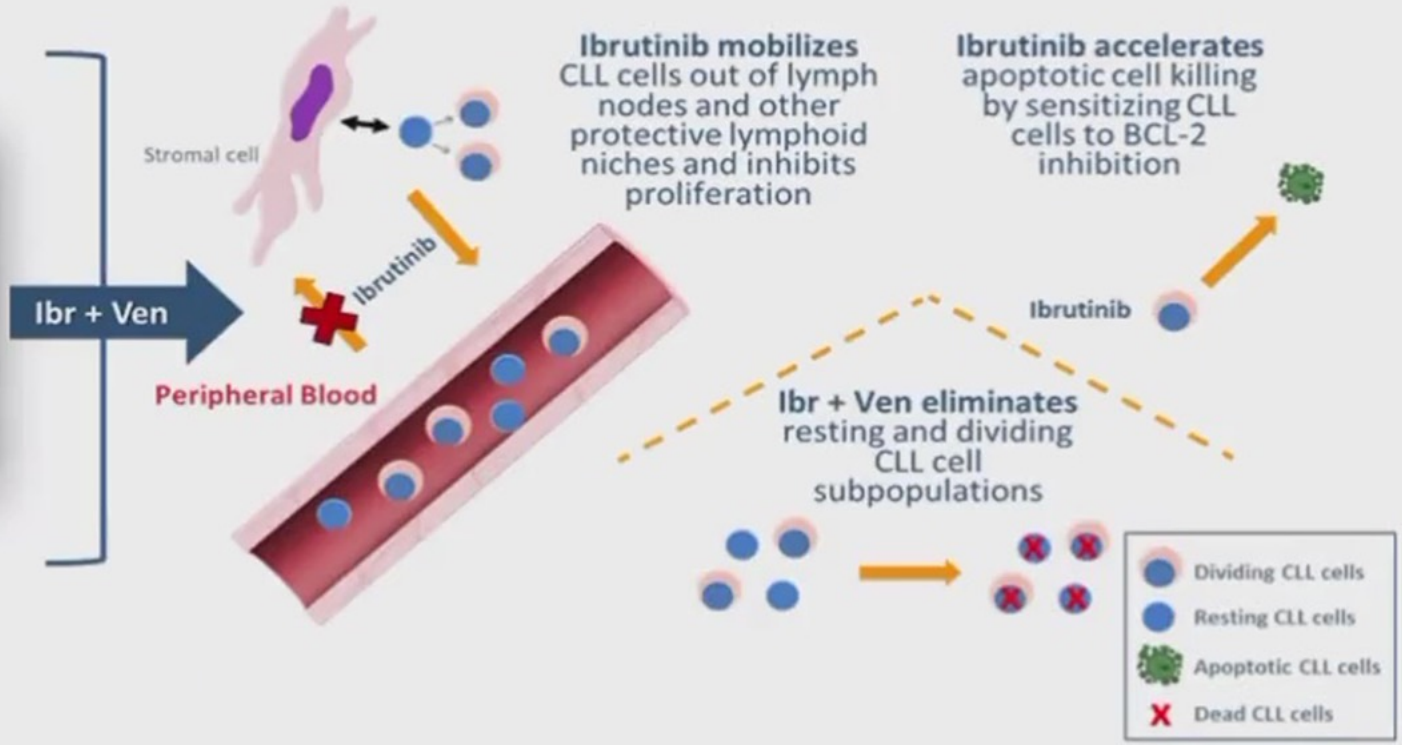
Leukemia (2017), 1–10

www.nature.com/leu

ORIGINAL ARTICLE

Bruton's tyrosine kinase inhibition increases BCL-2 dependence and enhances sensitivity to venetoclax in chronic lymphocytic leukemia

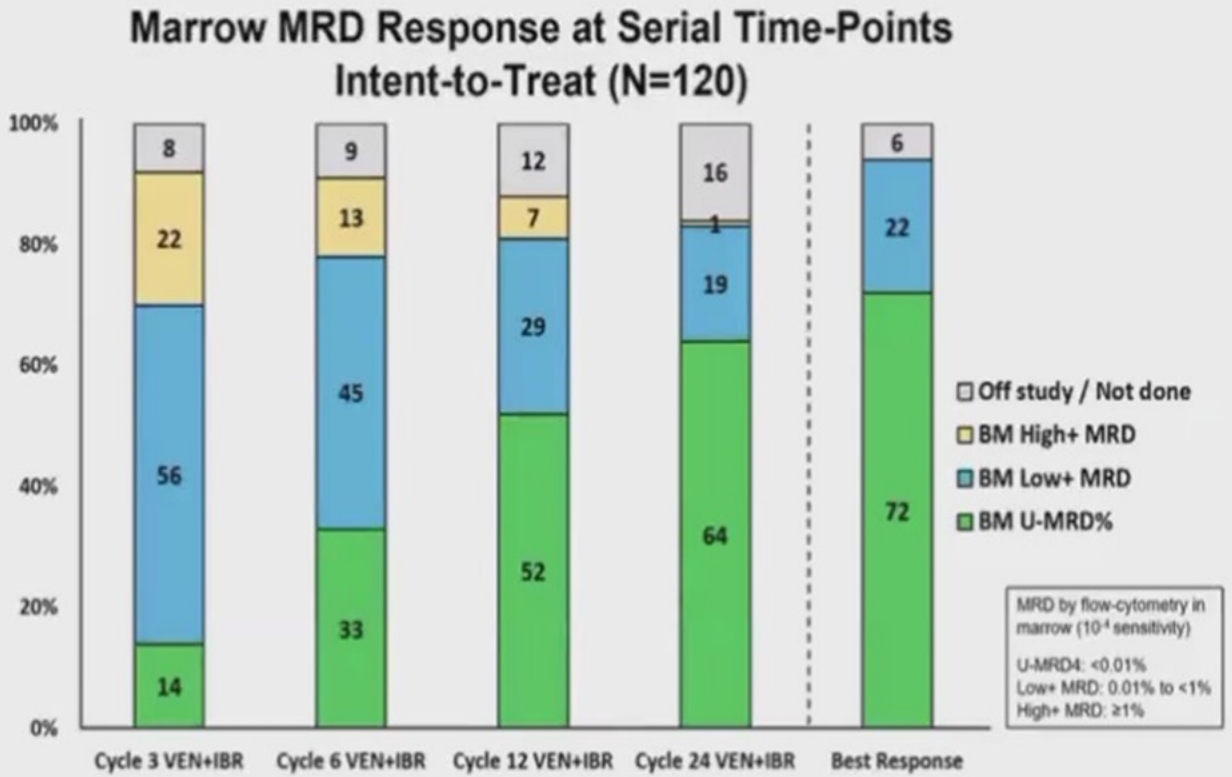
J Deng, E Isik, SM Fernandes, JR Brown, A Letai[1] and MS Davids[1]

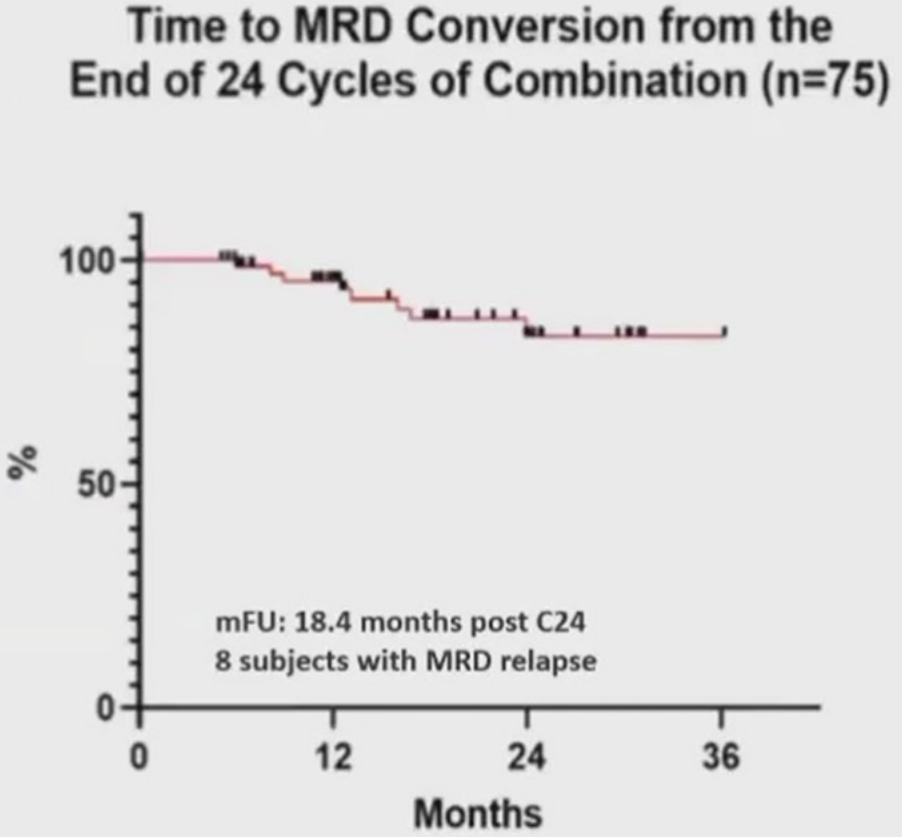


Deng et al., *Leukemia*, 2017

Adapted from: Allan et al EHA, 2021

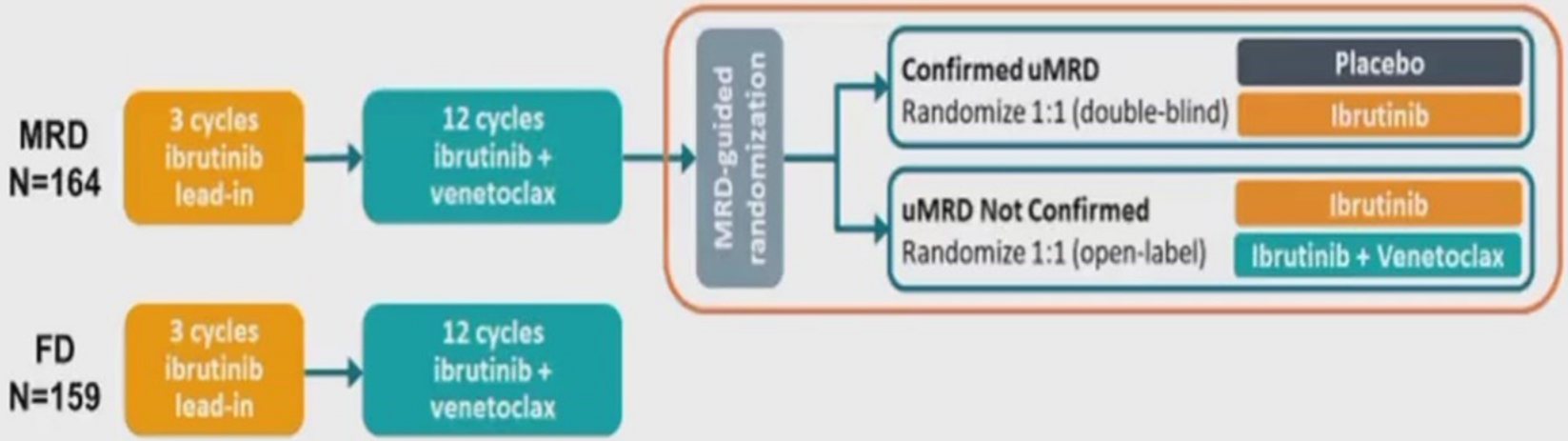
MD Anderson Ibr/Ven IST



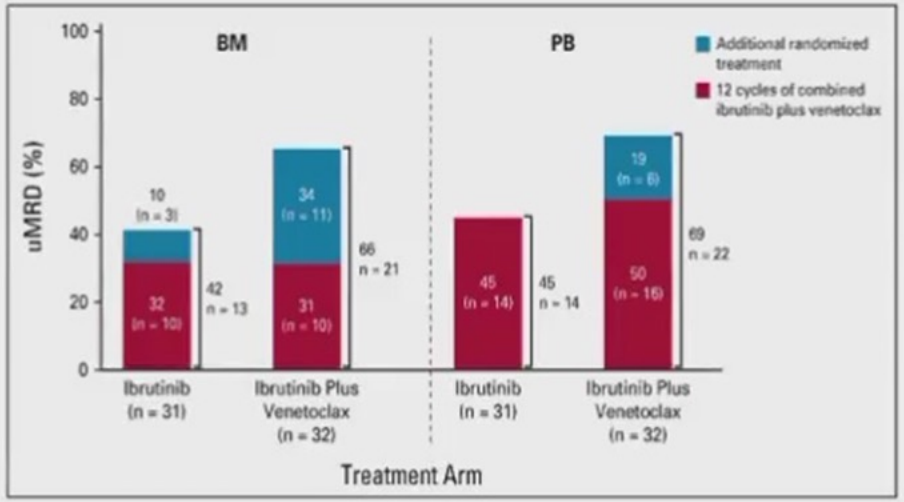


Jain et al., NEJM, 2019 and ASH 2021

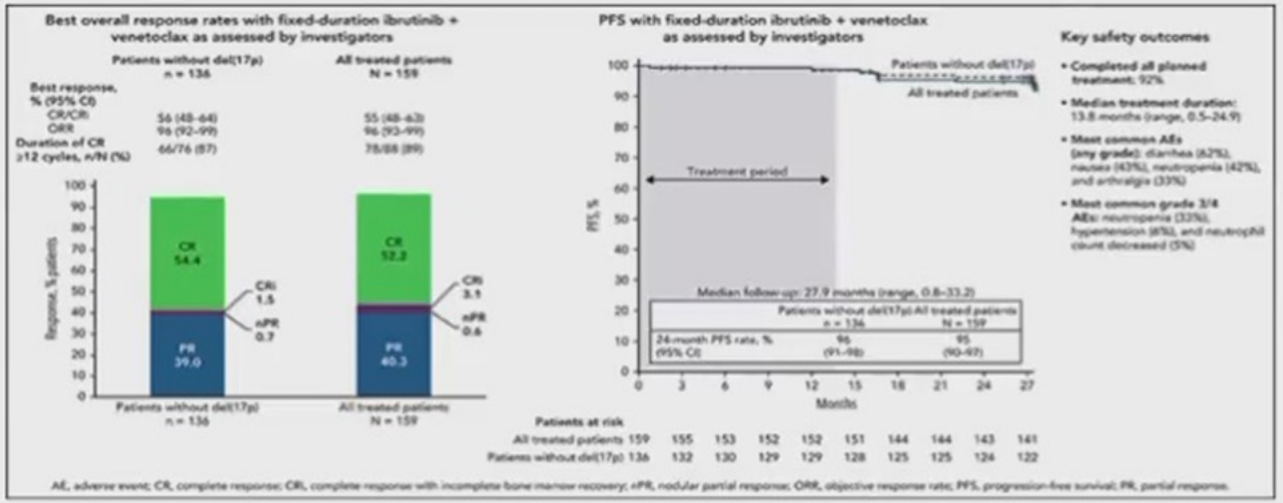
CAPTIVATE: Ibr/Ven in a younger, fit population



MRD Cohort



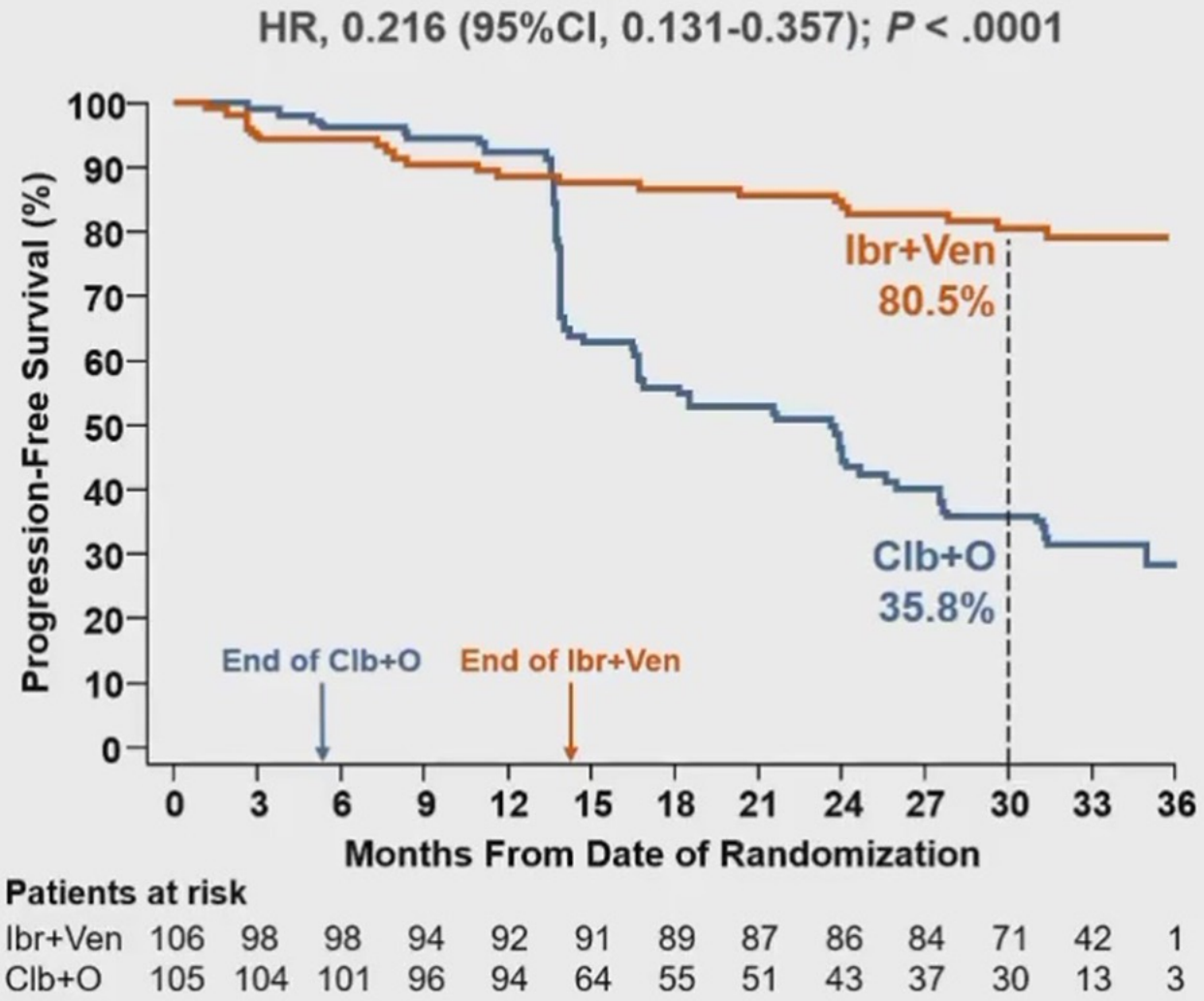
FD Cohort



MRD: Wierda et al., J Clin Oncol, 2021

FD: Tam et al., *Blood*, 2022

GLOW: Ibr/Ven in an older, co-morbid population



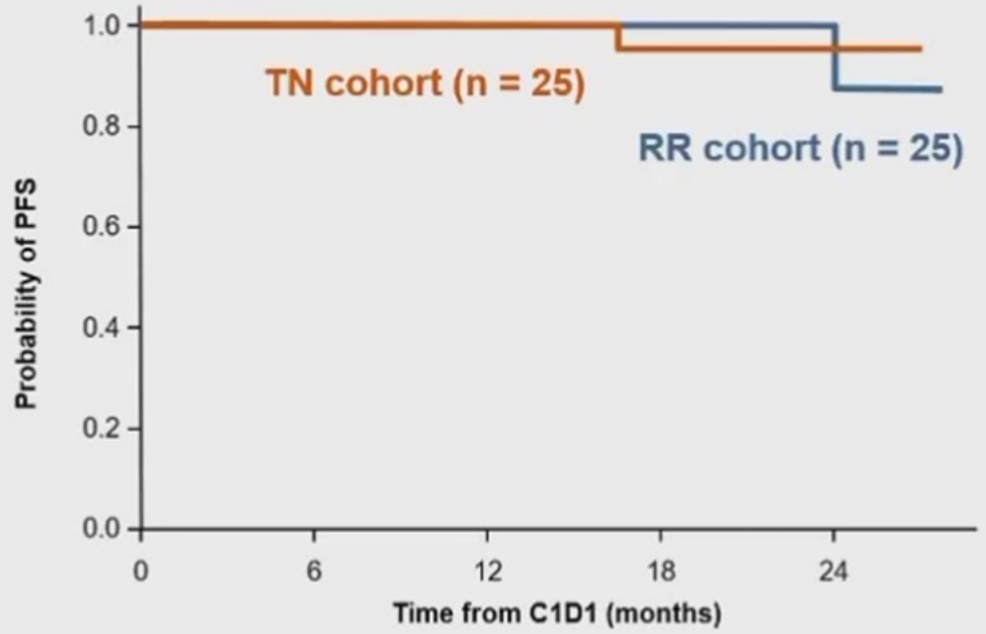
With median follow-up of 34.1 mos:

- OS: HR, 0.76 (95% CI, 0.35-1.64)
  - 11 deaths for Ibr+Ven vs 16 for Clb+O
  - 4 on treatment deaths due to CV complications in IV arm

Munir T. et al. Presented at: 2021 ASH Annual Meeting and Exposition; December 11-14, 2021; Atlanta, GA. Abstract 70.

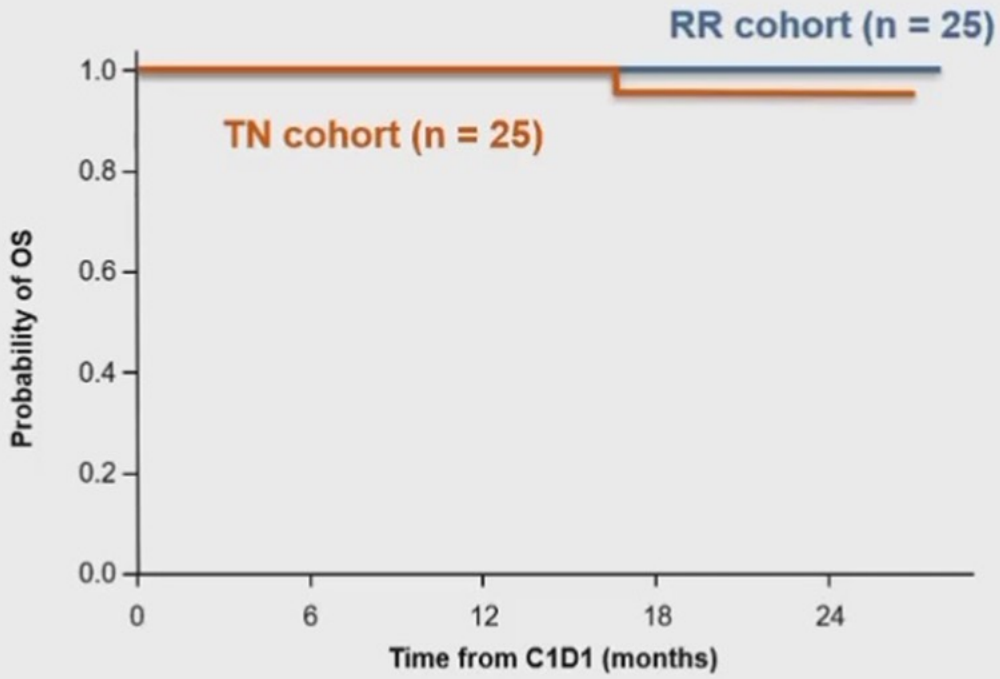
Triplet Therapy With IVO is Active, but Ibrutinib-Related Toxicities are Observed

PFS



No. at Risk					
RR cohort	25	24	23	18	8
TN cohort	25	25	23	18	13

OS



No. at Risk					
RR cohort	25	24	23	18	8
TN cohort	25	25	23	18	13

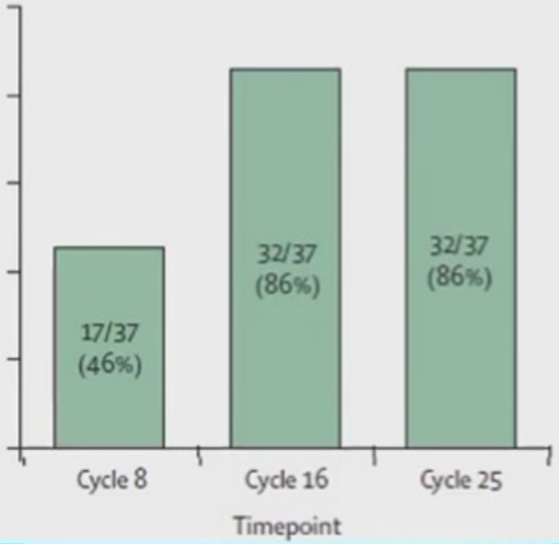
Cardiovascular toxicities were common: HTN: 82%; AFib: 10%

Rogers KA, et al. *J Clin Oncol*. 2020;38(31):3626-3637

Triplets with more specific BTKi are also active, well-tolerated

Phase 2 AVO Trial

BM MRD Response



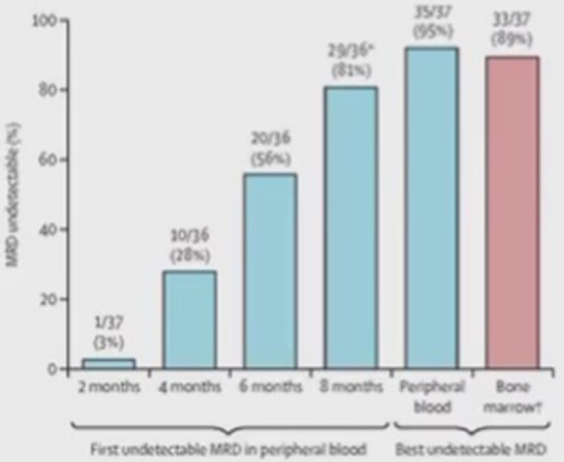
Safety profile

AEs (N=37), %		All Grades	Grade ≥3
Most frequent hematologic	Neutropenia	84	43
	Thrombocytopenia	81	27
	Anemia	59	5
Non-hematologic (≥50%)	Fatigue	89	3
	Headache	76	3
	Bruising	59	0
AEs of special interest	IRR	25	3
	Hypertension	11	0
	Atrial fibrillation	3	3
	Laboratory TLS	5	5

Davids MS, et al. *Lancet Oncol*. 2021.

Phase 2 BOVen Trial

MRD Response



Safety profile

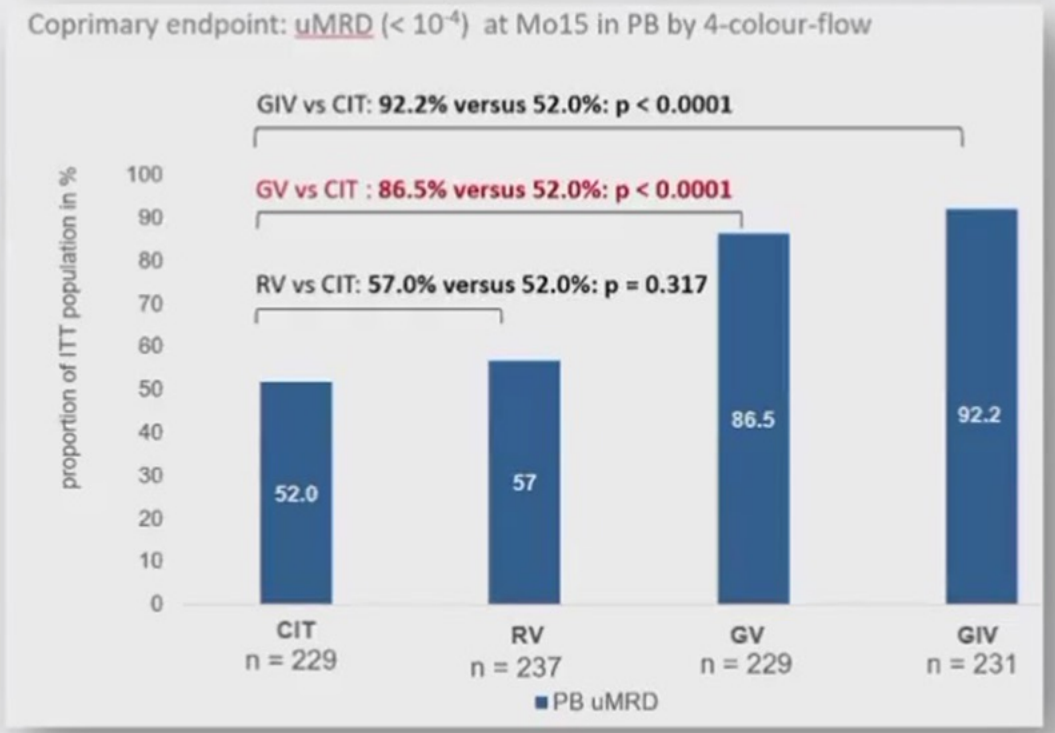
	Grade 1–2	Grade 3	Grade 4
Thrombocytopenia	20 (51%)	3 (8%)	0
Fatigue	20 (51%)	1 (3%)	0
Neutropenia	13 (33%)	2 (5%)	5 (13%)
Bruising	20 (51%)	0	0
Diarrhoea	18 (46%)	0	0
Infusion-related reaction	15 (39%)	1 (3%)	1 (3%)
Anaemia	16 (41%)	0	0
Cough	14 (36%)	0	0
Rash	10 (26%)	3 (8%)	0
Nausea	12 (31%)	0	0
Constipation	11 (28%)	0	0
Nasal congestion	10 (26%)	0	0
Gastroesophageal reflux disease	10 (26%)	0	0
Insomnia	9 (23%)	0	0
Myalgia	9 (23%)	0	0
Arthralgia	8 (21%)	0	0

Soumerai, JD, et al. *Lancet Haem*, 2021

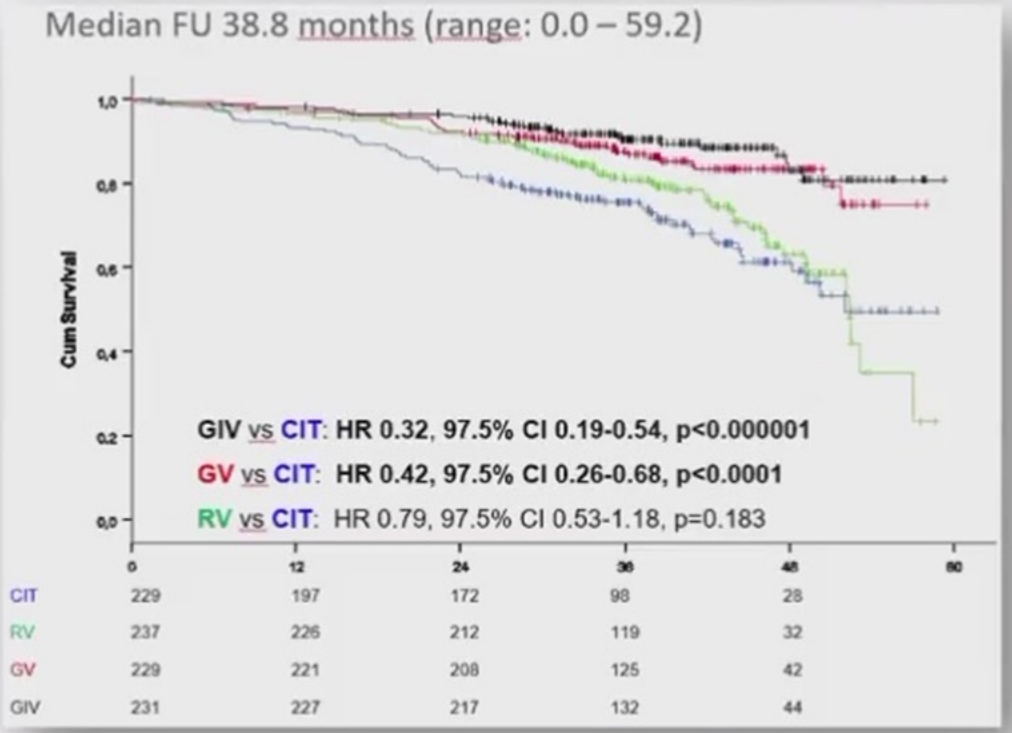
How do triplet combos compare to doublets?

CLL13

MRD



PFS



PFS	Median months	3y PFS (%)
CIT	52.0	75.5
RV	52.3	80.8
GV	Not reached	87.7
GIV	Not reached	90.5

Eichhorst B, et al. ASH 2021

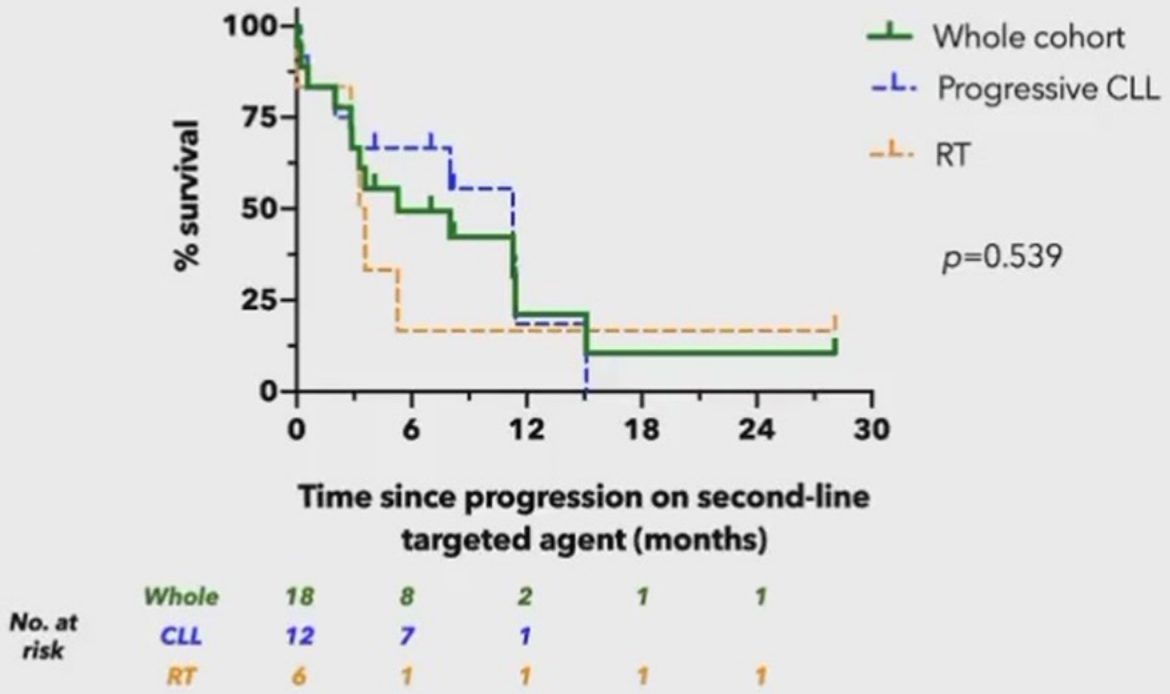
Eichhorst B, et al. EHA 2022

2023+

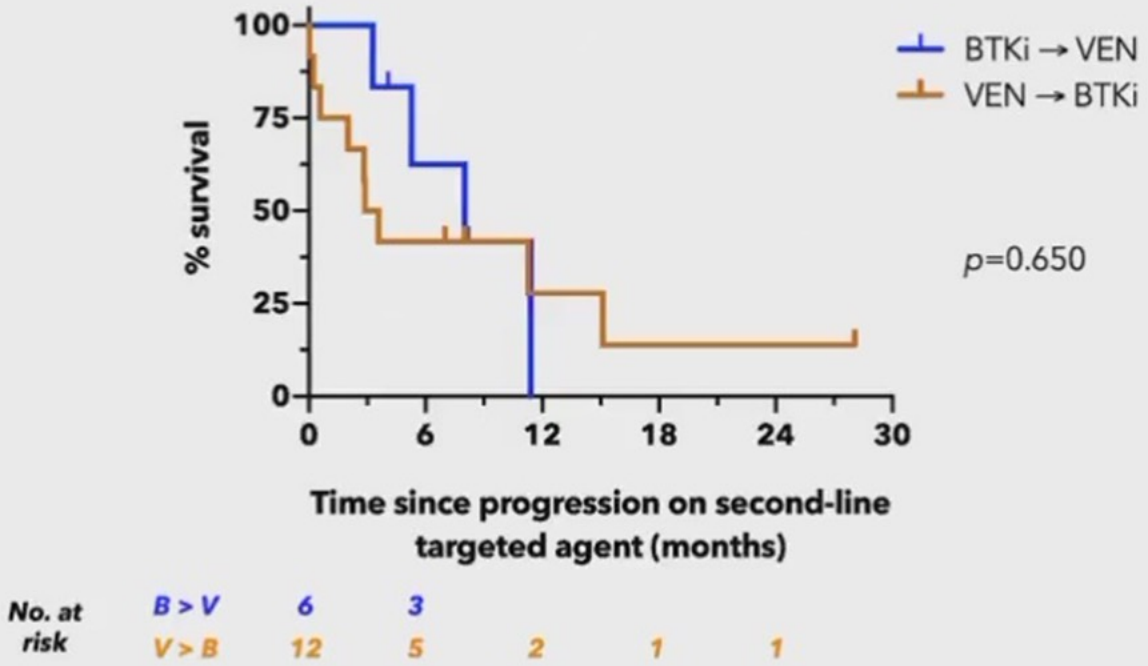
How can we treat patients progressing after covalent BTKi and BCL-2i?

Outcomes for “double class resistant” CLL are poor

2011 to 2020: 165 pts treated with Ven or BTKi → 42 double exposed → 18 double refractory



- Whole cohort median OS: 5.3 months
- No difference in OS between progressive CLL (11.3 months) and RT (3.4 months)

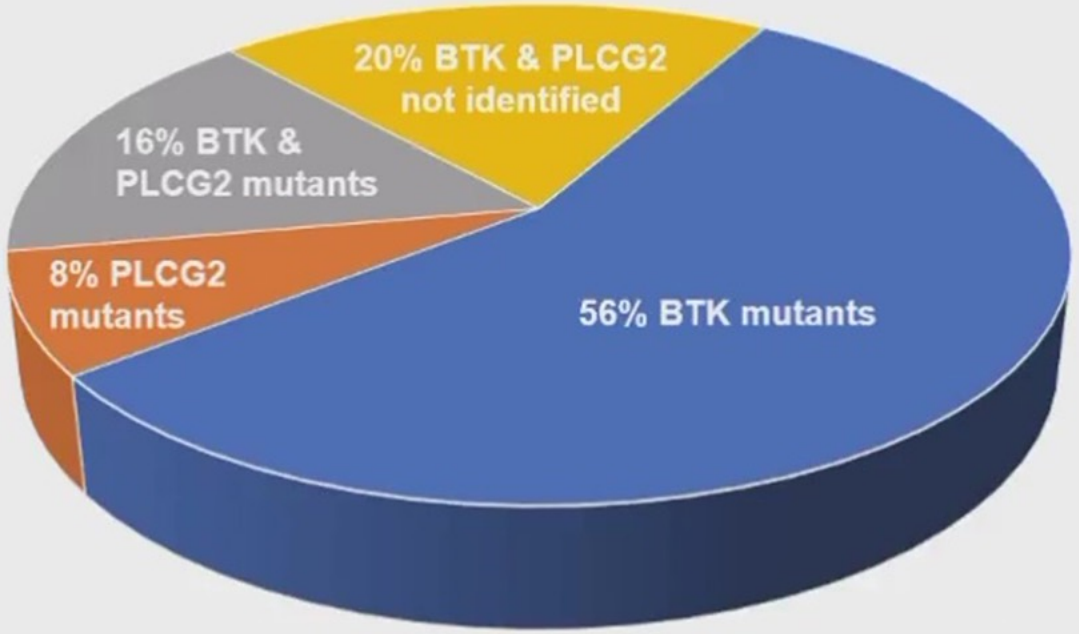


- No difference in OS between BTKi → VEN (8 months) and VEN → BTKi (3.2 months)

Lin VS et al. iwCLL 2021; updated from *Blood Adv*. 2021;5(20):4054-4508.

BTK mutations are a common cause of covalent BTKi resistance

Acquired Resistance to Ibrutinib in Patients With Progressive CLL[1]



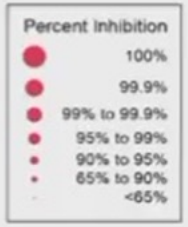
- *BTK* C481 mutations are the principal reason for progressive CLL after treatment with covalent BTK inhibitors (1)
- *BTK* C481 mutations impair target inhibition by covalent BTK inhibitors (2)
- *BTK* C481S is the most common mutation in progressors on ibrutinib and acalabrutinib (3)
- *BTK* L528W mutations recently described in 7/13 patients progressing on zanubrutinib (4)

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

1. Lampson BL. *Expert Rev Hematol*. 2018;11(3):185-194. 2. Mato AR. *Lancet*. 2021;397(10277):892-901. 3. Woyach et al., ASH 2019, 4. Blombery P, et al. *Blood Adv*, 2022

BTK Inhibitors Exhibit Differences in Kinase Selectivity

Covalent BTKi



Ibrutinib

Acalabrutinib

Zanubrutinib

Non-covalent BTKi

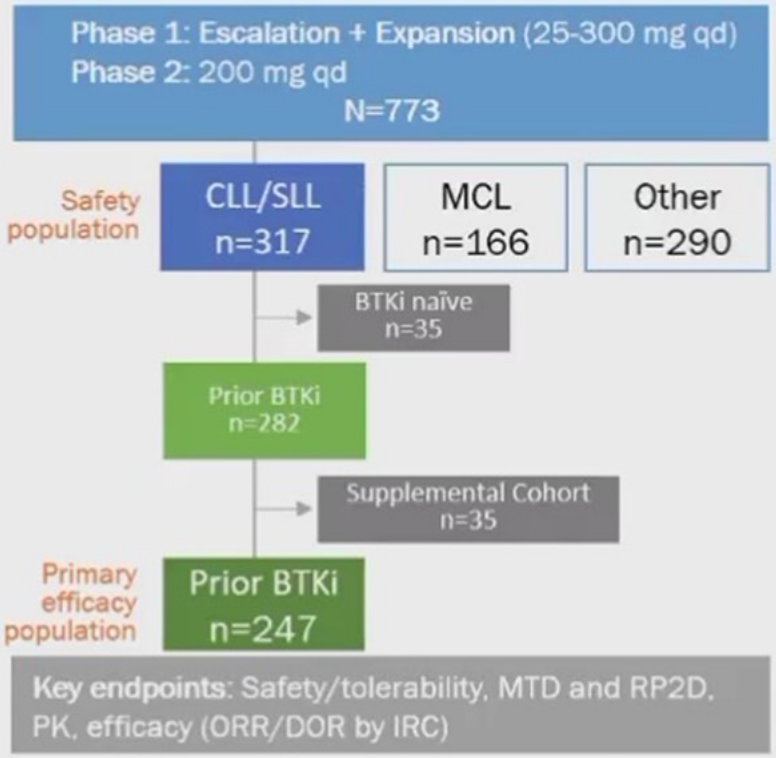
Nemtabrutinib

Pirtobrutinib

Kaptein A, de Bruin G, Emmelot-van Hoek M, et al. *Blood*. 2018;132(Suppl 1):1871.

Extended Follow-Up From the BRUIN Phase 1/2 Study of Pirtobrutinib in cBTKi-Pretreated Patients With R/R CLL/SLL – Study Design and Patients

Key Eligibility Criteria
- R/R CLL/SLL with prior BTKi treatment
- ECOG PS ≤2
- Received ≥1 dose of pirtobrutinib monotherapy



Patient Characteristics		n=247
Median age (range), years		69 (36-88)
Rai stage, n (%)	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 prior lines of therapy (range), n		3 (1-11)
Prior therapies, n (%)	BTKi	247 (100)
	Anti-CD20 mAb	217 (88)
	Chemotherapy	195 (79)
	BCL2i	100 (41)
	PI3Ki	45 (18)
	CAR T-cell therapy	14 (6)
	AlloSCT	6 (2)
Median time from diagnosis to 1st dose (IQR), years		11 (8-15)

Mutation Status, n/N (%)	
BTK C481mut	84/222 (38)
BTK C481wt	138/222 (62)
PLCG2mut	18/222 (8)
PLCG2wt	204/222 (92)
High-Risk Molecular Features, n/N (%)	
del(17p)	51/176 (29)
TP53mut	87/222 (39)
del(17p) and/or TP53mut	90/193 (47)
del(17p) and TP53mut	48/170 (28)
Unmutated IGHV	168/198 (85)
Complex karyotype	24/57 (42)
del(11q)	44/176 (25)
Reason for BTKi Discontinuation,[b] n (%)	
PD	190 (77)
Toxicity/other	57 (23)

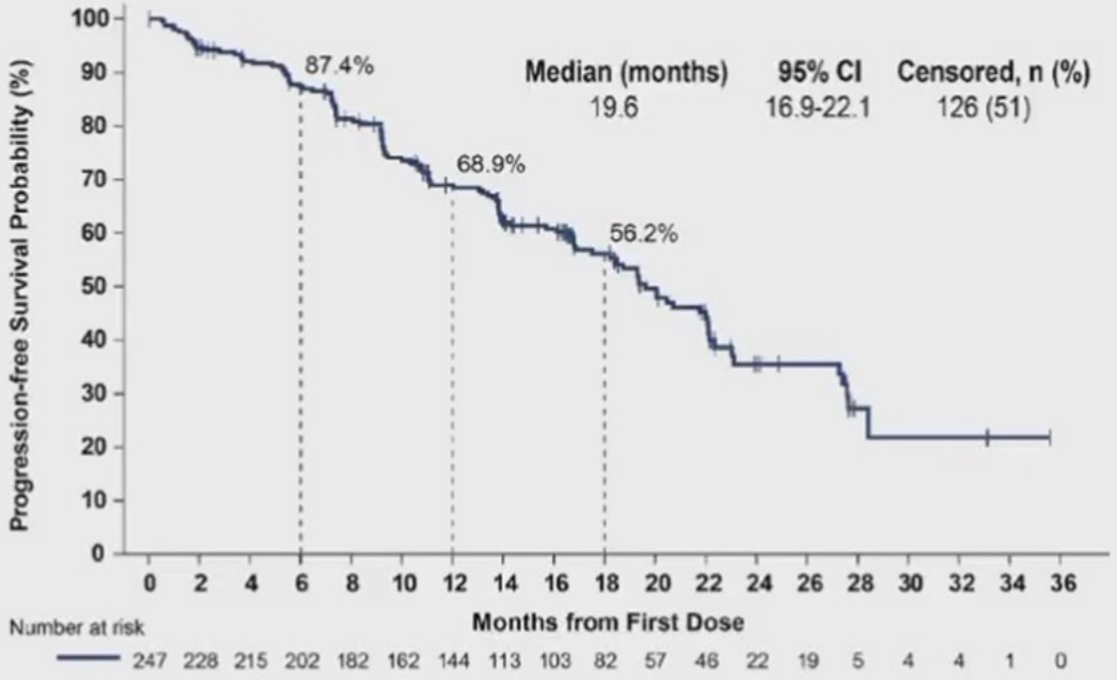
[a] To ensure adequate follow-up, the primary efficacy population included all patients with CLL/SLL who enrolled prior to November 5, 2021. [b] In the event more than 1 reason was noted for discontinuation, disease progression took priority.

Mato AR, et al. ASH 2022. Abstract 961.

Extended Follow-Up From the BRUIN Phase 1/2 Study of Pirtobrutinib in cBTKi-Pretreated Patients With R/R CLL/SLL – Efficacy

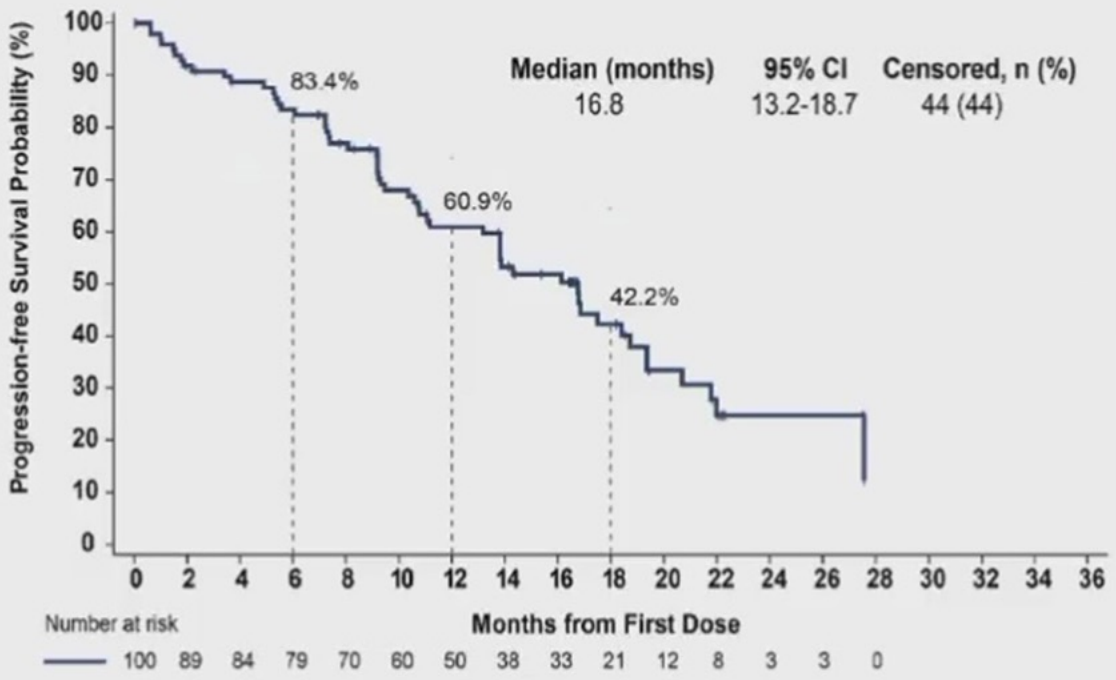
PFS by IRC in All Prior BTKi Patients

- Median prior lines of treatment (LOT): 3
- Median follow-up: 19.4 months



PFS by IRC in Prior BTKi and BCL2i Patients

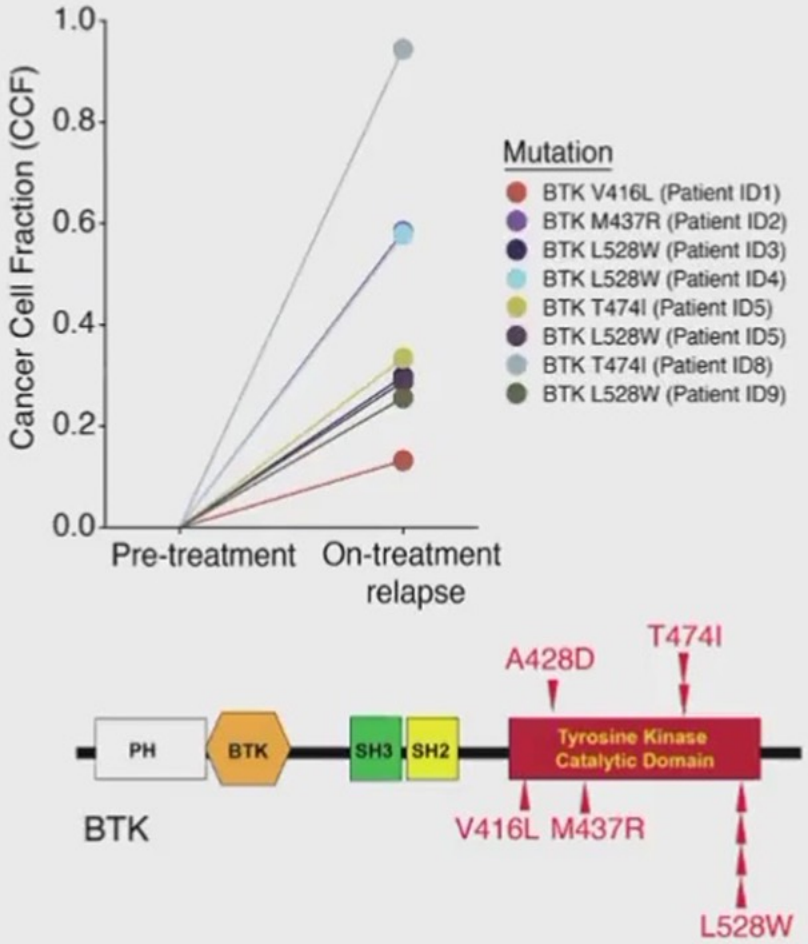
- Median prior LOT: 5
- Median follow-up: 18.2 months



Mato AR, et al. ASH 2022. Abstract 961.

Mechanisms of Resistance to Noncovalent BTKi

- Novel, acquired mutations in *BTK* identified in patients with CLL at the time of disease progression:
  - ***BTK L528W***
  - ***BTK V416L***
  - ***BTK M437R***
  - ***BTK T474I***
  - ***BTK A428D***
- These mutations cluster around the tyrosine kinase catalytic domain of BTK
- Several patients with progressive disease also had preexisting *PLCG2* mutations



Wang E, et al. *N Engl J Med.* 2022;386(8):735-743.

Continuous BTKi

Time-limited Ven-Combos

Where do we go from here?

The CLL17 trial is comparing continuous BTKi to time-limited venetoclax-based doublets

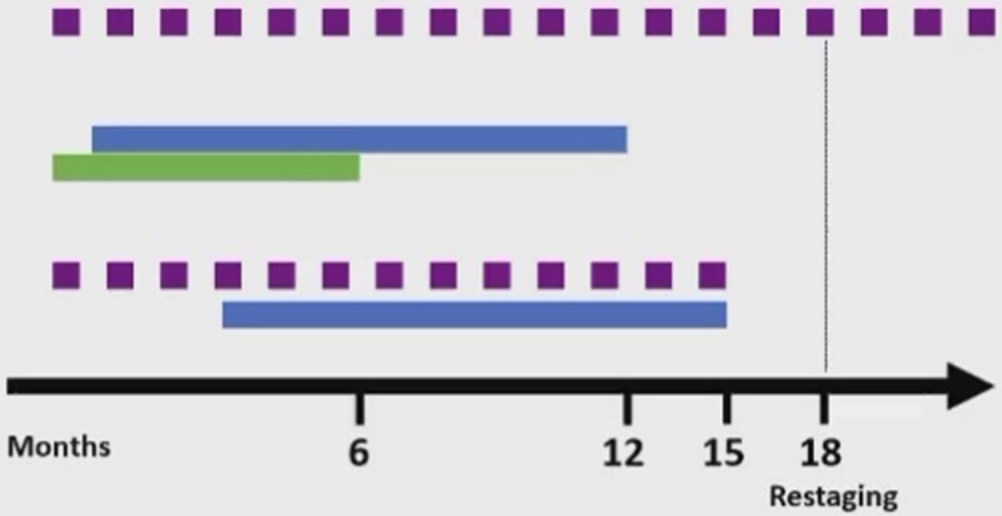
CLL17[1,2]

Phase 3 trial in 1L CLL, including those with adverse prognostic factors

- Ibr mono
- Ven + Obin
- Ven + I

Stratification by fitness, del(17p)/*TP53*^{mut}, IGHV

RANDOMIZATION[2]



Ibrutinib D1 420 mg PO daily until PD or intolerance

Venetoclax 400 mg PO daily (C1 D22 – C12 D28)
Obinutuzumab 1000 mg IV (C1 D1(2)/8/15, C2–6 D1)

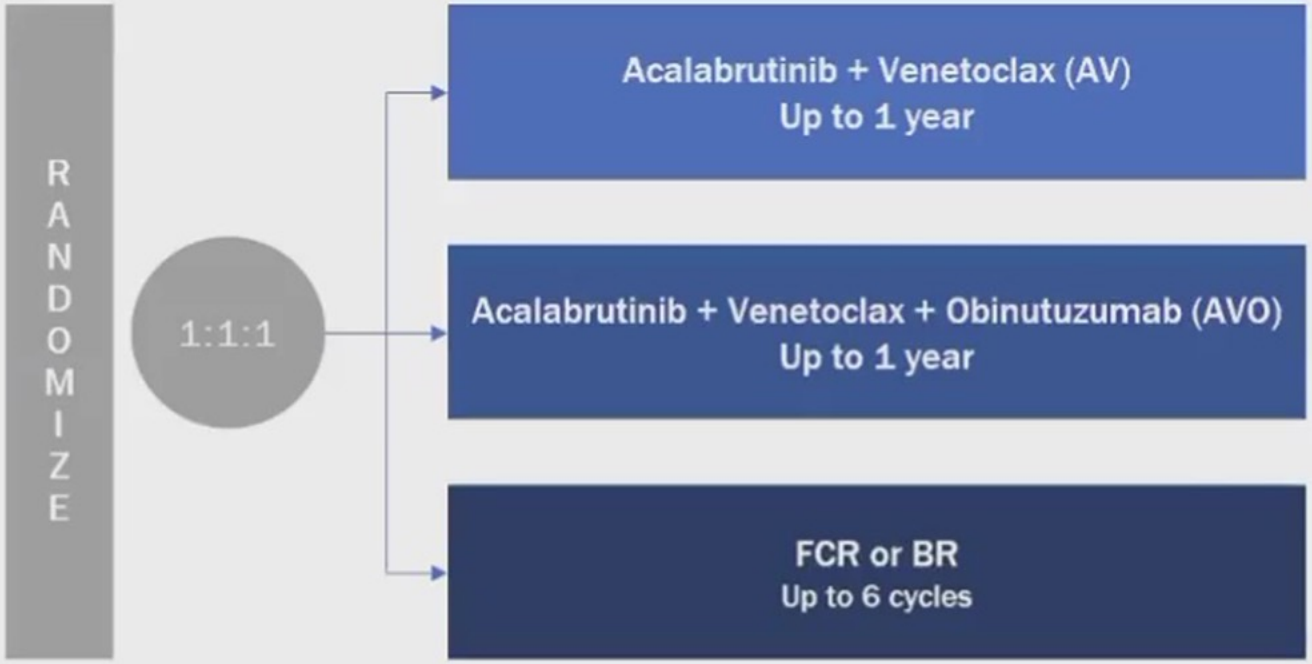
Ibrutinib 420 mg PO daily (C1 D1 – C15 D28)
Venetoclax 400 mg PO daily (C4 D1 – C15 D28)

1. ClinicalTrials.gov. NCT04608318. Available at: https://www.clinicaltrials.gov/ct2/show/NCT04608318 (accessed August 2021);
2. DCLLSG. CLL17 Trial. Available at: https://www.dcllsg.de/en/trial/cll17/CLL17_Synopsis_v1.2_20200923.pdf (accessed August 2021)

AMPLIFY (ACE-CL-311): Phase 3 Study of Acalabrutinib + Venetoclax ± Obinutuzumab vs FCR/BR in TN CLL Without Del(17p) or *TP53* Mutations

Key Eligibility Criteria

- Previously untreated CLL
- Without del(17p) or *TP53* mutations
- ECOG PS ≤2



Primary endpoint

- PFS (IRC assessed) of AV vs FCR/BR

Key secondary endpoints

- PFS (IRC assessed) of AVO vs FCR/BR
- PFS (INV assessed) of AV vs FCR/BR

ClinicalTrials.gov identifier: NCT03836261. Accessed October 4, 2022. https://clinicaltrials.gov/ct2/show/NCT03836261

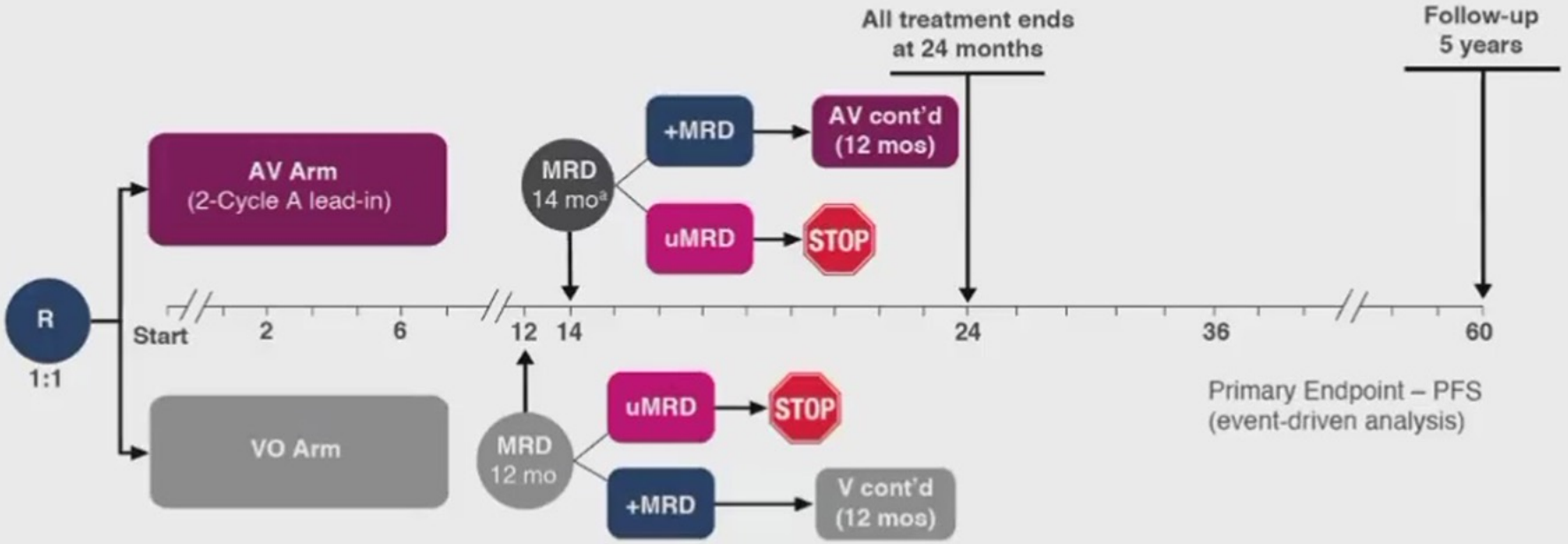
The global MAJIC phase 3 study seeks to define the optimal MRD-guided venetoclax doublet for frontline CLL treatment

- N=~750 patients to be recruited
- Global study with ~40 sites
- FPI: Sept 2022

Key Eligibility Criteria

- TN CLL/SLL requiring treatment per 2018 iwCLL guidelines
- ECOG PS 0-2
- Anti-thrombotic agents permitted except for warfarin or equivalent vitamin K antagonists

Primary endpoint: INV-assessed PFS



Davids et al., ASH, 2021. Abstract 1553

Conclusioni

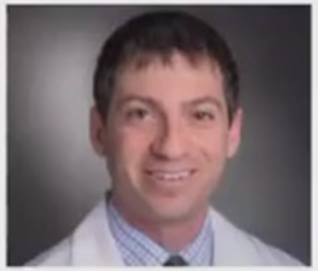
- The last 7 years have been a dynamic period for BTKi
- 2016-2019 was a Golden Age that established continuous BTKi as a safe and effective therapy for a broad population of patients with CLL
- 2019-2022 witnessed the approval of the first time-limited novel-agent therapy (ven/obin) and also the readout of 2 head-to-head BTKi trials
- 2023 and beyond will likely usher in a new era of BTKi + BCL-2i combos (+/- CD20) and non-covalent BTKi
- Active participation in clinical trials remain critical

Dana-Farber Cancer Institute

Harvard Medical School

DFCI CLL Center

Jennifer Brown, MD, PhD



Matthew Davids, MD, MMSc

Inhye Ahn, MD

Catherine Wu, MD

We hope to welcome you to Boston next fall!