Chronic Lymphocytic Leukemia

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CLL-”Best” initial therapy

- Is watchful waiting still the best option?
- Any role for chemotherapy?
- MRD negativity as a treatment goal
- Ongoing Treatment with BTKi
  - Which BTKi?
  - In combination?
  - Does this really need to continue forever?
- Fixed duration therapy – incorporating MRD

Watchful Waiting (worrying)

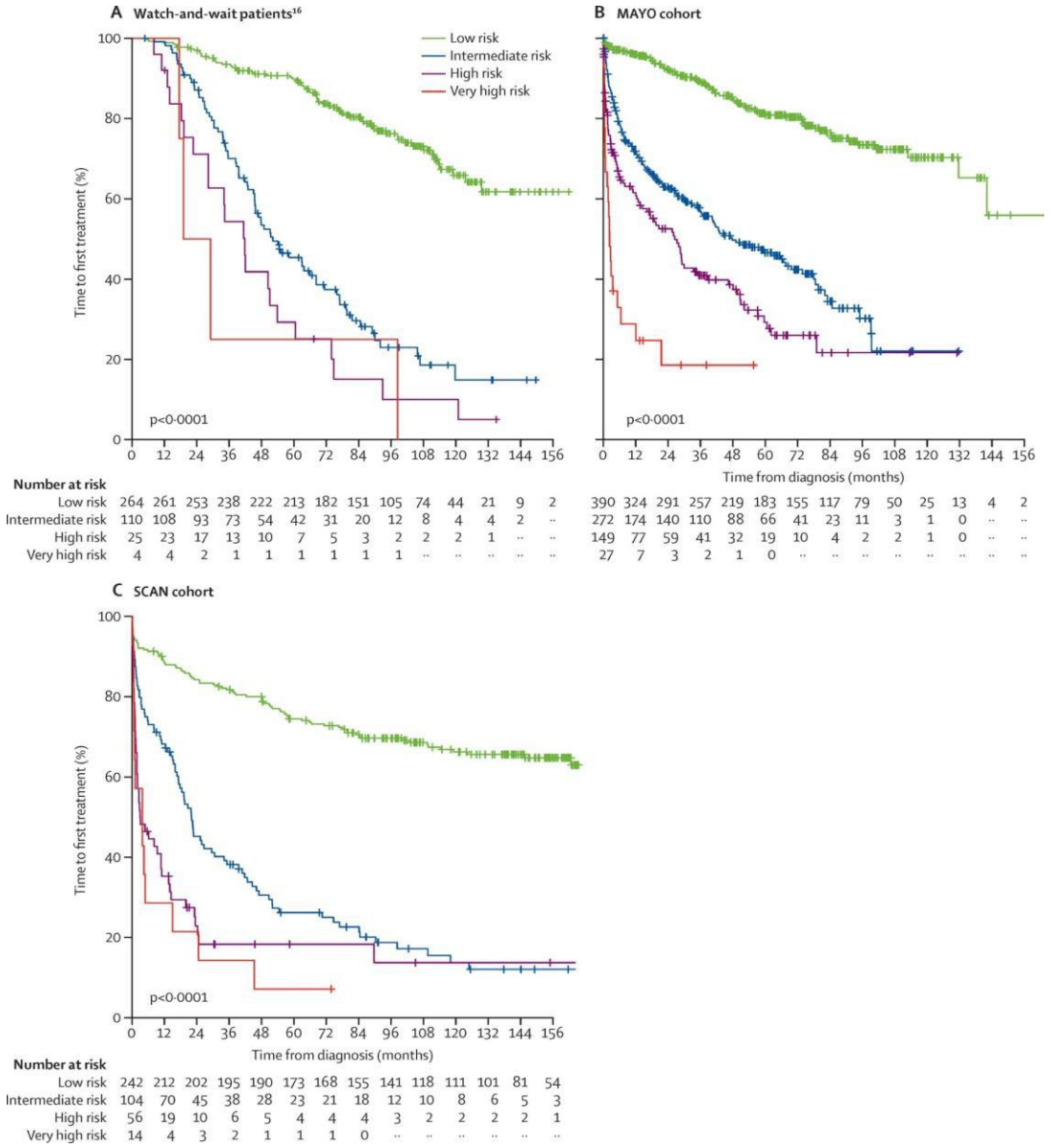
-original watchful waiting data based primarily on immediate treatment with chlorambucil

-Can we define a high risk subset that would benefit from earlier treatment

Defining High Risk Disease – CLL IPI

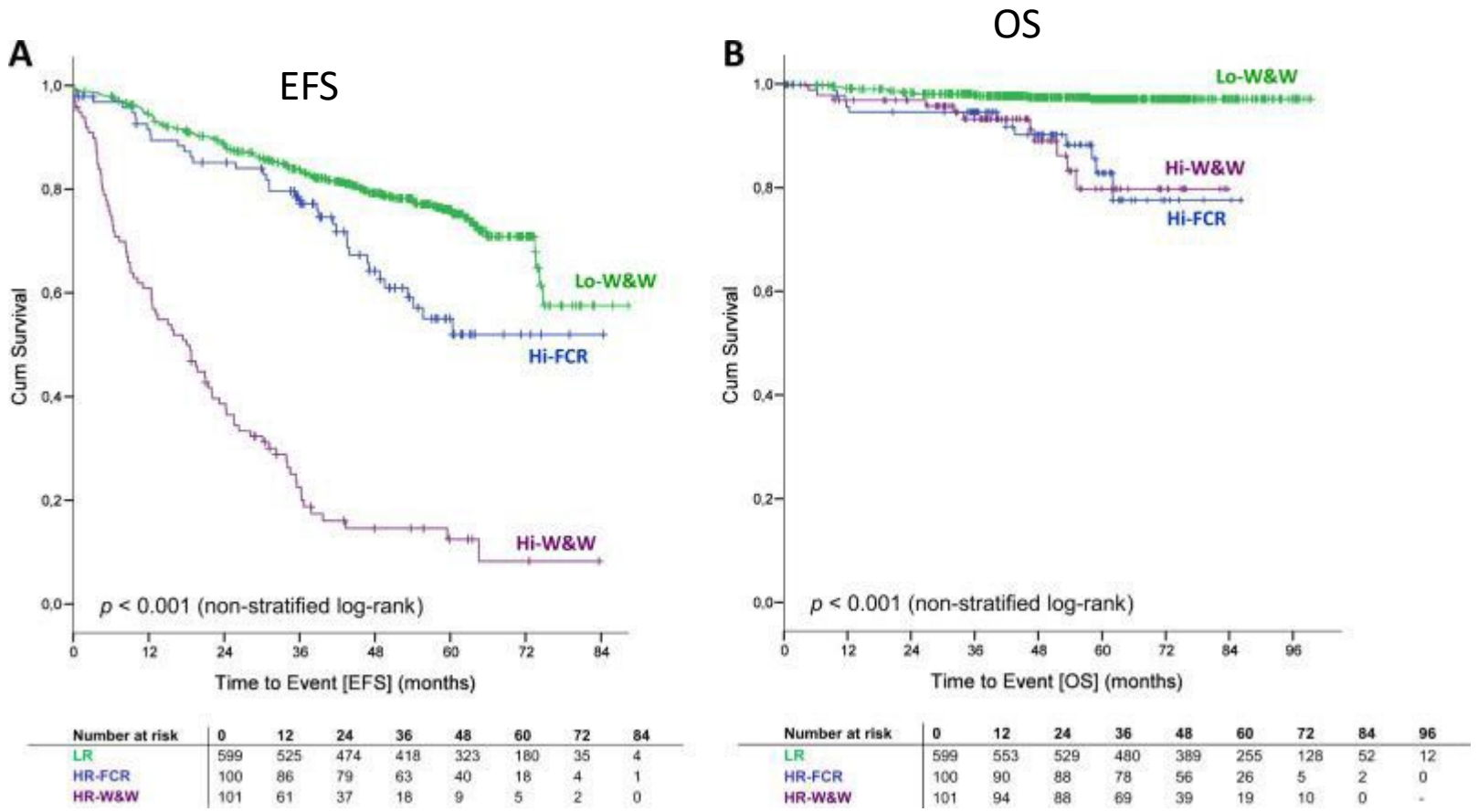
Characteristic	Points (10)
Age > 65	1
Rai Stage I-IV	1
B2M ≥ 3.5	2
IGHV UNmutated	2
17p deletion or p53 mutation	4

Low risk: 0-1
Intermediate Risk: 2-3
High Risk: 4-6
Very High Risk: 6-10



Lancet Oncology Volume 17, Issue 6, June 2016, Pages 779-790

Early treatment with FCR versus watch and wait in patients with stage Binet A high-risk chronic lymphocytic leukemia (CLL): a randomized phase 3 trial



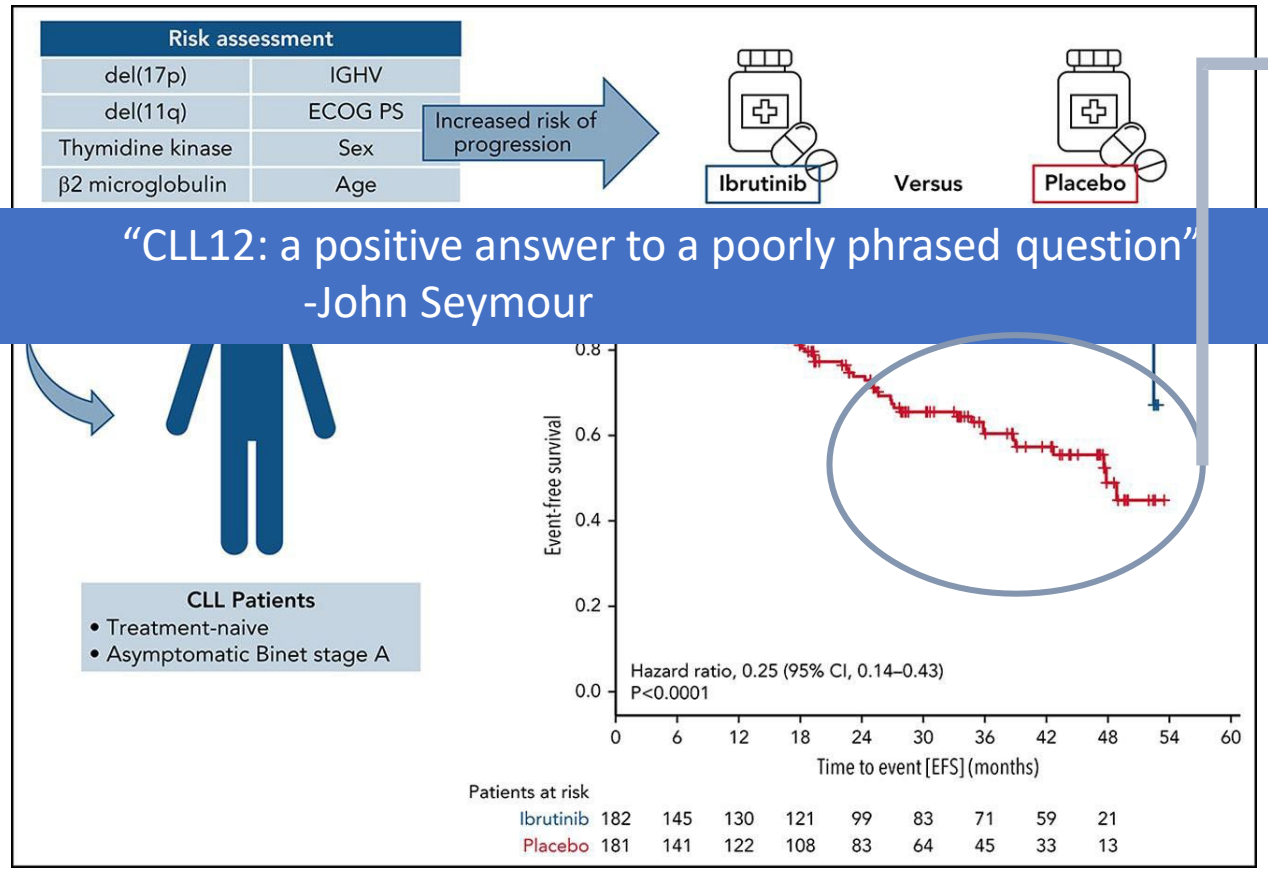
Number at risk	0	12	24	36	48	60	72	84
LR	599	525	474	418	323	180	35	4
HR-FCR	100	86	79	63	40	18	4	1
HR-W&W	101	61	37	18	9	5	2	0

Number at risk	0	12	24	36	48	60	72	84	96
LR	599	553	529	480	389	255	128	52	12
HR-FCR	100	90	88	78	56	26	5	2	0
HR-W&W	101	94	88	69	39	19	10	0	-

High risk = ≥ 2 risk factors: Doubling time <12 months, serum thymidine kinase >10 U/L, unmutated IGHV genes, and unfavorable cytogenetics (del(11q)/del(17p)/trisomy 12).

Leukemia. 2020; 34(8): 2038–2050.

The CLL12 trial: ibrutinib vs placebo in treatment-naïve, early-stage chronic lymphocytic leukemia



"CLL12: a positive answer to a poorly phrased question"
-John Seymour

Better than expected EFS

EVOLVE CLL (NCTN study)
Early vs. late Obi-Ven
CLL-IPI score ≥4 and/or complex cytogenetics
OS and QOL primary outcomes

Blood Volume 139, Issue 2, 13 January 2022, Pages 177-187

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NCCN Guidelines Treatment-naïve CLL

All recommendations are category 2A unless otherwise indicated

First-line without del(17p)/TP53 Mutation		First-line with del(17p)/TP53 Mutation
Frail with significant comorbidities or ≥65 and younger with significant comorbidities	<65 without significant comorbidities	
Ibrutinib (Category 1)		Ibrutinib
Acalabrutinib ± obinutuzumab (Category 1)		Acalabrutinib ± obinutuzumab
Venetoclax + obinutuzumab (Category 1)		Venetoclax + obinutuzumab
Other recommended regimens: Bendamustine + anti-CD20 mAb (not recommended for frail patients); chlorambucil + obinutuzumab; HDMP + rituximab (cat2B); ibrutinib + obinutuzumab (cat2B); obinutuzumab (cat2B); chlorambucil (cat3); rituximab (cat3)	**Other recommended regimens:** Bendamustine + anti-CD20 mAb; FCR (preferred for IGHV-mutated CLL); FR; HDMP + rituximab (cat2B); ibrutinib + rituximab (cat2B); PCR (cat3)	**Other recommended regimens:** alemtuzumab ± rituximab; HDMP + rituximab; obinutuzumab; zanubrutinib (for pts with contraindication to other BTKi)

NCCN. CLL/SLL Guidelines. v3.2021.

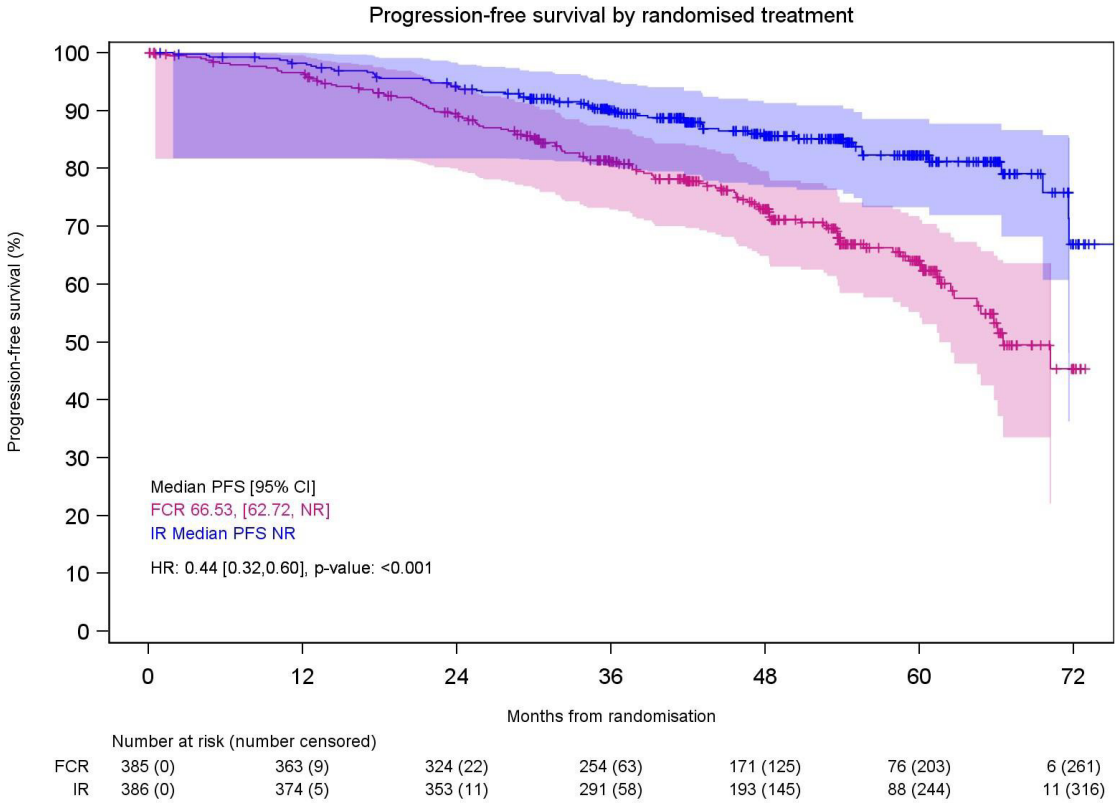
Ibrutinib based Regimens

Study	Arms	Clinical Data	Notes
E1912 Trial (Ph III) (<70 years old + no del17p) N=529	• **Ibrutinib**/ritux • FCR	**36 mo PFS:** 89% vs 73% **36 mo OS:** 99% vs 92%	• Ibrutinib/ritux superior to FCR • Outcomes independent of high-risk features (except IGHV-mutated)
A041202 (Ph III) (≥65 years old, including del17p) N=547	• **Ibrutinib** • **Ibrutinib**/ritux • BR	**24 mo PFS:** 87% vs 88% vs 74% (I vs IR vs BR) I vs BR (HR: 0.39); I vs IR (HR: 1.00) IR vs BR (HR: 0.38) **24 mo OS:** 90% vs 94% vs 95% (I vs IR vs BR)	• Ibrutinib and ibrutinib/ritux PFS are superior to BR [regardless of high-risk features (except ZAP70)]; no significant difference with ibrutinib vs ibrutinib/ritux • No statistically significant difference in OS

BTKi have largely supplanted chemotherapy

Woyach JA, et al. *N Engl J Med*. 2018; Shanafelt TD, et al. *N Engl J Med*. 2019; Moreno C, et al. *Lancet Oncol.* 2019; Tam CS, et al. *Hematologica*. 2020.

642 Ibrutinib Plus Rituximab Is Superior to FCR in Previously Untreated CLL: Results of the Phase III NCRI FLAIR Trial

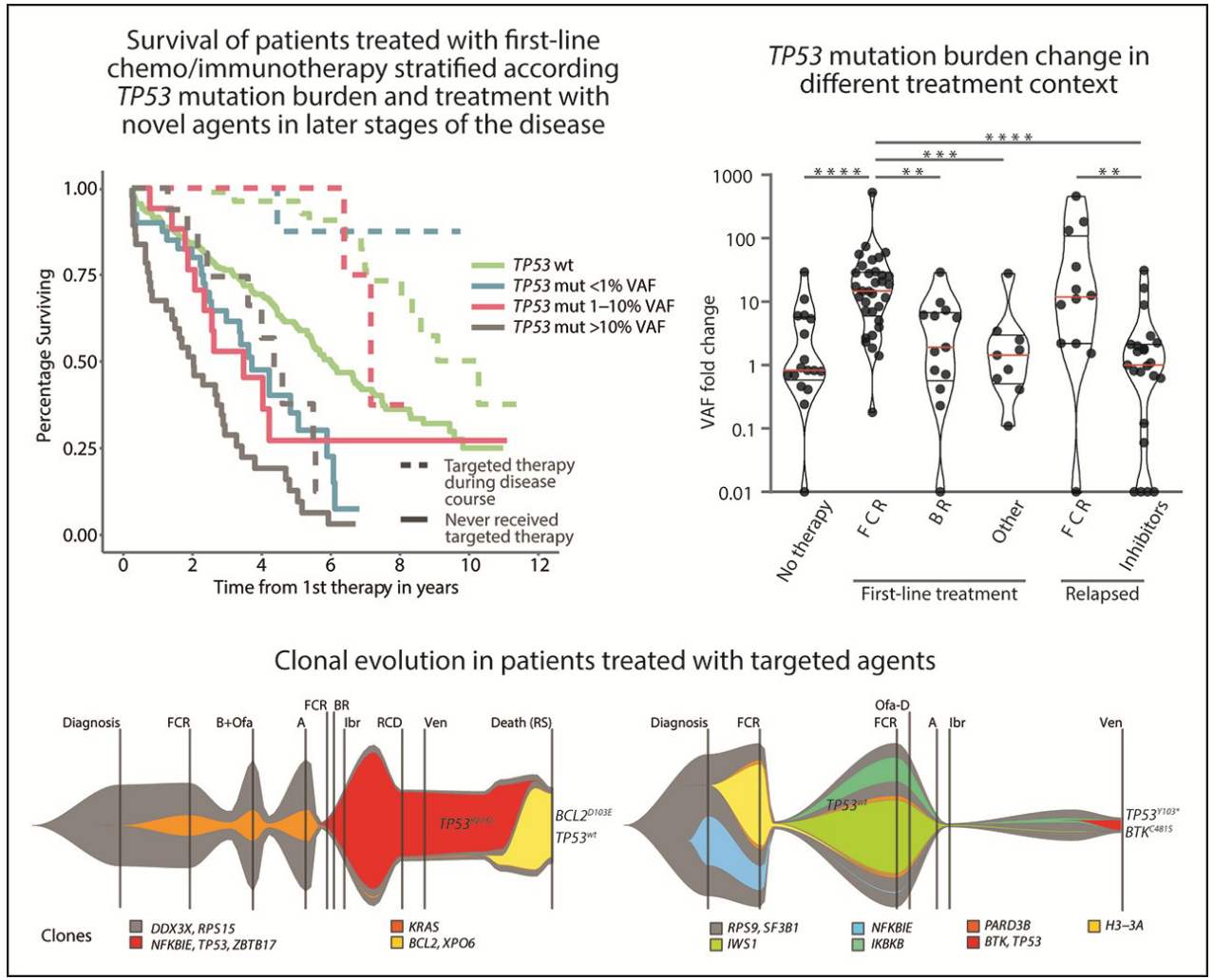


N = 771
Median age = 62
FCR vs. IR
Follow up = 57 months

- **The PFS significantly better for IR in patients with IGHV unmutated CLL (HR: 0.41; p<0.001), but not for patients with IGHV mutated CLL**
- No OS difference
  - **-8 vs. 2 cardiac/sudden deaths in ibrutinib arm (7 of 8 hx of HTN)**
  - -6 cases (1.6%) of MDS/AML in FCR (1 in IR)
  - -Significantly improved OS compared to prior FCR studies

Low-burden TP53 mutations in CLL: clinical impact and clonal evolution within the context of different treatment options

- Genomic complexity associated with inferior survival
- Clonal and subclonal TP53 and clonal NOTCH1 mutations predicted for shorter overall survival together with the IGHV mutational status.
- May occur in chemotherapy treated patients and Untreated patients



Blood. 2021 Dec 23;138(25):2670-2685

CLL-”Best” initial therapy

- Is watchful waiting still the best option? → YES, unless on study
- Any role for chemotherapy?→ not really….
- Ongoing Treatment with BTKi
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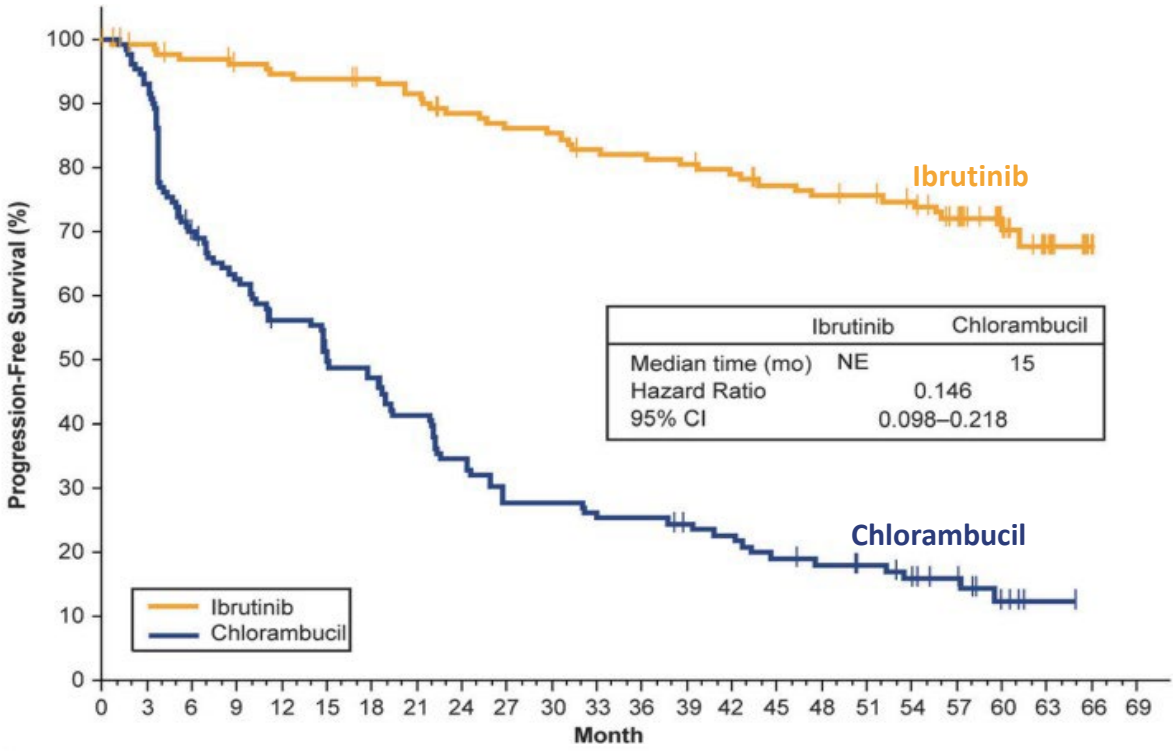
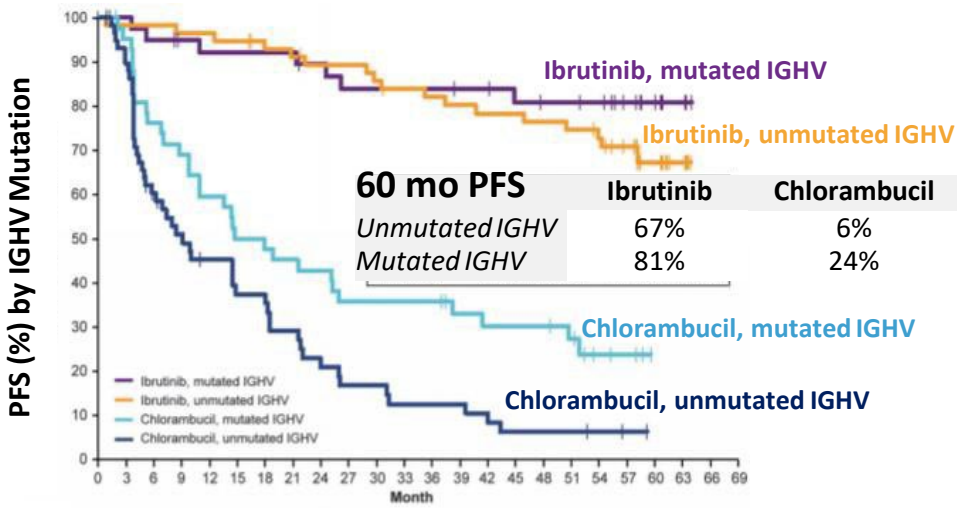
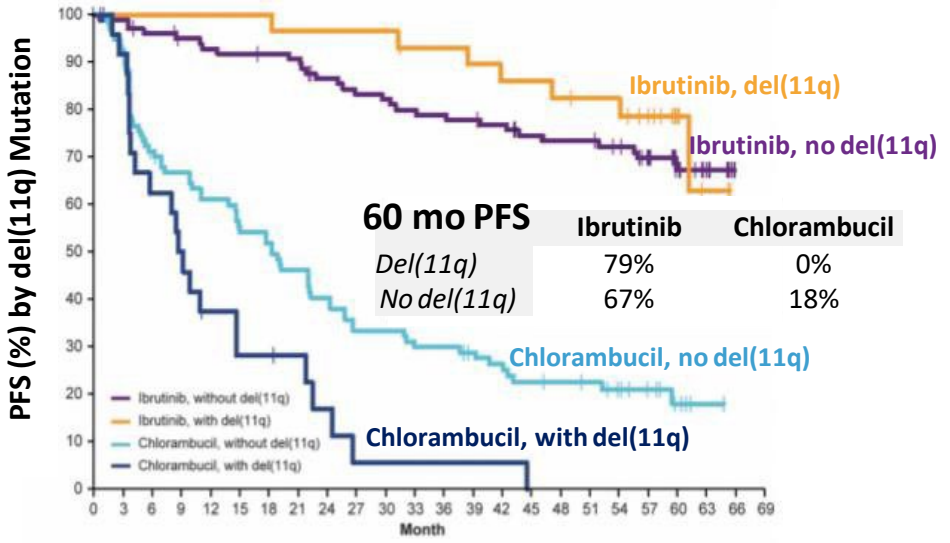
Ibrutinib Monotherapy in TN CLL
Phase III, RESONATE-2 Trial

≥65 years old; excluded del17p; N=269



60 mo PFS: 70% vs 12% (I vs C)
60 mo OS: 83% vs 68% (I vs C)

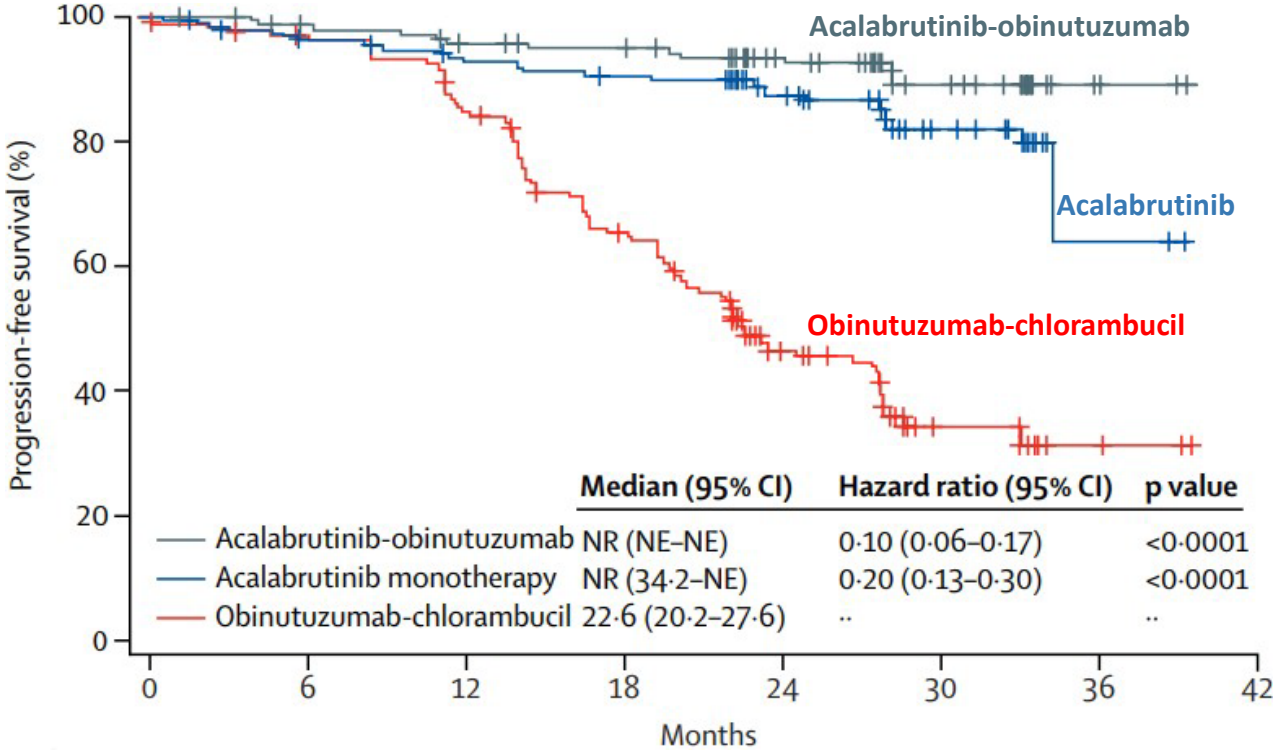




Burger JA, et al. *Leukemia*. 2020.

Acalabrutinib Monotherapy and Combination
Phase III, ELEVATE-TN Trial

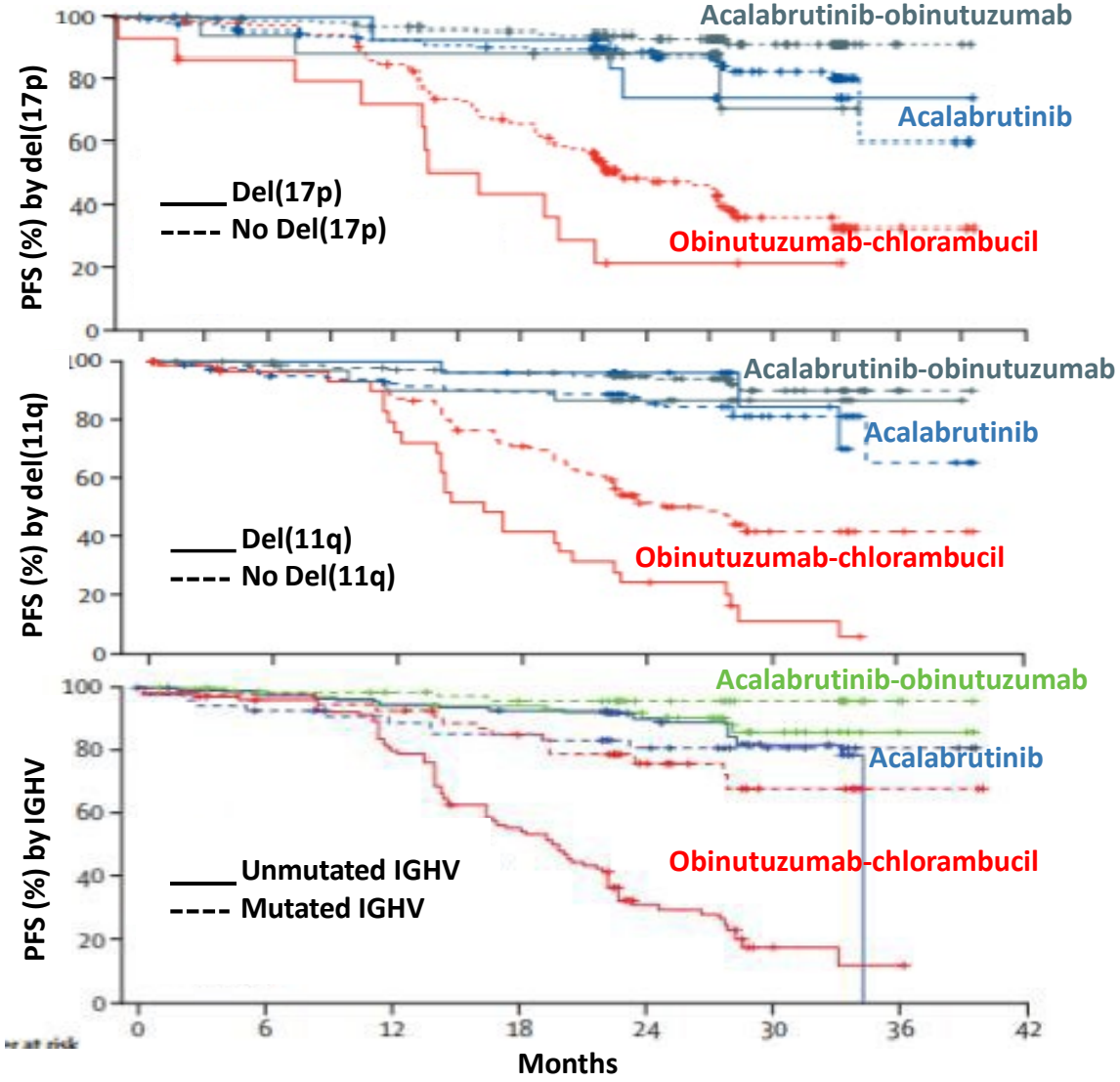
≥65 years or older or <65 years + coexisting conditions (N=535)



	Median (95% CI)	Hazard ratio (95% CI)	p value
Acalabrutinib-obinutuzumab	NR (NE–NE)	0·10 (0·06–0·17)	<0·0001
Acalabrutinib monotherapy	NR (34·2–NE)	0·20 (0·13–0·30)	<0·0001
Obinutuzumab-chlorambucil	22·6 (20·2–27·6)	..	..

24 mo PFS: 93% vs 87% vs 47% (AO vs A vs CO)

24 mo OS: 95% vs 95% vs 92% (AO vs A vs CO)



Sharman JP, et al. *Lancet*. 2020.

2636 Sudden or Cardiac Deaths on Ibrutinib-Based Therapy Were Associated with a Prior History of Hypertension or Cardiac Disease and the Use of ACE-Inhibitors at Study Entry: Analysis from the Phase III NCRI FLAIR Trial

Table 1: Contingency tables of sudden or cardiac death, hypertension or prior history of cardiac disorder and baseline ACE inhibitor-use in treated patients in the FLAIR trial.

Safety population (patients receiving at least one dose of study drug)

FCR arm		**Sudden or cardiac death**		
		No	Yes	Total
Hypertension or prior history of cardiac disorder (on treatment at trial entry)	No	291	2	293
	Yes	85	0	85
	Total	376	2	378
	Relative Risk NE* Fisher's Exact P NE*			

IR arm		**Sudden or cardiac death**		
		No	Yes	Total
Hypertension or prior history of cardiac disorder (on treatment at trial entry)	No	290	1	291
	Yes	86	7	93
	Total	376	8	384
	Relative Risk 23.6, 95%CI (2.9-490) Fisher's Exact P = 0.0003			

		No	Yes	Total
ACE inhibitor	No	339	2	341
	Yes	37	0	37
	Total	376	2	378
	Relative Risk NE* Fisher's Exact P NE*			

		No	Yes	Total
ACE inhibitor	No	336	1	337
	Yes	40	7	47
	Total	376	8	384
	Relative Risk 50.2, 95%CI (6.3-399) Fisher's Exact P < 0.0001			

*NE = not estimable

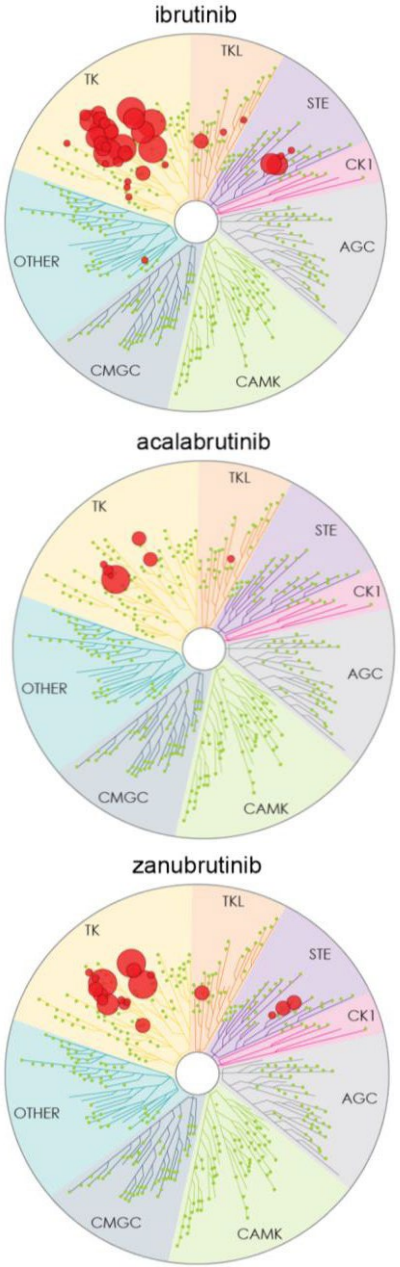
.3%

7.5%

15%

In the IR arm, none of the 46 pts receiving cardiac medication but not ACEi had a sudden or cardiac death suggesting that the risk was not simply a prior history of HT or cardiac disorder.

BTK Inhibitor Toxicity Differs Based on TKI Selectivity



All Grades

A

	Ibru	Acala	Zanu
Anemia	27	14	22
Neutropenia	23	10.6	53
Thrombocytopenia	16	7.3	32
Infection	83	79.4	75.8
Diarrhea	53	34.6	23.8
Fatigue	36	18.4	/
Upper respiratory infection	29	18.4	39
Arthralgia	22	15.6	17.4
Pneumonia	18	7.3	25
Hypertension	21	6.7	15.4
Headache	17	36.9	/
Atrial fibrillation	11	3.9	/
Rash	35	14	36
Bleeding/Bruising	55	39.1	28.4
Median treatment exposure	29mon	27.7mon	6mon
Numbers	330	179	118
Patients	CLL/SLL	CLL/SLL	MCL

≥40 ≥30 ≥20 ≥10

Grades 3–5

B

	Ibru	Acala	Zanu
Anemia	7	6.7	8
Neutropenia	18	9.5	15
Thrombocytopenia	6	2.8	5
Infection	31	14	10.8
Diarrhea	5	0.6	0.8
Fatigue	3	1.1	/
Upper respiratory infection	1	0	0
Arthralgia	2	0.6	3.4
Pneumonia	12	2.2	10
Hypertension	7	2.2	3.4
Headache	2	1.1	/
Atrial fibrillation	5	0	/
Rash	3	0.6	0
Bleeding/Bruising	6	1.7	3.4
Median treatment exposure	29mon	27.7mon	6mon
Numbers	330	179	118
Patients	CLL/SLL	CLL/SLL	MCL

≥10 ≥7.5 ≥5 ≥2.5

FDA Prescribing

ELEVATE-RR: Phase 3 Randomized Non-inferiority Open-Label Trial[1,2]

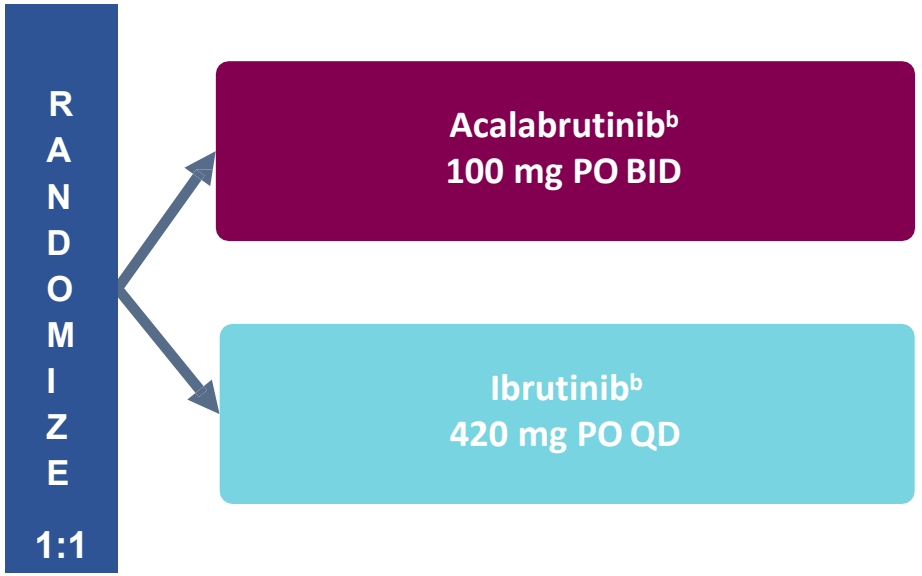
Patients (N=533)

Key Inclusion Criteria

- Adults with previously treated CLL requiring therapy (iwCLL 2008 criteria[1])
- Presence of del(17p) or del(11q)[a]
- ECOG PS of ≤2

Stratification

- del(17p) status (yes or no)
- ECOG PS (2 vs ≤1)
- No. prior therapies (1-3 vs ≥4)



Primary endpoint

- Noninferiority on IRC-assessed PFS[c]

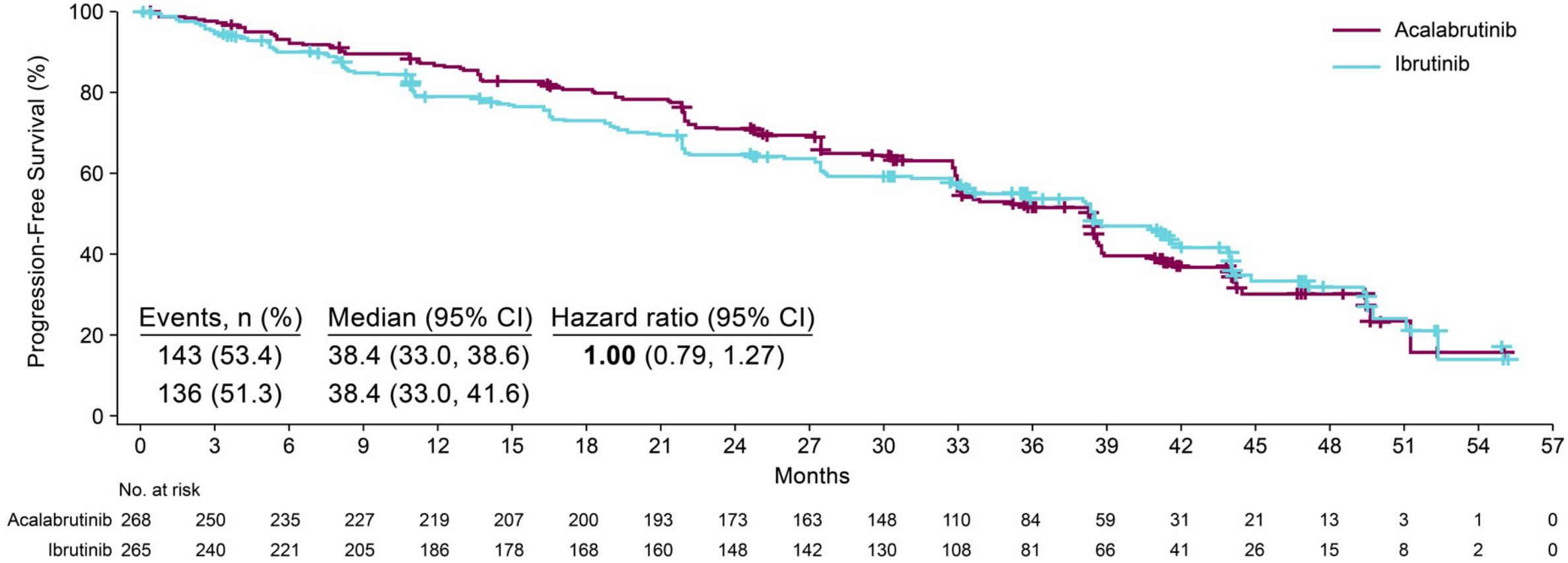
Secondary endpoints (hierarchical order):

- Incidence of Any Grade afib/flutter
- Incidence of Grade ≥3 infection
- Incidence of Richter transformation
- Overall survival

Key exclusion criteria: Significant CV disease; concomitant treatment with warfarin or equivalent vitamin K antagonist; prior treatment with ibrutinib, a BCR inhibitor, (eg, BTK , PI3K, or Syk inhibitors) or a BCL-2 inhibitor (eg, venetoclax)

NCT02477696 (ACE-CL-006). [a]By central laboratory testing. [b]Continued until disease progression or unacceptable toxicity. [c]Conducted after enrollment completion and accrual of ≈250 IRC-assessed PFS events.
Afib, atrial fibrillation; BCL-2, B-cell leukemia/lymphoma-2; BCR, B-cell receptor; BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CV, cardiovascular; del, deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; iwCLL, International Workshop on CLL; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PO, orally; QD, once daily; Syk, spleen tyrosine kinase.
1. Hallek M, et al. *Blood*. 2008;111:5446-56. 2. Byrd JC, et al. Presented at ASCO Virtual Annual Meeting; June 4-8, 2021.

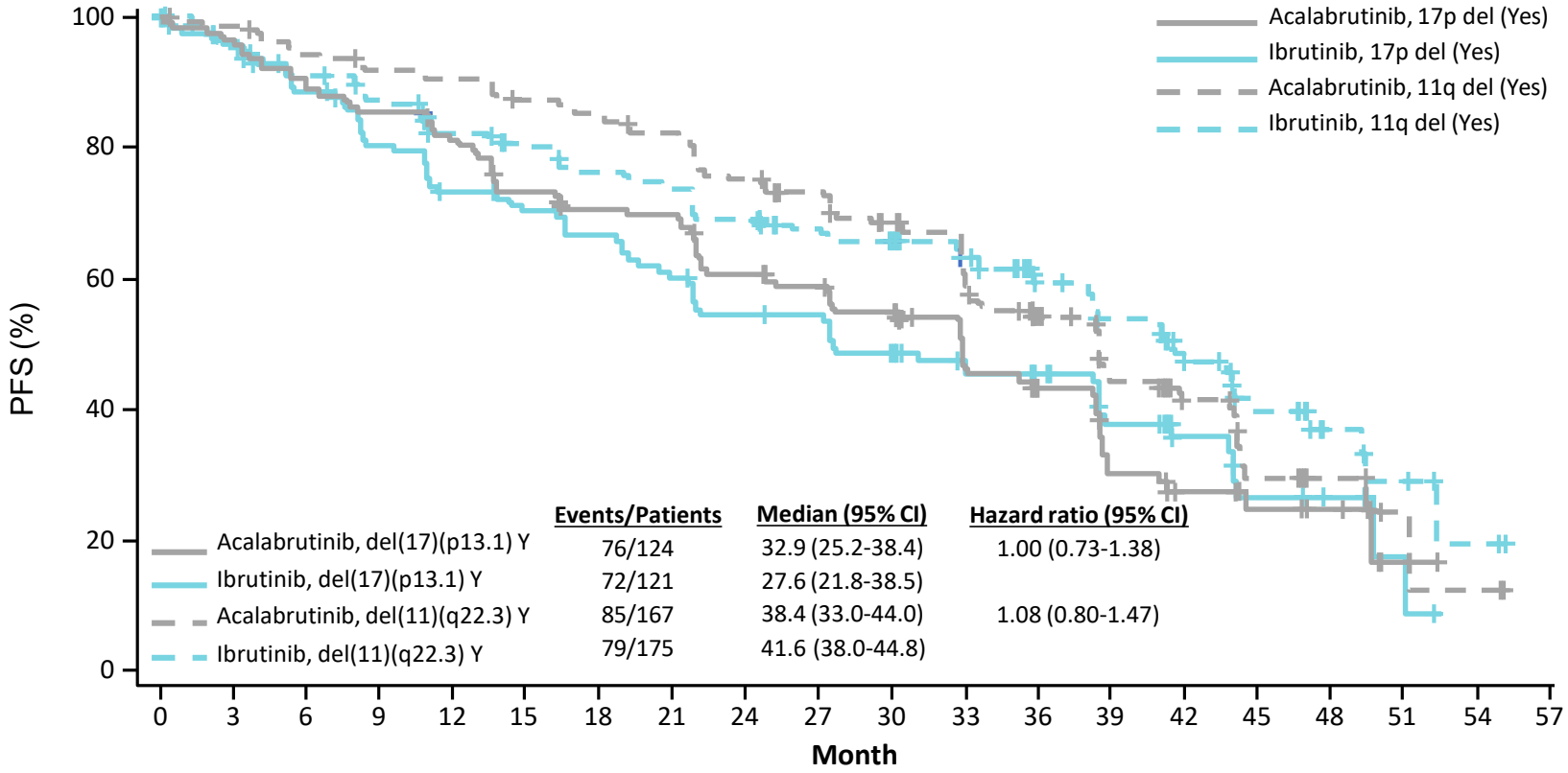
Primary Endpoint: Noninferiority Met on IRC-Assessed PFS



Median follow-up: 40.9 months (range, 0.0-59.1)

CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.
Byrd JC, et al. Presented at ASCO Virtual Annual Meeting; June 4-8, 2021.

IRC-Assessed PFS in Patients With del(17p) or del(11q)



Number at risk

Acalabrutinib 17p del (Yes)	124	113	104	100	94	84	79	78	66	63	58	43	35	23	14	10	7	1	0
Ibrutinib 17p del (Yes)	121	112	100	89	80	75	71	64	57	56	49	43	38	29	16	11	7	2	0
Acalabrutinib 11q del (Yes)	167	159	151	146	144	138	135	129	118	110	100	74	55	40	20	12	7	2	1	0
Ibrutinib 11q del (Yes)	175	157	147	139	127	123	115	111	104	99	95	78	55	47	30	18	10	7	2	0

CI, confidence interval; del, deletion; IRC, independent review committee; PFS, progression-free survival.

Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

Secondary Endpoints

ITT population	Acalabrutinib (n=266)	Ibrutinib (n=263)	Difference in TEAE incidence rates [acalabrutinib minus ibrutinib], %	*P* value[b]
Atrial fibrillation/flutter, all Grades, n (%) 95% CI[a]	25 (9.4) (6.4-13.5)	42 (16.0) (12.0-20.9)	**−6.6** (−12.2-−0.9)	**0.0228**
Infections, Grade ≥3, n (%) 95% CI[a]	82 (30.8) (25.6-36.6)	79 (30.0) (24.8-35.8)	+0.8 (−7.1-8.6)	0.8777
Richter's transformation, n (%) 95% CI[a]	10 (3.8) (2.1- 6.8)	13 (4.9) (2.9- 8.3)	−1.2 (−4.7-2.3)	0.5131

≥5% difference between arms are highlighted; **green** favors acalabrutinib, **red** favorsibrutinib.
[a]95% CI based on Normal approximation (with use of Wilson's score).
[b]Based on Cochran-Mantel-Haenzel test stratified by del(17p) status (yes vs no) and number of prior therapies (1 to 3 vs ≥4).

BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; del, deletion; ITT, intention to treat; TEAE, treatment-emergent adverse event.

Events of Clinical Interest

Events, n (%)	Any Grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Cardiac events	64 (24.1)	79 (30.0)	23 (8.6)	25 (9.5)
Atrial fibrillation[a,f]	25 (9.4)	**42 (16.0)**	13 (4.9)	10 (3.8)
Ventricular arrhythmias[b]	0	3 (1.1)	0	1 (0.4)
Bleeding events[f]	101 (38.0)	**135 (51.3)**	10 (3.8)	12 (4.6)
Major bleeding events[c]	12 (4.5)	14 (5.3)	10 (3.8)	12 (4.6)
Hypertension[d, f]	25 (9.4)	**61 (23.2)**	11 (4.1)	**24 (9.1)**
Infections[e]	208 (78.2)	214 (81.4)	82 (30.8)	79 (30.0)
ILD/pneumonitis[f]	7 (2.6)	**17 (6.5)**	1 (0.4)	2 (0.8)
SPMs excluding NMSC	24 (9.0)	20 (7.6)	16 (6.0)	14 (5.3)

All Grade cardiac arrhythmias of unspecified origin were reported including tachycardia (2.6%), arrhythmia (0.8%) and extrasystoles (0.8%) for acalabrutinib; tachycardia (2.7%), arrhythmia (0.8%), and extrasystoles (0.4%) for ibrutinib

Higher incidence indicated in **bold red** for terms with statistical differences.

[a]Includes events with preferred terms atrial fibrillation and atrial flutter.

[b]Includes events with preferred terms: ventricular arrhythmia, ventricular extrasystoles, and ventricular fibrillation.

[c]Defined as any hemorrhagic event that was serious, Grade ≥3 in severity, or a central nervous system hemorrhage (any severity grade).

[d]Included events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.

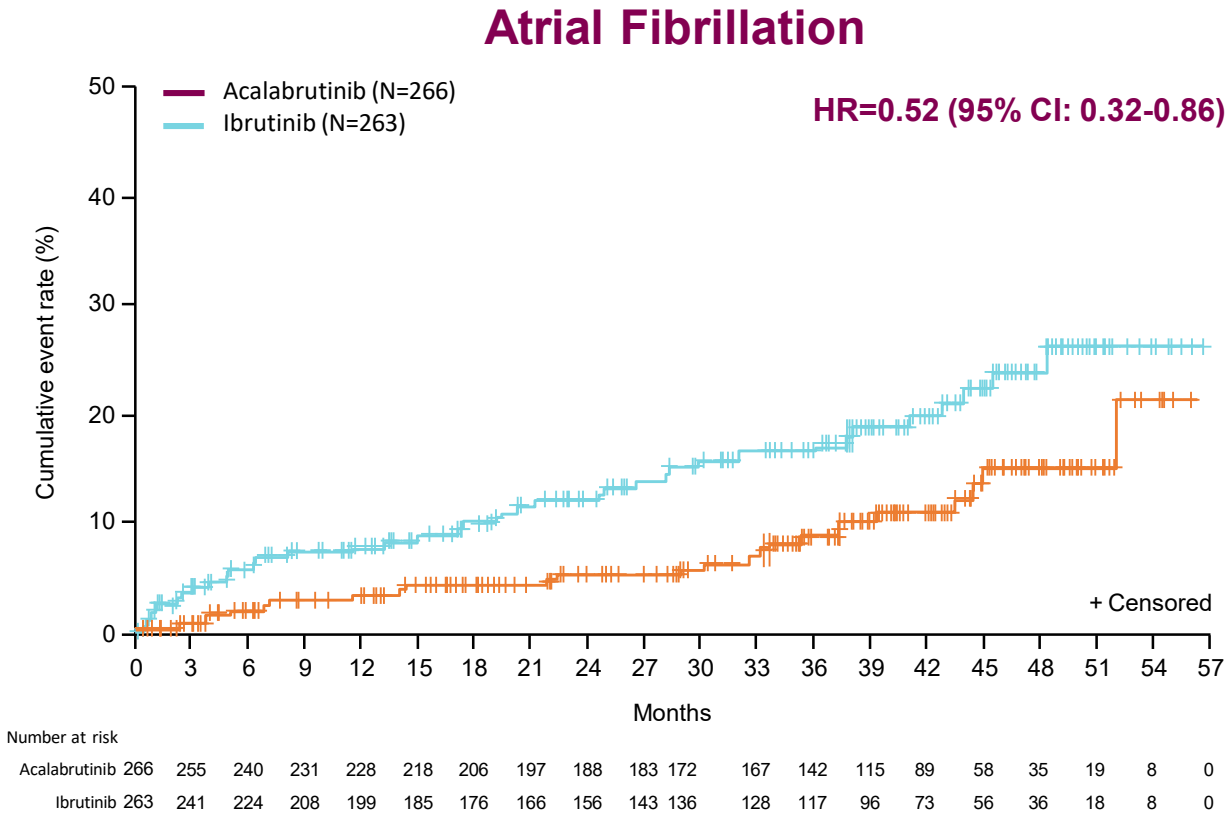
[e]Most common Grade ≥3 infections were pneumonia (acalabrutinib, 10.5%; ibrutinib, 8.7%), sepsis (1.5% vs 2.7%, respectively), and UTI (1.1% vs 2.3%).

[f]Two-sided *P* value for event comparisons <0.05 without multiplicity adjustment.

ILD, interstitial lung disease; NMSC, nonmelanoma skin cancer; SPM, second primary malignancy; UTI, urinary tract infection.

Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

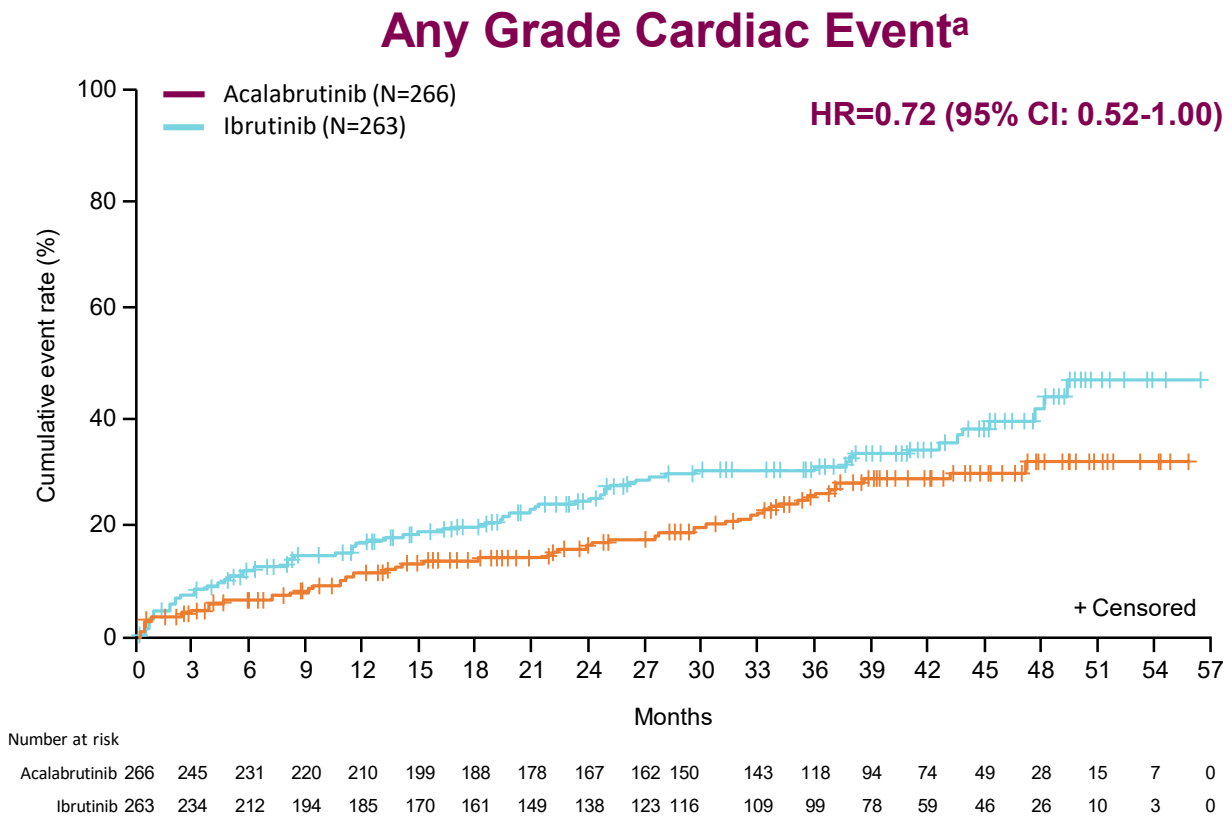
Cumulative Incidence and Summary of Atrial Fibrillation/Flutter of Any Grade



n (%)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Afib/flutter	**25 (9.4)[a,c]**	**42 (16.0)[a]**
Events/100 person-months	0.366	0.721
Time to onset, median (range), months	28.8 (0.4-52.0)	16.0 (0.5-48.3)
Leading to treatment discontinuation[b]	0	7 (16.7)
Subgroup analysis		
Patients without prior history of afib/flutter	15/243 (6.2)	37/249 (14.9)
Afib/flutter events at 24 months, %	4.5	10.3

[a]Grade ≥3 afib/flutter was reported in 13 (4.9%) in the CALQUENCE arm vs 10 (3.8%) in the ibrutinib arm.
[b]Among patients with events of afib/flutter.
[c]Difference in Any Grade incidence rates: −6.6% (95% CI: −12.2 to −0.9); *P*=0.02.
Afib, atrial fibrillation; CI, confidence interval; HR, hazard ratio.
Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

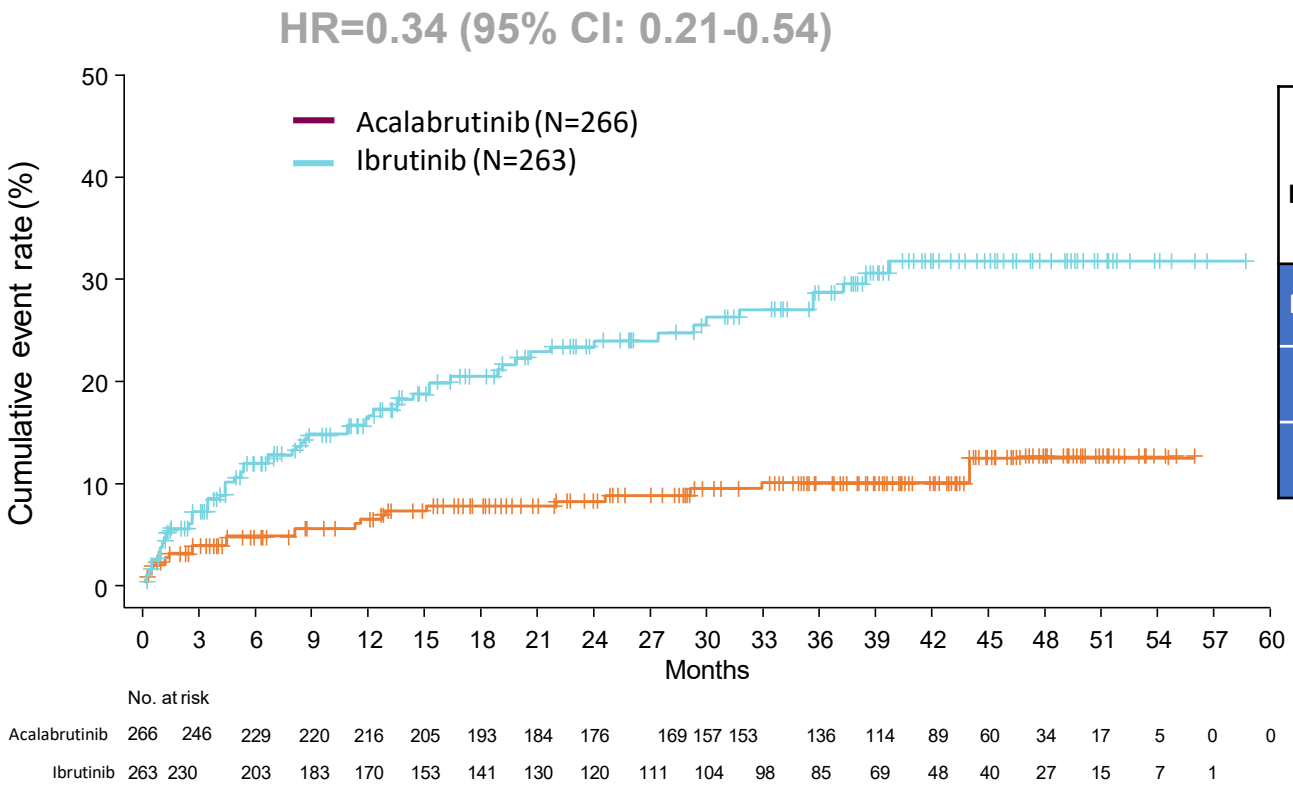
Cumulative Incidence of Cardiac Events



[a]Cardiac events include cardiac arrhythmias, cardiac disorders, signs and symptoms not elsewhere classifiable, coronary artery disorders, heart failures, pericardial disorders, cardiac valve disorders, and myocardial disorders. CI, confidence interval; HR, hazard ratio.

Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

Cumulative Incidence and Summary of HTN



Events	Acalabrutinib (n=266)		Ibrutinib (n=263)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
HTN events[a]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Events/100 person-months	0.444	0.133	1.243	0.435
Patients with a history of HTN	16 (64.0)	9 (81.8)	30 (49.2)	16 (66.7)

Percentages are based on the number of patients with the event.

[a]Includes events with the preferred terms of hypertension, blood pressure increased, and blood pressure systolic increased.
CI, confidence interval; HR, hazard ratio; HTN, hypertension.

Byrd JC, et al. *J Clin Oncol*. 2021;39(31):3441-3452.

Zanubrutinib on the way

OncLive
Bringing the Global Oncology Community Together

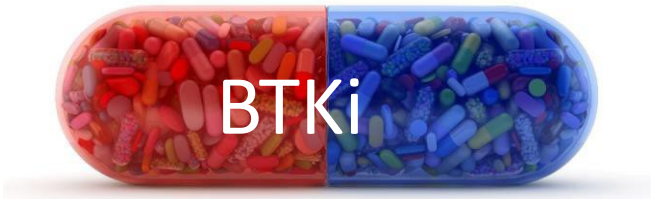
Final Response Analysis of ALPINE Trial Shows Superior ORR With Zanubrutinib Vs Ibrutinib in CLL

April 11, 2022
Kristi Rosa

	ORR	12 month PFS	Afib/aflutter	discontinuation
Zanubrutinib	80.4%	94.9%	4.6%	13%
Ibrutinib	72.9%	84%	12.0%	17.6%

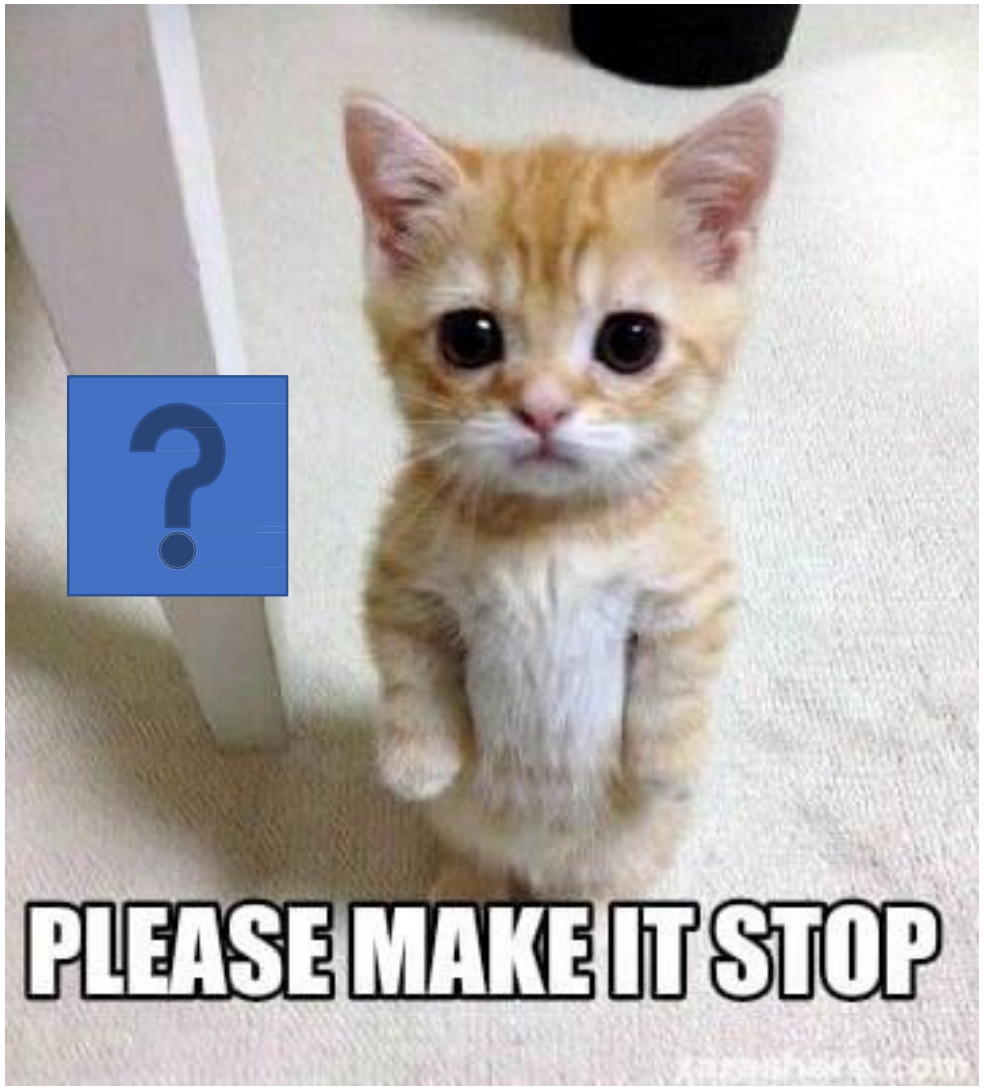
Median f/u 24 months

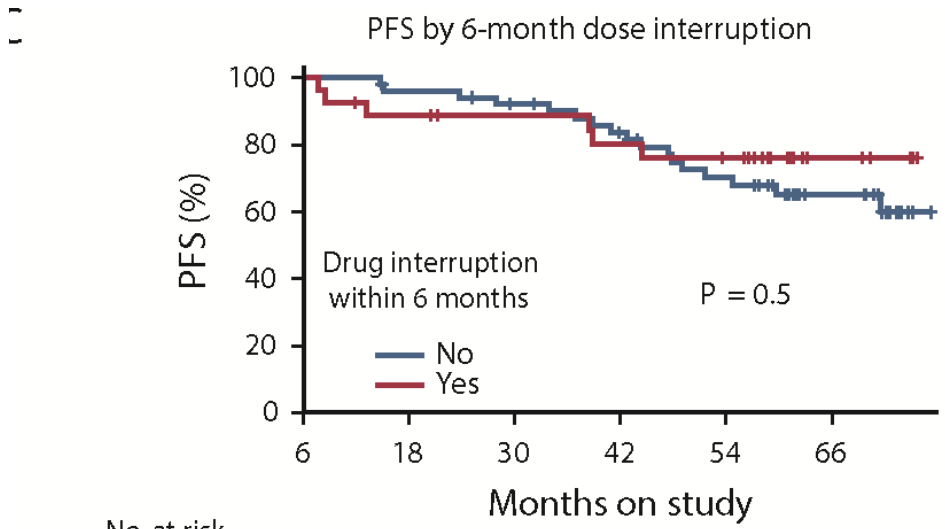
Phase 3 Alpine study in R/R CLL, n = 415, median age 67


BTKi

+

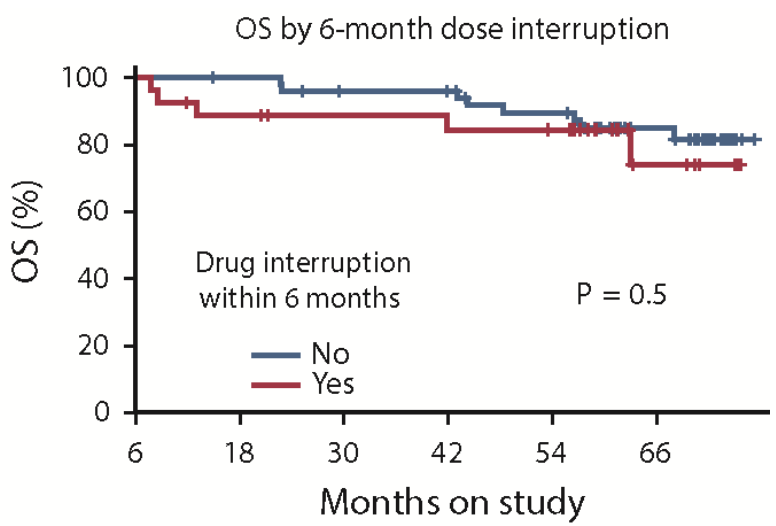
=


?
PLEASE MAKE IT STOP



No. at risk						
No Interruption	52	49	45	39	31	18
Interruptions	27	23	21	19	17	5

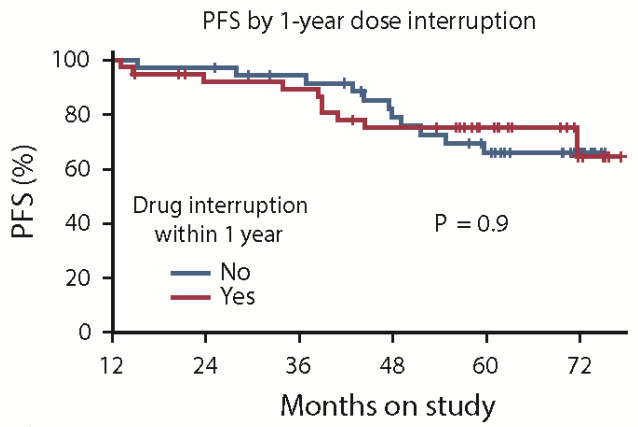
D



No. at risk						
No Interruption	52	51	47	46	41	24
Interruptions	28	24	21	20	19	6

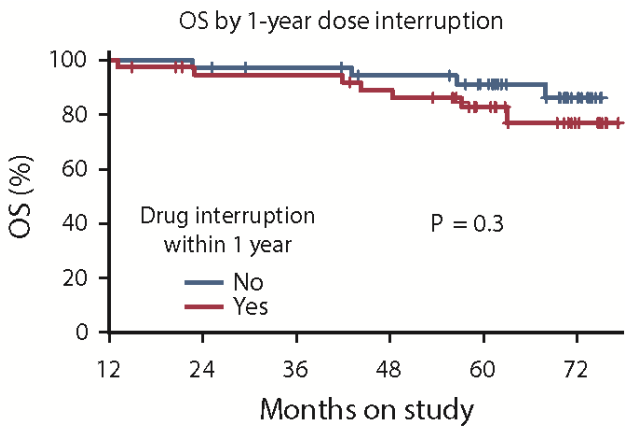
Missed ibrutinib:
> 8 days 68%
> 15 days 48%

E



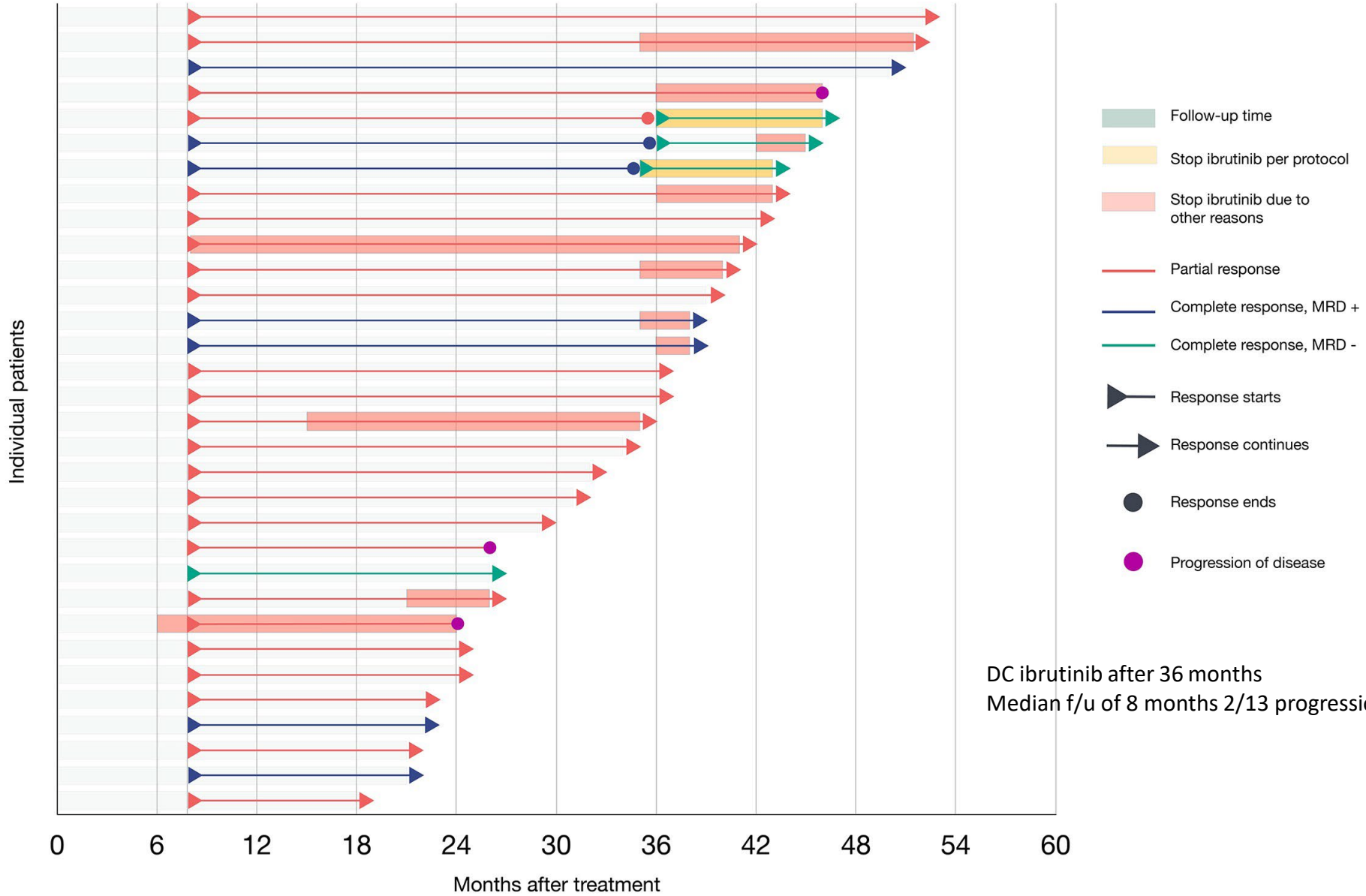
No. at risk						
No Interruption	37	36	32	25	18	8
Interruptions	39	33	32	26	16	5

F



No. at risk						
No Interruption	37	36	34	31	25	9
Interruptions	40	35	34	31	19	7

Blood (2019) 133 (22): 2452–2455.



DC ibrutinib after 36 months
Median f/u of 8 months 2/13 progression (10 months and 17 months)

Figure 1. Swimmers plot of patients enrolled
This figure provides a snapshot of all patients enrolled in the study that received medication. Each bar represents one subject in the study. Patients started treatment at time point zero. First response assessment occurred eight months after initiation of therapy according to iWCLL 2018 guidelines.

Blood 2020 Suppl (1) 33-34

CLL-”Best” initial therapy

- Is watchful waiting still the best option? → YES, unless on study
- Any role for chemotherapy?→ not really….
- Ongoing Treatment with single agent BTKi
  - Which BTKi? → acalabrutinib
  - In combination? → no
  - Treatment interruption? → ? Perhaps ?
- MRD negativity as a treatment goal
- Fixed duration therapy

MRD- Is this the goal of CLL directed therapy?

MRD = minimal residual disease

MRD

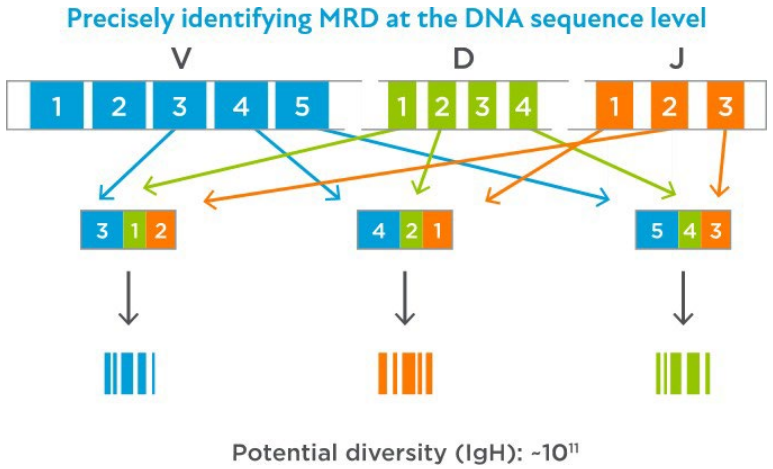
- Not applicable to continuous BTKi
- MRD negativity is associated with longer PFS with fixed duration therapy

  -FCR, MCF* (10^{-4}) in marrow gold standard

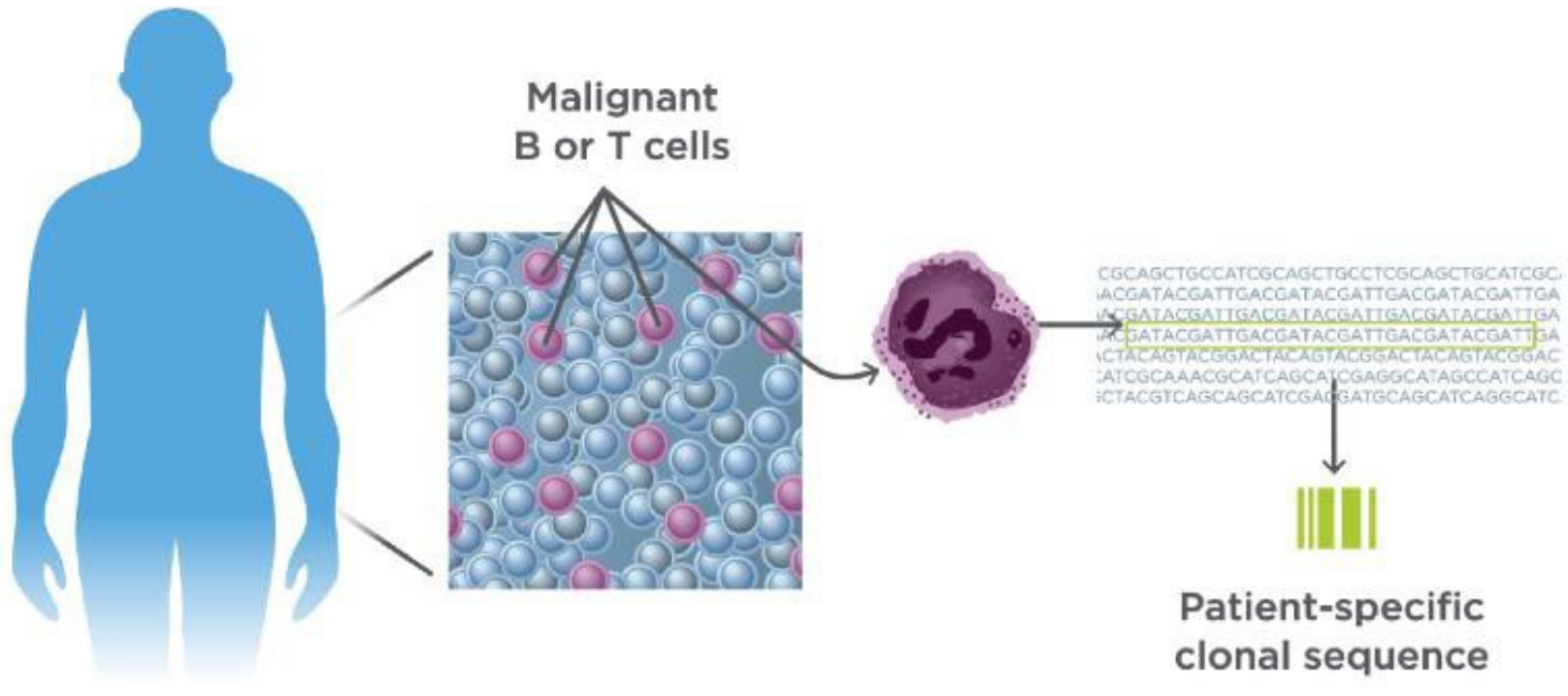
  -outcomes the same irrespective of number of FCR cycles
- What is the best platform to use?
  - MCF or NGS?
- What should one do with the information?
- Should I monitor MRD serially?

MCF = 6 color multi color flow cytometry

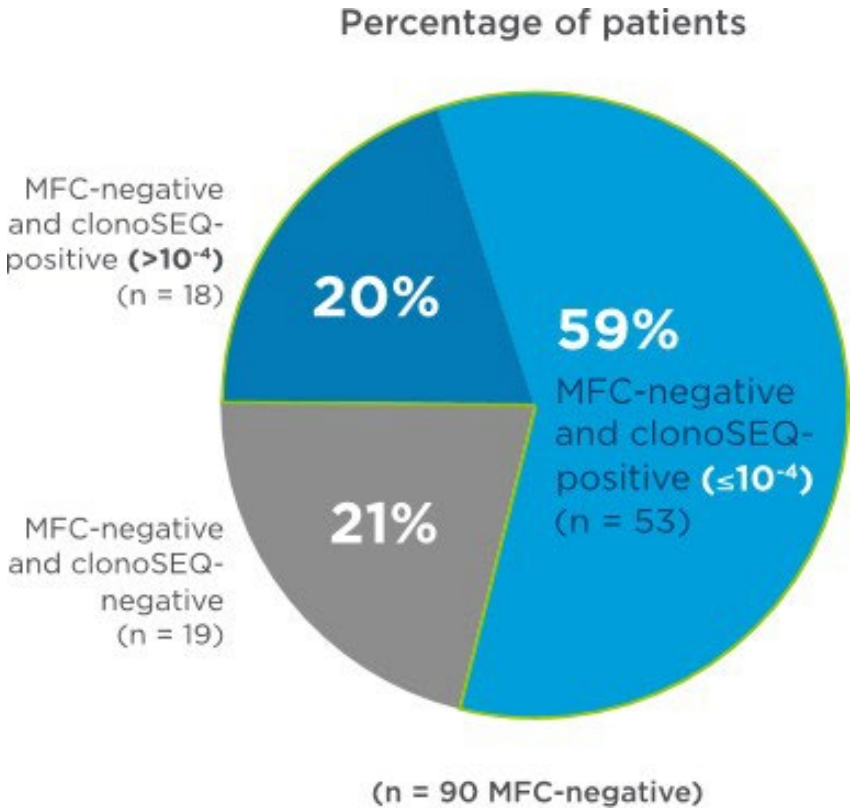
clonoSEQ
By Adaptive

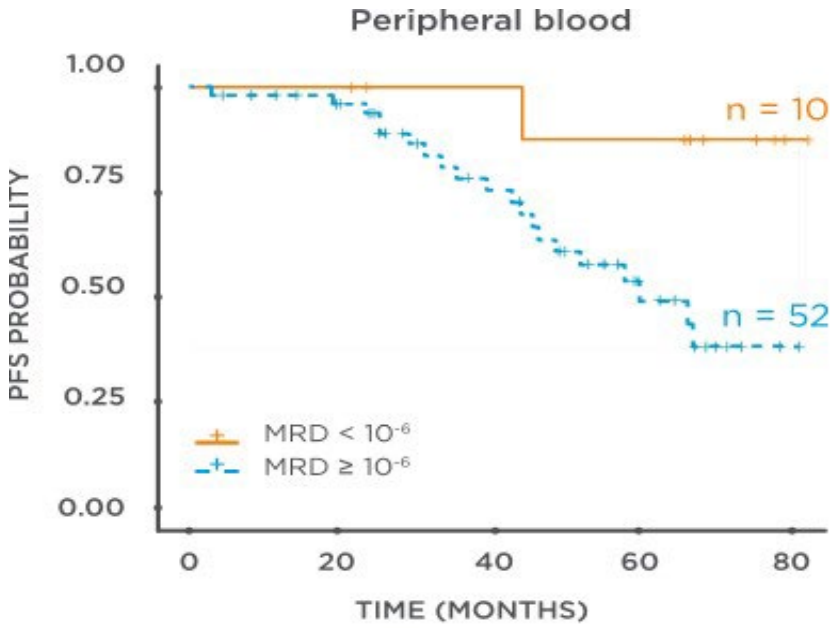


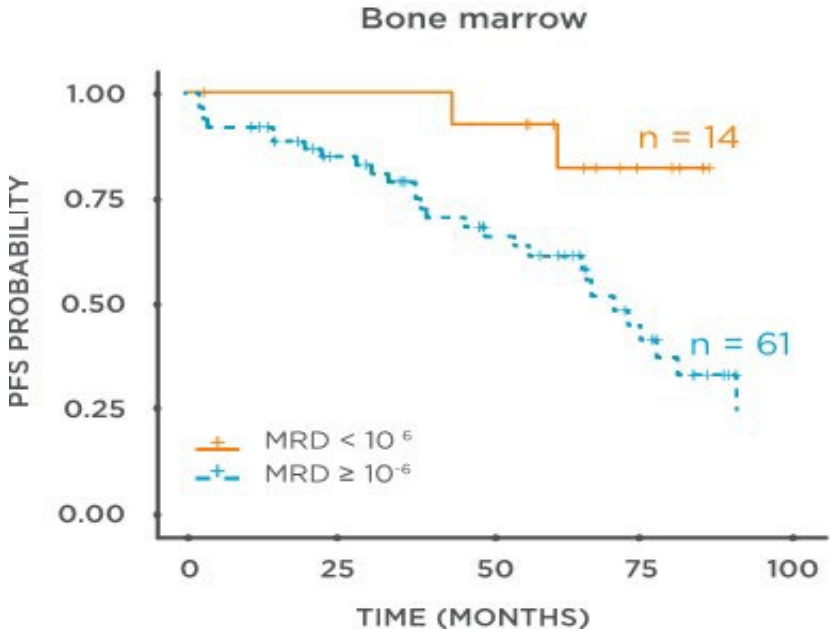
Potential diversity (IgH): ~10^{11}



NGS more sensitive than MCF





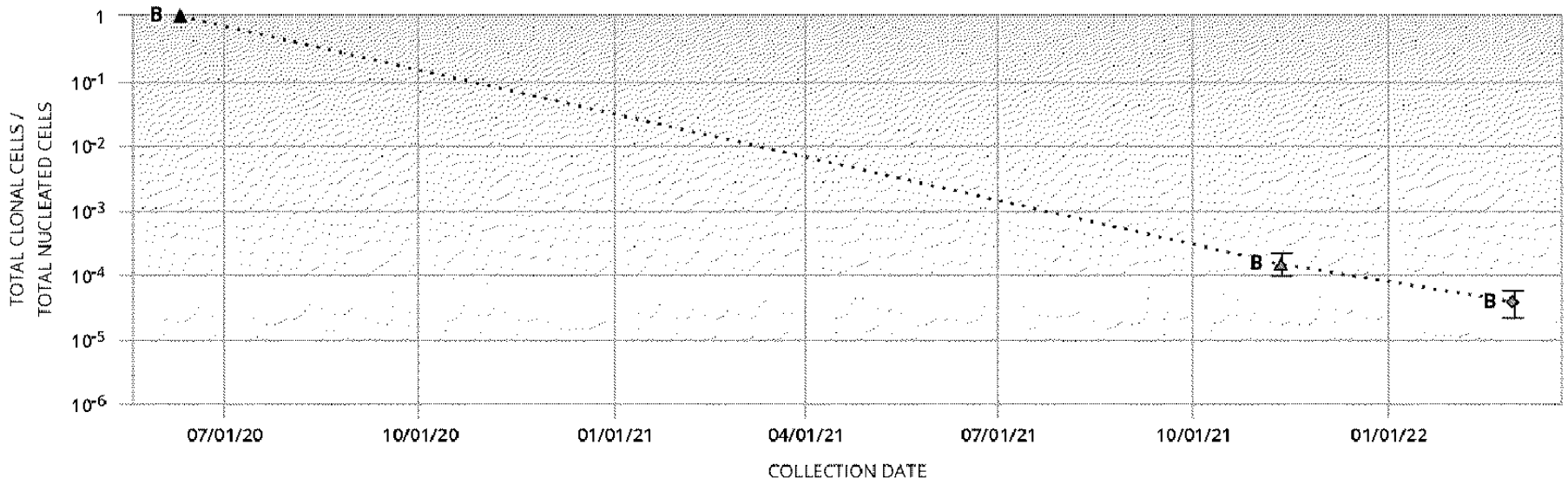


clonoSEQ is quantitative

RESULTS SUMMARY

- Genomic DNA was extracted from a blood sample.
- 6 of the 6 dominant sequences identified in a diagnostic sample from this patient were still present in this current sample.
- 121 copies of the dominant sequence determining the MRD result (IGK Sequence C) were observed out of 3,275,992 total nucleated cells evaluated from this sample.
- **The results obtained from this assay should always be used in combination with the clinical examination, patient medical history, and other findings.**

SAMPLE-LEVEL MRD TRACKING *(shows only the sequence determining the MRD result for each time point)*



Fixed Duration Therapy

MRD as a meaningful endpoint

71 A Randomized Phase III Study of Venetoclax-Based Time-Limited Combination Treatments (RVe, GVe, GIVe) Vs Standard Chemoimmunotherapy (CIT: FCR/BR) in Frontline Chronic Lymphocytic Leukemia (CLL) of Fit Patients: First Co-Primary Endpoint Analysis of theInternational Intergroup GAIA (CLL13) Trial

Figure 1. Comparison of uMRD rates by flow and treatment responses (CR: complete response; CRi: complete response with incomplete bone marrow recovery; PR: partial response; SD: stable disease; PD: progressive disease)

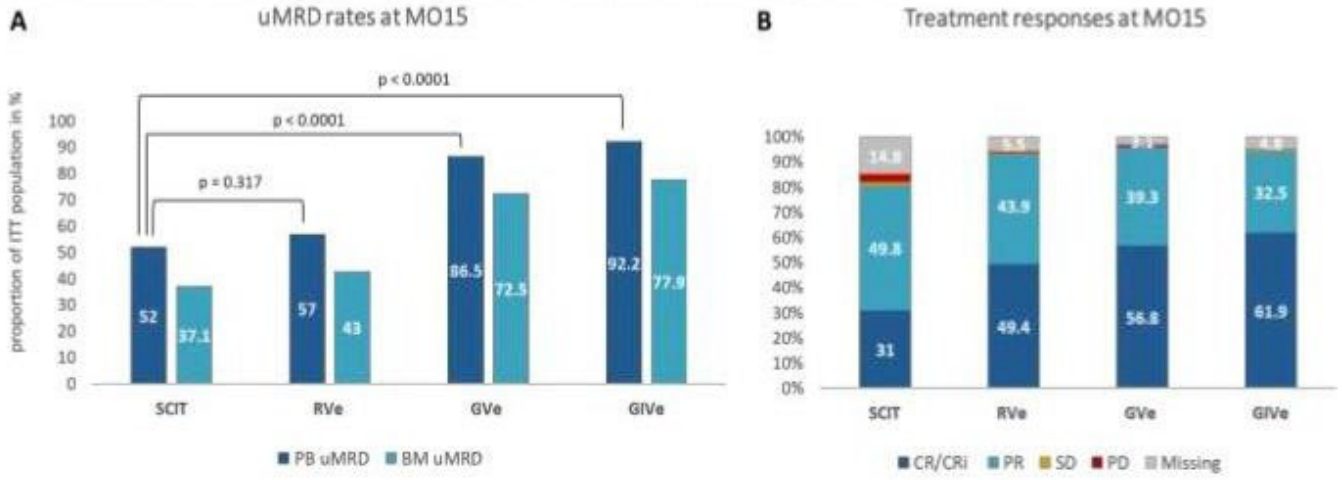


Table 1. Treatment-emergent AEs according to the common toxicity criteria (CTC) that occurred in ≥5% (grades 3-5) of pts plus AEs of interest

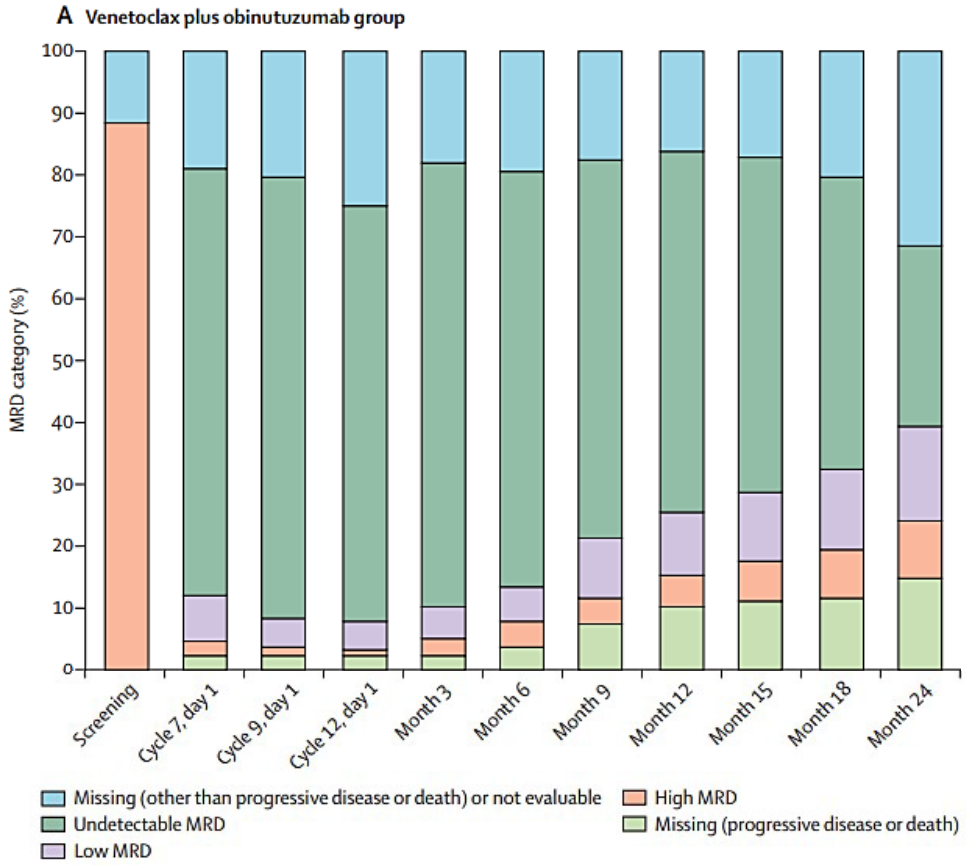
Treatment-emergent adverse events	SCIT	RVe	GVe	GIVe	Total
All pts [safety population], N	**216**	**237**	**228**	**231**	**912**
Max CTC grade, N (%)					
Max. grade 1 – 2	42 (19.4)	60 (25.3)	32 (14.0)	38 (16.5)	172 (18.9)
Max. grade 3	81 (37.5)	111 (46.8)	113 (49.6)	107 (46.3)	412 (45.2)
Max. grade 4	84 (38.9)	51 (21.5)	74 (32.5)	74 (32.0)	283 (31.0)
Max. grade 5	5 (2.3)	7 (3.0)	6 (2.6)	9 (3.9)	27 (3.0)
Anemia	31 (14.4)	20 (8.4)	19 (8.3)	21 (9.1)	91 (10.0)
Grade 3 and higher	16 (7.4)	9 (3.8)	11 (4.8)	9 (3.9)	45 (4.9)
Neutropenia	120 (55.6)	126 (53.2)	134 (58.8)	131 (56.7)	511 (56.0)
Grades 3 and higher	113 (52.3)	109 (46.0)	127 (55.7)	112 (48.5)	461 (50.5)
Thrombocytopenia	41 (19.0)	24 (10.1)	53 (23.2)	69 (29.9)	187 (20.5)
Grades 3 and higher	22 (10.2)	10 (4.2)	42 (18.4)	37 (16.0)	111 (12.2)
Febrile neutropenia	24 (11.1)	10 (4.2)	8 (3.5)	18 (7.8)	60 (6.6)
Grades 3 and higher	24 (11.1)	10 (4.2)	7 (3.1)	18 (7.8)	59 (6.5)
Infections	131 (60.6)	141 (59.5)	155 (68.0)	174 (75.3)	601 (65.9)
Grades 3 and higher	43 (19.9)	27 (11.4)	32 (14.0)	51 (22.1)	153 (16.8)
Pneumonia	20 (9.3)	9 (3.8)	22 (9.6)	30 (13.0)	81 (8.9)
Grades 3 and higher	14 (6.5)	5 (2.1)	13 (5.7)	16 (6.9)	48 (5.3)
Infusion-related reaction	70 (32.4)	82 (34.6)	119 (52.2)	53 (22.9)	324 (35.5)
Grades 3 and higher	12 (5.6)	18 (7.6)	26 (11.4)	10 (4.3)	66 (7.2)
Tumor lysis syndrome	10 (4.6)	29 (12.2)	26 (11.4)	19 (8.2)	84 (9.2)
Grades 3 and higher	9 (4.2)	24 (10.1)	20 (8.8)	15 (6.5)	68 (7.5)
Bleeding events	13 (6.0)	12 (5.1)	23 (10.1)	64 (27.7)	112 (12.3)
Grades 3 and higher	1 (0.5)	1 (0.4)	1 (0.4)	4 (1.7)	7 (0.8)
Atrial fibrillation	4 (1.9)	2 (0.8)	2 (0.9)	18 (7.8)	26 (2.9)
Grades 3 and higher	1 (0.5)	1 (0.4)	0 (0.0)	6 (2.6)	8 (0.9)

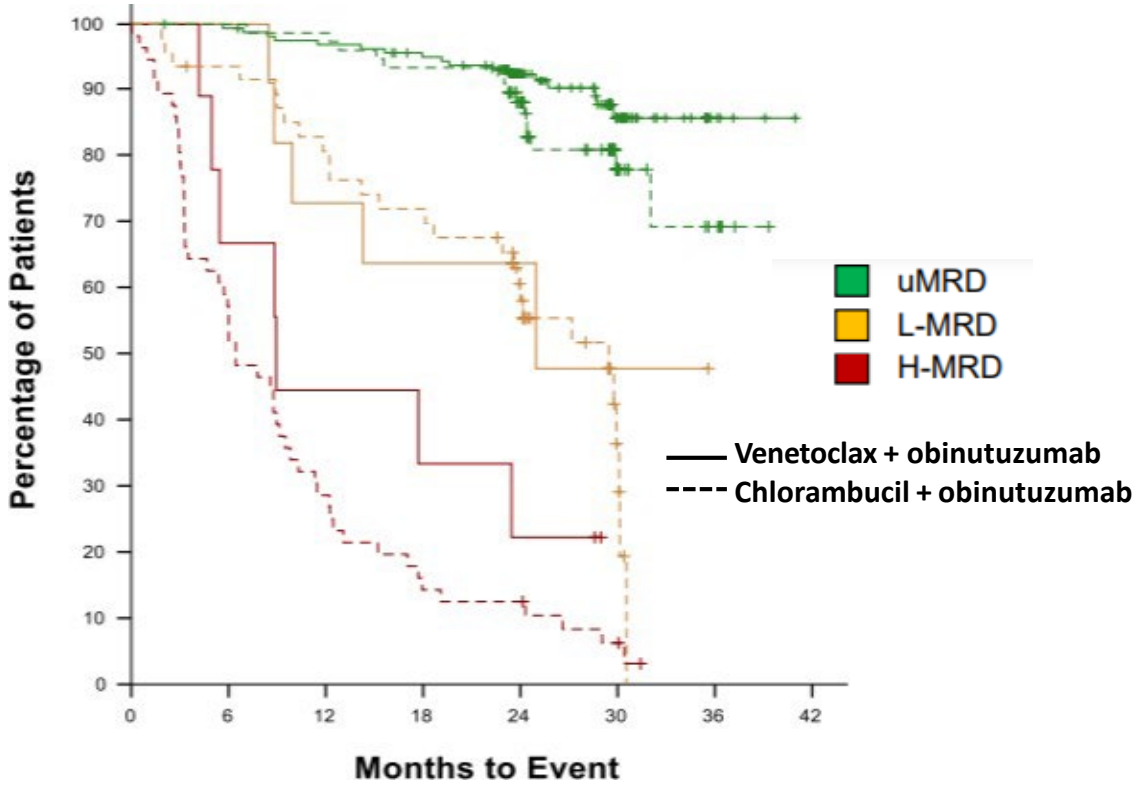
N=926 pts (CIT: 229 (150 FCR, 79 BR), RVe: 237, GVe: 229, GIVe: 231

Venetoclax + Obinutuzumab in TN CLL

Phase III, CLL14 Trial

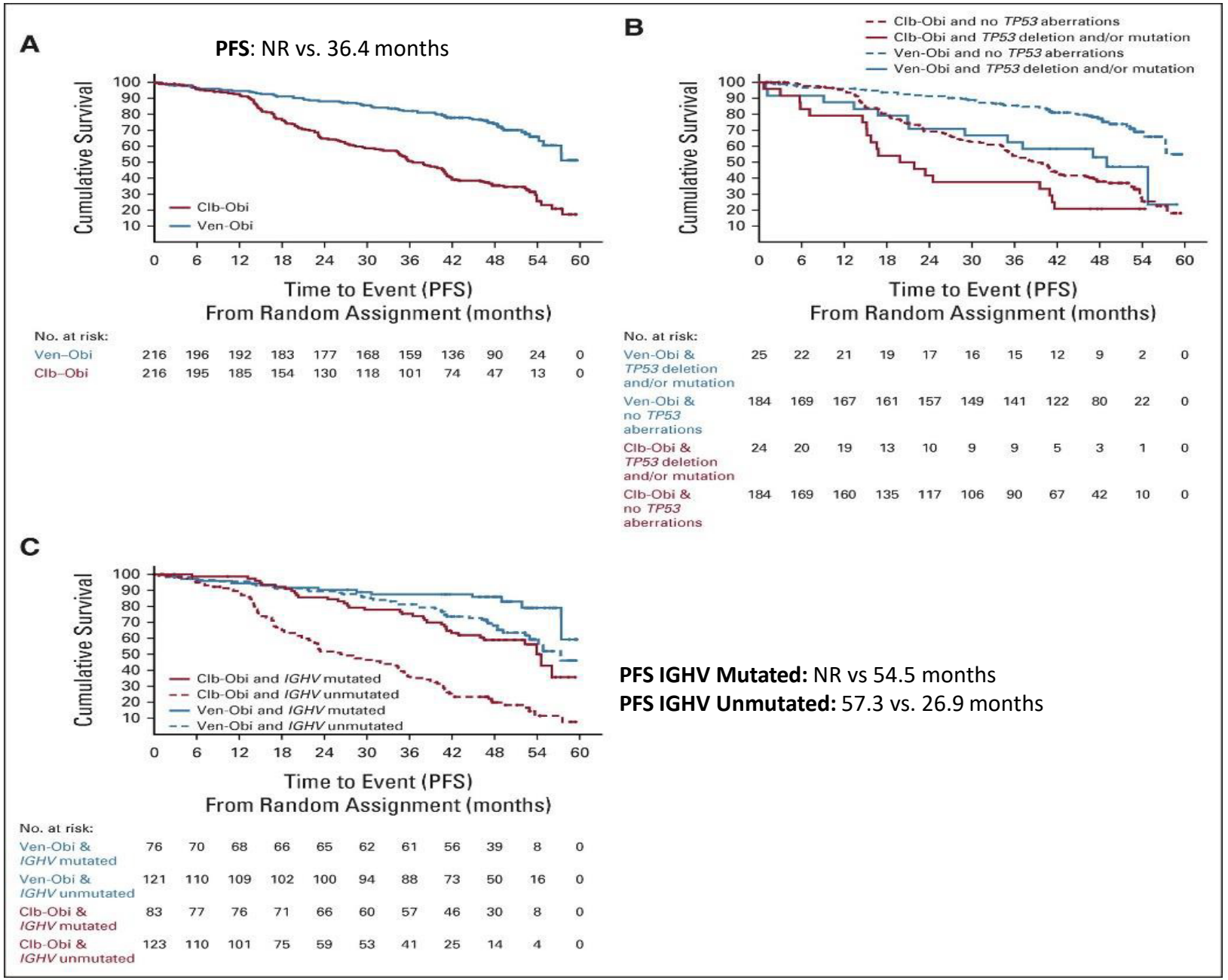
≥65 years or older or <65 years + coexisting conditions (N=432)





Conclusion: MRD negative disease with venetoclax correlates with improved PFS

Fischer K, et al. *N Engl J Med*. 2019; Al-Sawaf O, et al. *Lancet Oncol*. 2020.



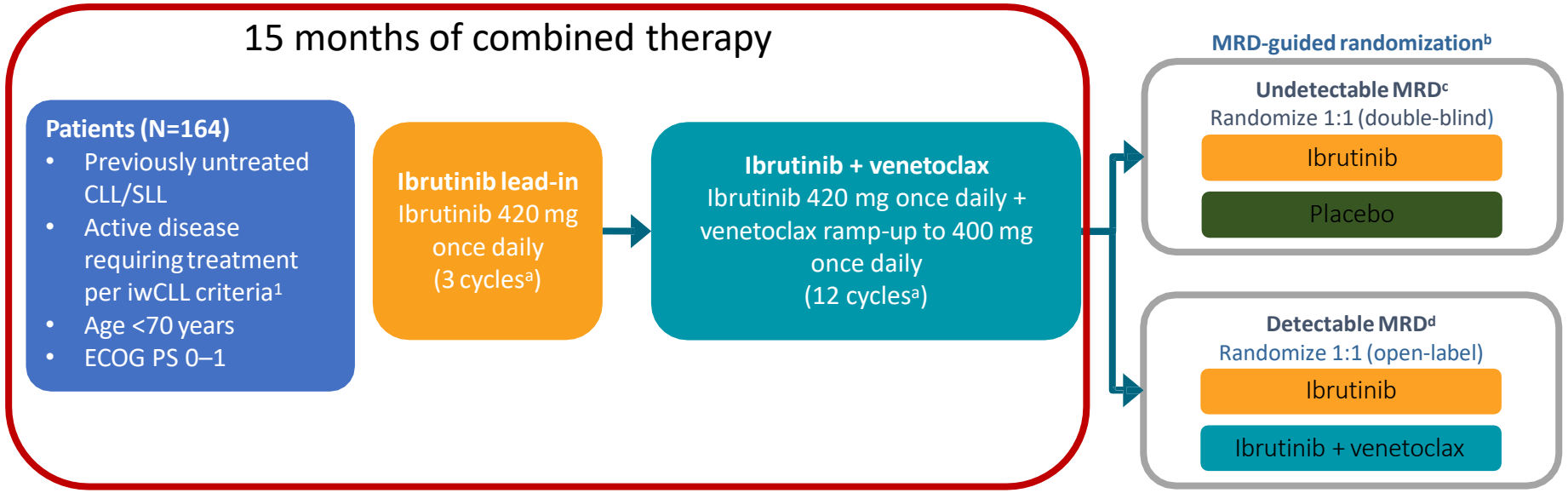
PFS 17p/p53: 49 vs 21 months (p = .03)

PFS IGHV Mutated: NR vs 54.5 months
PFS IGHV Unmutated: 57.3 vs. 26.9 months

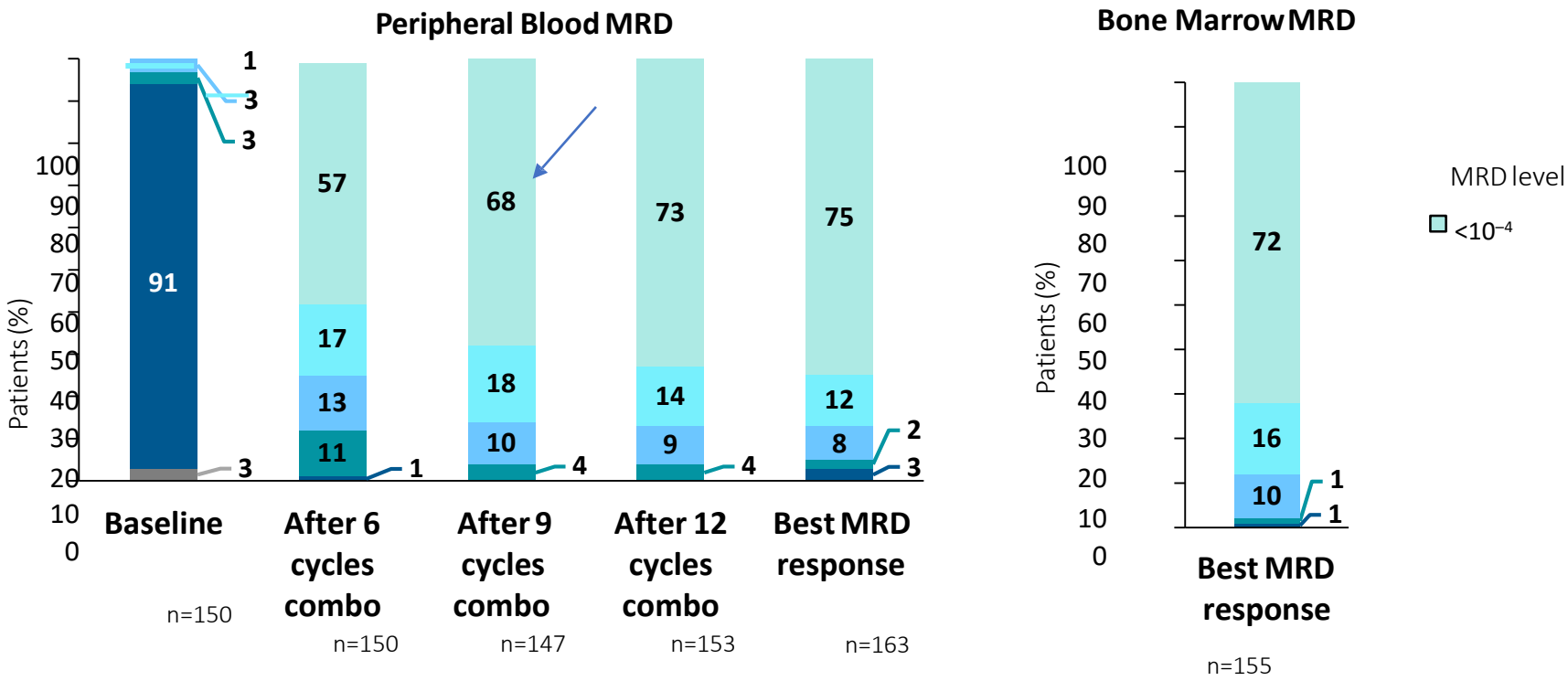
Median follow up 52.4 months

J. Clin Onc. 2021 Dec 20;39(36):4049-4060

Ibrutinib plus venetoclax
CAPTIVATE-MRD Cohort: Study Design



High Rates of Undetectable MRD Sustained Over Time in MRD-Evaluable Patients

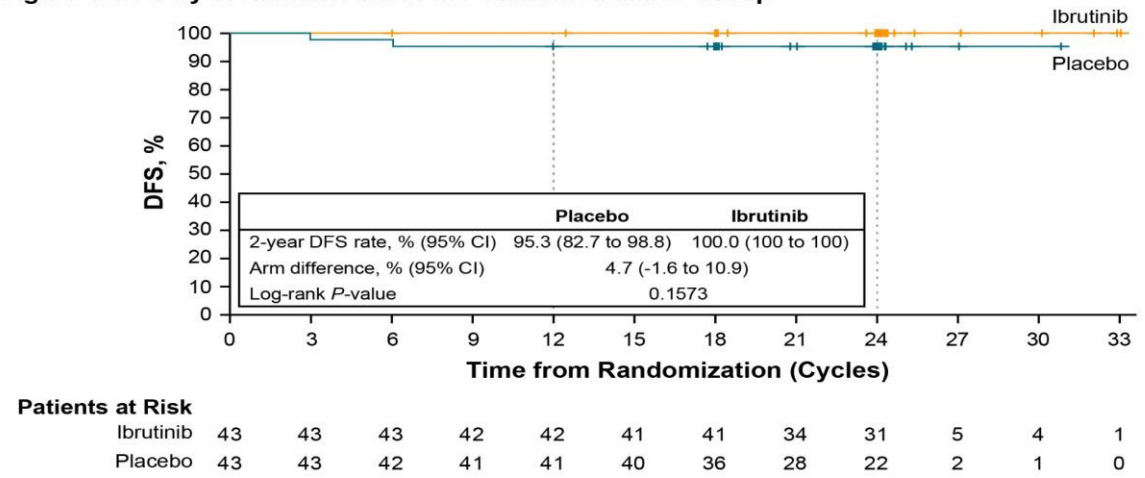


- Proportion of patients with undetectable MRD in peripheral blood increased over the 12 cycles of combination therapy
- In patients with undetectable MRD at cycle 16 in peripheral blood with matched bone marrow samples, 93% had undetectable MRD in both peripheral blood and bone marrow

First-Line Treatment with Ibrutinib (Ibr) Plus Venetoclax (Ven) for Chronic Lymphocytic Leukemia (CLL): 2-Year Post-Randomization Disease-Free Survival (DFS) Results from the Minimal Residual Disease (MRD) Cohort of the Phase 2 Captivate Study

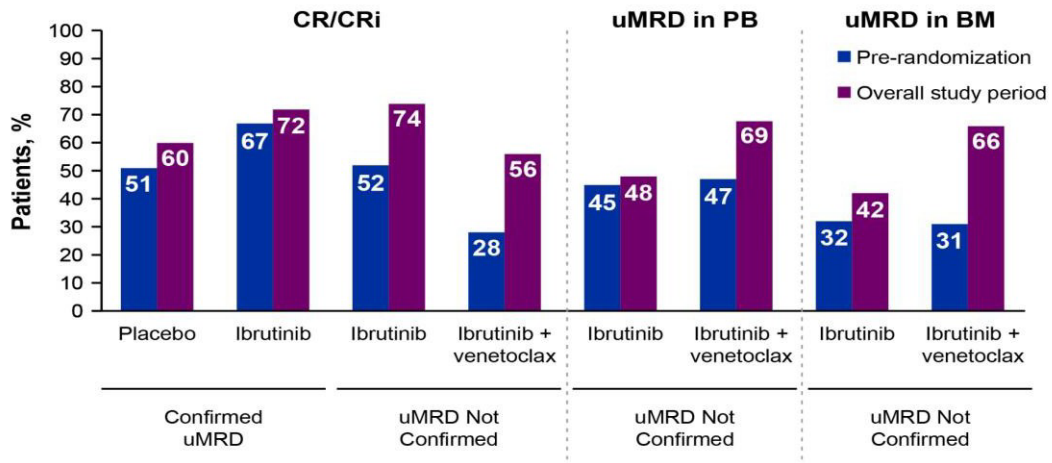
Undetectable MRD[c]
Randomize 1:1 (double-blind)
- Ibrutinib
- Placebo

Figure 1. DFS by Treatment Arm in the Confirmed uMRD Group



Detectable MRD[d]
Randomize 1:1 (open-label)
- Ibrutinib
- Ibrutinib + venetoclax

Figure 2. Change in Best Response Rates Post-randomization



Similar Study with zanubrutinib Fully accrued in poor risk patients (**SEQUOIA (BGB-3111-304) Trial)**

Blood (2021) 138 (Supplement 1): 68.

67 Zanubrutinib in Combination with Venetoclax for Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia (CLL) or Small Lymphocytic Lymphoma (SLL) with del(17p): Early Results from Arm D of the SEQUOIA (BGB-3111-304) Trial

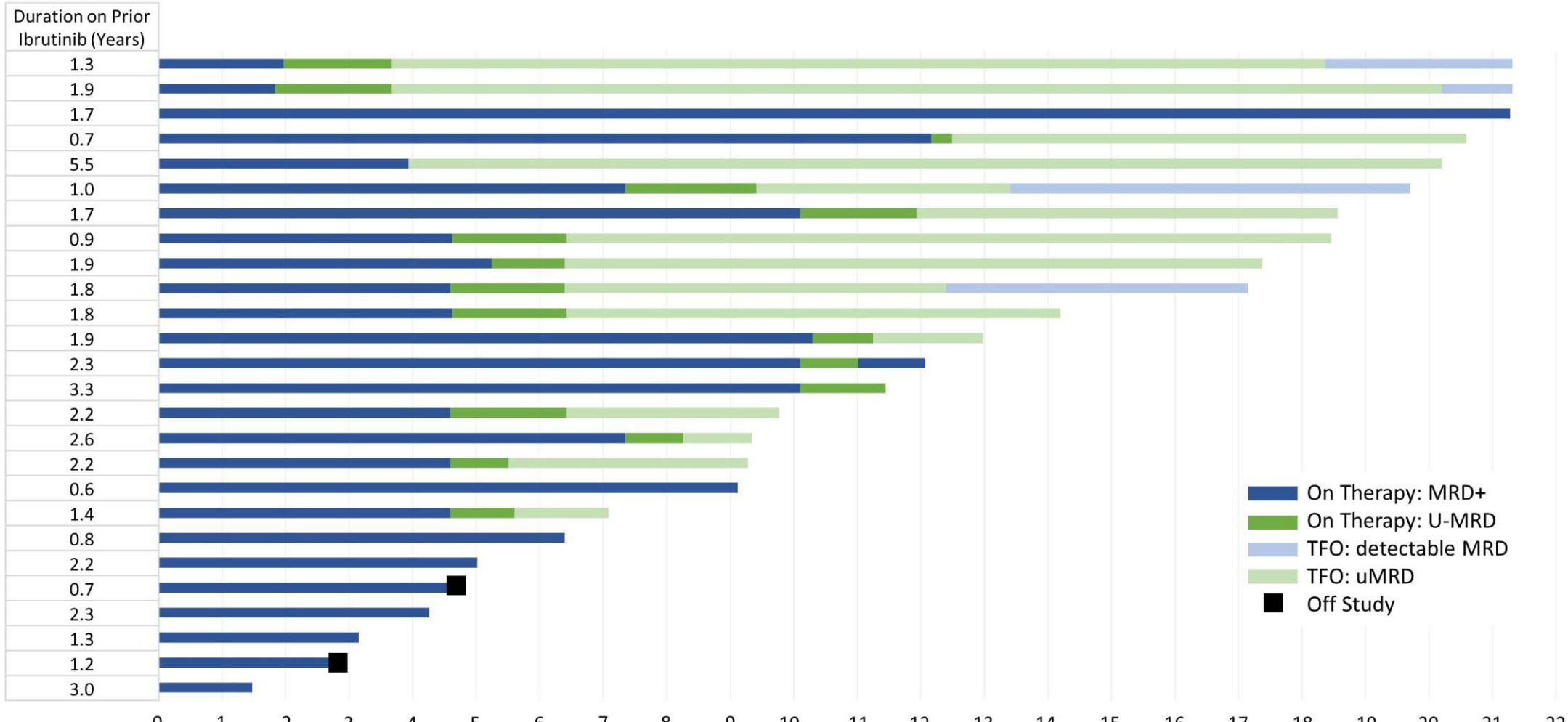
Table: Preliminary Summary of Safety and Efficacy

Safety	
	TN del(17p) CLL/SLL (n = 35)
Median follow-up, mo (range)	9.72 (4.53–16.36)
Any AE, n (%)	29 (82.9)
Grade ≥3 AE, n (%)	13 (37.1)
Serious AE, n (%)	4 (11.4)
Treatment discontinuation due to AE, n (%)	1 (2.9)
Fatal AE, n (%)	1 (2.9)
Efficacy (Best Response)	
	TN del(17p) CLL/SLL (n = 31)
Median follow-up, mo (range)	11.2 (3.0–18.5)
ORR (CR/CRi, PR, or PR-L), n (%) [95% CI]	30 (96.8) [69.7–95.2]
CR/CRi	4 (12.9)
PR	22 (71.0)
PR-L	4 (12.9)
SD	1 (3.2)
PD	0 (0)

AE, adverse event; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete hematological recovery; ORR, overall response rate; PD, progressive disease; PR, partial response; PR-L, PR with lymphocytosis; SD, stable disease; SLL, small lymphocytic lymphoma; TN, treatment-naïve.

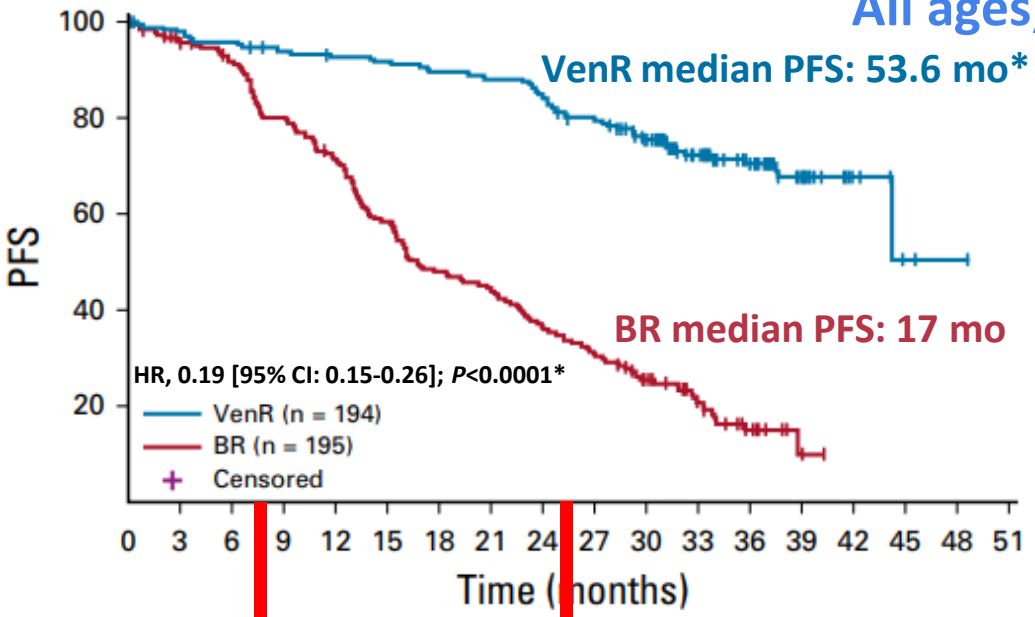
A Phase 2 Study Evaluating the Addition of Ublituximab and Umbralisib (U2) to Ibrutinib in Patients with Chronic Lymphocytic Leukemia (CLL): A Minimal Residual Disease (MRD)-Driven, Time-Limited Approach

Figure 1 Prior Ibrutinib treatment, MRD status, and time on therapy



MRD in the relapsed setting: Venetoclax + Rituximab in R/R CLL *Phase III, MURANO Trial*

All ages; (median age: 65); N=389

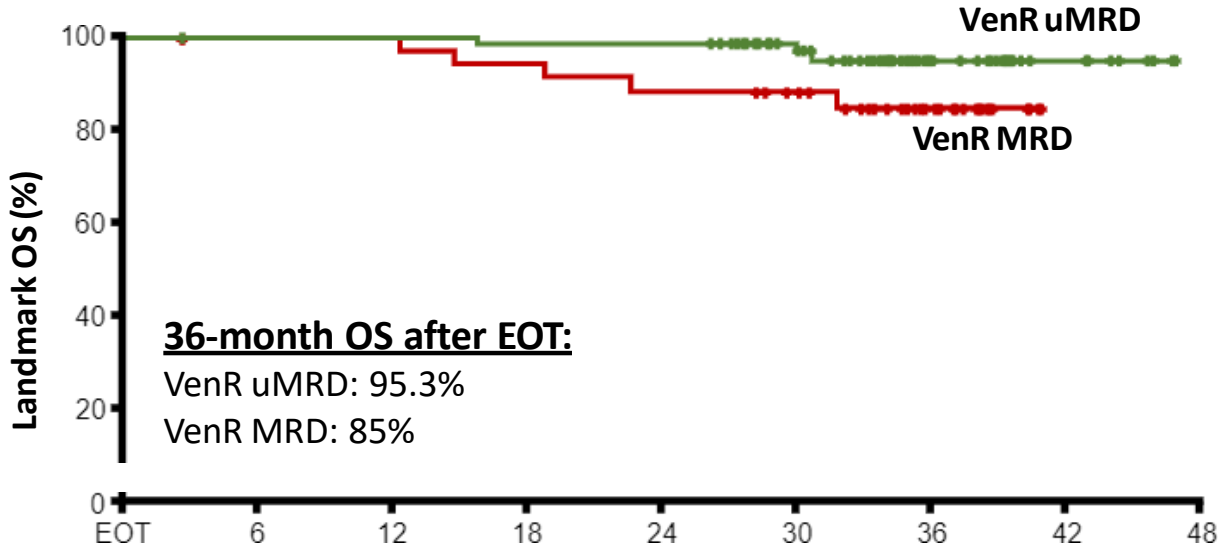


62% of VenR arm had uMRD at EOCT

48% of VenR arm had uMRD at EOT

Baseline del17p, unmutated IGVH, genomic complexity (≥3 copy # variations) associated with increased risk of MRD conversion post-EOT

Landmark OS by PB MRD Status at EOT in Patients that Completed Ven Tx without PD



High rates of uMRD with venetoclax combination correlates with improved OS

*Updated ASH 2020

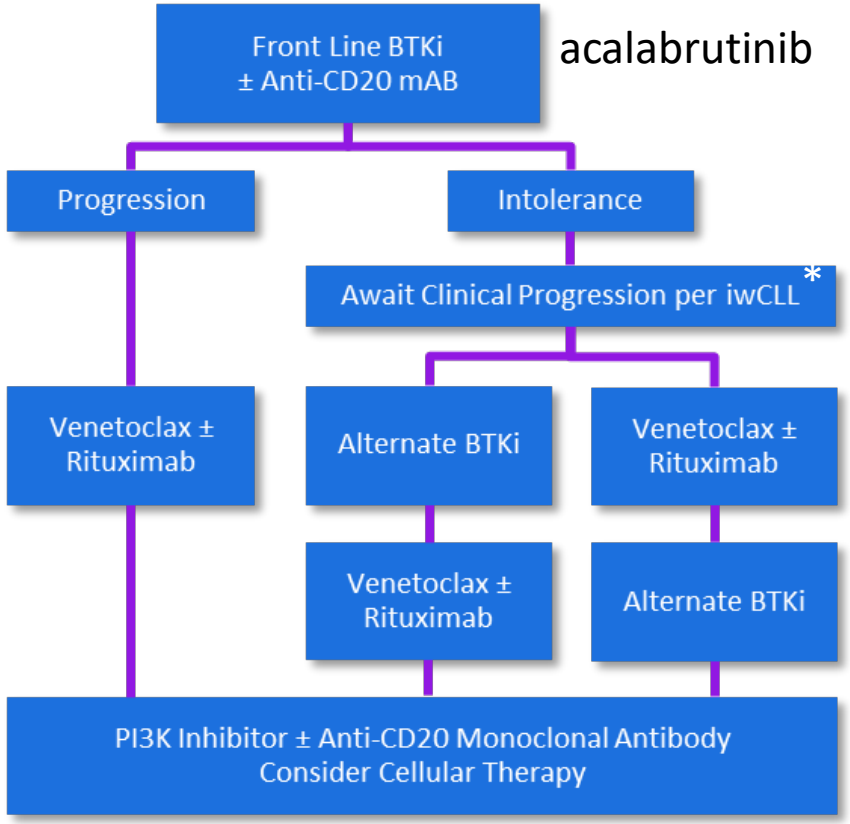
uMRD, undetectable minimalresidual disease; EOCT, end of combination therapy; EOT, end of therapy; NR, not reached.

Kater AP, et al. *J Clin Oncol*. 2019; Kater AP, et al. *ASH.* 2020. Abstract 125.

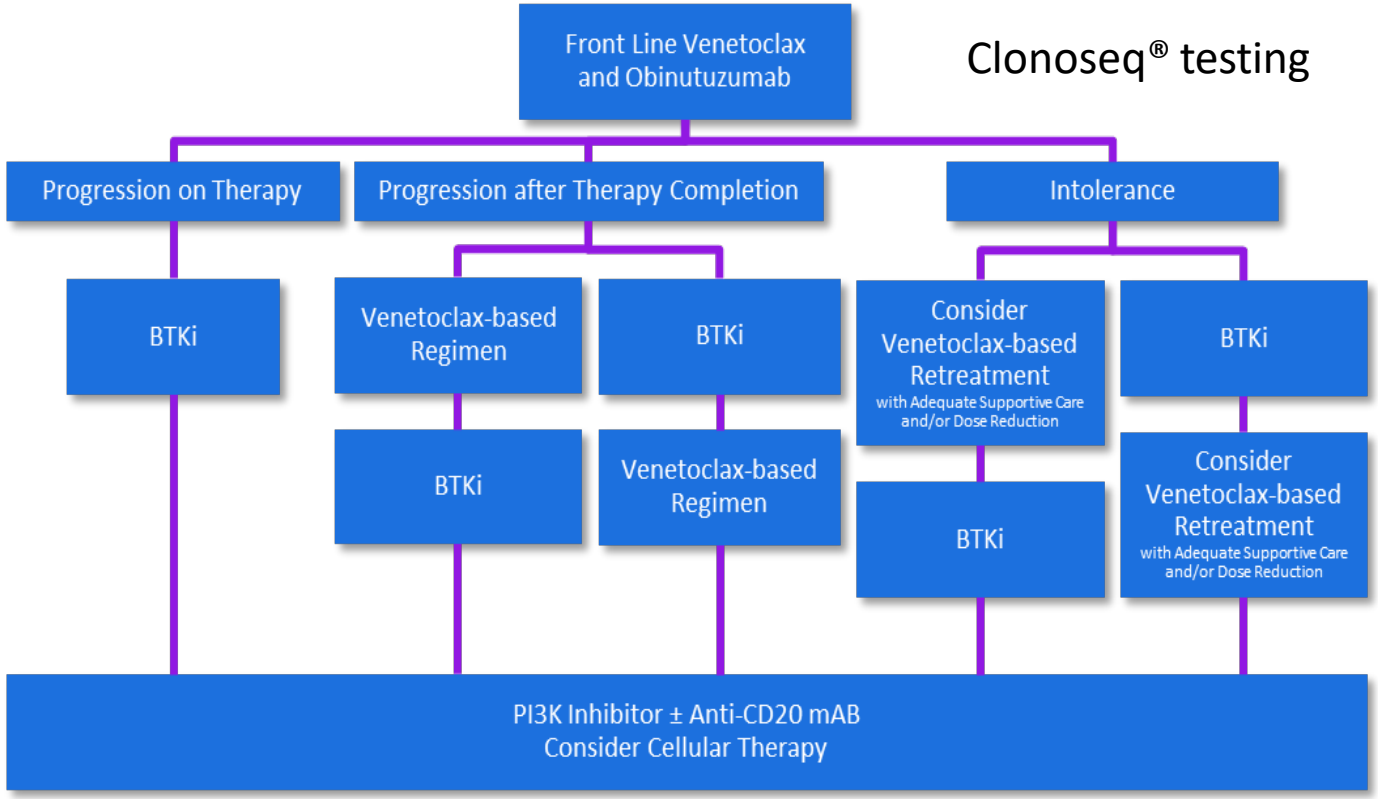
Fixed Duration and How do I use MRD in 2022

- Prefer clonoSEQ platform
  - Avoids the need for BM bx, quanititative
- Can I stop treatment early?
- Continue therapy in high risk patients and/or those who continue to have a response
- No role for continuous/surveillance monitoring in the majority of patients outside of a clinical trial
  - exception: patients with history of AIHA/ITP?

UM IgHV
17p/p53
Complex karyotype



Mutated IgHV
Major cardiac risk factors

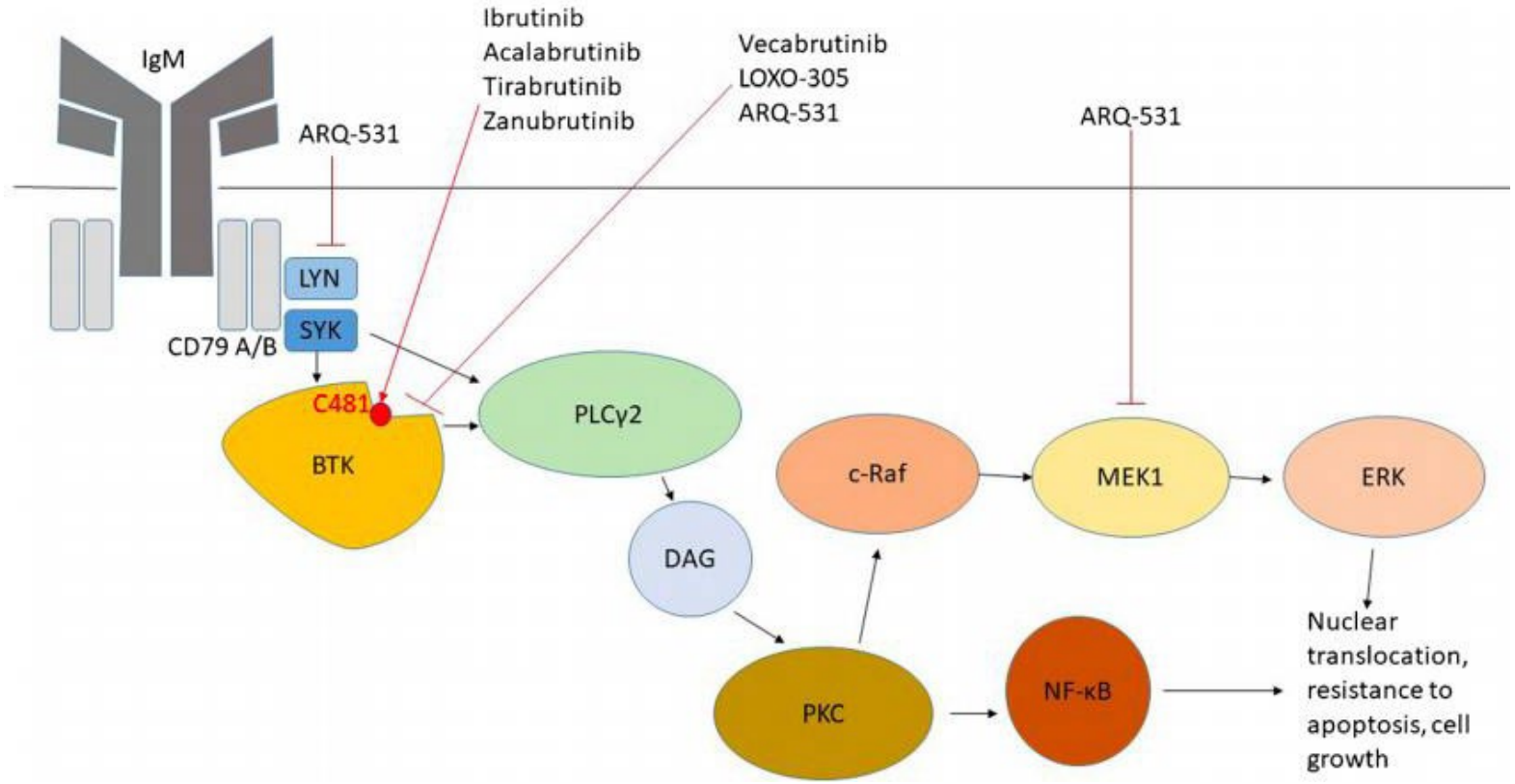


*If early in disease course, change BTKI, dose reduction

Roeker LE, Mato AR. *Hematology Am Soc Hematol Educ Program.* 2020.

The Next Phase

Drugs in Development

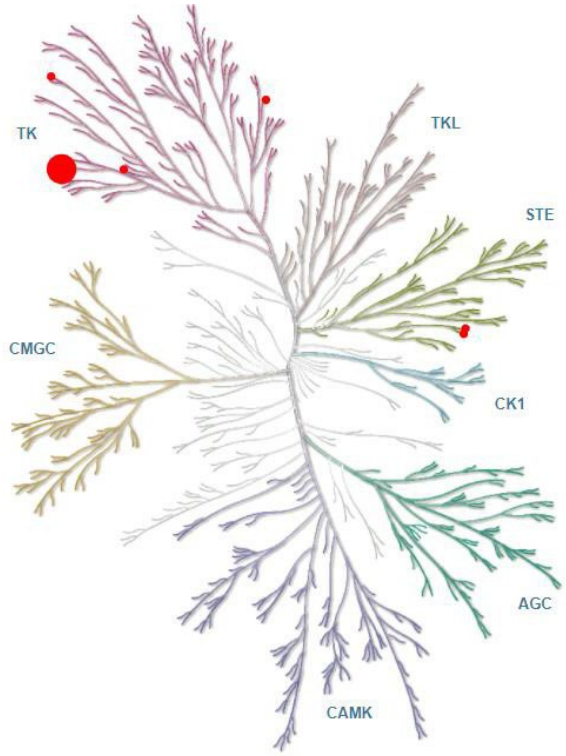


Bond DA, Woyach JA. *Curr Hematol Malig Rep.* 2019.

Pirtobrutinib is a Highly Potent and Selective Non-Covalent (Reversible) BTK Inhibitor

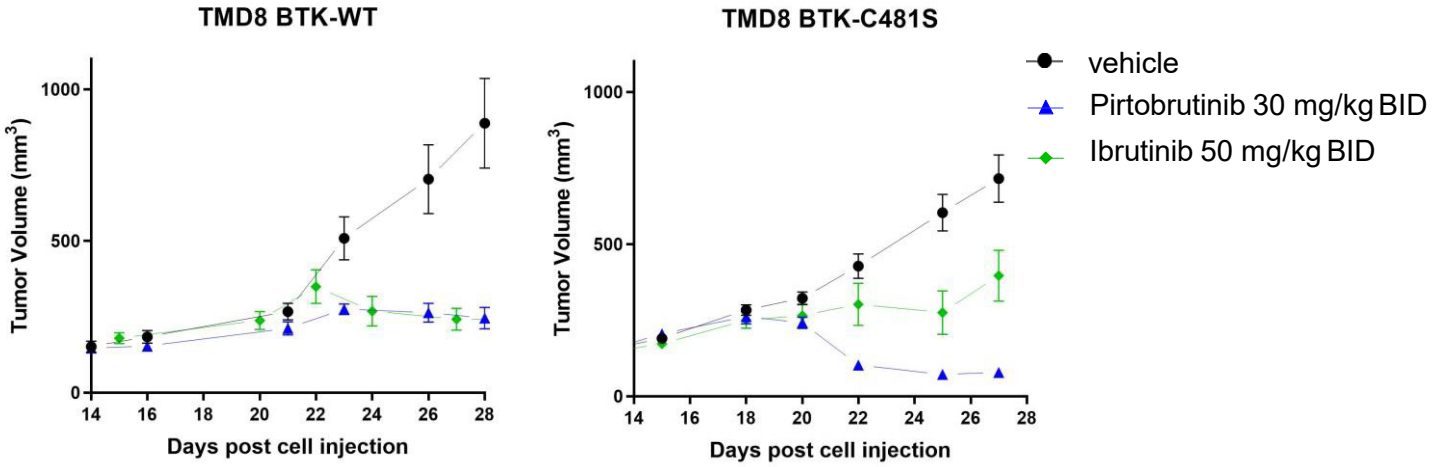
Kinome selectivity[1]

Highly selective for BTK



Xenograft models

In vivo activity similarly efficacious as ibrutinib in WT; superior in C481S



- Nanomolar potency against WT & C481-mutant BTK in cell and enzyme assays[2]
- >300-fold selectivity for BTK vs 370 other kinases[2]
- Due to reversible binding mode, BTK inhibition not impacted by intrinsic rate of BTK turnover[2]
- Favorable pharmacologic properties allow sustained BTK inhibition throughout dosing interval[2]

BID, twice-daily; BTK, Bruton tyrosine kinase. [1]Mato et al, *Lancet*, 2021:397:892-901. [2]Brandhuber BJ, et al. *Clin. Lymphoma Myeloma Leuk*. 2018.18:S216. Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com).

Pirtobrutinib, A Highly Selective, Non-covalent (Reversible) BTK Inhibitor In Previously Treated CLL/SLL: Updated Results From The Phase 1/2 BRUIN Study

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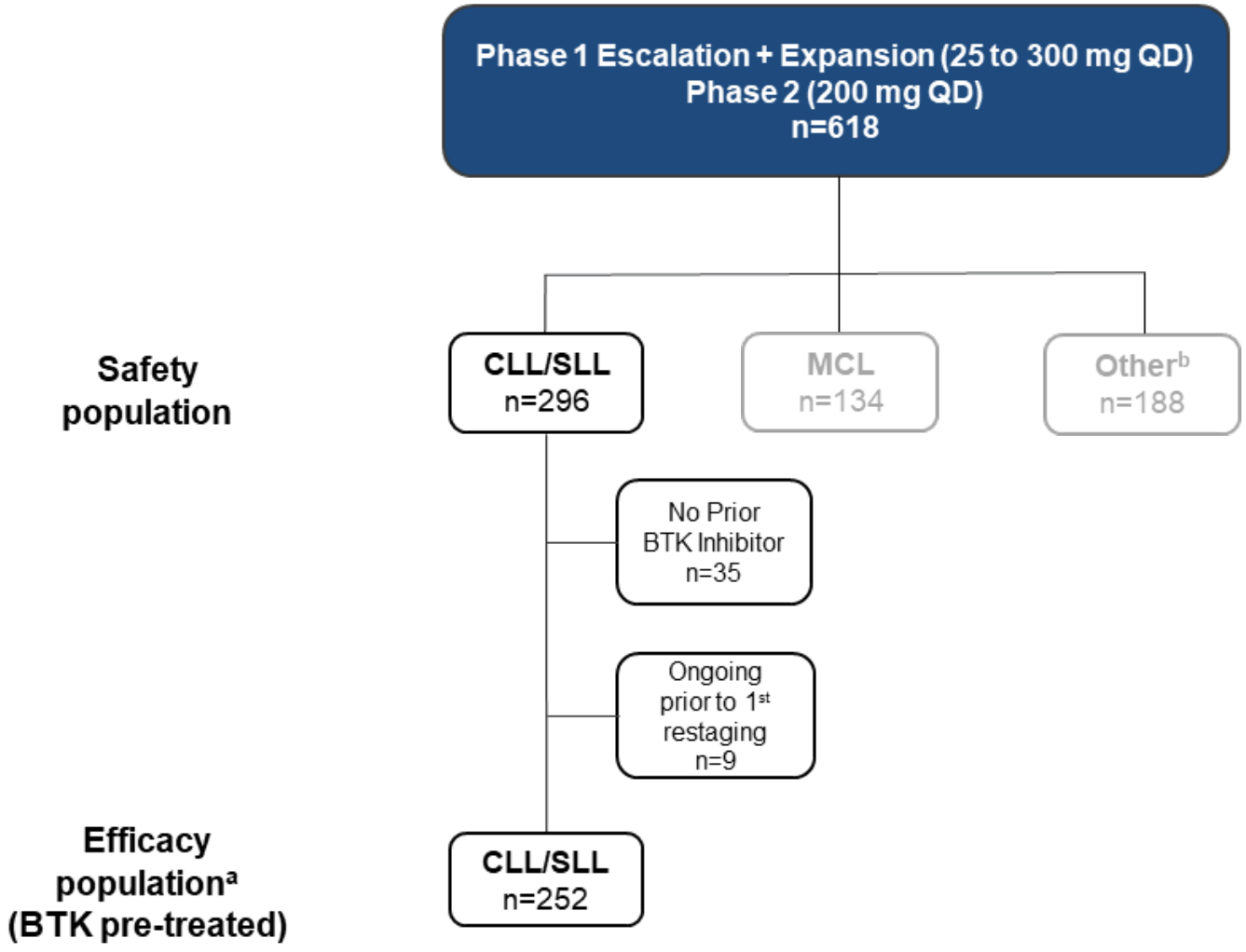
Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

- Age ≥18
- ECOG 0-2
- CLL or other B-cell NHL
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD & recommended phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR & DoR based on disease criteria (iwCLL, IWWM, Lugano)

Data cutoff date of 16 July 2021. [a]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline response assessment. [b]Other includes DLBCL, WM, FL, MZL, Richter's transformation, B-PLL, Hairy Cell Leukemia, PCNSL, and other transformation.

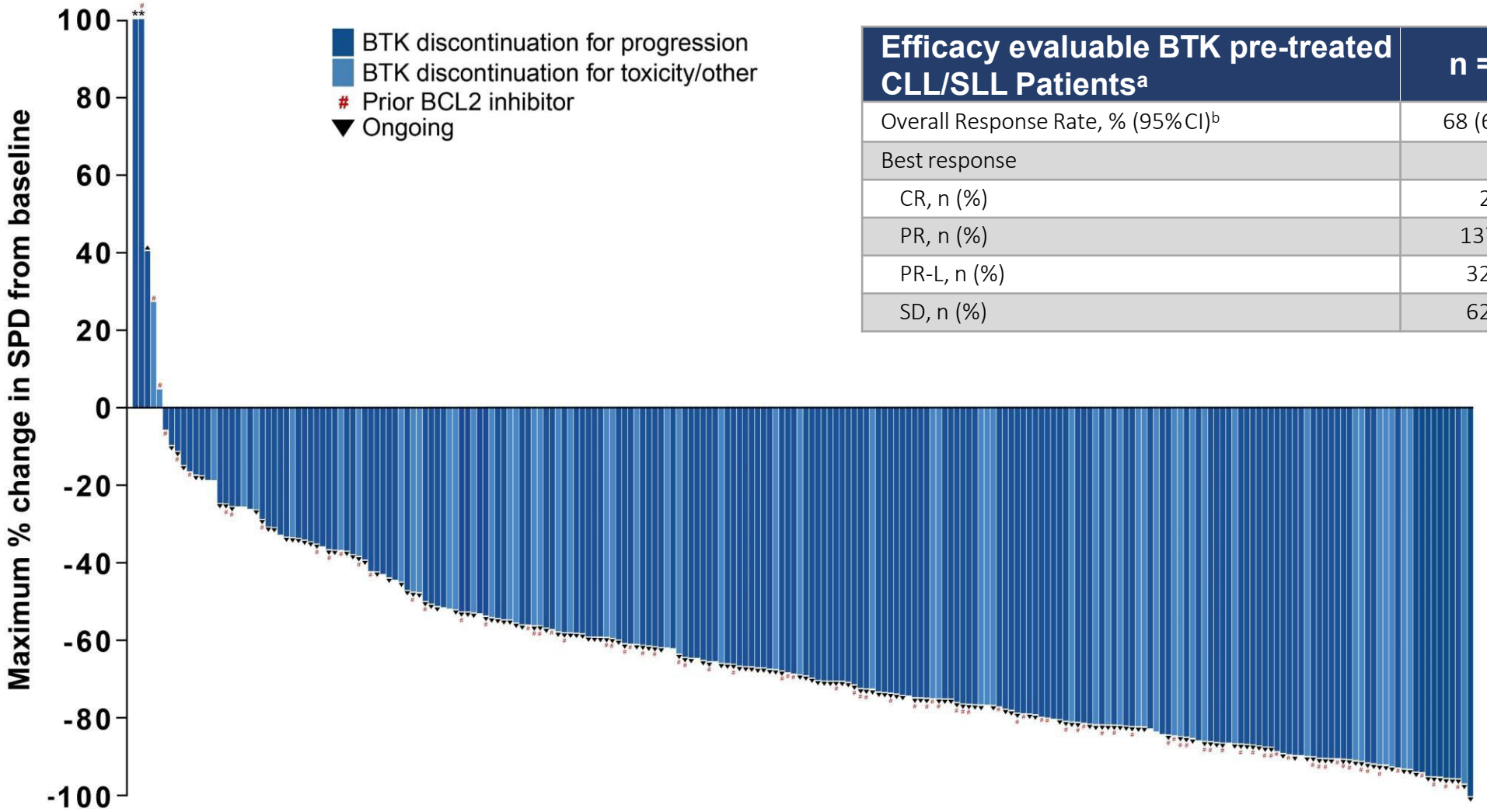
BTK Pre-treated CLL/SLL Patient Characteristics

Characteristics	N = 261
Median age, years (range)	69 (36-88)
Female, n (%)	84 (32)
Male, n (%)	177 (68)
ECOG PS[a], n (%)	
0	138 (53)
1	104 (40)
2	19 (7)
Median number of prior lines of systemic therapy (range)	3 (1-11)
Prior therapy, n (%)	
BTK inhibitor	261 (100)
Anti-CD20 antibody	230 (88)
Chemotherapy	207 (79)
BCL2 inhibitor	108 (41)
PI3K inhibitor	51 (20)
CAR-T	15 (6)
Stem cell transplant	6 (2)
Allogeneic stem cell transplant	5 (2)
Autologous stem cell transplant	1 (<1)
Reason discontinued prior BTKi, n (%)	
Progressive disease	196 (75)
Toxicity/Other	65 (25)

Baseline Molecular Characteristics[a]	
Mutation status, n (%)	
BTK C481-mutant	89 (43)
BTK C481-wildtype	118 (57)
PLCG2-mutant	33 (16)
High Risk Molecular Features, n (%)	
17p deletion	51 (28)
TP53 mutation	64 (37)
17p deletion or TP53 mutation	77 (36)
Both 17p deletion and TP53 mutation	38 (27)
IGHV unmutated	168 (84)
11q deletion	45 (25)

Data cutoff date of 16 July 2021. Total % may be different than the sum of the individual components due to rounding. [a]Molecular characteristics were determined centrally, in those patients with sufficient sample to pass assay quality control. 207 patients were tested for BTK and PLCG2, 180 patients for 17p deletion, 175 patients for TP53, 143 patients for 17p deletion + TP53, 200 patients for IGHV and 180 patients for 11q deletion.

Pirtobrutinib Efficacy in BTK Pre-treated CLL/SLL Patients

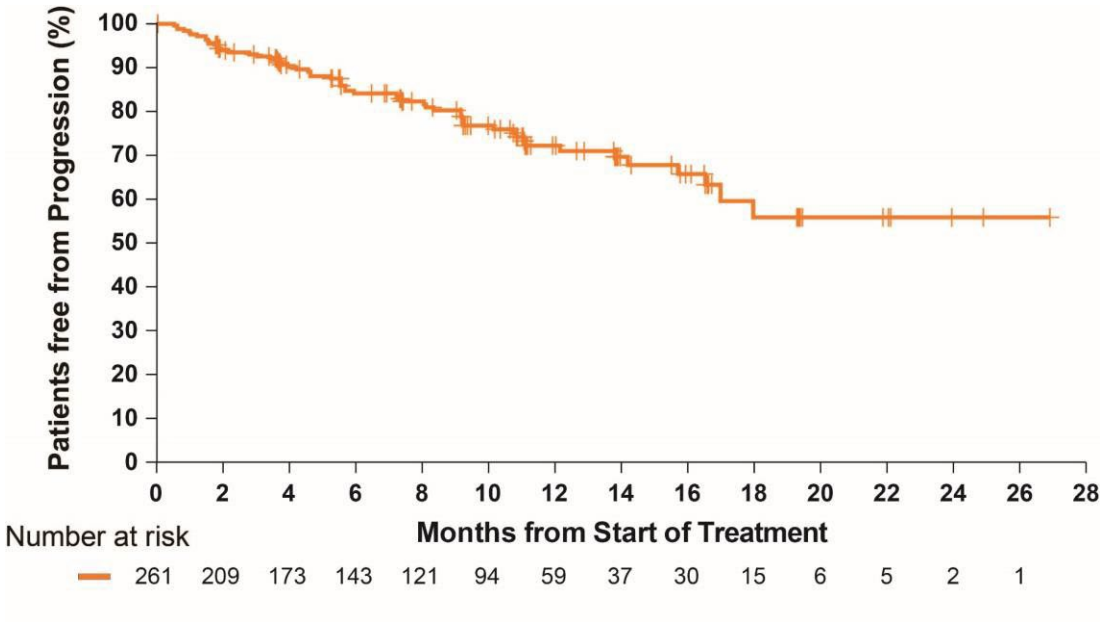


Efficacy evaluable BTK pre-treated CLL/SLL Patients[a]	n = 252
Overall Response Rate, % (95% CI)[b]	68 (62 – 74)
Best response	
CR, n (%)	2 (1)
PR, n (%)	137 (54)
PR-L, n (%)	32 (13)
SD, n (%)	62 (25)

Data cutoff date of 16 July 2021. *Patients with >100% increase in SPD. Data for 30 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]Efficacy evaluable patients are those who had at least one post-baseline response assessment or had discontinued treatment prior to first post-baseline 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 % may be different than the sum of the individual components due to rounding.

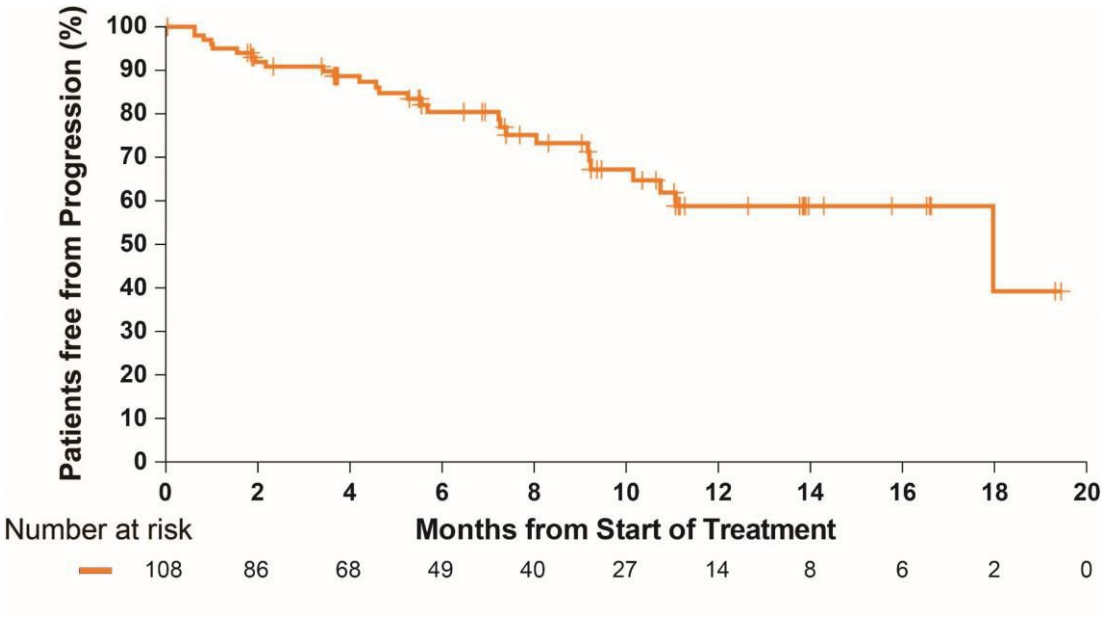
Progression-free Survival in BTK Pre-treated CLL/SLL Patients

PFS in at least BTK pre-treated patients
Median prior lines = 3



Median PFS: Not Estimable (95% CI: 17.0 months – Not Estimable)

PFS in at least BTK and BCL2 pre-treated patients
Median prior lines = 5

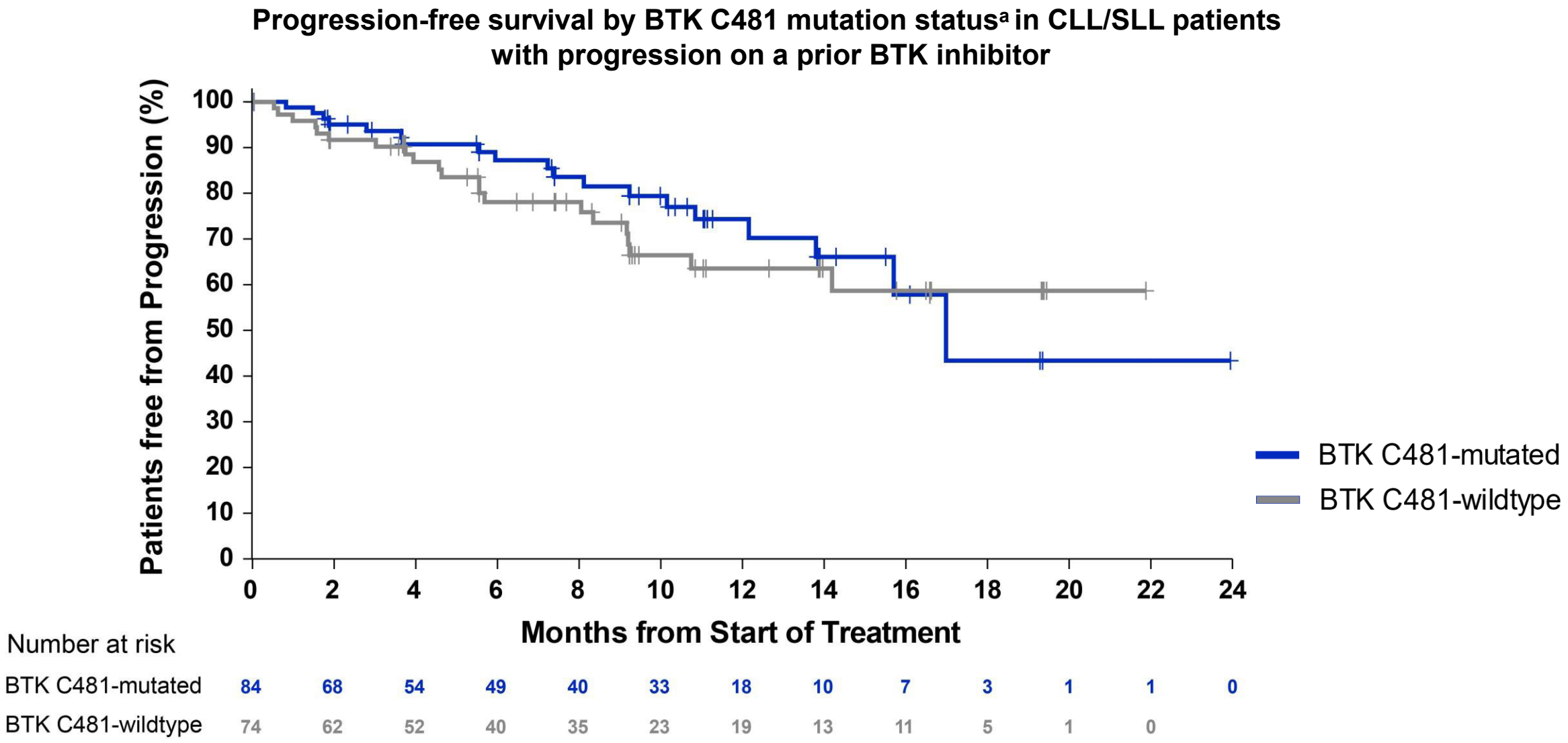


Median PFS: 18 months (95% CI: 10.7 months – Not Estimable)

- 74% (194/261) of BTK pre-treated patients remain on pirtobrutinib
- Median follow-up of 9.4 months (range, 0.3 – 27.4) for all BTK pre-treated patients

Data cutoff date of 16 July 2021. Response status per iwCLL 2018 according to investigator assessment.

BTK C481 Mutation Status is not Predictive of Pirtobrutinib Benefit



Data cutoff date of 16 July 2021. Response status per iwCLL 2018 according to investigator assessment. [a]BTK C481 mutation status was centrally determined and based on pre-treatment samples.

Pirtobrutinib Safety Profile

	All doses and patients (n=618)						
	Treatment-emergent AEs, (≥15%), %					Treatment-related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

No DLTs reported and MTD not reached

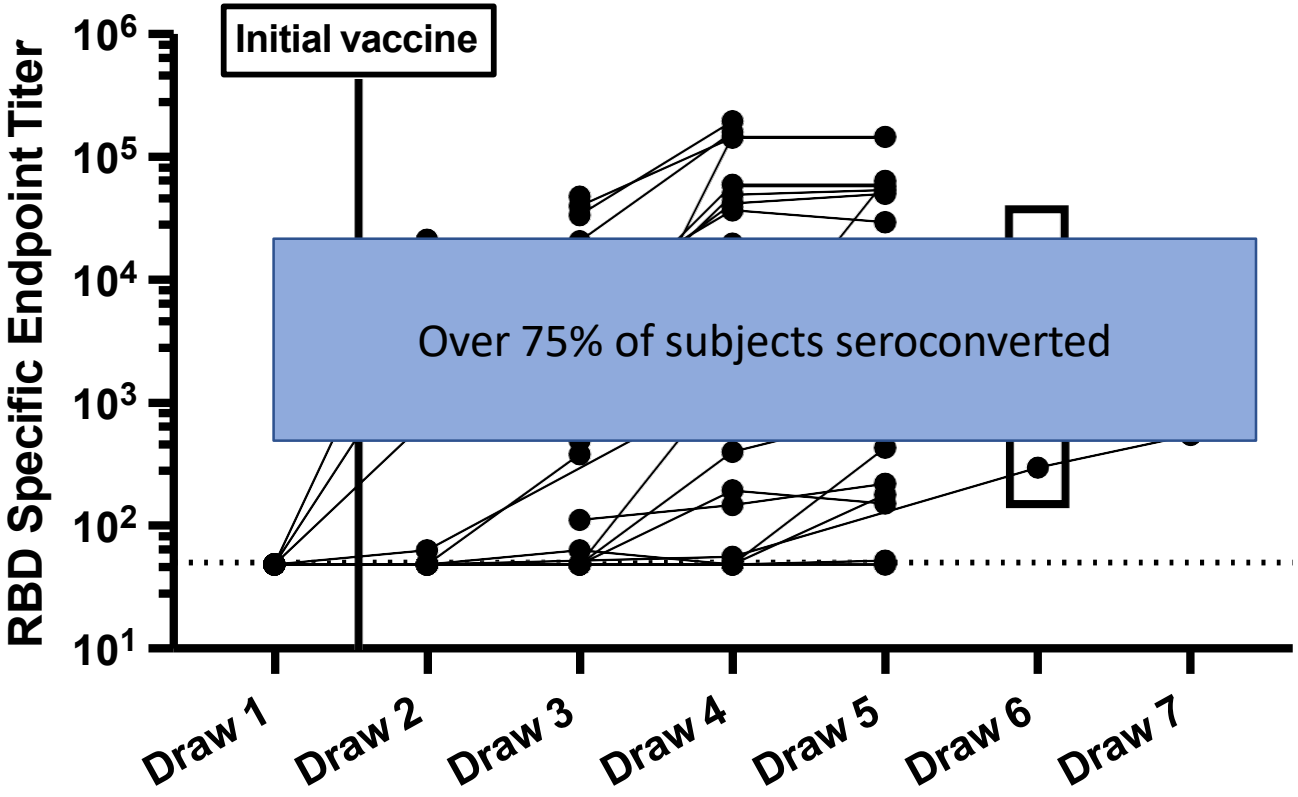
96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily

1% (n=6) of patients permanently discontinued due to treatment-related AEs

COVID and CLL

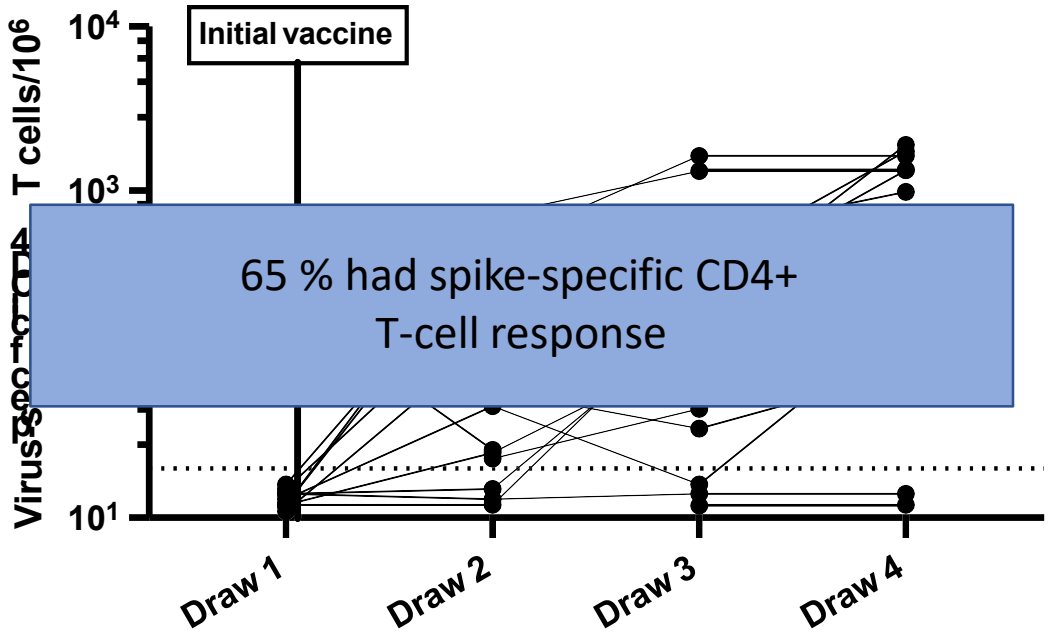
- ≈ 70-90% hospitalized, 25-30% die from COVID (pre-vaccine)[1,2]
  - Age > 75 and co-morbidities increase risk for death
- Patients may have active infection for months
- Survival in CLL patients has improved over the course of the pandemic[3]
- Antibody response rate 39% (15-80%) after initial series[4,5]
  - Low IgG, BTKi, mAb within 1 year
  - Improved with 3rd dose (25% seroconversion)

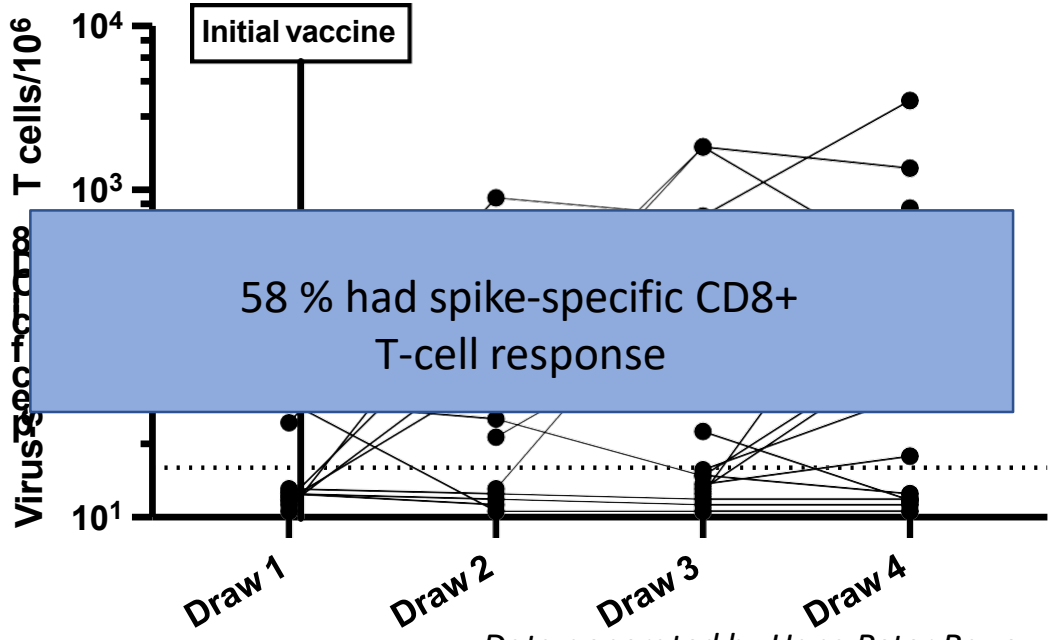
1. *Blood*. 2020 Sep 3;136(10):1134-1143
2. Leukemia. 2020 Sep;34(9):2354-2363.
3. *Blood* (2021) 138 (18): 1768–1773.
4. *Blood* 2022 Feb 3;139(5):678-685.
5. Blood. 2021 Jun 10;137(23):3165-3173



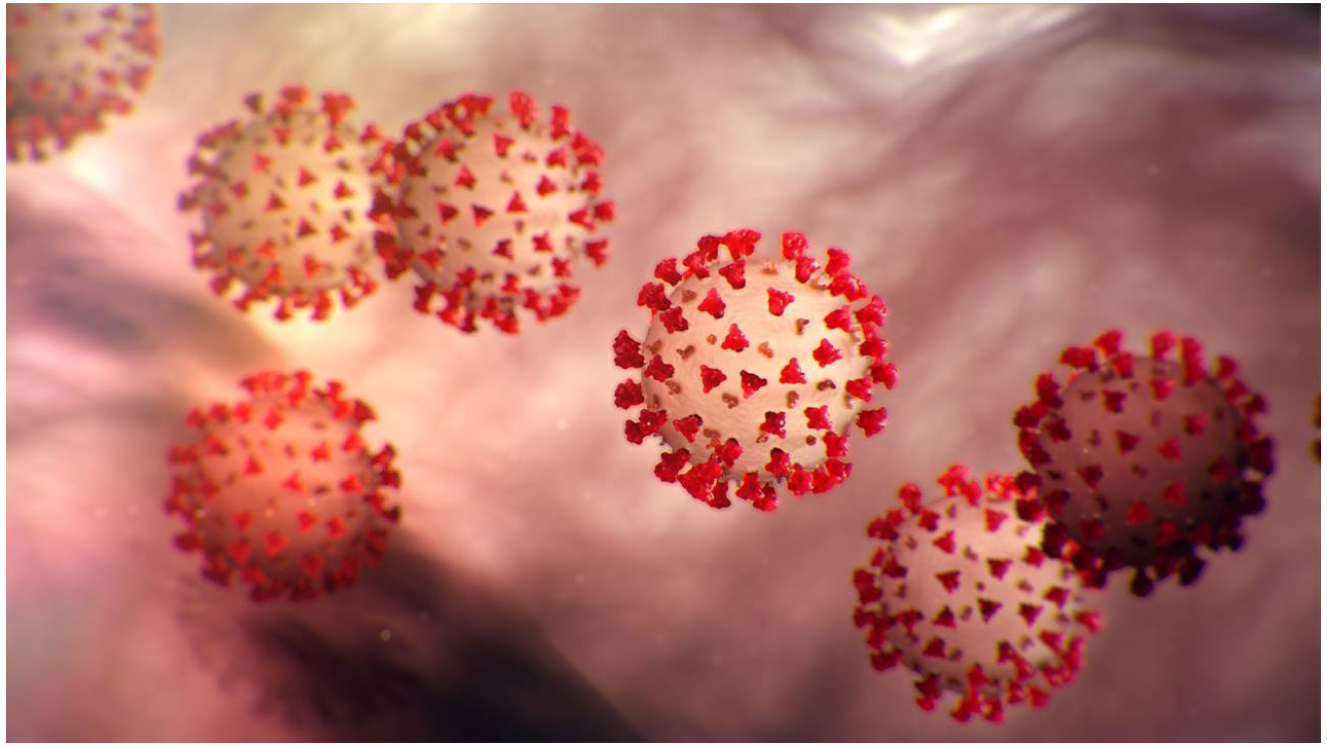
These antibody responses are neutralizing

Data generated by David Xthona Lee





Data generated by Hans-Peter Raue



Revaccinate all patients (including boosters) receiving mAb within 12 months
Administer Evusheld for
-all patients on active treatment
-watchful waiting patients without an immune response
Counsel on importance of rapid/early testing
Administer paxlovid

THANK YOU

2022.....

Immunotherapy

Bi-specific antibodies

CAR-NK and CAR-T