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Hematologic Malignancies

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What Are the Latest Strategies for Relapsed CLL and What Is on the Horizon?

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Disclosures

- Consultant–AbbVie, Acerta/AstraZeneca, Alloplex Biotherapeutics, BeiGene,Genentech/Roche, Grifols Worldwide Operations, Hutchmed, iOnctura, Janssen, Kite, Loxo/Lilly, Merck,Numab Therapeutics, Pfizer, Pharmacyclics
- Grant/Research Support–BeiGene, Gilead, iOnctura, Loxo/Lilly, MEI Pharma, SecuraBio, TG Therapeutics

Learning Objectives

- Assess the current treatment options for CLL beyond the current chemoimmunotherapy (CIT) standard
- Evaluate the mechanism of action, safety/efficacy data, and potential drug-drug interactions associated with Bruton's tyrosine kinase (BTK) inhibitors and BCL2 inhibitors
- Incorporate guideline recommendations for minimal residual disease (MRD) monitoring into the care of patients with CLL/SLL

The Changing Landscape of Relapsed CLL

- Patients relapsing after minimal therapy (ab, clb)
- Patients relapsing after effective CIT
  - *Most of our data: RESONATE, HELIOS, ASCEND, MURANO, ELEVATE-RR, ALPINE*
- Patients exposed to BTK inhibitors:
  - (Off for adverse events (AEs)
  - Progressed during therapy
- Patients relapsing after venetoclax (or PI3Ki)
  - Time-limited or during therapy
- Patients relapsing after BTKi and BCL-2

CLL = chronic lymphocytic leukemia.

The Changing Landscape of Relapsed CLL

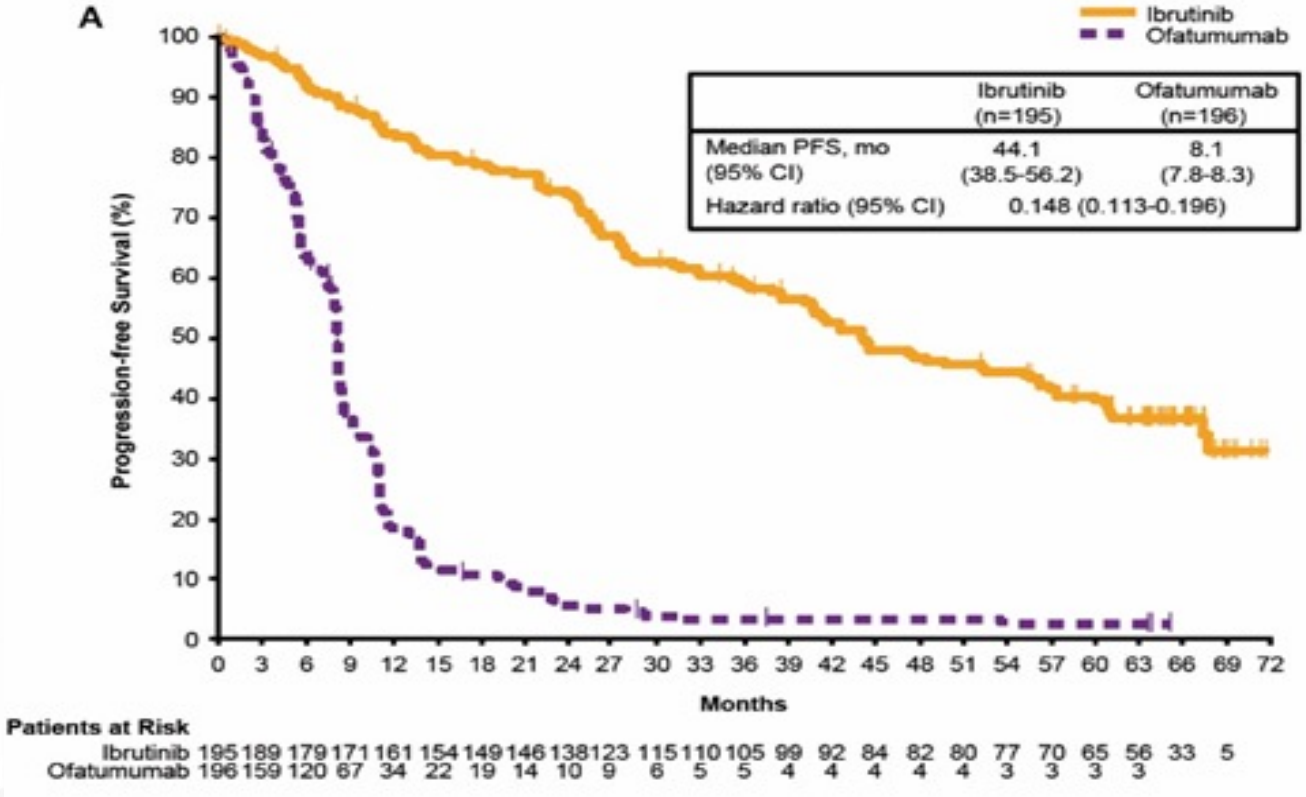
- Patients relapsing after minimal therapy (mAb, clb)
- Patients relapsing after effective CIT
- Patients exposed to ibrutinib:
  - Off for adverse events (AEs)
  - Progressed during ibrutinib therapy
- Patients relapsing after venetoclax
- Patients relapsing after BTKi and BCL-2

CIT = chemoimmunotherapy.

The Changing Landscape of Relapsed CLL

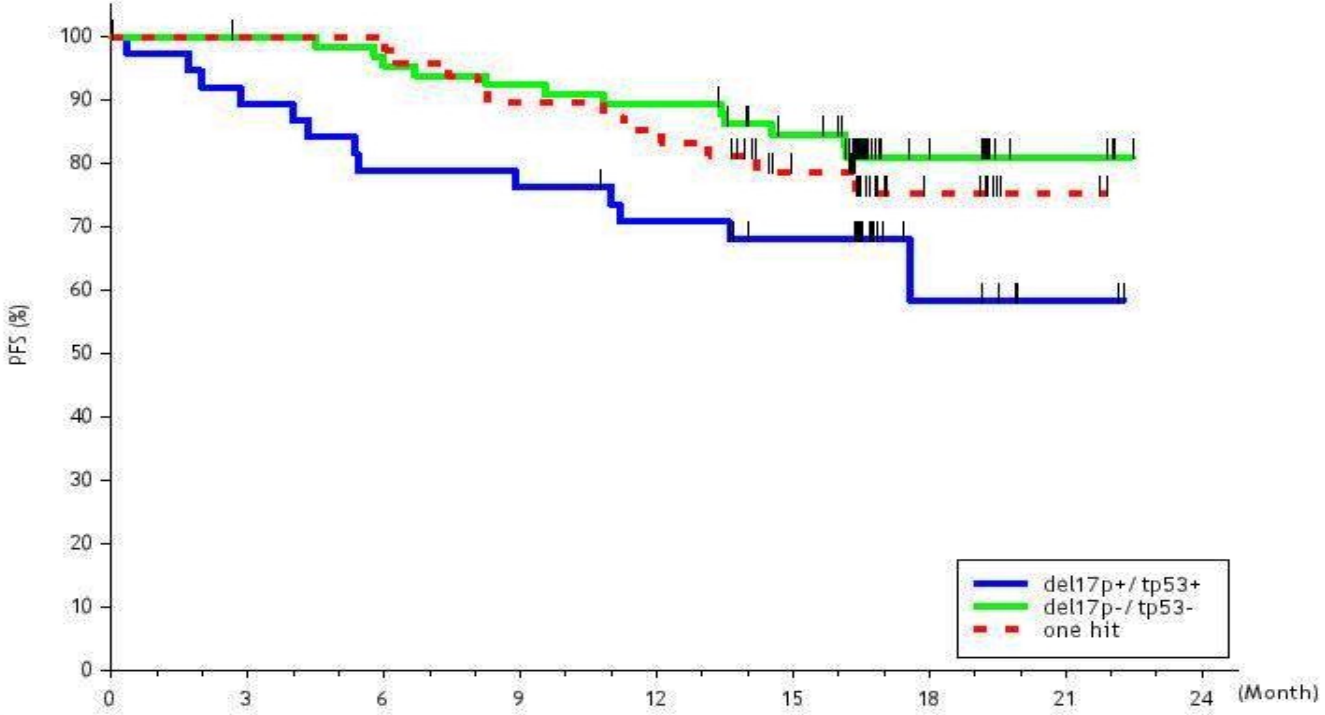
- Patients relapsing after minimal therapy (mAb, clb)
- Patients relapsing after effective CIT
- Patients exposed to BTK inhibitors:
  - Off for adverse events
  - Progressed during therapy
- Patients relapsing after venetoclax
- Patients relapsing after BTKi and BCL-2

Final Analysis of RESONATE
Median 65 Mo F/U



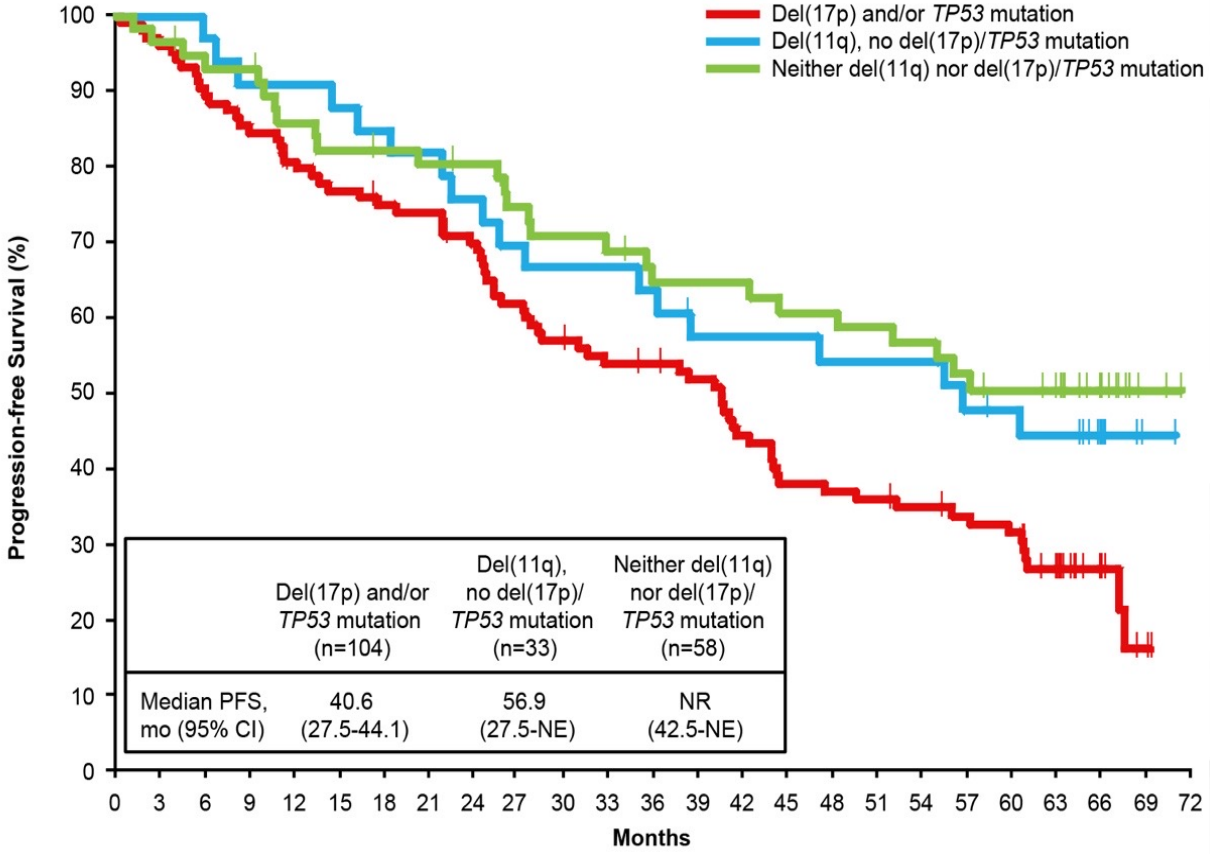
Munir T, et al. *Am J Hematol*. 2019;94(12):1353-1363.

PCYC 1112 RESONATE: PFS by TP53 / Del17p



Brown JR, et al. *Leukemia*. 2018;32(1):83-91.

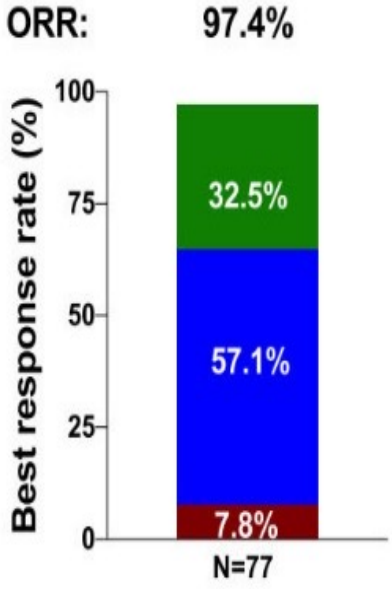
Final Analysis of RESONATE: TP53 or 11q Median 65 Mo F/U

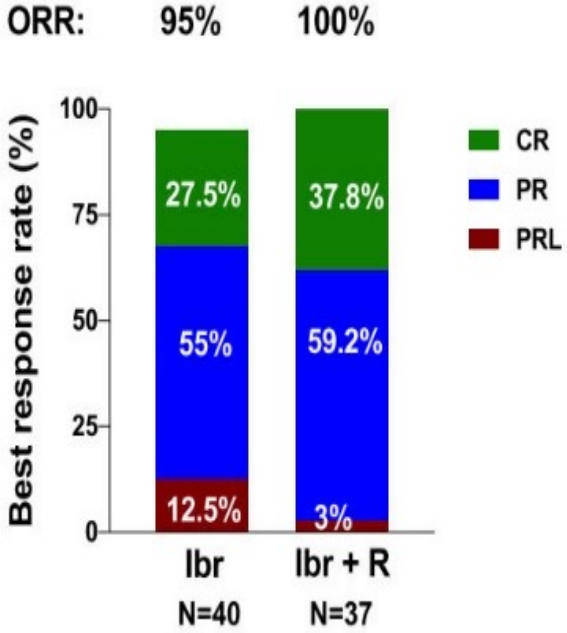


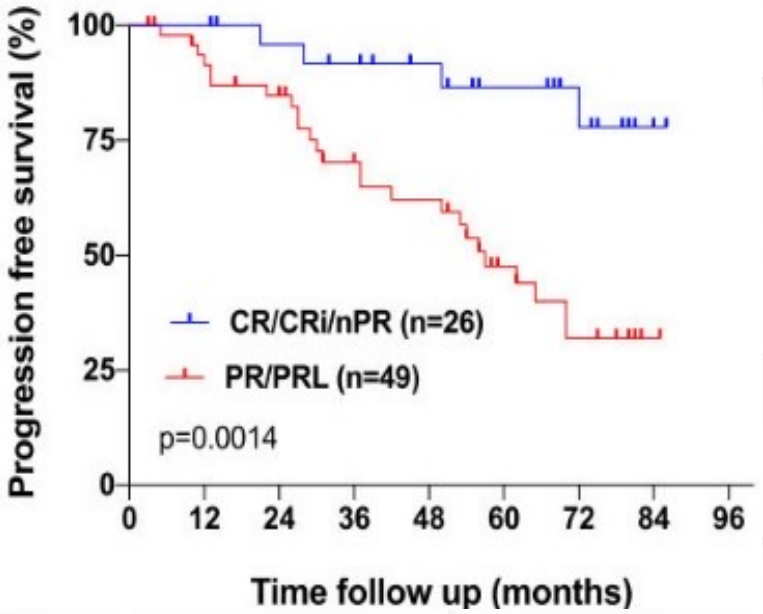
	Del(17p) and/or *TP53* mutation (n=104)	Del(11q), no del(17p)/ *TP53* mutation (n=33)	Neither del(11q) nor del(17p)/ *TP53* mutation (n=58)
Median PFS, mo (95% CI)	40.6 (27.5-44.1)	56.9 (27.5-NE)	NR (42.5-NE)

Munir T, et al.
***Am J Hematol*.**
2019;94(12):1353-1363.

Best Response to I+/-R Treatment in CLL Patients with *TP53* Aberrations



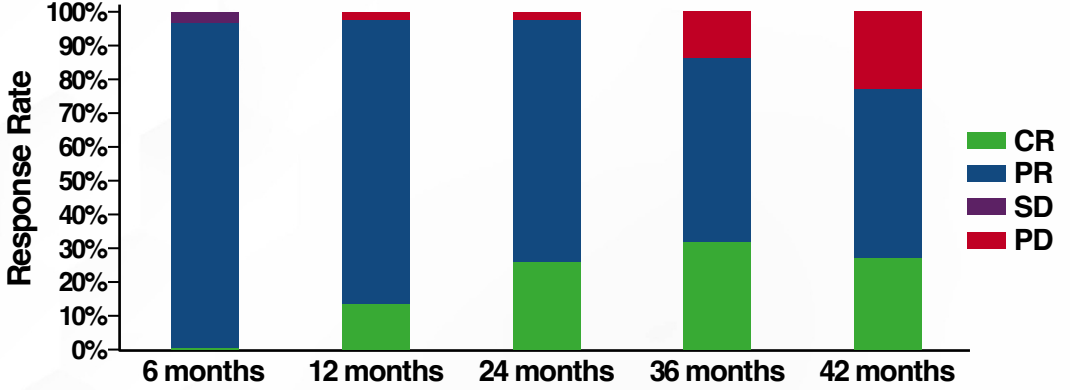


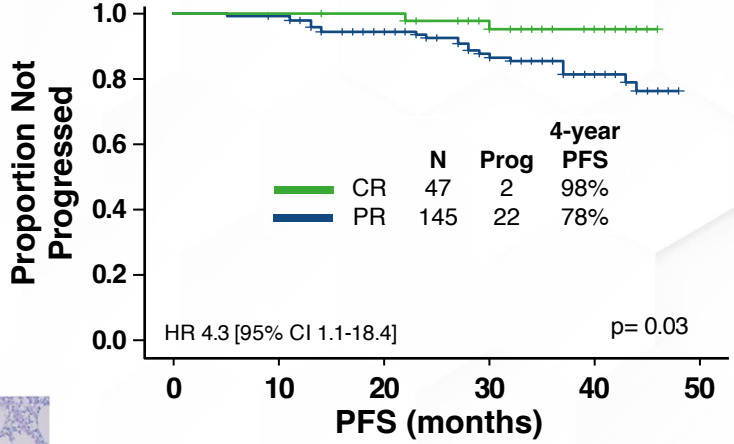


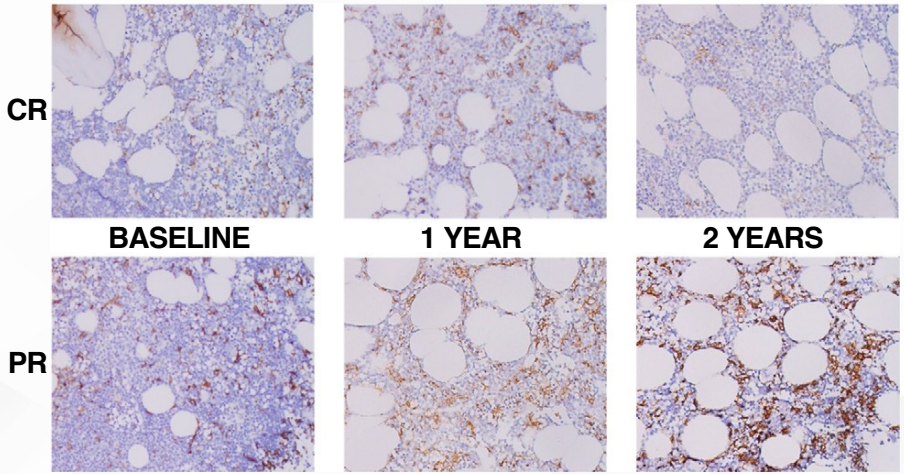
Five =ear Follow-up from a Phase 2 Study

Burger JA, et al. Presented at: ASH;2021. Abstract 2218.

Achieving CR in CLL Patients Treated with Ibrutinib Leads to Better PFS







Strati P, et al. *Blood.* 2020; 135(7): 510-513.

Severe CV Toxicities and Ibrutinib

- Case reports of ventricular arrhythmias and deaths in the setting of Ibrutinib
- CV Adverse drug reactions with overreporting in the WHO VigiBase

TABLE 1 Disproportionality Analysis in VigiBase

	Ibrutinib	Entire Database (Since Inception)	IC/IC_{02} $_{5}$	Entire Database (Since 2013)	ROR ($_{95}$CI)
Total number of ICSRs available	13,572	16,343,451		8,318,890	
Number of ICSRs and statistics by CV-ADR subgroups					
Cardiac supraventricular arrhythmias	959 (7.07)	68,597 (0.42)	4.06/3.97	28,242 (0.34)	23.1 (21.6-24.7)
CNS hemorrhagic events	505 (3.72)	179,621 (1.10)	1.76/1.63	85,402 (1.03)	3.7 (3.4-4.1)
Heart failure	363 (2.67)	142,502 (0.87)	1.61/1.46	65,680 (0.79)	3.5 (3.1-3.8)
Cardiac ventricular arrhythmias	70 (0.52)	33,504 (0.20)	1.32/0.96	9,220 (0.11)	4.7 (3.7-5.9)
Cardiac conduction disorders	50 (0.37)	26,008 (0.16)	1.19/0.76	8,834 (0.11)	3.5 (2.7-4.6)
CNS ischemic events	254 (1.87)	161,618 (0.99)	0.92/0.73	70,529 (0.85)	2.2 (2.0-2.5)
Hypertension and related end-organ damages	295 (2.17)	239,232 (1.46)	0.57/0.40	109,148 (1.31)	1.7 (1.5-1.9)

Salem J-E, et al. Accessed May 12, 2023. https://www.sciencedirect.com/science/article/pii/S0735109719361558.

Kinome Selectivity among Covalent BTKis

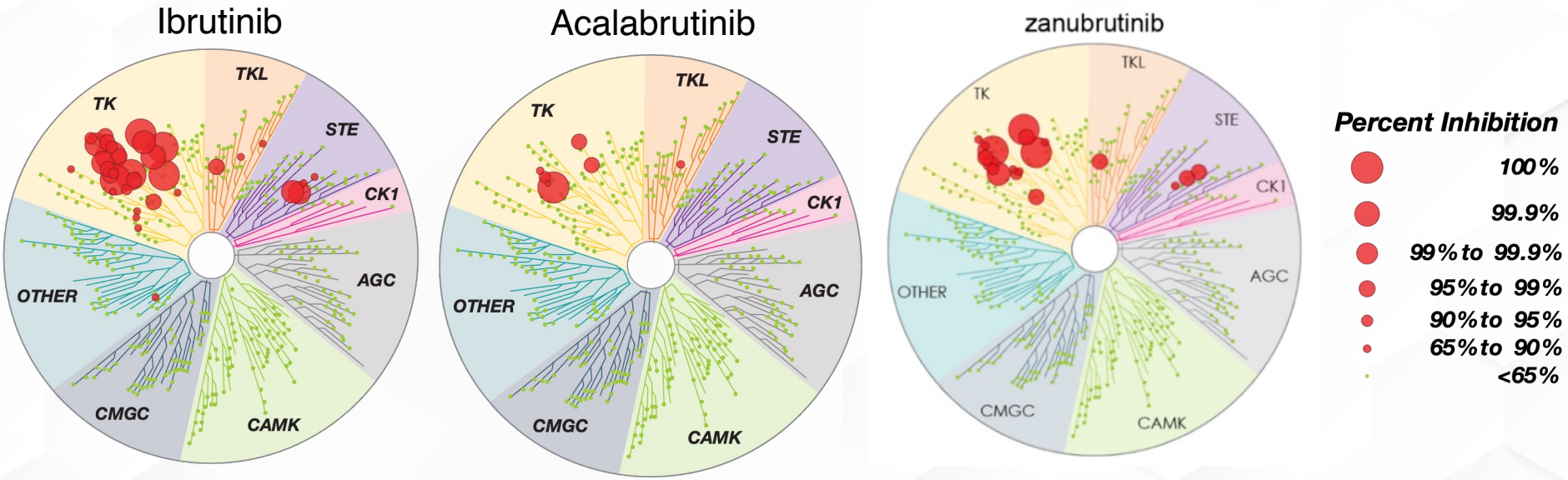
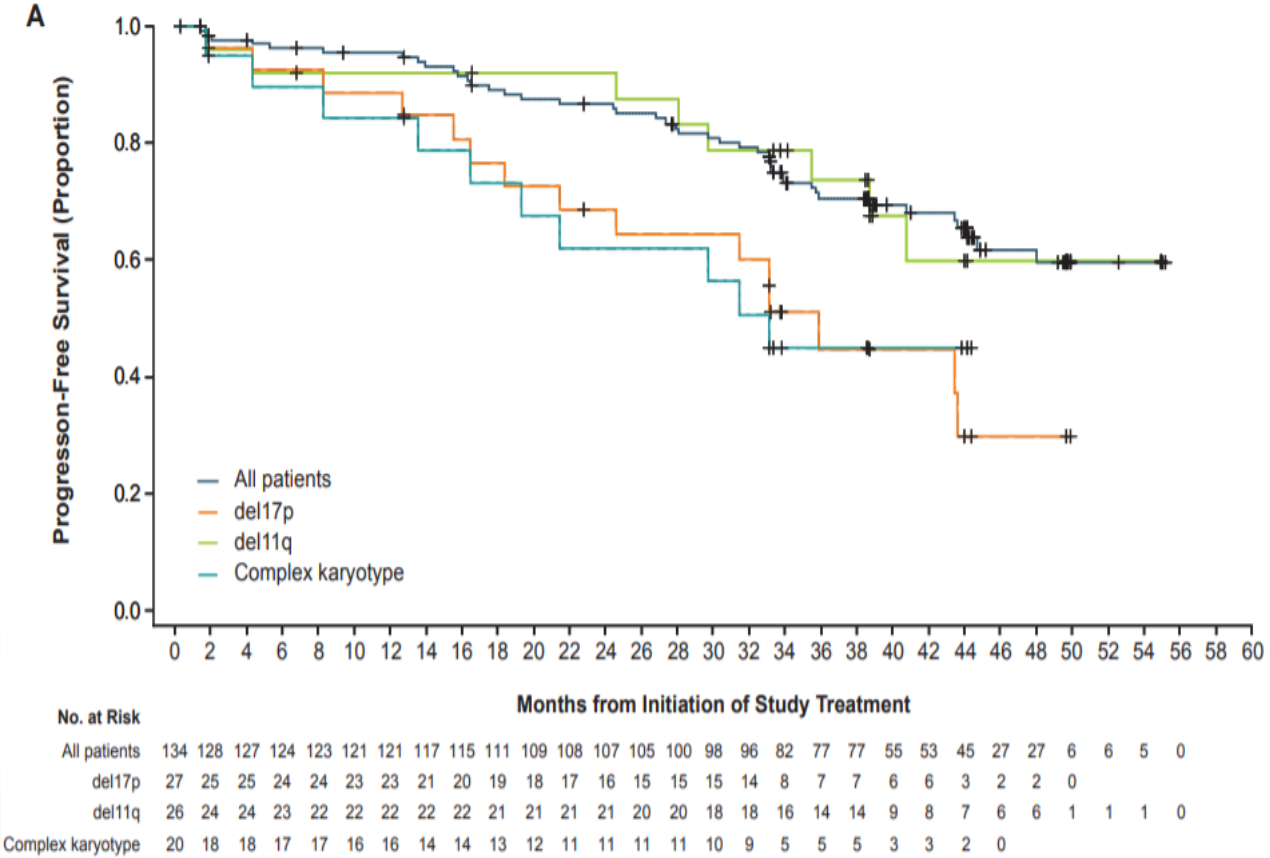


Figure 1. Kinome profiling at a single dose of 1 μM (KINOMEscan, Eurofins DiscoverX)

Brown JR, et al. Accessed May 12, 2023. https://cllroadmap.md-education.com/wp-content/uploads/2022/05/Jennifer-Brown-Slides.pdf.

Acalabrutinib Ph 2 PFS, R/R CLL



Byrd JC, et al. *Blood*. 2020;135(15):1204-1213.

ASCEND Study Design and Assessments

Relapsed/Refractory CLL (N=310)

Stratification:

Presence of del(17p)
ECOG PS 0-1 vs 2
1-3 vs ≥4 prior therapies

RANDOMIZE

1:1

Acalabrutinib (n=155)
100 mg PO BID[a]

Idelalisib plus Rituximab (IdR; n=119)
Idelalisib 150 mg PO BID[a] + rituximab[b]

Or

Bendamustine plus Rituximab (BR; n=36)
Bendamustine 70mg/m² IV[c] + rituximab[d]

Primary endpoint:
- **PFS[e]**

Key secondary endpoints:
- **ORR**
- **OS**
- **Safety**

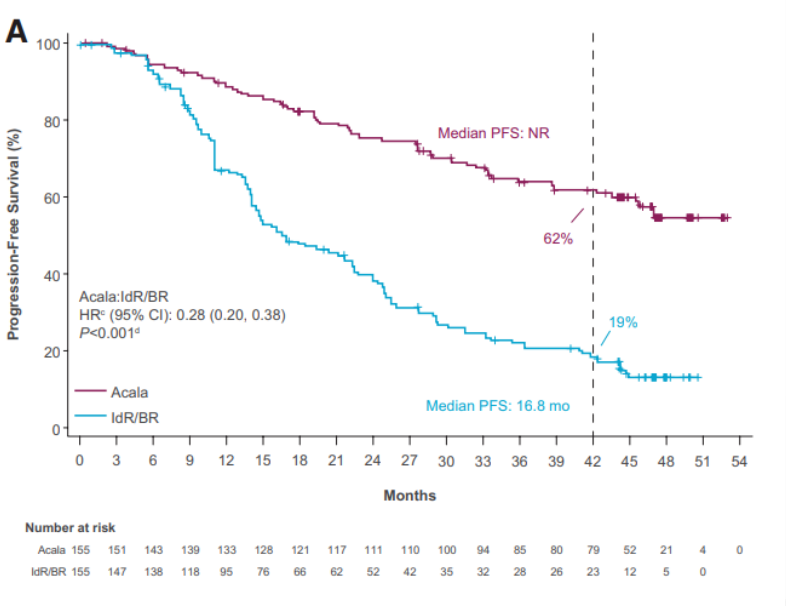
Crossover from IdR/BR arm allowed after confirmed disease progression

The data cutoff date for this analysis was August 1, 2019

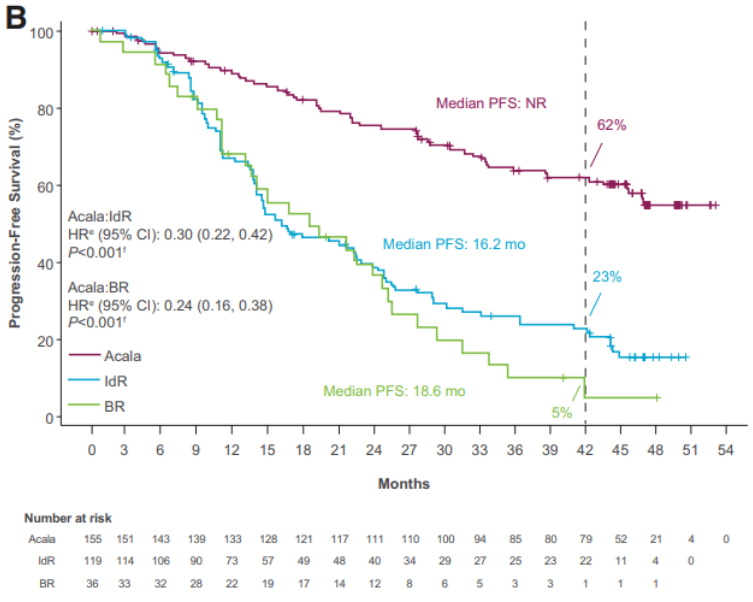
NCT00135226. Updated December 1, 2022. Accessed May 12, 2023. https://clinicaltrials.gov/ct2/show/NCT00135226.

ASCEND: Final PFS by Investigator Assessment

Final PFS Analysis



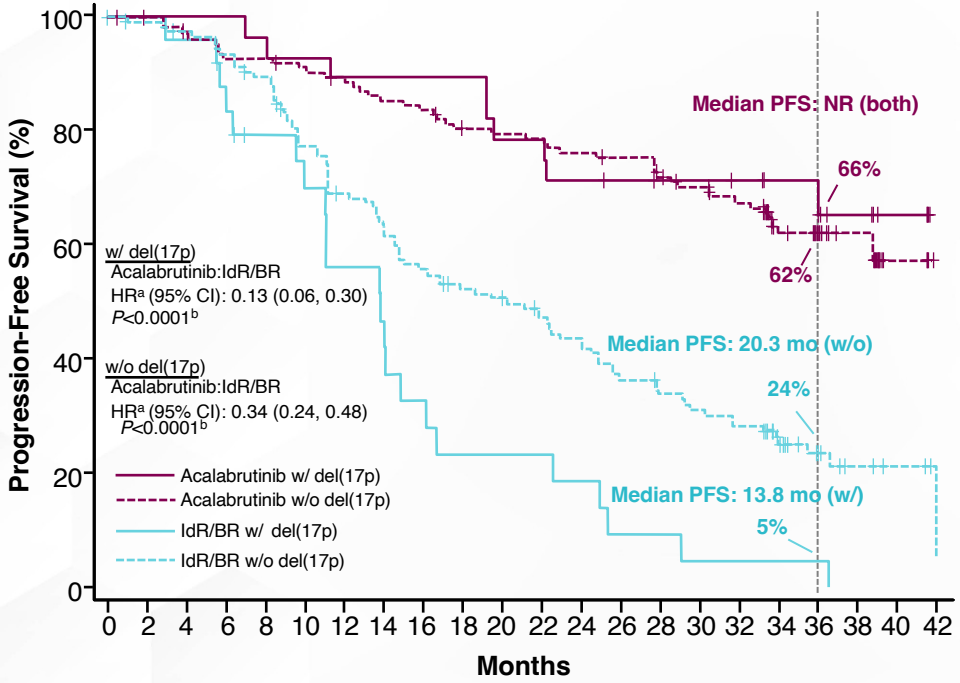
PFS By Treatment Received



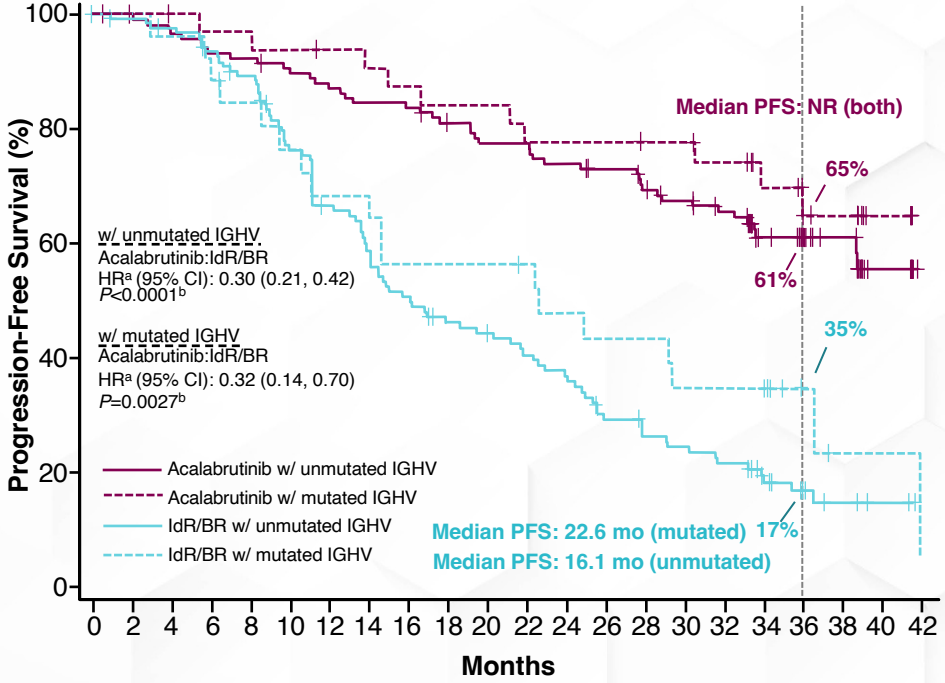
Ghia P, et al. *Hemasphere*. 2022;6(12):e801.

ASCEND: Investigator-Assessed PFS in Patients with High-Risk Features

PFS by del(17p)



PFS by IGHV



- **Acalabrutinib prolonged PFS in patients with del(17p)/*TP53* mutations and unmutated IGHV**

Ghia P, et al. *Hemasphere*. 2022;6(12):e801.

ELEVATE-RR: Phase 3 Randomized Non-Inferiority Open-Label Trial

Patients (N=533)

Key Inclusion Criteria

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

Stratification

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

RANDOMIZE 1:1

- **Acalabrutinib 100 mg PO BID**
- **Ibrutinib 420 mg PO QD**

Primary endpoint

- Non-inferiority on IRC-assessed PFS

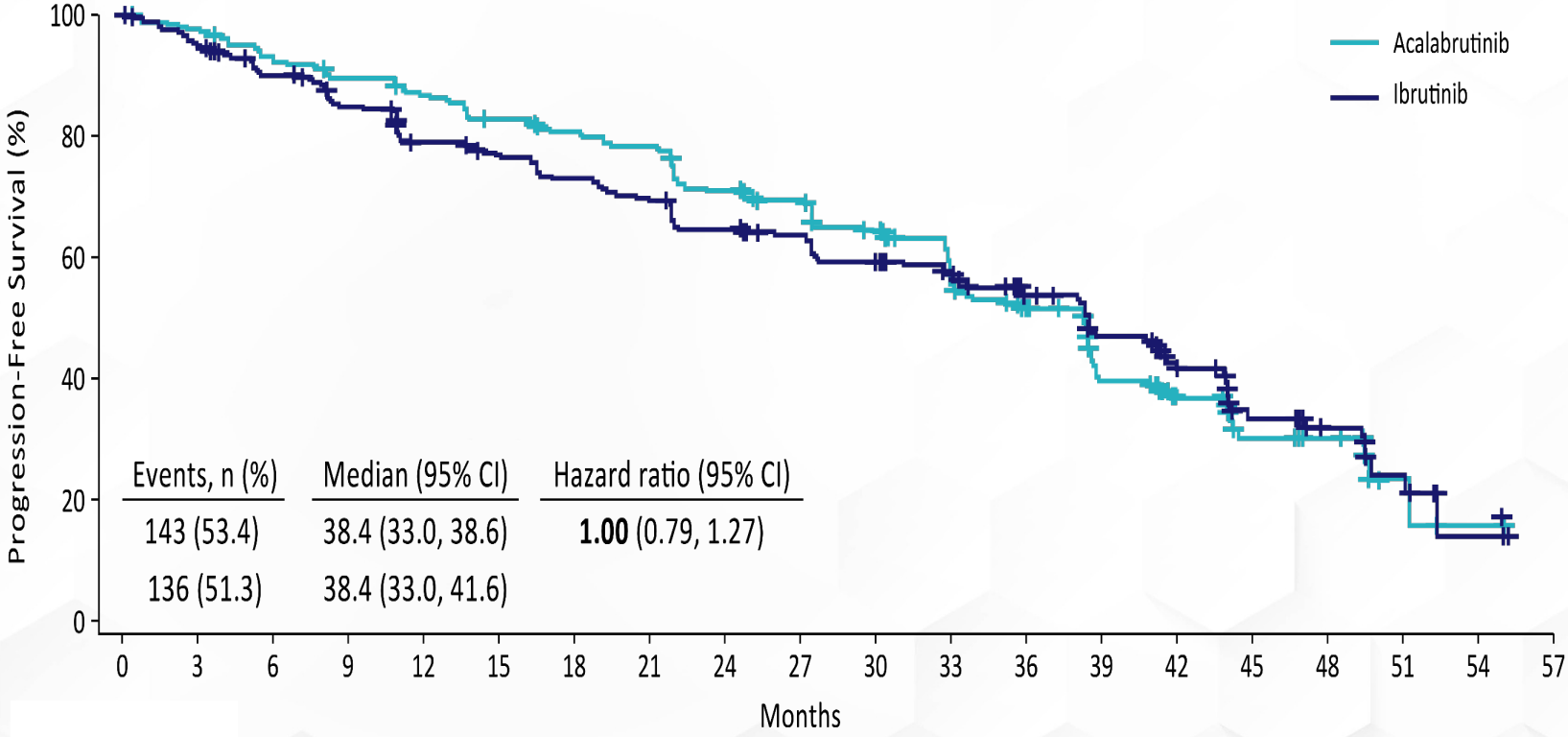
Secondary endpoints (hierarchical order):

- Incidence of any grade atrial fibrillation/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. Updated March 15, 2023. Accessed May 12, 2023. https://clinicaltrials.gov/ct2/show/NCT02477696.

ELEVATE RR: Non-inferiority Primary Endpoint Met on IRC-Assessed PFS

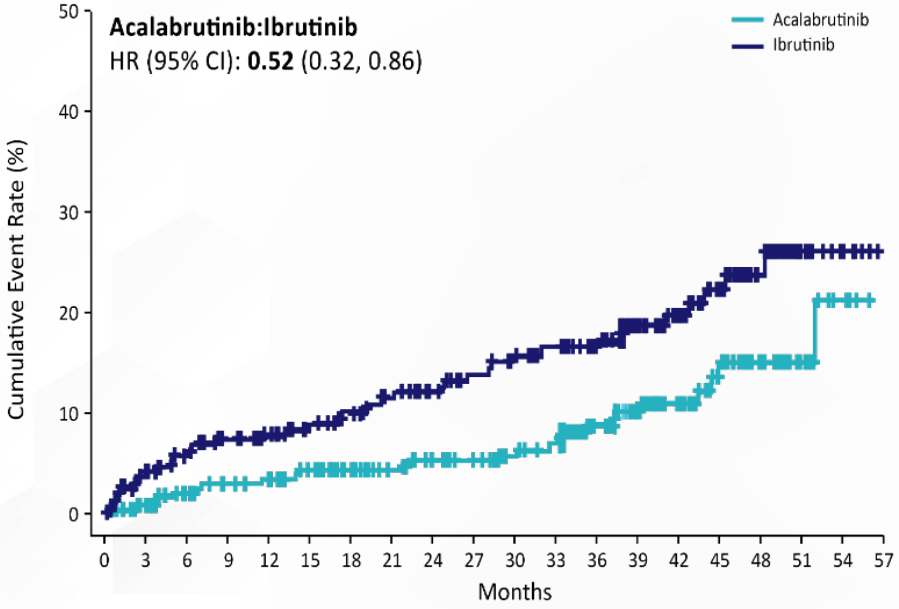


Median follow-up: 40.9 months (range, 0.0–59.1).

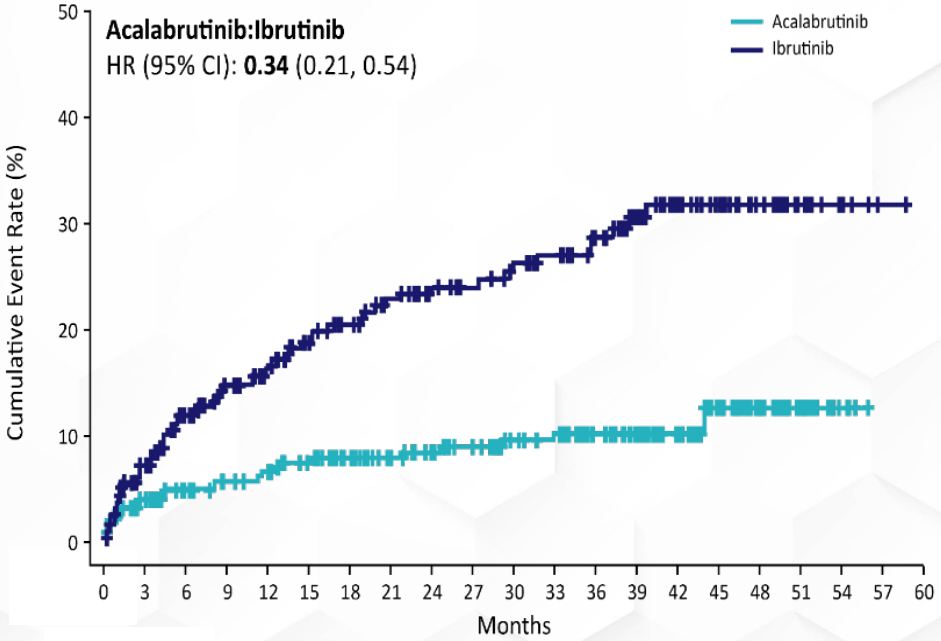
Hillmen P, et al. Presented at: EHA:2021. Abstract S145.

ELEVATE RR: Lower Cumulative Incidence of Atrial Fibrillation and Hypertension With Acalabrutinib

Afib/Flutter, Any Grade



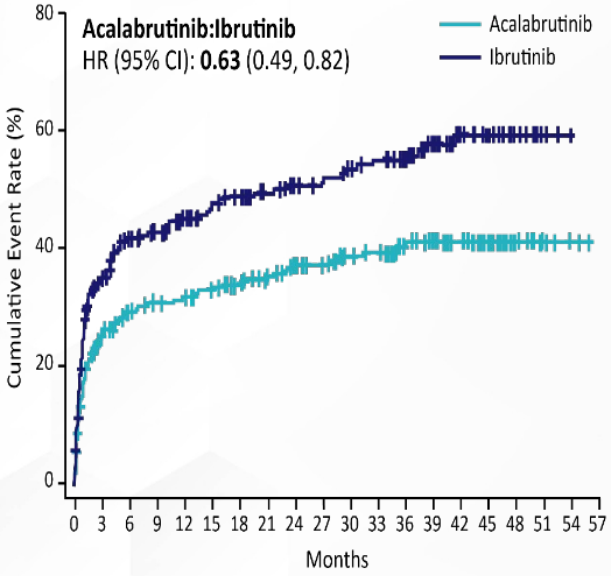
Hypertension, Any Grade



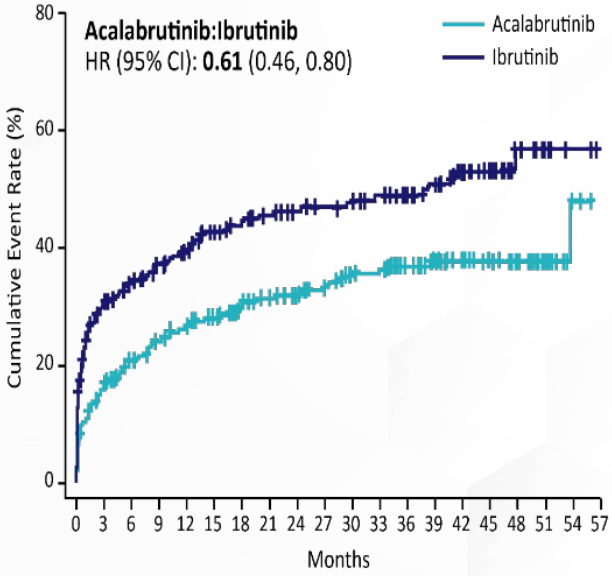
Hillmen P, et al. Presented at: EHA:2021. Abstract S145.

ELEVATE-RR: Lower Cumulative Incidence of Any-Grade Bleeding, Diarrhea, and Arthralgia Events with Acalabrutinib

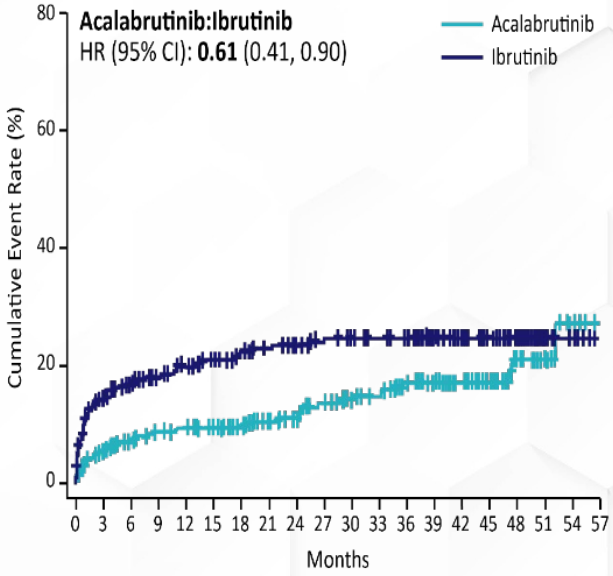
Bleeding Events



Diarrhea



Arthralgia

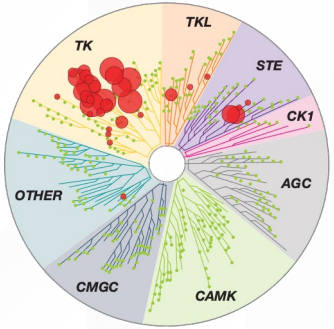


Hillmen P, et al. Presented at: EHA:2021. Abstract S145.

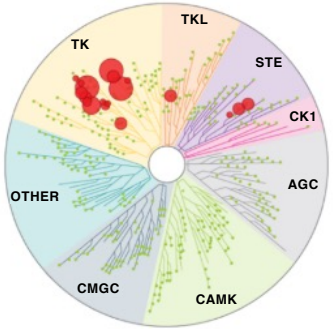
Pharmacokinetics and Selectivity of Zanubrutinib and Ibrutinib

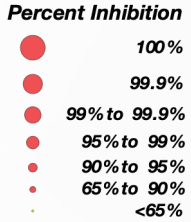
Whole Kinase Panel Selectivity Profiles

Ibrutinib

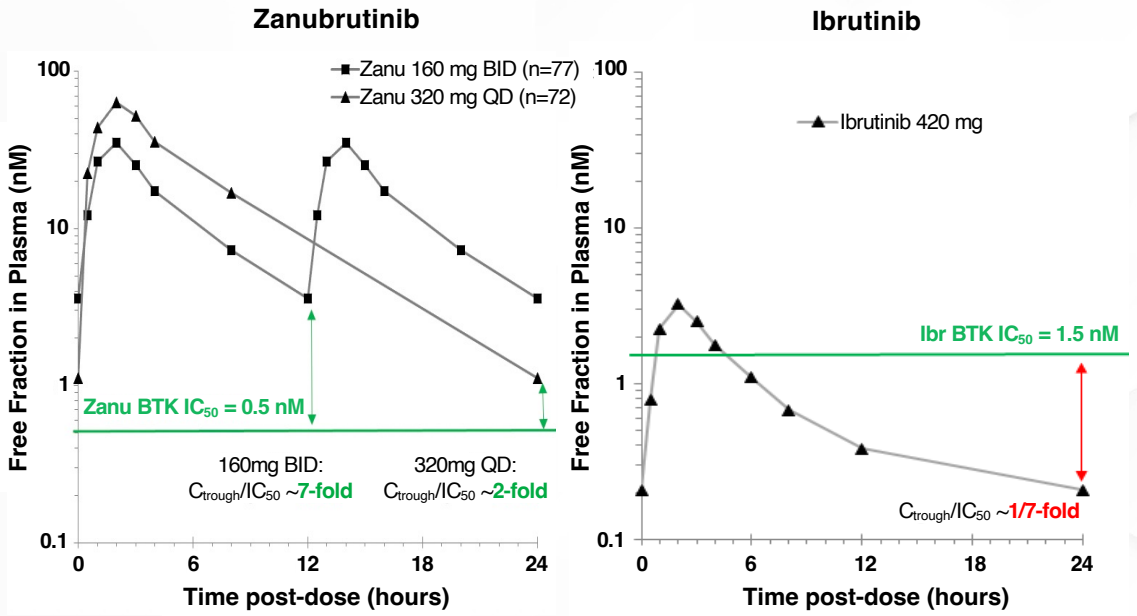


Zanubrutinib





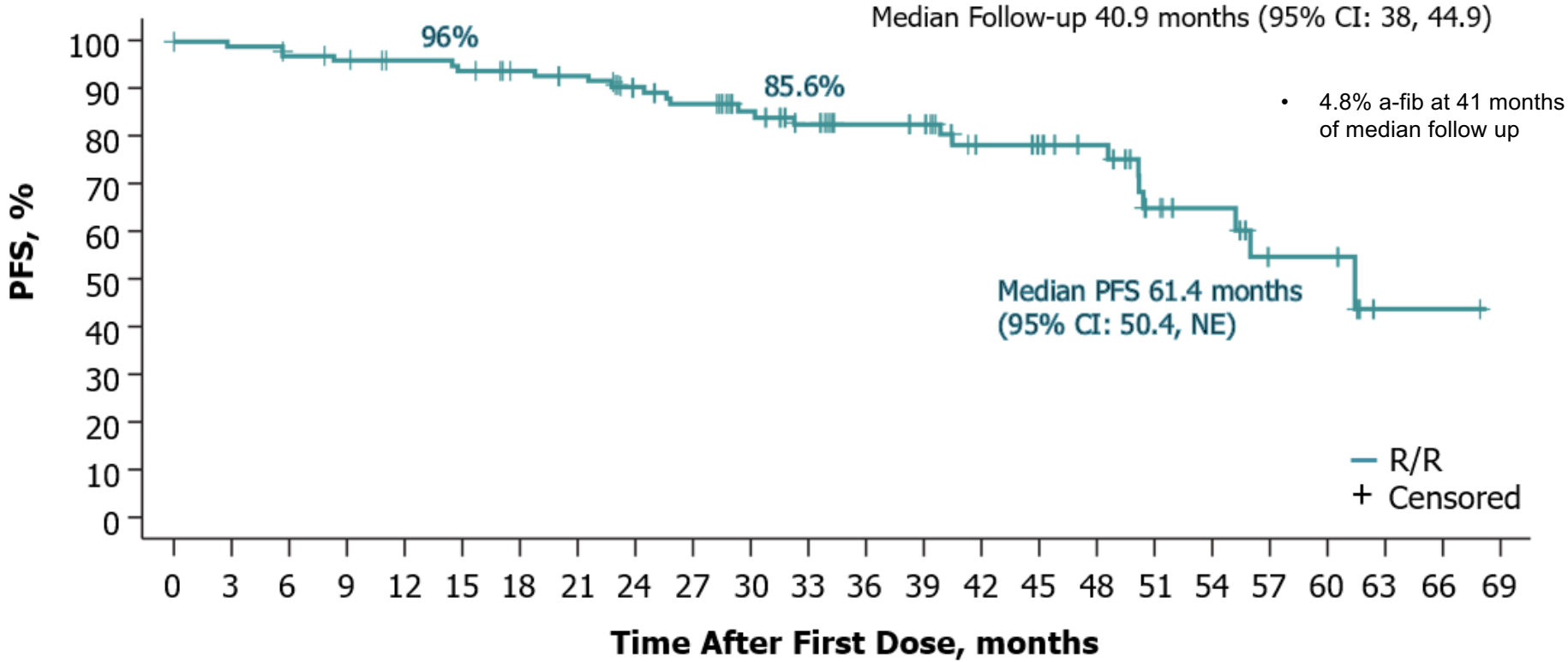
Free Drug Concentration Time Profiles Relative to IC_{50}



Note: These data are from separate analyses. Limitations of cross-trial comparisons apply.

Hillmen P, et al. Presented at: EHA;2021. LB1900.

Zanu Long-Term R/R CLL Data



- 4.8% a-fib at 41 months of median follow up

Hillmen P, et al. Presented at: EHA;2021. Abstract LB1900.

ALPINE Study Design

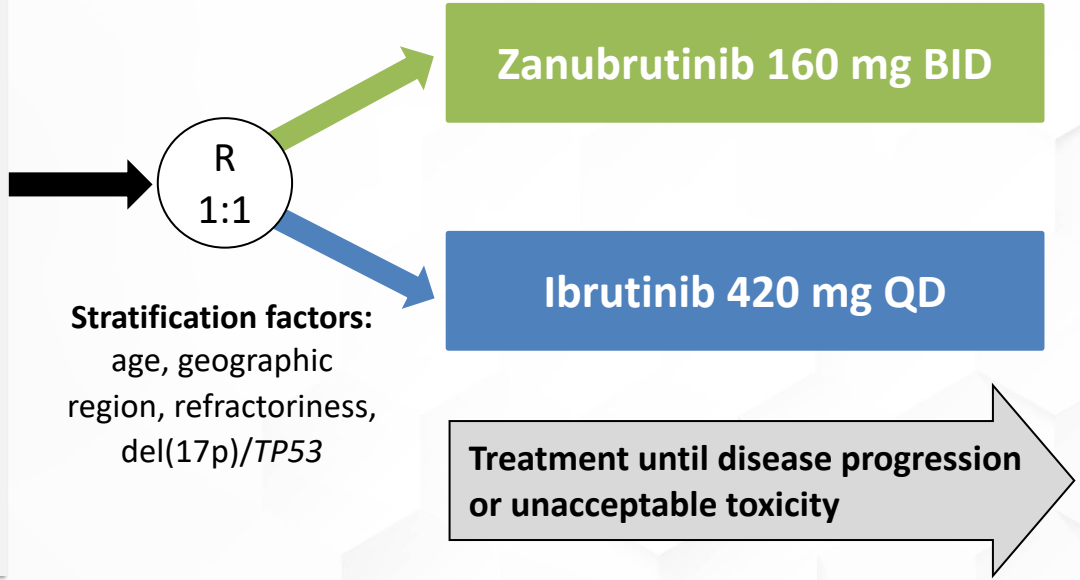
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

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

Key Exclusion Criteria

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



Hillmen P, et al. Presented at: EHA;2021. Abstract LB1900.

Endpoints and Statistical Design

Primary Endpoint

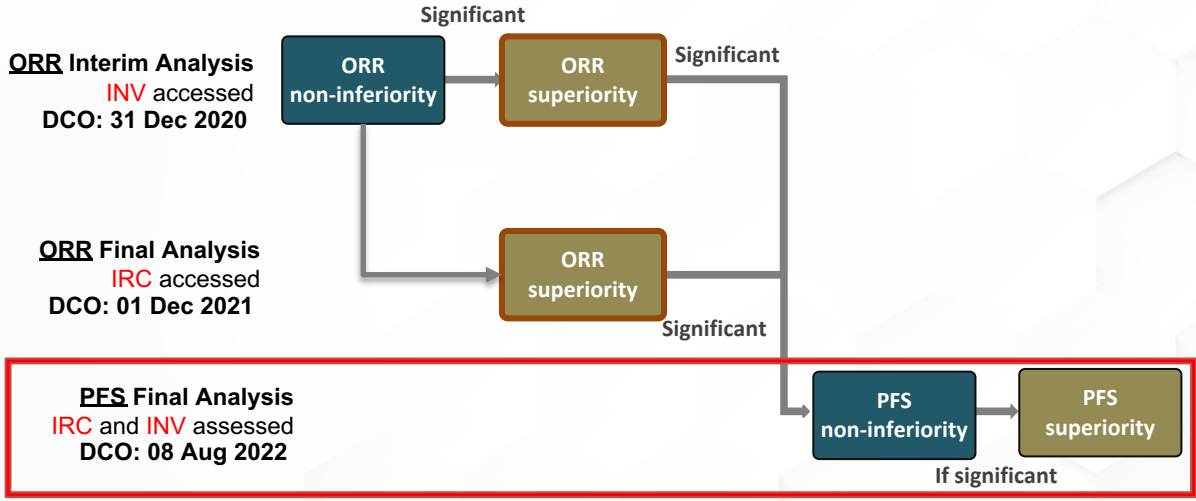
- ORR (PR+CR) noninferiority and superiority (by investigator)

Key Secondary Endpoints

- PFS
- Incidence of atrial fibrillation

Other Secondary Endpoints

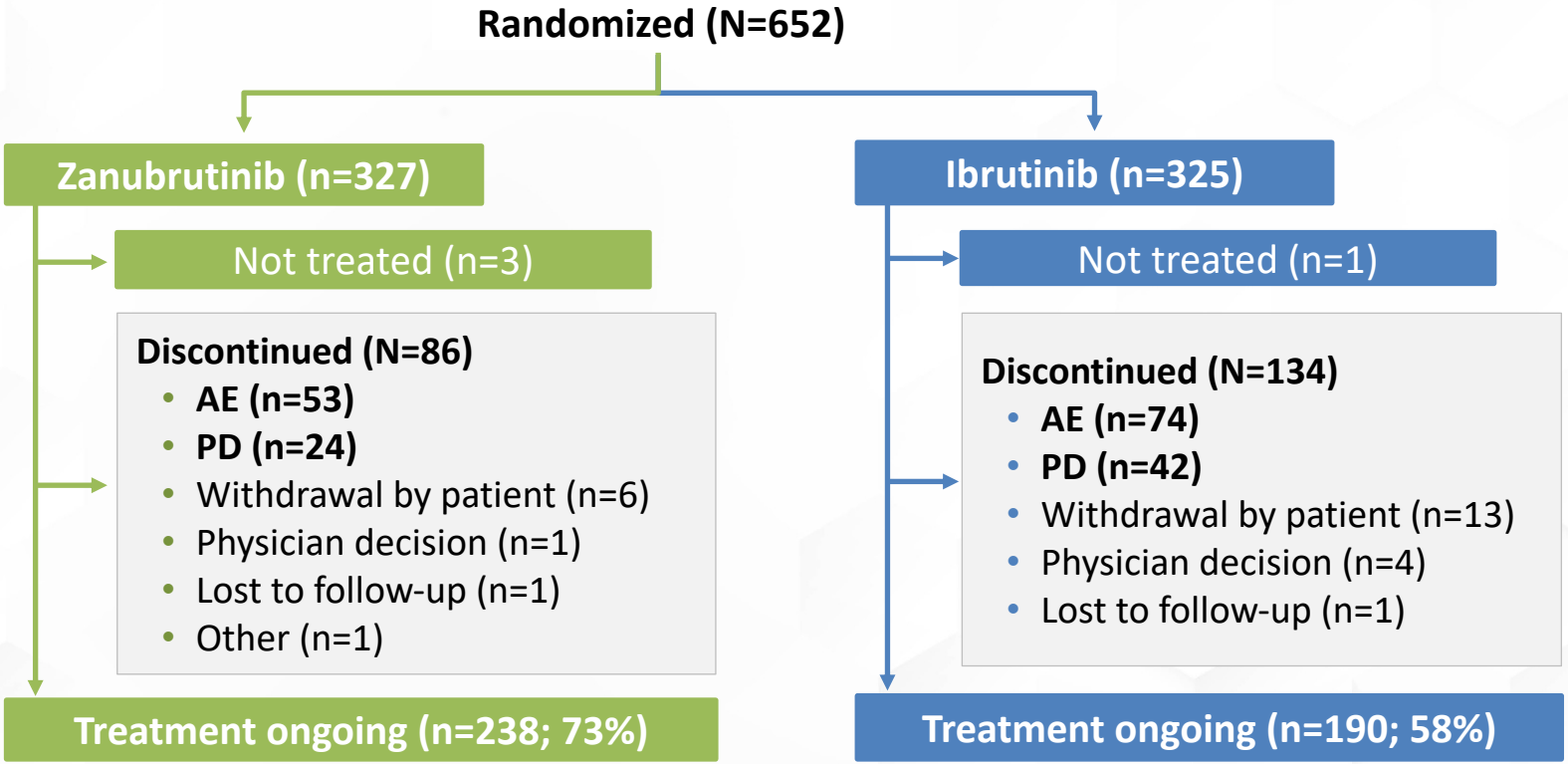
- DoR, OS
- Time to treatment failure
- PR-L or higher
- Patient-reported outcomes
- Safety



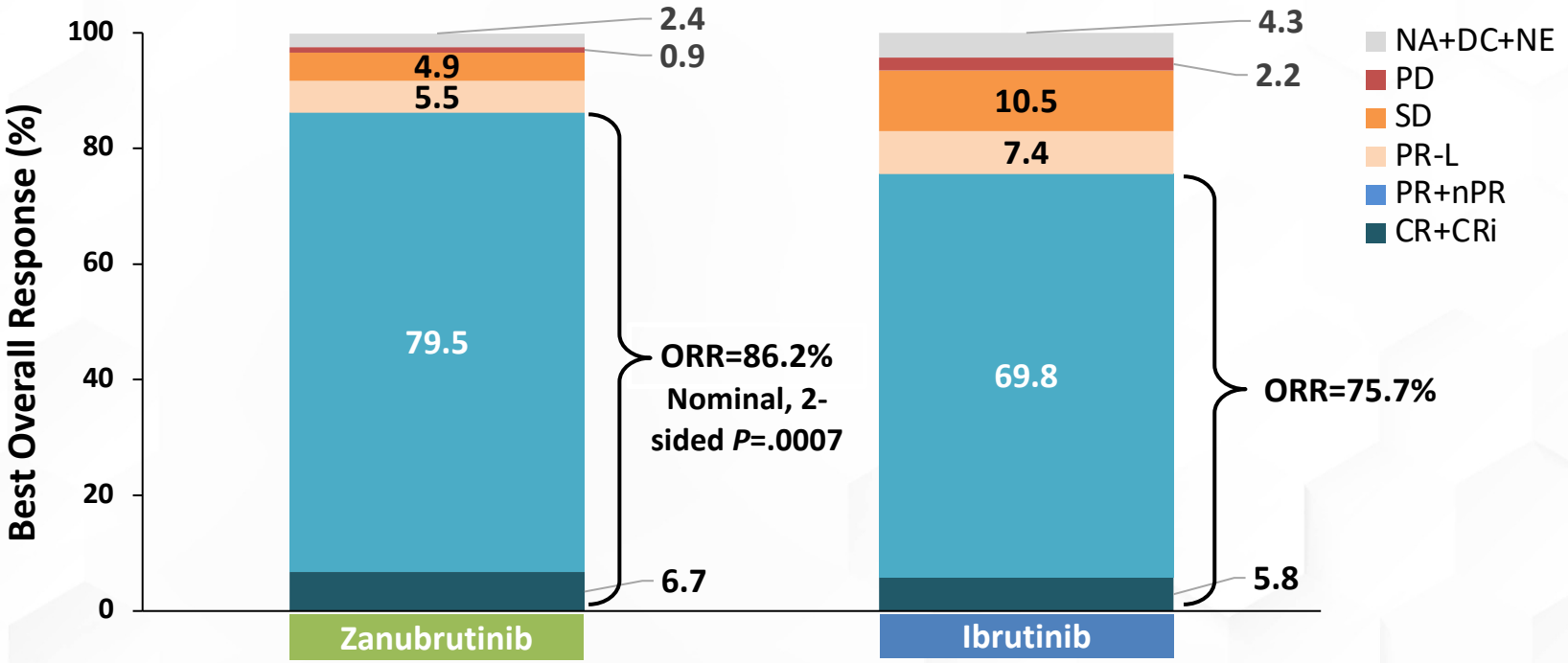
Overall response rate noninferiority and superiority were demonstrated in the ORR interim and final analyses; PFS was tested for noninferiority under hierarchical testing when 205 events had occurred

Hillmen P, et al. Presented at: EHA;2021. Abstract LB1900.

Patient Disposition



Zanubrutinib Showed Higher ORR Assessed by IRC

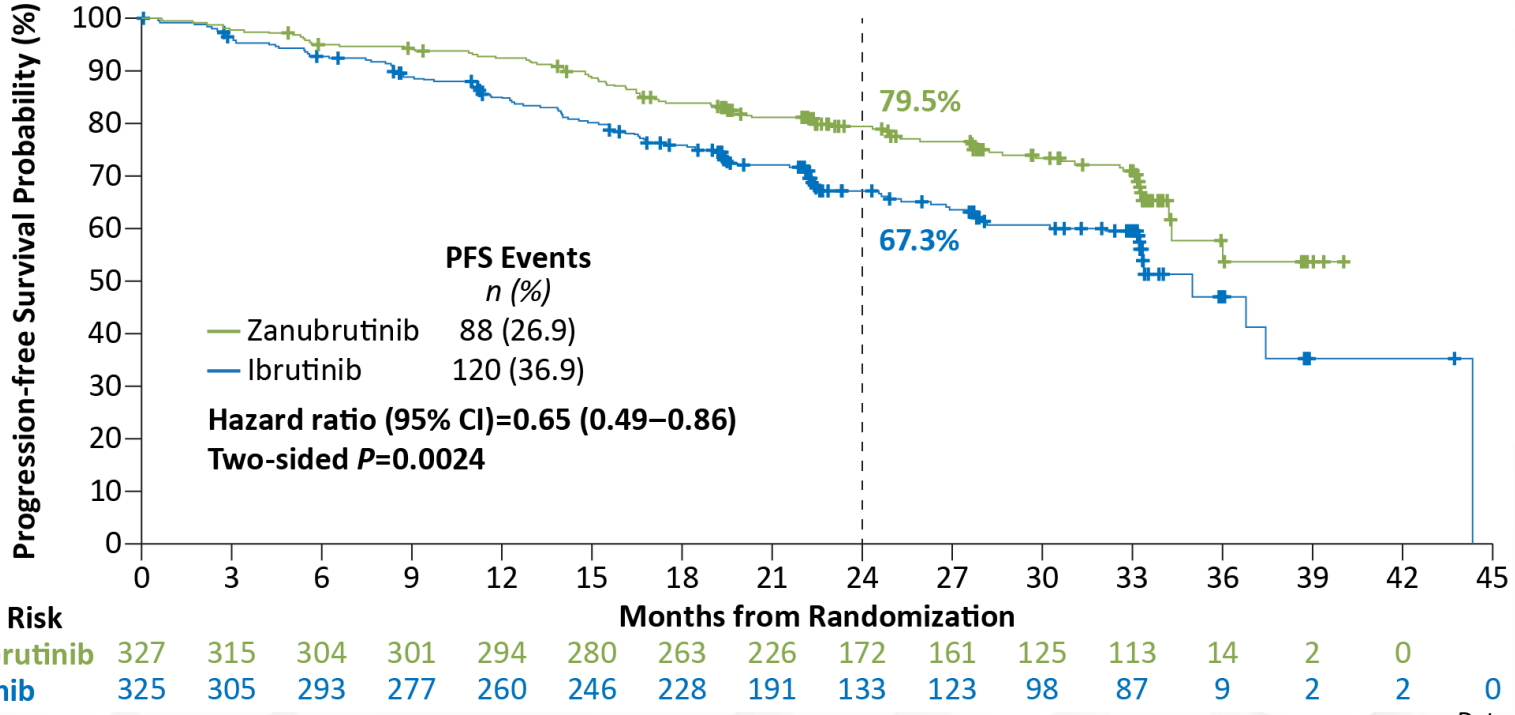


CR, complete response; CRi, complete response with incomplete bone marrow recovery; nPR, nodular partial response; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable response; PD, progressive disease; NA, not assessed; DC, discontinued prior to first assessment; NE, not evaluable.

Data cutoff: 8 Aug 2022

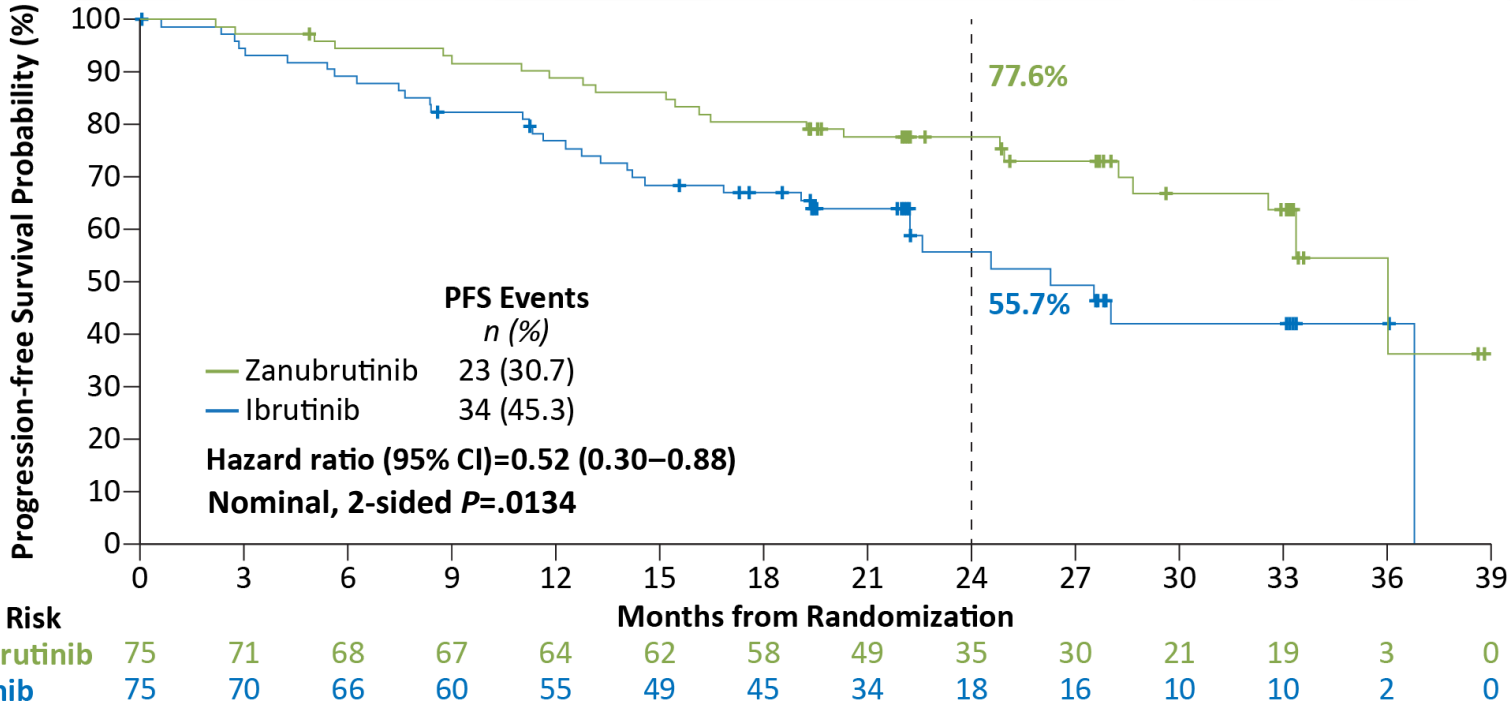
Zanubrutinib PFS by IRC Significantly Superior to Ibrutinib

Median study follow-up of 29.6 months



Data cutoff: 8 Aug 2022

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



PFS data assessed by IRC

Data cutoff: 8 Aug 2022

Zanubrutinib Had a Favorable Cardiac Profile

Lower rate of cardiac events, serious cardiac events, treatment discontinuation, and deaths

- Lower rate of serious cardiac adverse events reported with zanubrutinib
  - A fib/flutter (n=2)
  - MI/ACS (n=2)
  - CHF (n=2)
- **Fatal cardiac events:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

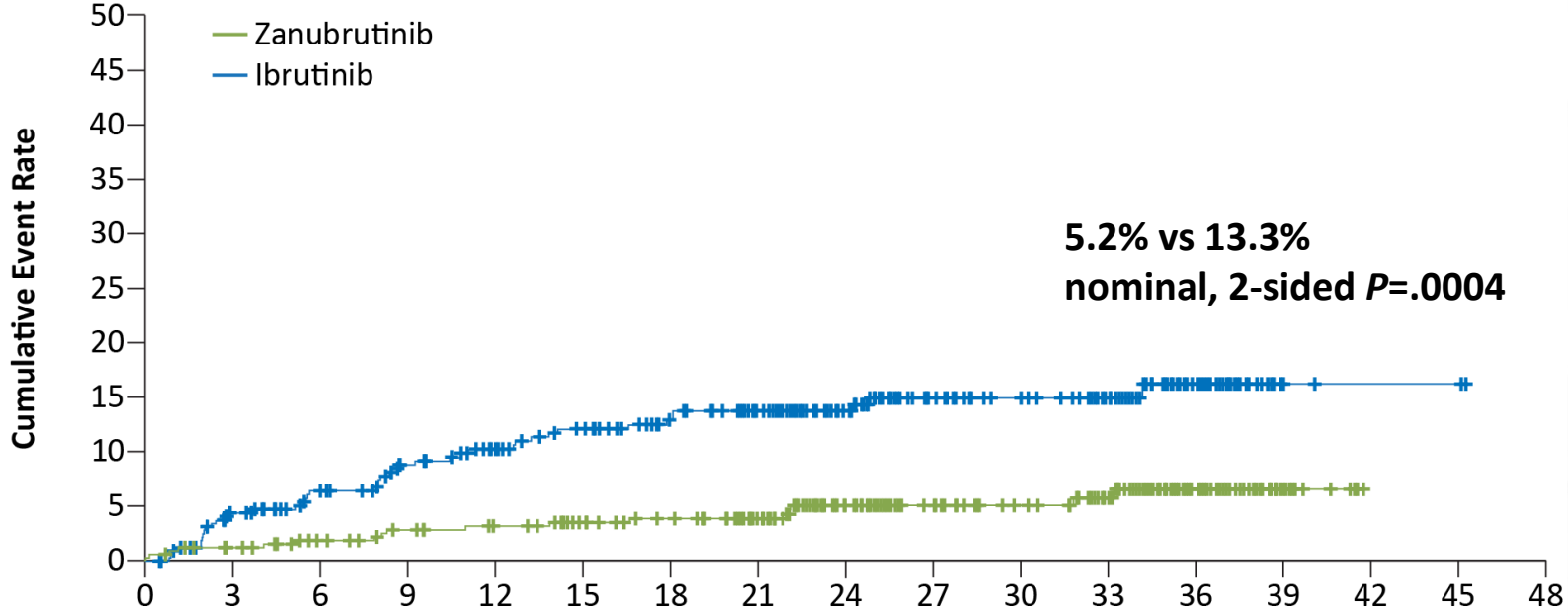
	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**69 (21.3%)**	**96 (29.6%)**
Serious cardiac adverse events	**6 (1.9%)**	**25 (7.7%)**
Cardiac adverse events leading to treatment discontinuation	**1 (0.3)**	**14 (4.3)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation	0	5 (1.5)
Cardiac arrest	0	2 (0.6)*
Cardiac failure	0	2 (0.6)
Cardiac failure acute	0	1 (0.3)*
Congestive cardiomyopathy	0	1 (0.3)*
Myocardial infarction	0	1 (0.3)*
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

*Cardiac deaths. One death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.

Data cutoff: 8 Aug 2022

Hillmen P, et al. *J Clin Oncol*. 2023;41(5):1035-1045.

Fewer Atrial Fibrillation/Flutter Events with Zanubrutinib



No. at Risk																	
Zanubrutinib	324	312	302	294	288	277	268	249	199	164	148	120	51	10	0		
Ibrutinib	324	295	278	260	247	230	211	193	153	121	108	89	40	3	2	1	0

Data cutoff: 8 Aug 2022

Considerations with BTK Inhibitors

- Toxicity of ibrutinib increases with age
  - Cardiac comorbidities
    - Difficult to control hypertension, atrial fibrillation, CHF ---- sudden death

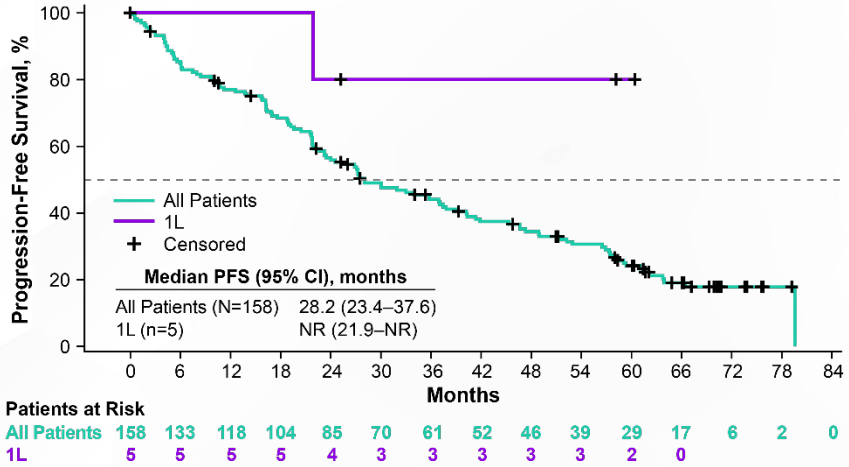
- Bleeding risk due to platelet dysfxn, including lack of data if plts <30K
  - Hold 3-7 days for procedures
  - Avoid anticoagulants if possible esp. warfarin, prefer NOACs
  - Avoid dual antiplatelet therapy

- Active infection, esp. fungal
  - Usually hold drug to control infection

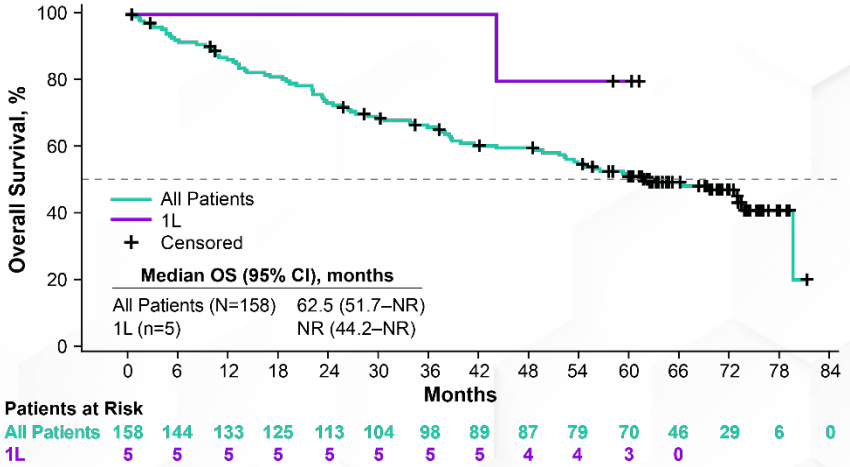
- Strong CYP3A4 inhibitors: generally avoid
  - Moderate CYP3A4 inhibitors or voriconazole: dose reduction required

Venetoclax in Deletion 17p Relapsed CLL Patients: PFS and OS (Median Follow-up, 70 Months)

Progression-Free Survival



Overall Survival



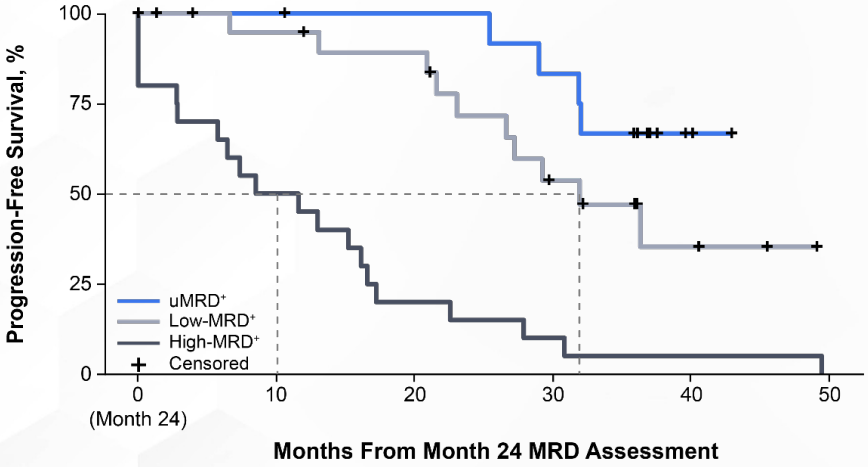
– **Median PFS was 28.2 months and median OS was 62.5 months**

NCT01889186. Updated December 16, 2021. Accessed May 12, 2023. https://clinicaltrials.gov/ct2/show/NCT01889186.

Venetoclax in Deletion 17p Relapsed CLL Patients:
PFS and OS Landmark Analysis by MRD Status at Month 24

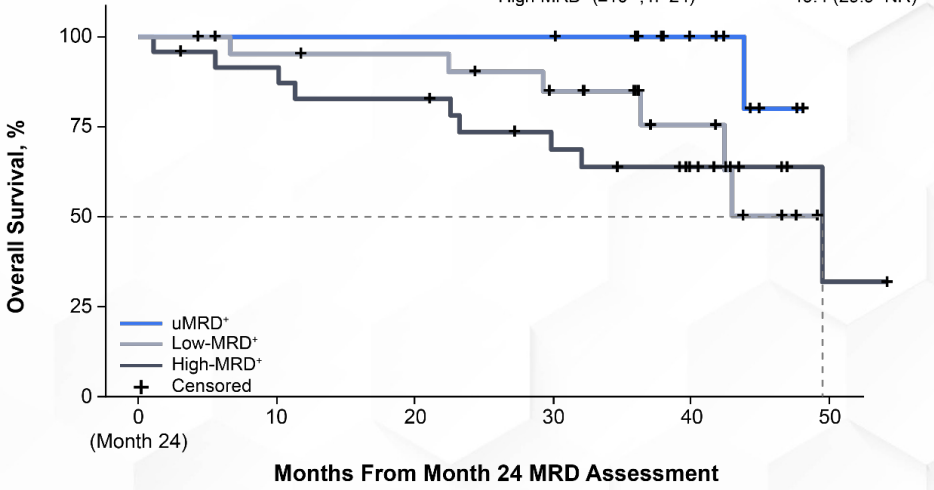
Progression-Free Survival

Median PFS (95% CI), months	
uMRD⁺ (10^{-4}; n=15)	NR (29.0–NR)
Low-MRD⁺ (10^{-4}–10^{-2}; n=20)	31.9 (23.1–NR)
High-MRD⁺ (≥10^{-2}; n=20)	10.1 (2.8–16.6)



Overall Survival

Median OS (95% CI), months	
uMRD⁺ (10^{-4}; n=15)	NR (43.8–NR)
Low-MRD⁺ (10^{-4}–10^{-2}; n=22)	NR (36.3–NR)
High-MRD⁺ (≥10^{-2}; n=24)	49.4 (29.9–NR)



MRD = minimal residual disease.

NCT01889186. Updated December 16, 2021. Accessed May 12, 2023. https://clinicaltrials.gov/ct2/show/NCT01889186.

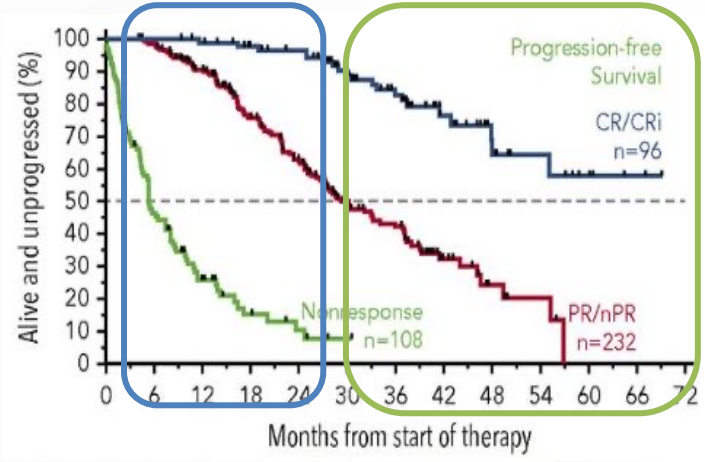
Clinical Patterns of CLL Resistance to Continuous Venetoclax Depend on Timing

Early Progression

Presentation enriched for:
- Richter Transformation
- Highly proliferative CLL

Pre-therapy Features
- Very bulky nodes (>10cm)
- BTK inhibitor resistant

Associated Genomic Changes
- Karyotypic Complexity
- Loss of *CDKN2A/B*
- *BTG1* mutation
- *NOTCH1* mutation



Late Progression

Presentation = Progressive CLL

Pre-therapy Features
- Adenopathy <10cm
- BTK inhibitor sensitive / naïve

Associated Genomic Changes
- **BCL2 mutation**
- MCL1 (1q) amplification
- Increased OXPHOS
- BCLXL overexpression

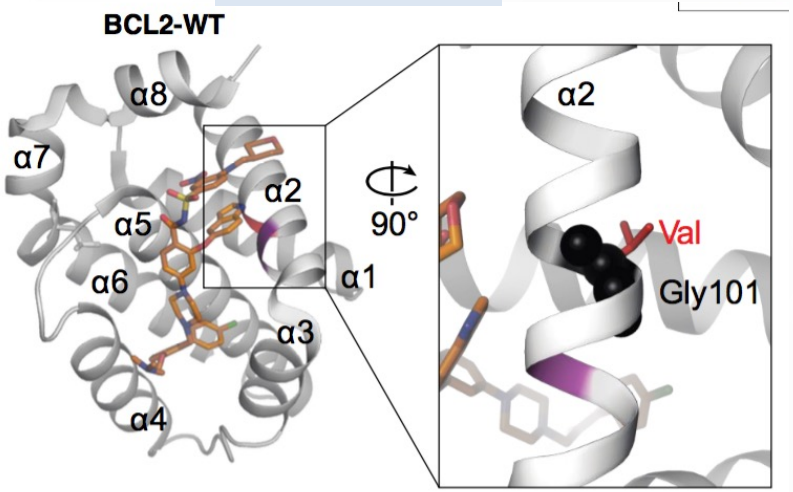
(slide adapted from M. Anderson, M Davids)

Anderson MA, et al. *Blood*. 2017;129(25):3362-3370, Herling CD, et al. *Nat Commun*. 2018;9(1):727. Bloombery P, et al. *Cancer Discov*. 2019;9(3):342-353. Tausch E, et al. *Haematologica*. 2019;104(9):e434-e437. Birkinshaw RW, et al. *Nat Commun*. 2019;10(1):2385, Guièze R, et al. *Cancer Cell*. 2019;36(4):369-384.e13, Roberts AW, et al. *Blood*. 2019;134(2):111-122.

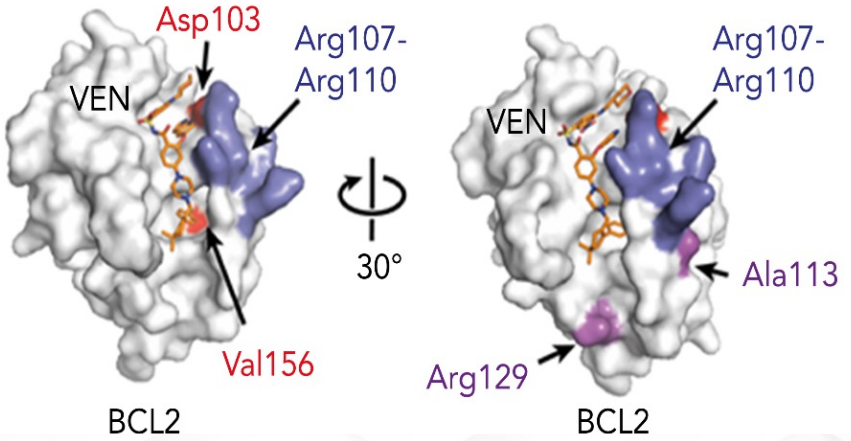
Multiple *BCL-2* Mutations Are Associated with Venetoclax Resistance

- ***BCL2*** **Gly101Val: 7 / 15 (46%) pts with CLL-type progression on venetoclax**

VENETOCLAX



- **Highly conserved residue**
- **Faces away from inside of binding groove**
- **Proximal to P4 pocket**



10 of 11 pts w Gly101 Val had a median 3 additional BCL2 mutations

Blombery P, et al. *Cancer Discov*. 2019;9(3):342-353. Blombery P, et al. *Blood.* 2020;135(10):773-777.

Ven-R: Long-Term Update of Ph1b Study

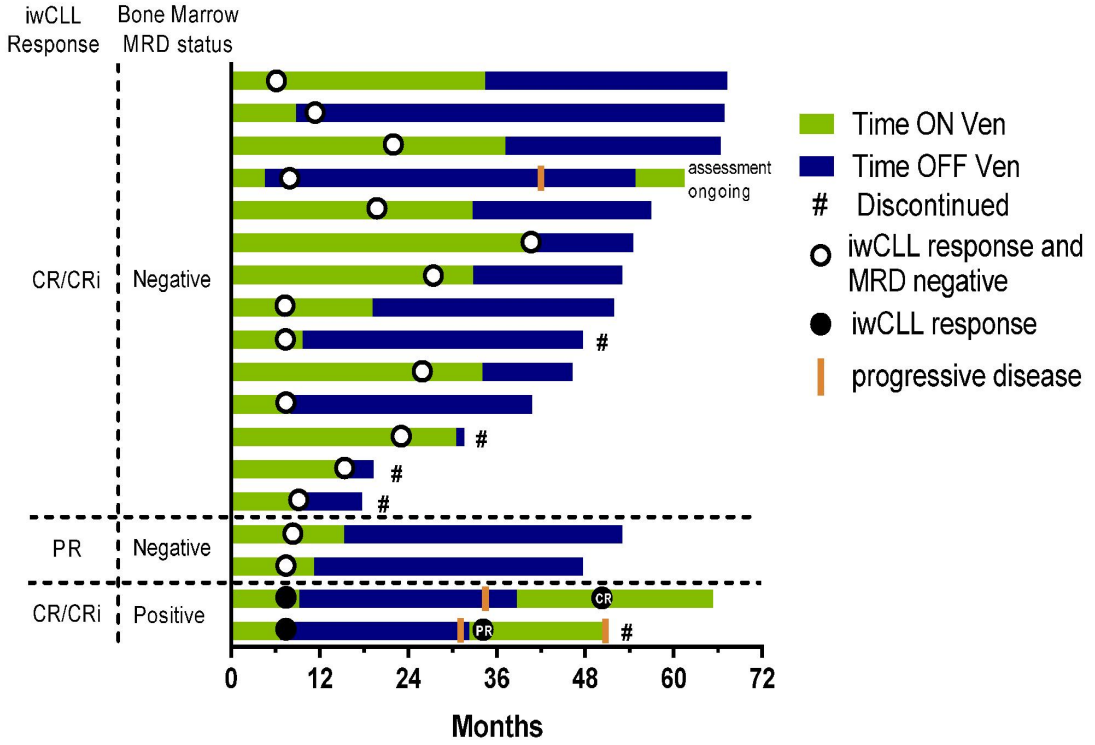
- N=49
- Median 2 priors

- Median time on study 4.1 y
- Median time on ven 2.5 y

- ORR 86%, CR 51%
- BM uMRD 61%

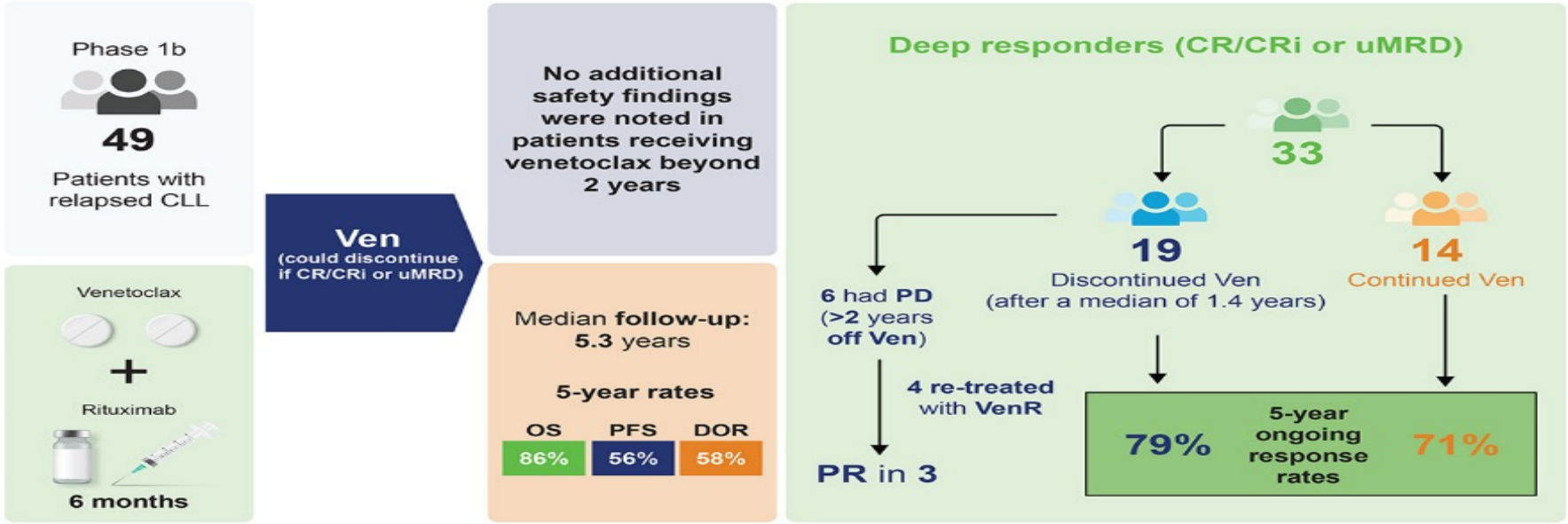
- PFS 61%
- DOR 88% if BM uMRD

Figure. Current Status of Patients who Discontinued Venetoclax and Remained on Study



Brander DM, et al. Accessed May 15, 2023. https://www.sciencedirect.com/science/article/pii/S0006497118609656.

Efficacy of venetoclax plus rituximab for relapsed CLL: Five-year follow-up of continuous or limited-duration therapy

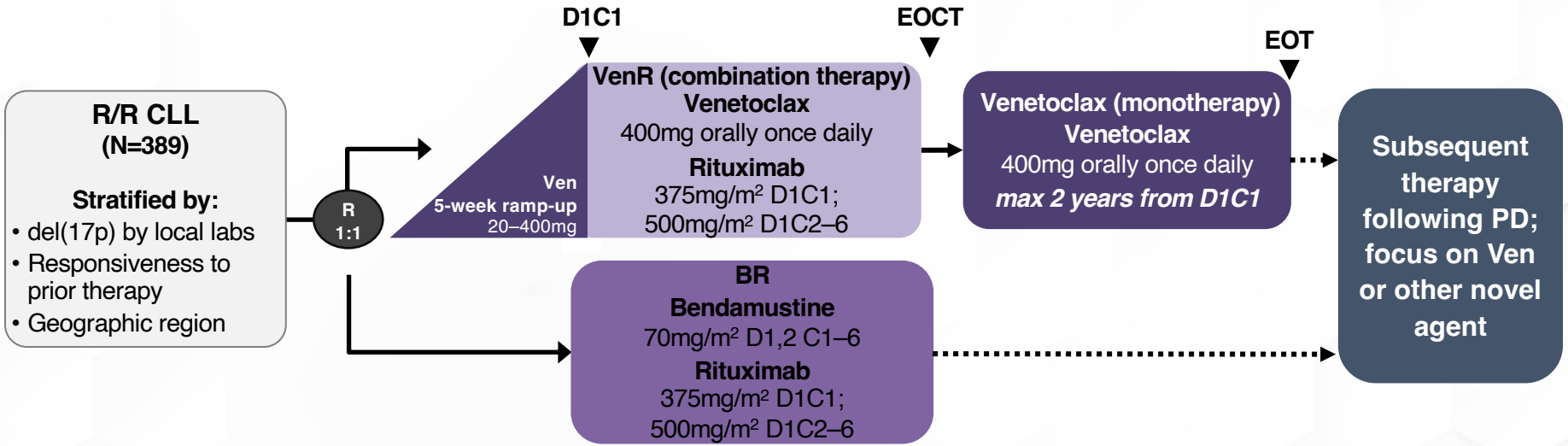


Long-term follow-up of patients with relapsed CLL receiving VenR demonstrates durable clinical benefit in patients receiving either continuous or limited-duration therapy

CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete marrow recovery; DOR, duration of response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; uMRD, undetectable minimal residual disease; Ven, venetoclax; VenR, venetoclax plus rituximab.

Ma S, et al. *Blood*. 2021;138(10):836–846.

MURANO Study Design

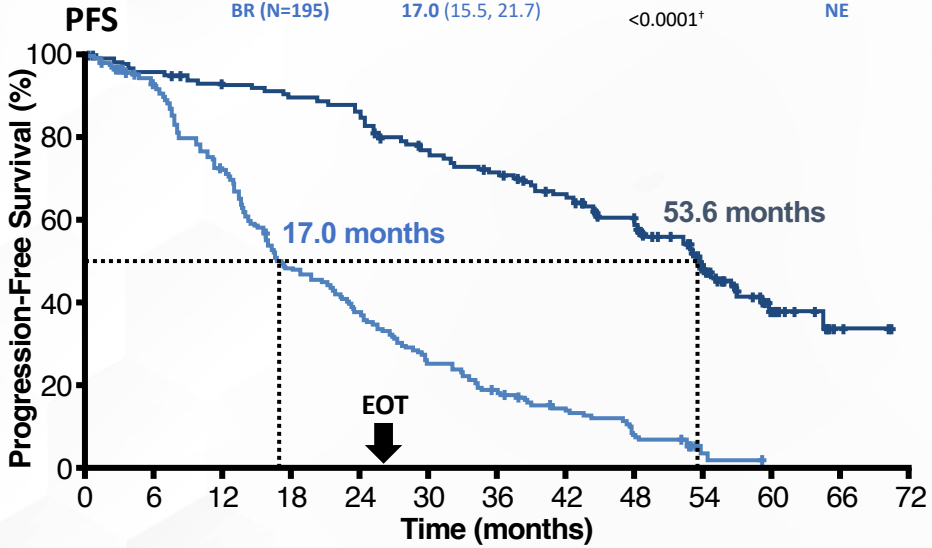


- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoint:** rates of clearance of MRD
- Clinical response and MRD* in PB during Ven monotherapy and follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD

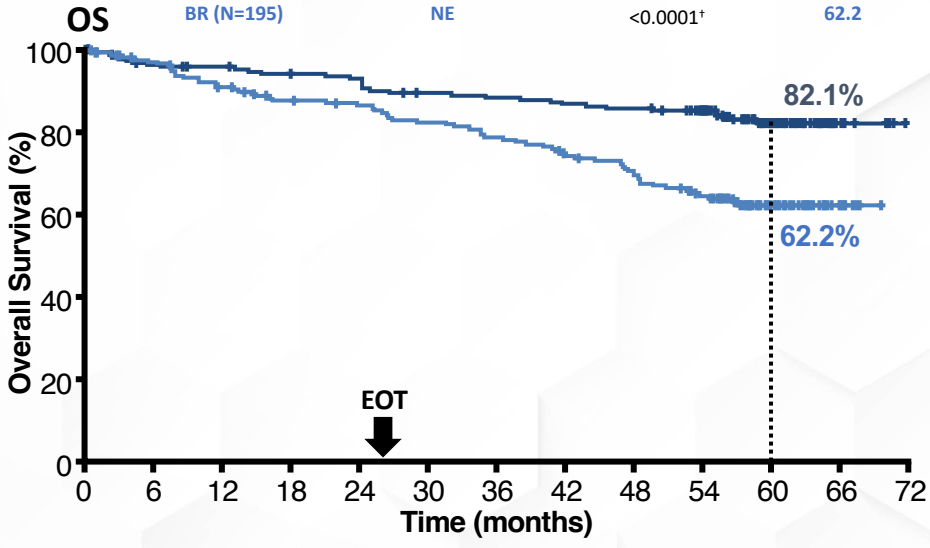
Kater AP, et al. Presented at: ASH;2020. Abstract 125.

PFS and OS Benefit with VenR Over BR Is Sustained 3 Years After EOT

	Median PFS (95% CI), months	HR* (95% CI)	5-yr PFS (%)
VenR (N=194)	**53.6** (48.4, 57.0)	**0.19** (0.15, 0.26) Stratified P-value <0.0001†	37.8
BR (N=195)	**17.0** (15.5, 21.7)		NE



	Median OS (95% CI), months	HR‡ (95% CI)	5-yr OS (%)
VenR (N=194)	NE	**0.40** (0.26, 0.62) Stratified P-value <0.0001†	82.1
BR (N=195)	NE		62.2



- With this 5-year update we can now accurately define the median PFS of VenR-treated patients
- No new safety signals were identified 3 years after EOT with longer follow up and patients are outside of the adverse event reporting window

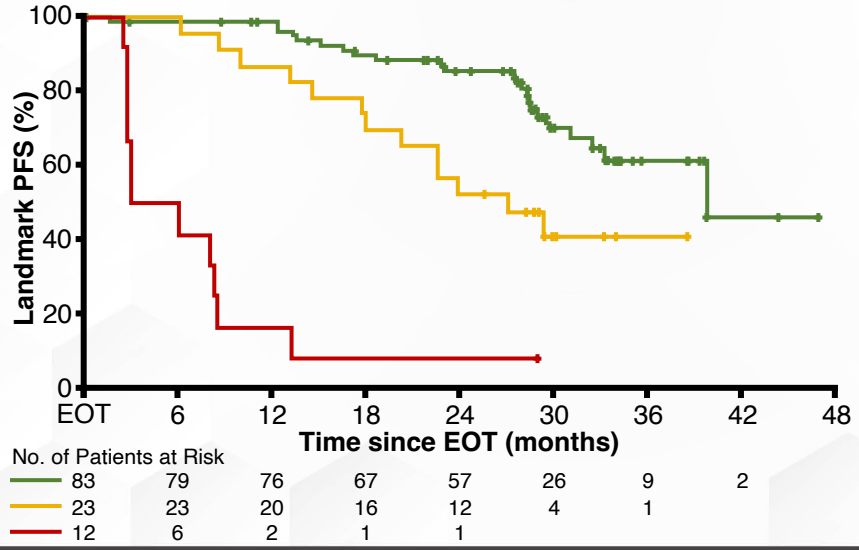
Kater AP, et al. Presented at: ASH;2020. Abstract 125.

uMRD at EOT Is Associated with Improved PFS

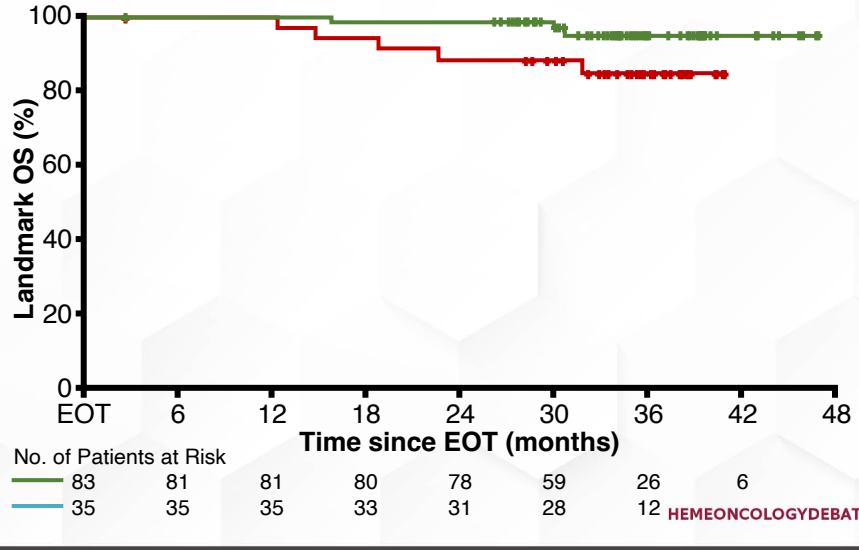
	PFS (95% CI) since EOT	
Category	**24 month**	**36 month**
uMRD ($<10^{-4}$)* (N=83)	85.4% (77.4, 93.4)	61.3% (47.3, 75.2)
Low-MRD+ (10^{-4}–10^{-2}) (N=23)	52.2% (31.8, 72.6)	40.7% (19.2, 62.2)
High-MRD+ ($>10^{-2}$) (N=12)	8.3% (0.0, 24.0)	NE
	HR (95% CI)	**P-value**
uMRD vs Low-MRD+	0.40 (0.18, 0.91)	0.0246
uMRD vs High-MRD+	0.02 (<0.01, 0.18)	<0.0001
Low-MRD+ vs High-MRD+	0.32 (0.10, 0.99)	0.0410

	OS (95% CI) since EOT	
Category	**24 month**	**36 month**
uMRD ($<10^{-4}$)* (N=83)	98.8% (96.4, 100.0)	95.3% (90.0, 100.0)
MRD ($\geq 10^{-4}$) (N=35)	88.6% (78.0, 99.1)	85.0% (72.8, 97.2)
	HR (95% CI)	**P-value**
uMRD vs MRD	NS	NS

PFS post-EOT

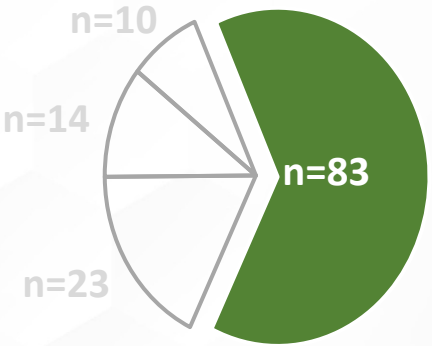


OS post-EOT



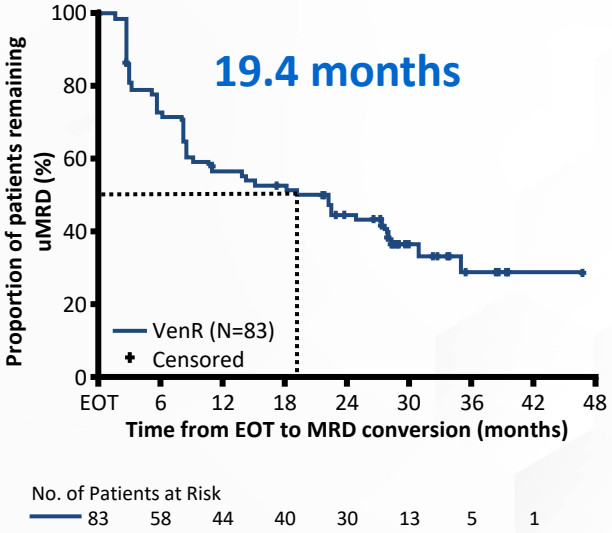
Delay between MRD Conversion and Clinical Progression

MRD status at EOT (N=130)



Time from EOT to MRD Conversion

Median 19.4 months
(95% CI 8.7; 28.3)

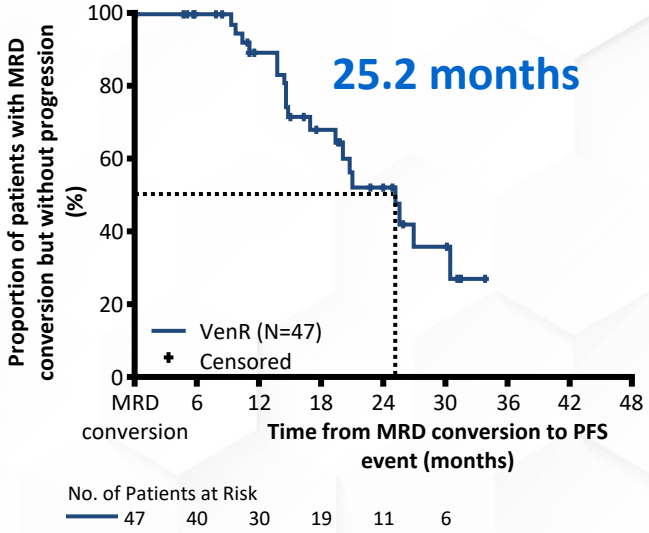


No. of Patients at Risk

VenR	83	58	44	40	30	13	5	1

Time from MRD conversion to PD*

Median 25.2 months
(95% CI 19.4; 30.4)



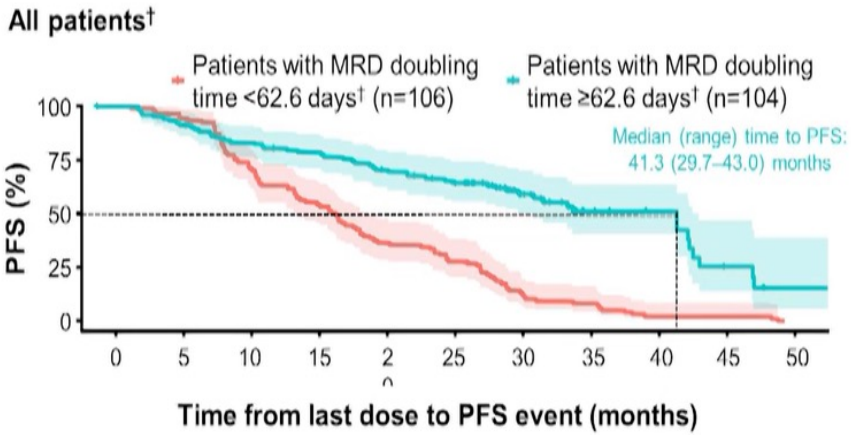
No. of Patients at Risk

VenR	47	40	30	19	11	6	

Kater AP, et al. Presented at: ASH;2020. Abstract 125.

CLL Clonal Growth Rate

Longer MRD doubling time* was predictive for longer PFS



The numerical shift observed in time from uMRD to MRD+ conversion supported the findings of the MRD growth model

Time to MRD+ conversion§ in subgroups who were all treated with VenR and had a difference in MRD doubling time

	Median doubling time, days	Median (95% CI), months
IGHV-mut, n=23	74	22.6 (8.1–NE)
IGHV-unmut, n=56	57	18.2 (8.4–28.0)
***TP53*-WT**, n=69	64	22.3 (8.6–28.4)
***TP53*-mut**, n=13	56	18.2 (8.3–NE)
≥65 years, n=45	66	22.6 (8.7–NE)
<65 years, n=38	53	15.2 (8.4–28.0)
Low/medium tumor burden, n=57	64	22.3 (8.6–35.1)
High tumor burden, n=23	53	12.2 (5.6–27.5)

Venetoclax: Be Aware

- TUMOR LYSIS: careful dose escalation with hydration
  - Often occurs during obinutuzumab in the ven obin regimen
- Renal failure

  Risk of tumor lysis, difficulty with fluids during dose escalation

- High tumor burden, bulky lymphadenopathy

- Pre-existing cytopenias, particularly neutropenia, due to hypocellular bone marrow or myeloid disorder

- CYP3A4 inhibitors / P-gp inhibitors: avoid during escalation
  - STRONG CYP3A4: after escalation, reduce dose to 70-100 mg
  - MODERATE CYP3A4 or P-gp inhibitors: after escalation, 50% dose reduction and ven taken 6 hrs after P-gp inhibitor
- No contra-indication to anticoagulation, but will increase serum warfarin concentration

Choice between BTKi and Ven R as First Novel Agent?

- ***Favors BTKi:***
  - Longer follow-up data (only with ibrutinib)
  - Use of next-gen BTKi improves toxicity profile (only with next gen)
  - Prospective data with ven after BTKi vs less data on the reverse
  - Intense early monitoring with ven
- ***Favors Ven R:***
  - High CR and undetectable MRD
  - Fewer long term side effects
  - Time-limited therapy, ?avoid selection pressure for resistance
  - Patient preference
  - Less cost
  - Potential for retreatment

Does the Sequence of Therapies Matter?

- Only prospective sequencing data showed that venetoclax has a 65% response rate and median 2 yrs PFS in pts with disease progression on prior BTKi
- Real-world data suggest ven followed by BTKi is also effective
  - But might allow for ven re-treatment before moving to BTKi
- Interest in time-limited combinations is designed to extend benefit of each class of therapy

Phase 2 TAP CLARITY: Ibrutinib + Venetoclax for Patients with R/R CLL

Key eligibility criteria
- ECOG PS ≤2
- Patients with CLL after ≥1 prior therapy
- No prior treatment with Ibr, Ven, or other BTKi or BCL-2i

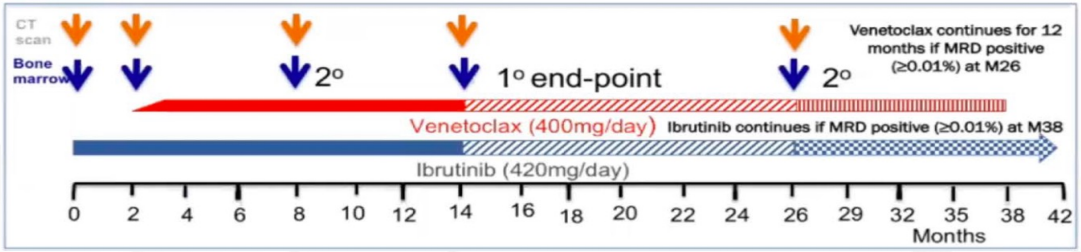
Primary endpoint:
MRD eradication (<0.01% CLL cells; MRD4) in BM after 12 months of I+V

Secondary endpoints:
MRD eradication in BM after 6 and 24 months of I+V, ORR, PFS, OS, safety

Duration of Ven: 3 consecutive MRD4 in PB and confirmed in BM
MRD <0.01% at:
- M8: stop I+V at M14
- M14: stop I+V at M26
- M26: stop I+V at M26

MRD ≥0.01%: continue Ibr

Amended treatment schedule and stopping rules allowed 3rd year of Ven



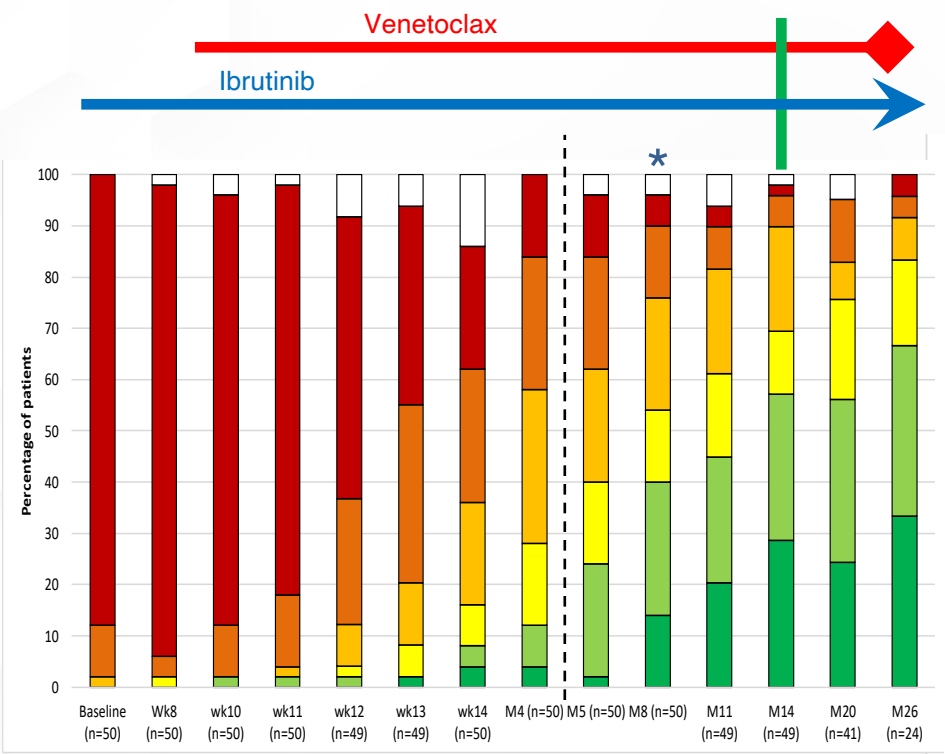
Patient Characteristics		(N=54)
Median age (range), years		64 (31-83)
Binet stage, n (%)	A	12 (22)
	B	18 (33)
	C	22 (41)
Bulky LNs (≥5 cm), n (%)		4 (8)
ECOG PS, n (%)	0	32 (59)
	1	18 (33)
	2	3 (6)
Unmutated *IgVH*, n (%)		40 (74)
del(17p), n/N (%)		10/50 (20)
del(11q), n/N (%)		13/51 (25)
Median prior therapies (range), n		1 (1-6)
Previous FCR or BR, n/N (%)		44/54 (82)
Relapse ≤3 years, n/N (%)		22/44 (50)
Previous idelalisib, n/N (%)		11/54 (20)

Data lock: 06 Nov 2020.

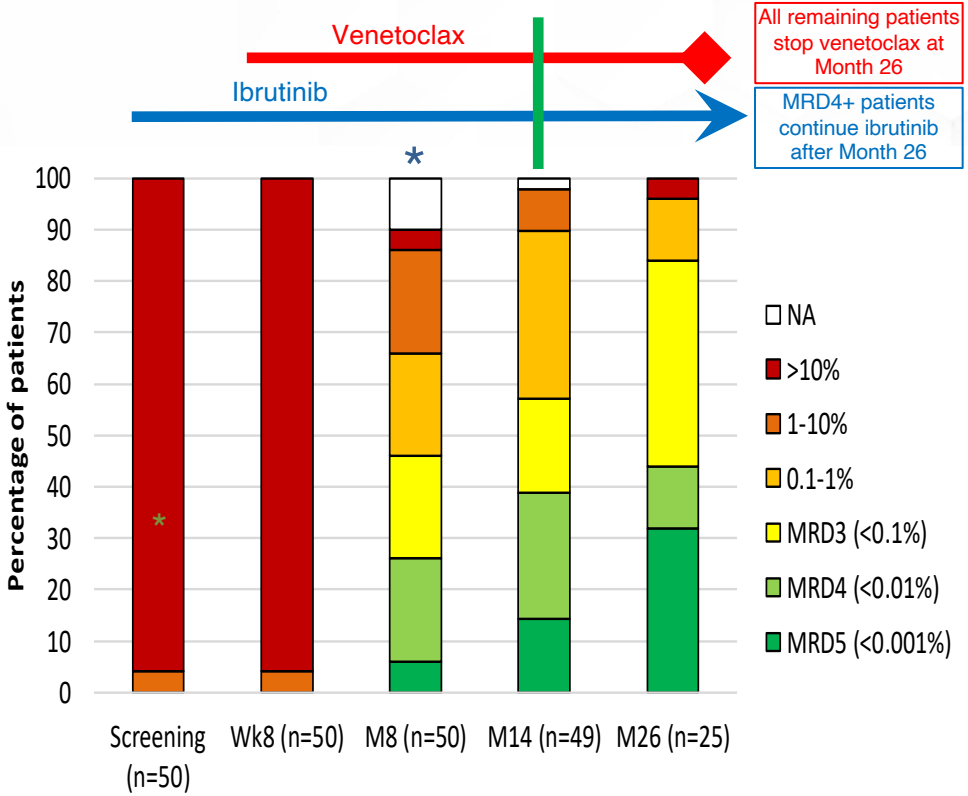
Munir T, et al. Presented at: ASH;2020. Abstract 124.

PB and BM MRD Level by Time-Point (up to Month 26)

Peripheral Blood



Bone Marrow

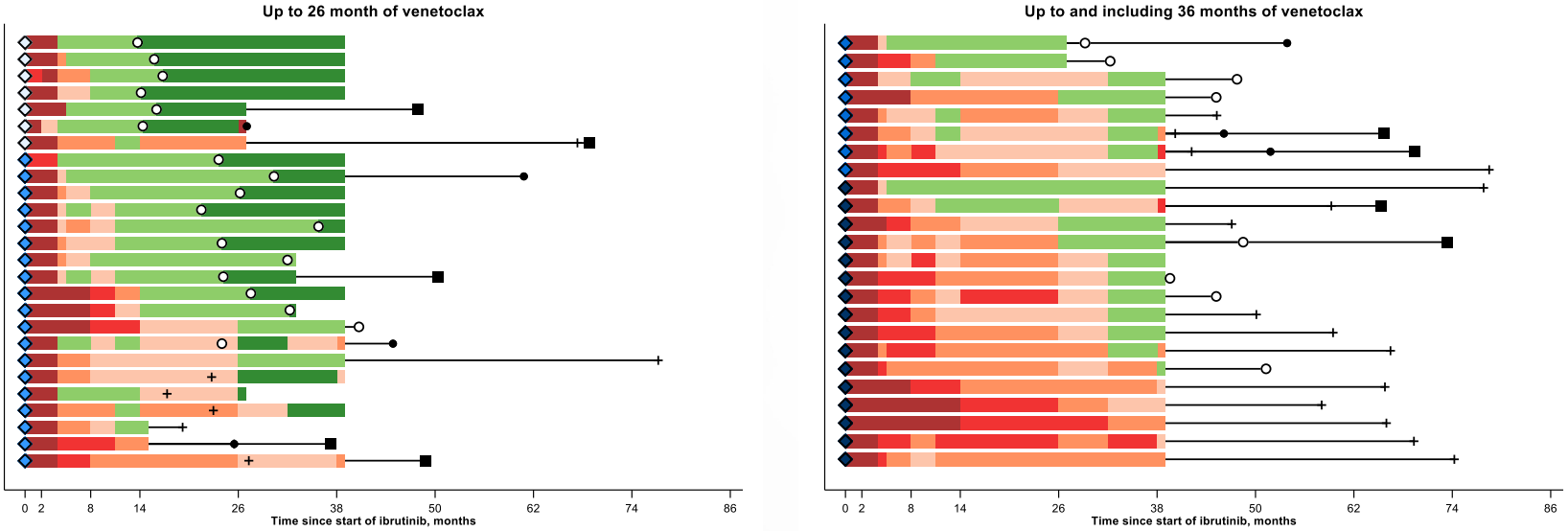


*PB & BM MRD negative pts at Month 8 & 14 stop I+V → All 6 reaching M26 remain MRD negative to date

Hillmen P, et al. *Blood.* 2018;132(Suppl 1):182.

Date of data lock: 05 November 2018

Higher MRD 4/5 Rates in Group Receiving 12-24 Months of Combination



Hillmen P, et al. *Blood.* 2018;132(Suppl 1):182.

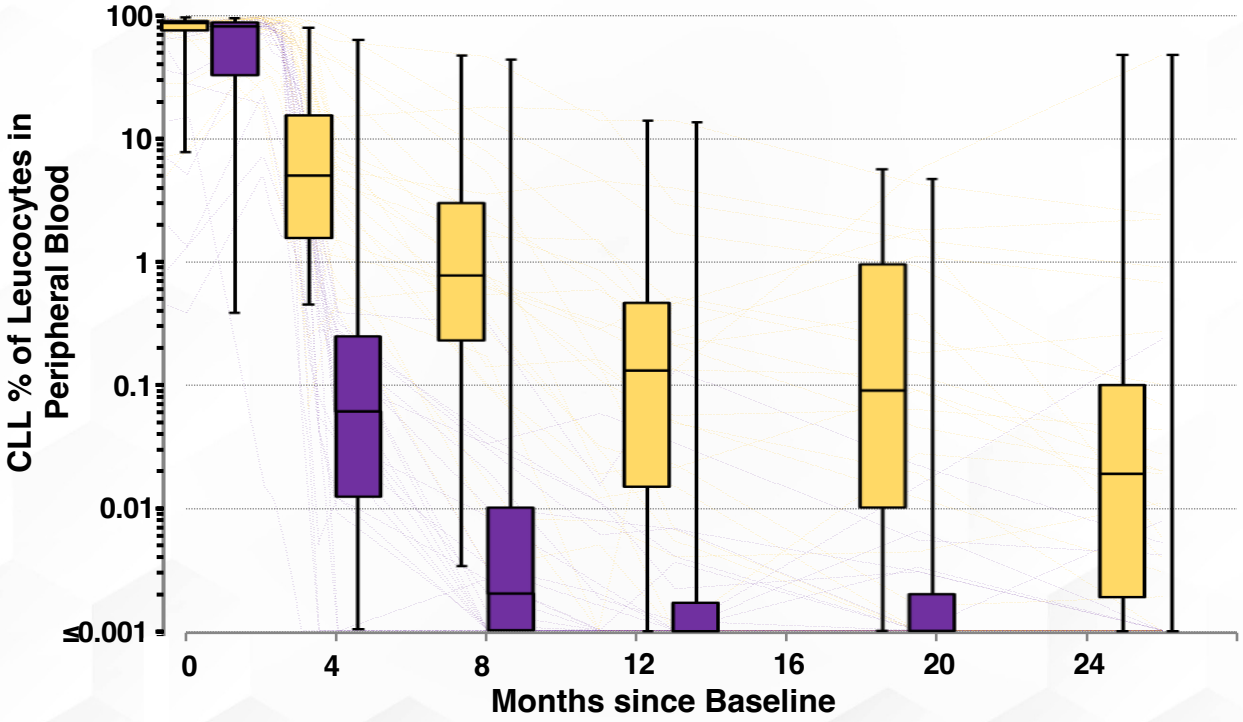
Date of data lock: 01-Nov-2022

Response Correlates with Initial Depletion Rate

IBR

VEN

Treatment continues until MRD <0.01% for 6M in PB confirmed in BM



Log depletion during first 2 months of VEN

<2 log depletion (n=25/50)

>2 log depletion (n=25/50)

Date of data lock: 19-May-2020

Rawstron A, et al. Presented at: EHA;2020. Abstract S164.

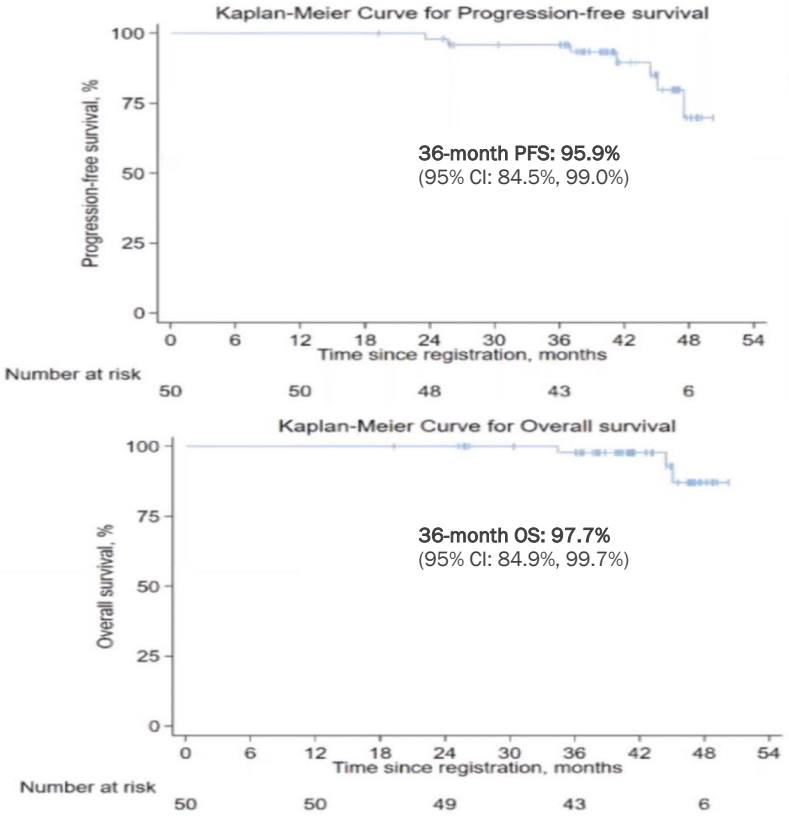
CLARITY Trial of Ibrutinib + Venetoclax for R/R CLL: Efficacy

23 patients have stopped treatment because of achieving sustained MRD <0.01% in both PB & BM. At one year after treatment discontinuation:

- **15/23 continue to have <0.01% PB MRD**
- 6/23 have between 0.01% - 1% PB MRD
- 2/23 have >1% MRD (both had 0.001 – 0.01% MRD at treatment discontinuation)

13 patients paused VEN for >6 months prior to trial amendment, of which 11/13 had a PB MRD evaluation during the pause:

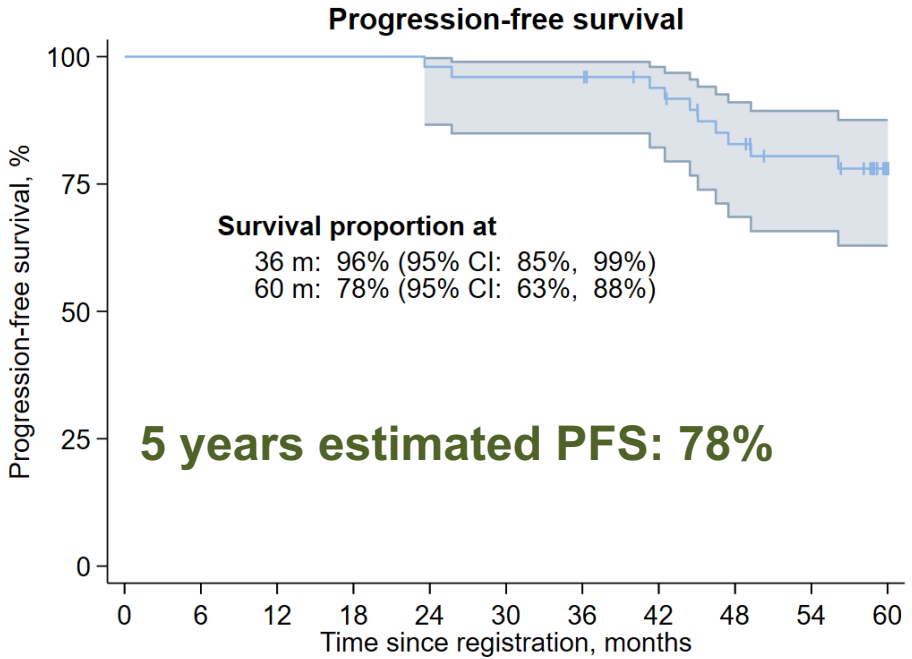
- 10/11 had stable MRD levels (<1log change)
- 1/11 MRD increased from 0.0039% to 0.045%

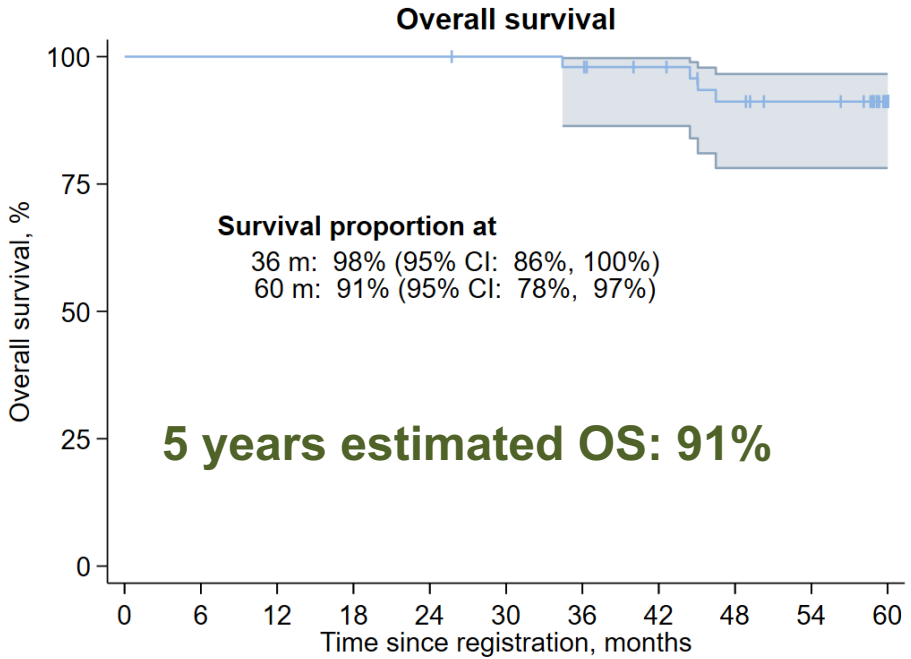


Munir T, et al. Presented at: ASH;2020. Abstract 124.

Progression Free and Overall Survival (n=50)

Median PFS and OS not reached by 60 months

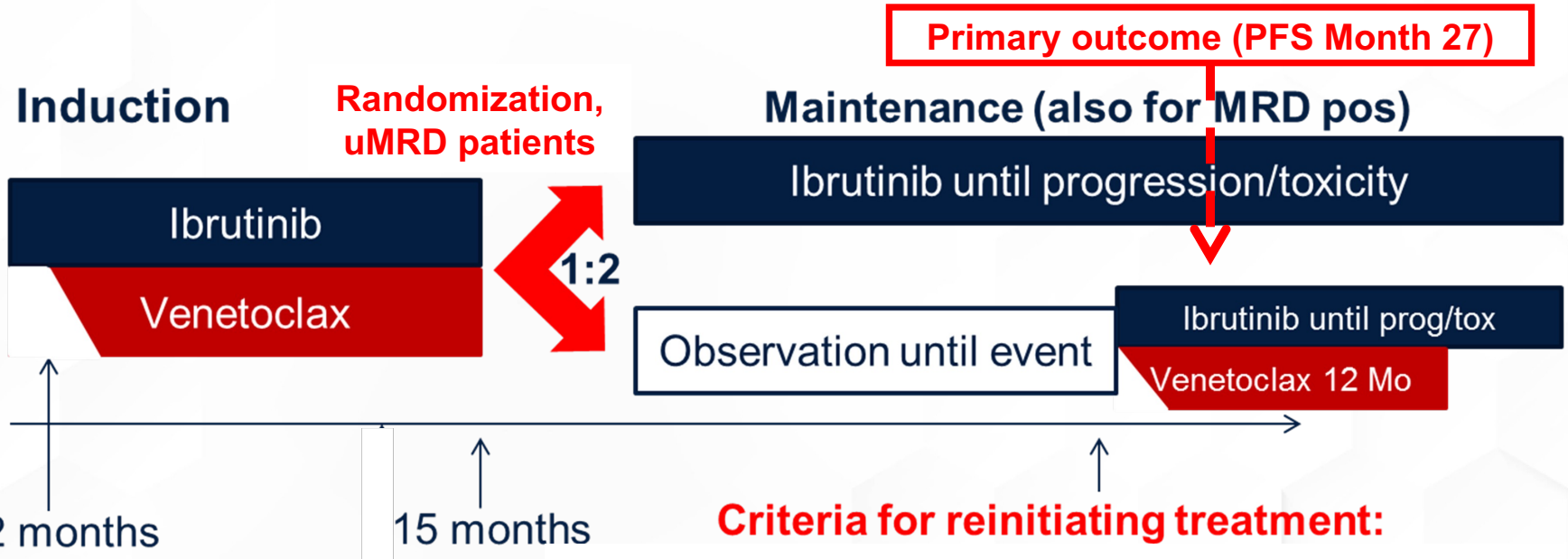




Munir T, et al. Presented at: ASH;2022. Abstract 91.

Date of data lock: 01-Nov-2022

HOVON Phase 2 VISION Trial: MRD Guided Stop / Start in RR CLL



Criteria for reinitiating treatment:

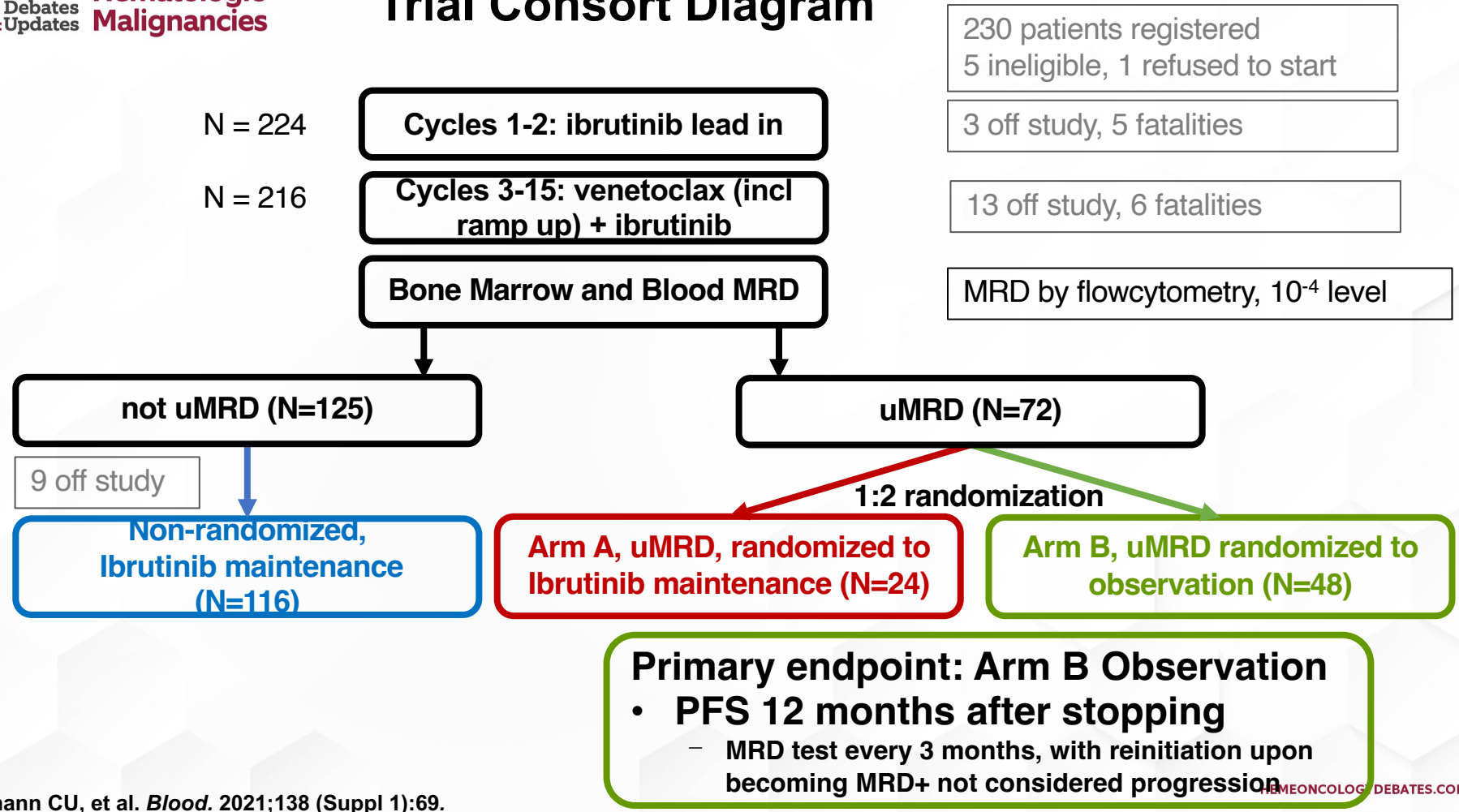
CLL progression according to iwCLL criteria or MRD >10^{-3} + MRD >10^{-2} ≥1 month later

Main Inclusion / Exclusion Criteria:

- Relapsed or Refractory CLL or SLL
- Performance status 0-3, all degrees of fitness / comorbidity allowed
- No prior venetoclax or ibrutinib

Niemann CU, et al. *Blood.* 2021;138 (Suppl 1):69.

Trial Consort Diagram

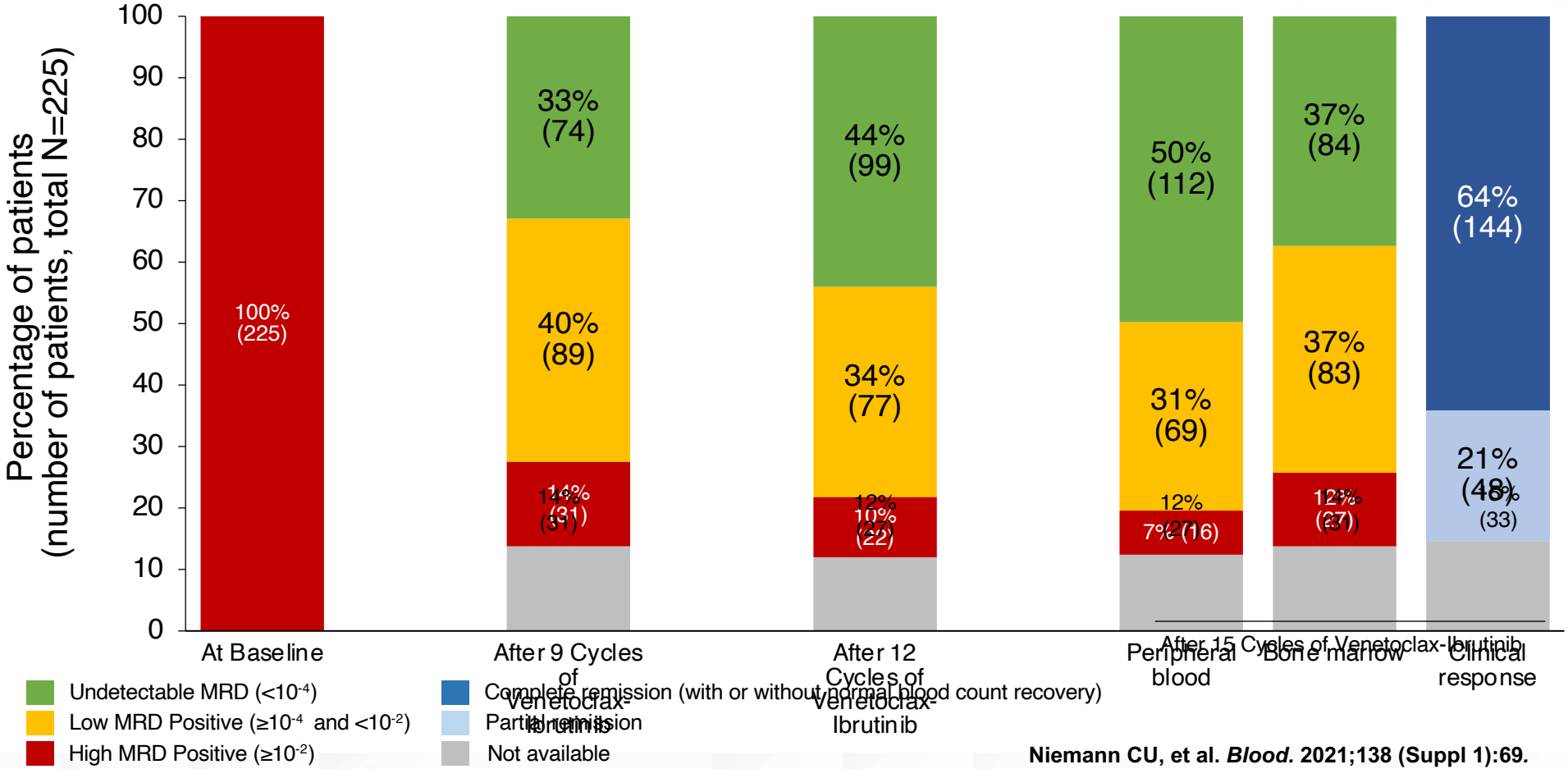


Primary endpoint: Arm B Observation

- **PFS 12 months after stopping**
  - **MRD test every 3 months, with reinitiation upon becoming MRD+ not considered progression**

Niemann CU, et al. *Blood.* 2021;138 (Suppl 1):69.

MRD and Response, 15 Cycles Ibrutinib-Venetoclax, Induction



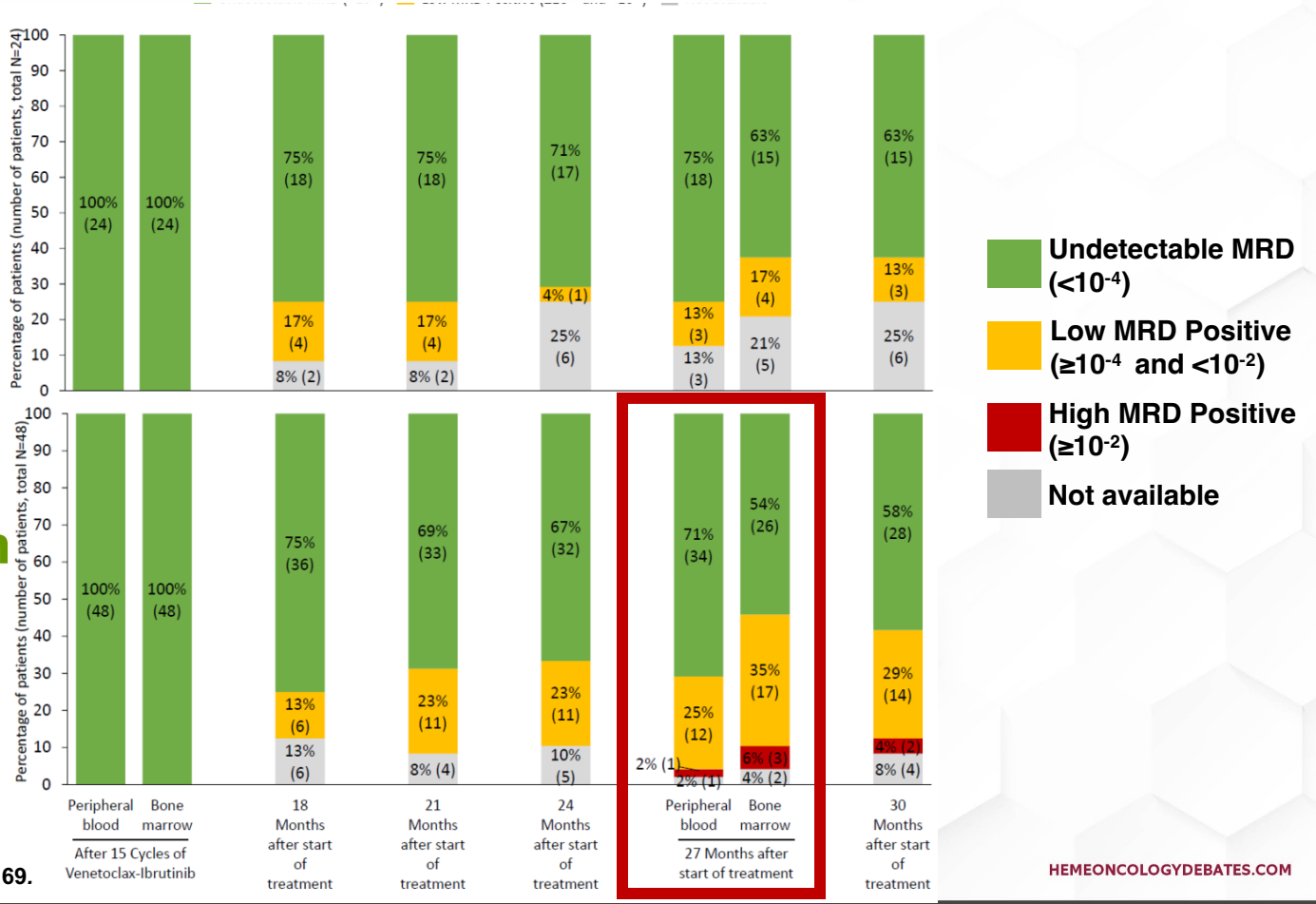
Niemann CU, et al. *Blood.* 2021;138 (Suppl 1):69.

MRD Over Time from C15, Arm A, Ibrutinib and Arm B, Observation

Arm A, Ibrutinib

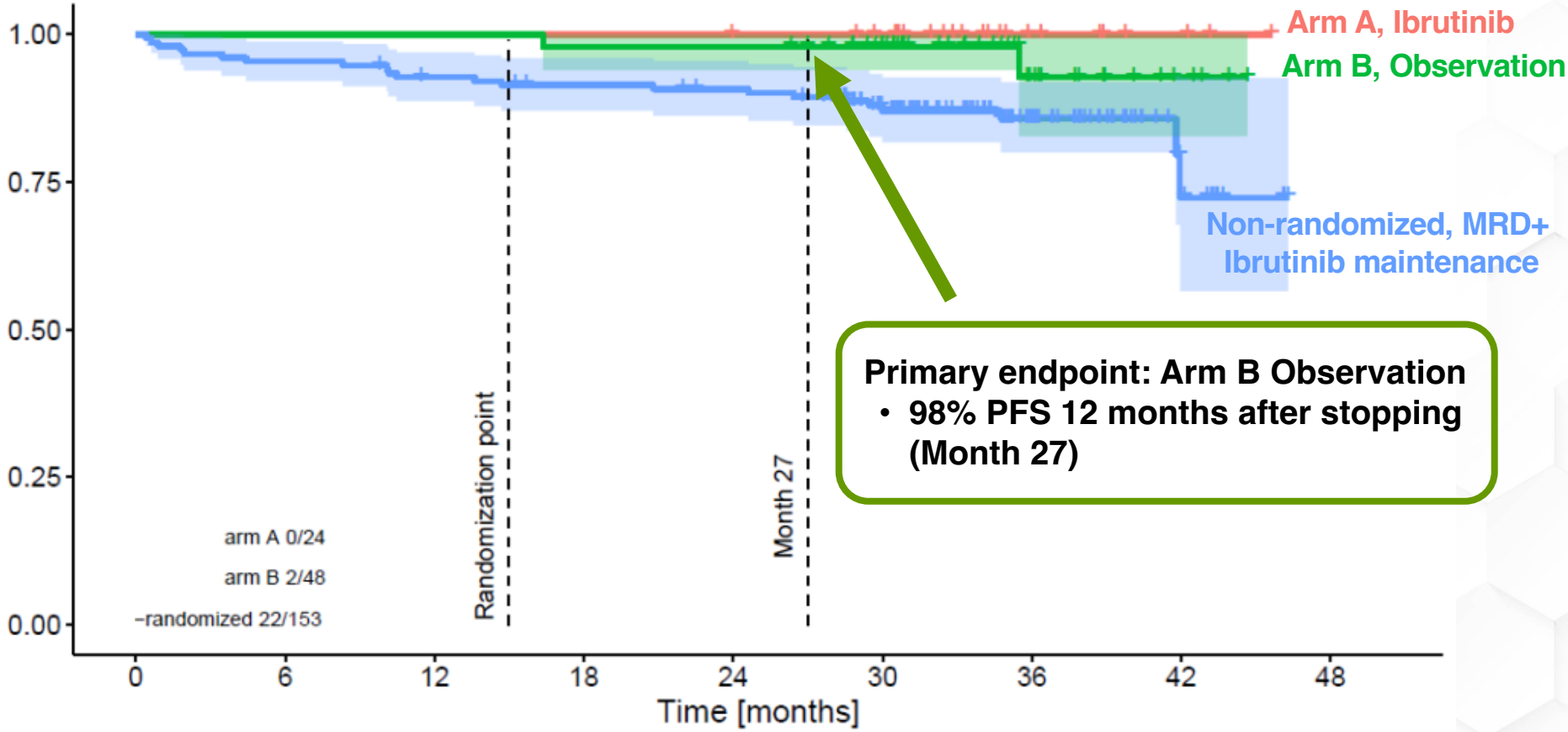
Arm B, Observation

Primary Endpoint



Niemann CU, et al. *Blood.* 2021;138 (Suppl 1):69.

Progression Free Survival (PFS)



Primary endpoint: Arm B Observation

- **98% PFS 12 months after stopping (Month 27)**

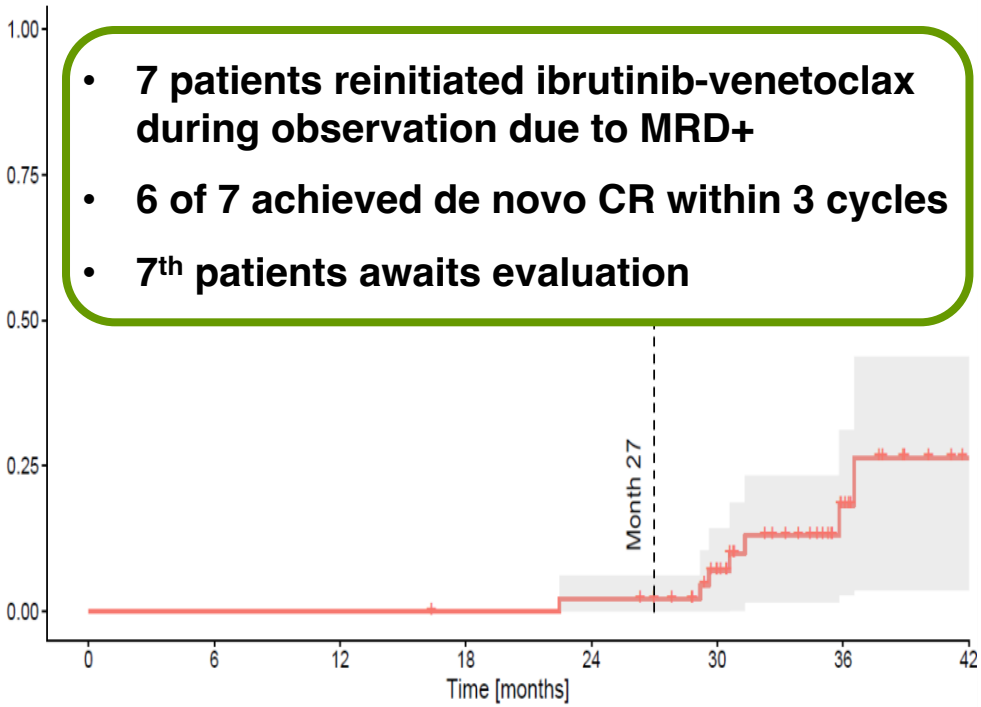
All patients with events prior to cycle 15 included in non-randomized group

Niemann CU, et al. *Blood.* 2021;138 (Suppl 1):69.

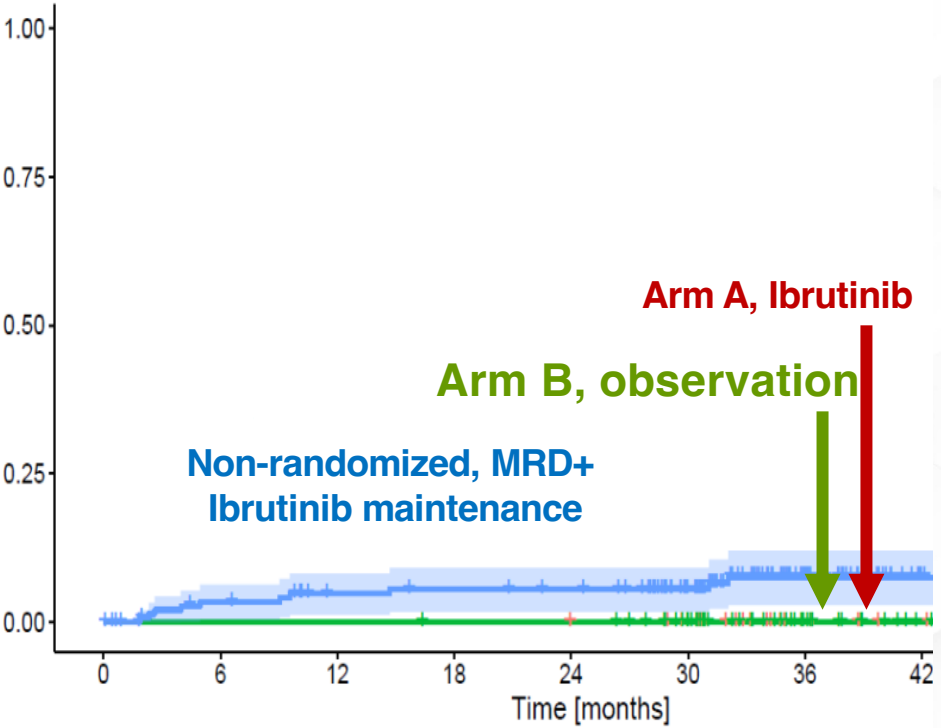
HOVON Vision Trial

Reinitiation, Arm B: Observation and Time To Next Treatment

- 7 patients reinitiated ibrutinib-venetoclax during observation due to MRD+
- 6 of 7 achieved de novo CR within 3 cycles
- 7th patients awaits evaluation



Reinitiation, Arm B: observation



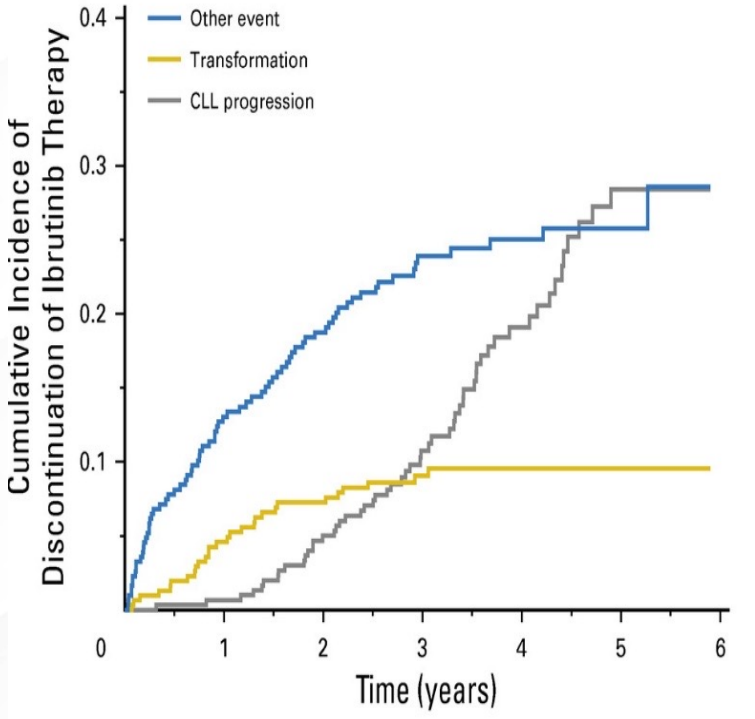
Time To Next Treatment

Niemann CU, et al. *Blood.* 2021;138 (Suppl 1):69.

The Changing Landscape of Relapsed CLL

- Patients relapsing after minimal therapy (mAb, clb)
- Patients relapsing after effective CIT
- Patients exposed to BTK inhibitors:
  - Off for adverse events
  - Progressed during therapy
- Patients relapsing after venetoclax
- Patients relapsing after BTKi and BCL-2

OSU Experience: Long-Term Ibrutinib



Cumulative Incidence	At 2 Yrs	At 3 Yrs	At 4 Yrs	Predictors
CLL progression	5.0%	10.8	19.1	Complex karyo (CK), 17p, age <65
Richters	7.3%	9.1	9.6	CK, MYC
Other event	18.7%	23.9	25.0	Age>=65 > 3 prior tx

Woyach J, et al. *J Clin Oncol*. 2017;35(13):1437-1443.

Retrospective Analysis of Toxicities and Outcomes for Ibrutinib-Treated Patients:

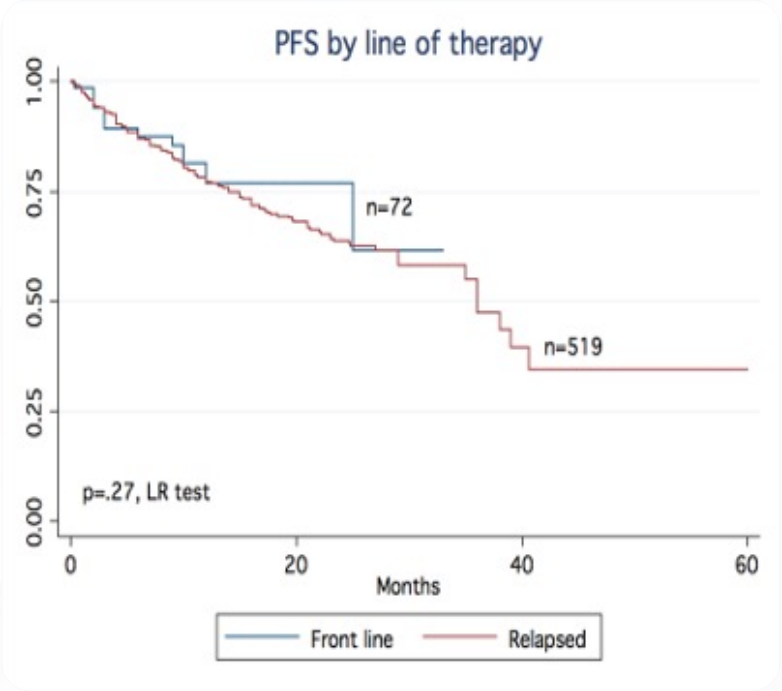
Discontinuations due to Toxicity

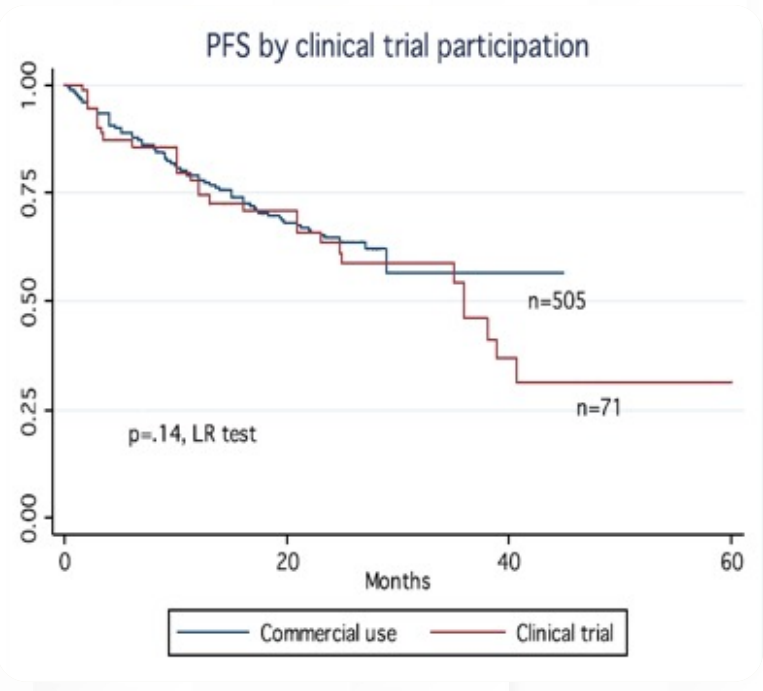
- Ibrutinib toxicity was the most common reason for discontinuation in all settings
  - In front line CLL, most commonly due to: arthralgia (42%), atrial fibrillation (25%), and rash (17%)
  - In R/R CLL, most commonly due to: atrial fibrillation (12%), infection (11%), pneumonitis (10%), bleeding (9%), and diarrhea (7%)
- Ibrutinib starting dose (420 mg/day vs. <420 mg/day) did not impact the proportion of patients who discontinued due to toxicity (51% vs 50%)

Months to discontinuation, median	Toxicity
Bleeding	8
Diarrhea	7.5
Atrial fibrillation	7
Infection	6
Arthralgia	5
Pneumonitis	4.5
Rash	3.5

Mato AR, et al. *Blood*. 2016;128(22):3222.

Retrospective Analysis of Toxicities and Outcomes for Ibrutinib-Treated Patients



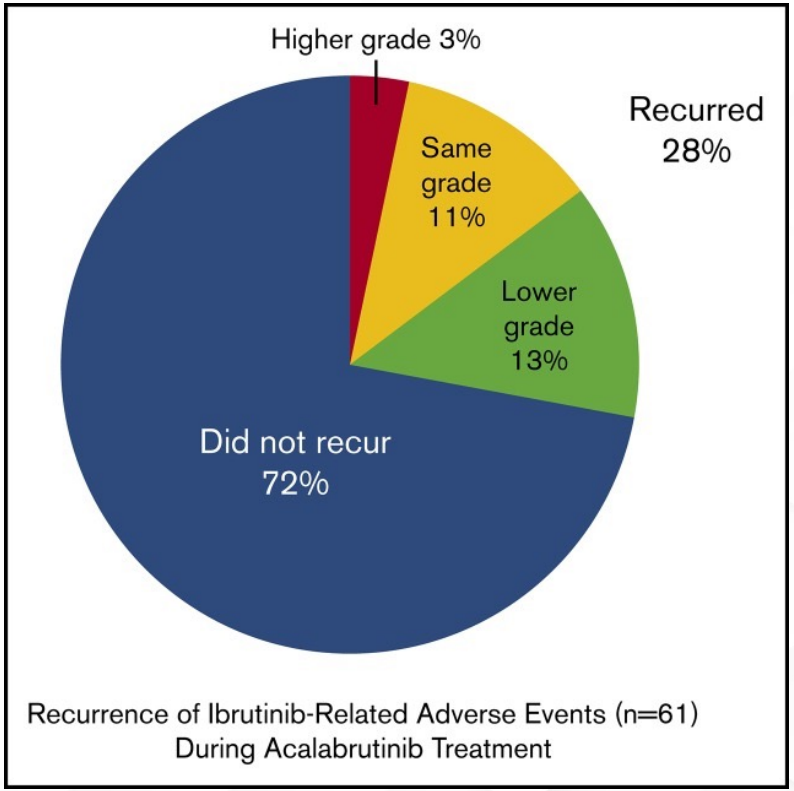


Median PFS and OS for entire cohort were 36 months and NR, respectively (median follow-up 17 months)

Mato AR, et al. *Blood*. 2016;128(22):3222.

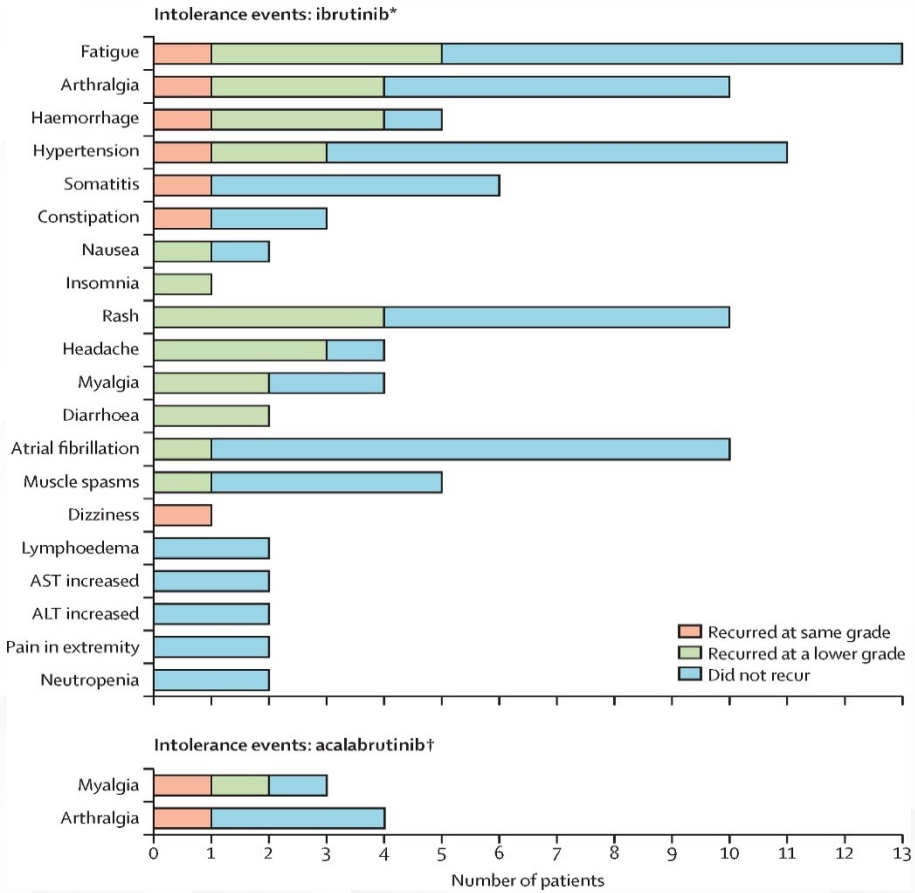
Phase I/II ACE-CL-001 Trial: Acalabrutinib in Ibrutinib-Intolerant Cohort

- Among 33 patients who could not tolerate ibrutinib, 23 remained on acalabrutinib
- No acalabrutinib dose reductions occurred
- Of 61 ibrutinib-related AEs, 72% did not recur and 13% recurred at a lower grade with acalabrutinib
- ORR: 76%
- Median PFS: not reached
- 1-yr PFS: 83.4%



Awan FT, et al. *Blood Adv*. 2019;3(9):1553-1562.

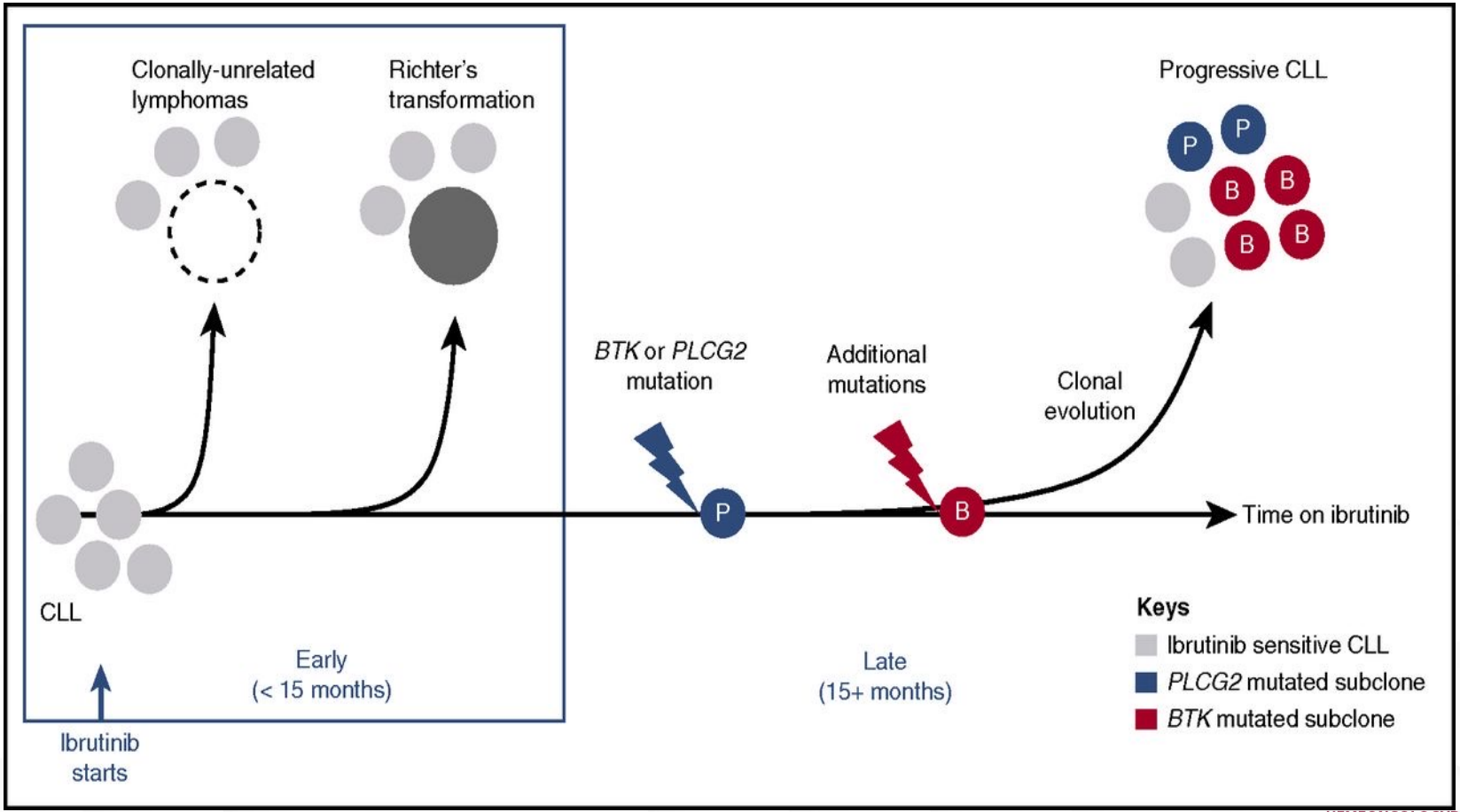
Low Recurrence of BTKi Intolerance on Zanubrutinib



- **Intolerable AEs experienced on ibrutinib or acalabrutinib were unlikely to recur with zanubrutinib**
  - **75% of ibrutinib and acalabrutinib intolerance events did not recur with zanubrutinib**
  - **<10% recurrence of a prior intolerance event led to zanubrutinib discontinuation**
- **Zanubrutinib was effective; 90% of patients' disease was controlled or responded to therapy**

Shadman M, et. al. *Lancet Haematol*. 2023;10(1):e35-e45.

Molecular Model of Ibrutinib Resistance



Ahn IE, et al. *Blood.* 2017;129:1469-1479.

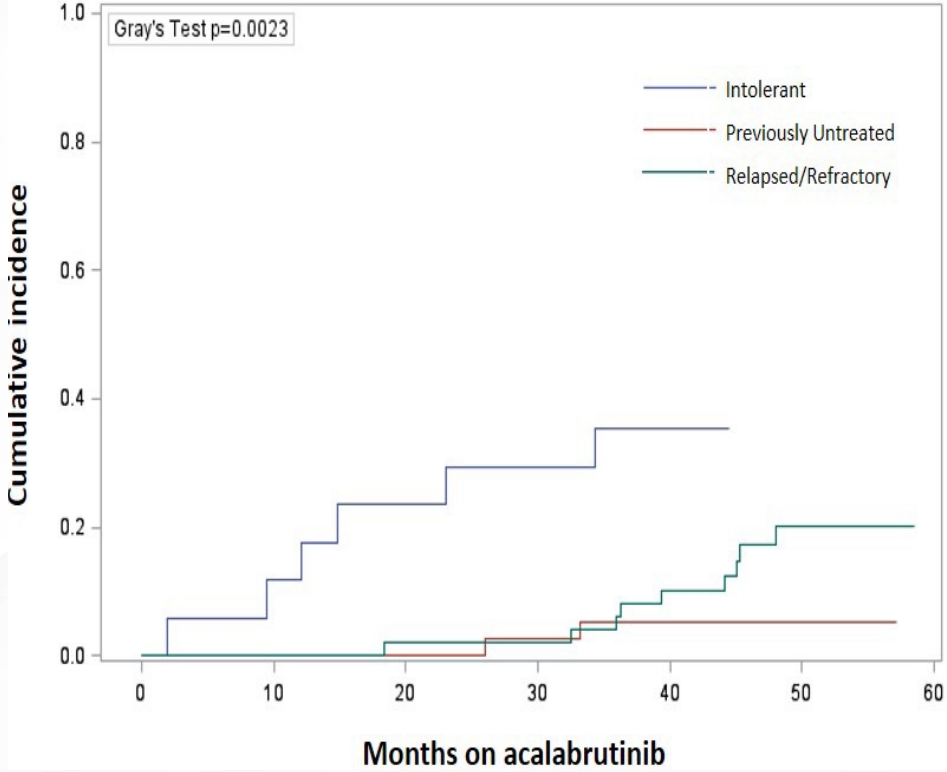
Progression on Ibrutinib Associated with BTK and PLCG2 Mutations

		Number (%) of Patients with Indicated Mutations				Number of Patients with summed *BTK/PLCG2* VAFs at resistance of:		
Study	N	BTK only	PLCG2 only	BTK and PLCG2	No identified BTK or PLCG2 mutation	< 10%	10-30%	> 30%
Maddocks	11	7 (64%)	2 (18%)	2 (18%)	0 (0%)	2 (18%)	2 (18%)	7 (64%)
Woyach	35	25 (71%)	1 (3%)	3 (8.6%)	6 (17%)	5 (17%)	7 (24%)	17 (59%)
Ahn	10	2 (20%)	1 (10%)	5 (50%)	2 (20%)	3 (43%)	0 (0%)	4 (57%)
Kadri	3	1 (33%)	0 (0%)	0 (0%)	2 (67%)	0 (0%)	0 (0%)	1 (100%)
Burger	5	1 (20%)	1 (20%)	0 (0%)	3 (60%)	Not reported		
Totals	64	36 (56%)	5 (7.8%)	10 (16%)	13 (20%)	10 (21%)	9 (19%)	29 (60%)

Lampson BL, Brown JR. *Expert Opin Investig Drugs*. 2017;26(11):1267-1279.

Resistance to Acalabrutinib:
OSU Experience

Figure 1: Cumulative Incidence of Progression



Of 16 progressors,
11 had C481x mutns
2 also PLCG2

103 pts were screened
22 had mutns at median 32 mos

Median time to relapse p mutn
12 mos

Woyach JS, et al, *Blood* (2019) 134 (Suppl_1): 504.

Resistance to Zanubrutinib

- 37 pts treated, 24 with ibrutinib, 13 with zanubrutinib
- *BTK* L528W in 1/24 ibrutinib PD vs 7/13 zanu PD
- BTK C481 mutations in 24/24 ibrutinib vs 10/13 zanu

- 8 progressors
- 6 Cys481, 1 Leu528Trp

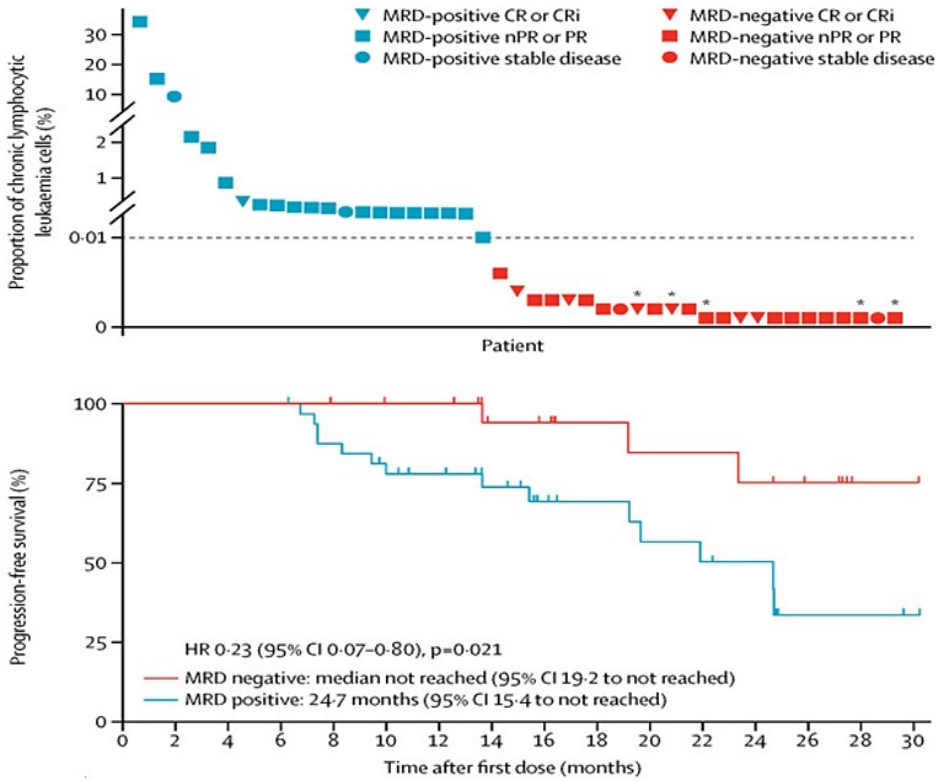
Blombery P, et al. *Blood Adv*. 2022;6(20):5589-5592. Zhu et al. Presented at: ASH;2023.

M14-032 Prospective Evaluation of Venetoclax in CLL Patients Progressing After Ibrutinib

- N 91
- Median age 66
- Median 4 prior tx

- 75% IGHV UM
- 47% del17p

- Median 20 mos on ibrutinib



ORR 65%

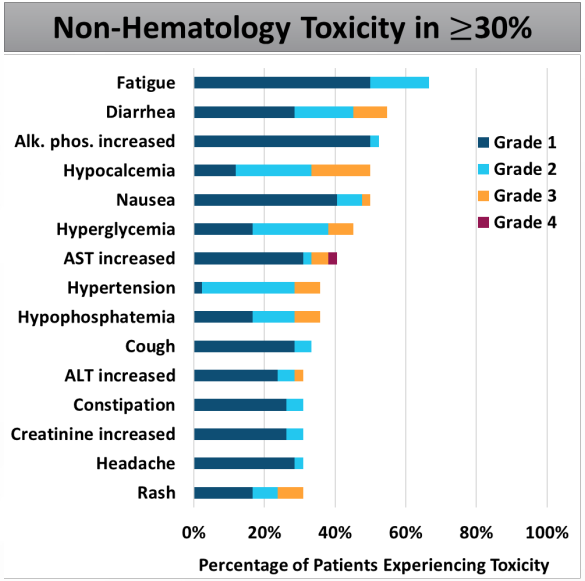
CR 9%

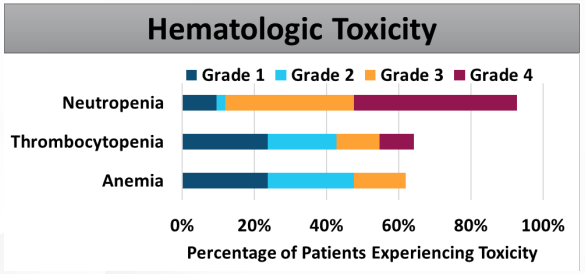
uMRD in PB: 42%

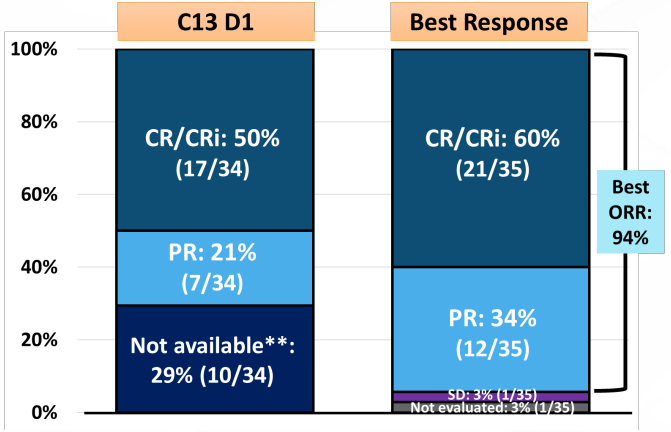
(of 57 pts)

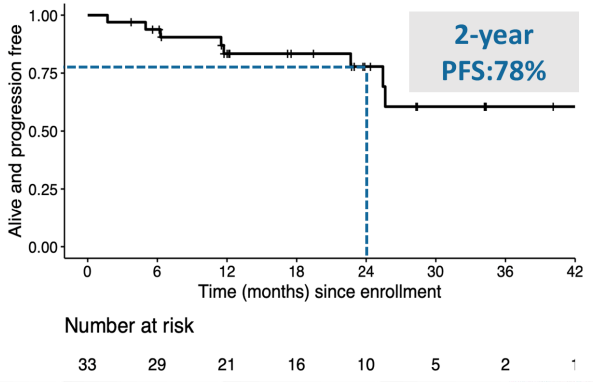
NCT02141282. Updated December 19, 2022. Accessed May 15, 2022. https://clinicaltrials.gov/ct2/show/NCT02141282.

Duvelisib + Venetoclax: Highly Active in R/R CLL Including Post-BTKi, Though Characteristic Toxicities Occur







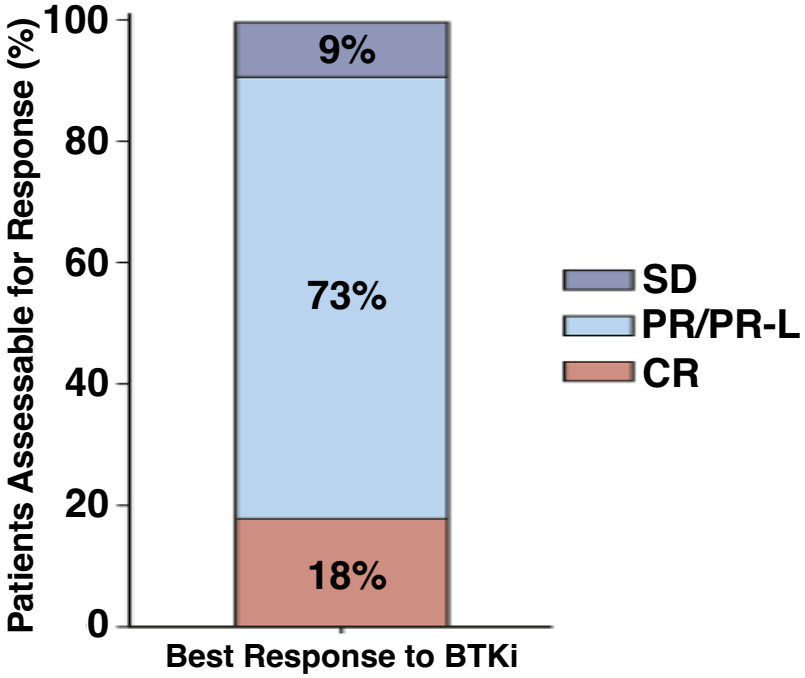


Ryan C, et al. *Blood*. 2022;140(Suppl):9871–9872.

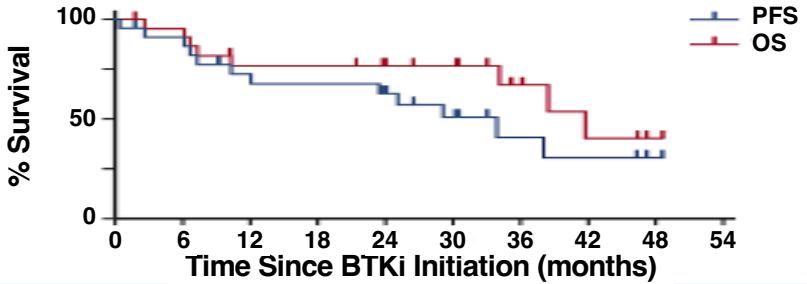
The Changing Landscape of Relapsed CLL

- Patients relapsing after minimal therapy (ab, clb)
- Patients relapsing after effective CIT
- Patients exposed to ibrutinib:
  - Off for AEs
  - Progressed during ibrutinib therapy
- Patients relapsing after venetoclax
- Patients relapsing after BTKi and BCL-2

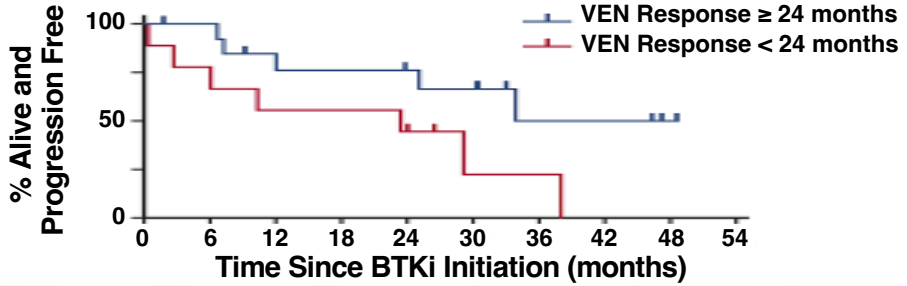
BTK Inhibitor Therapy is Effective in Patients with CLL Resistant to Venetoclax



BTK inhibitors are effective against venetoclax-resistant CLL



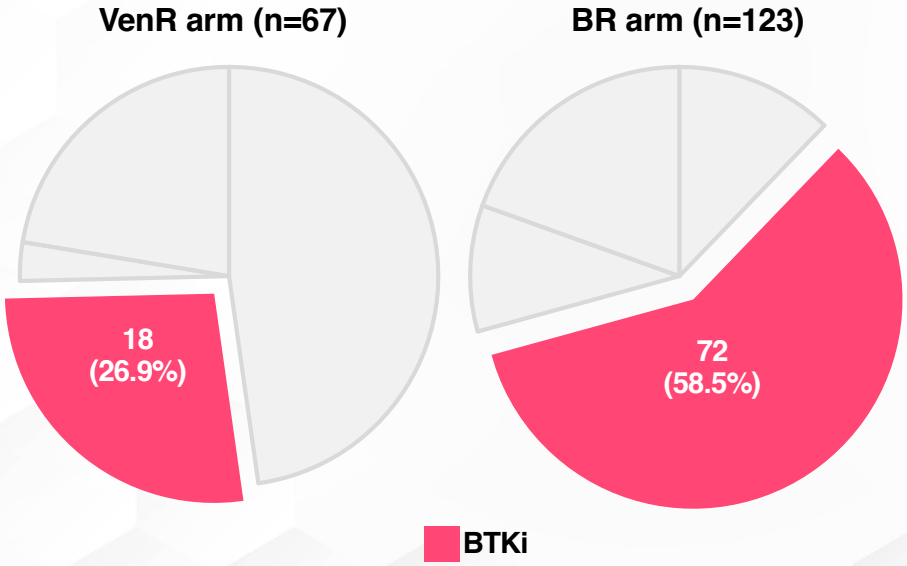
Durability of response to BTK inhibitor is associated with length of remission to prior venetoclax therapy



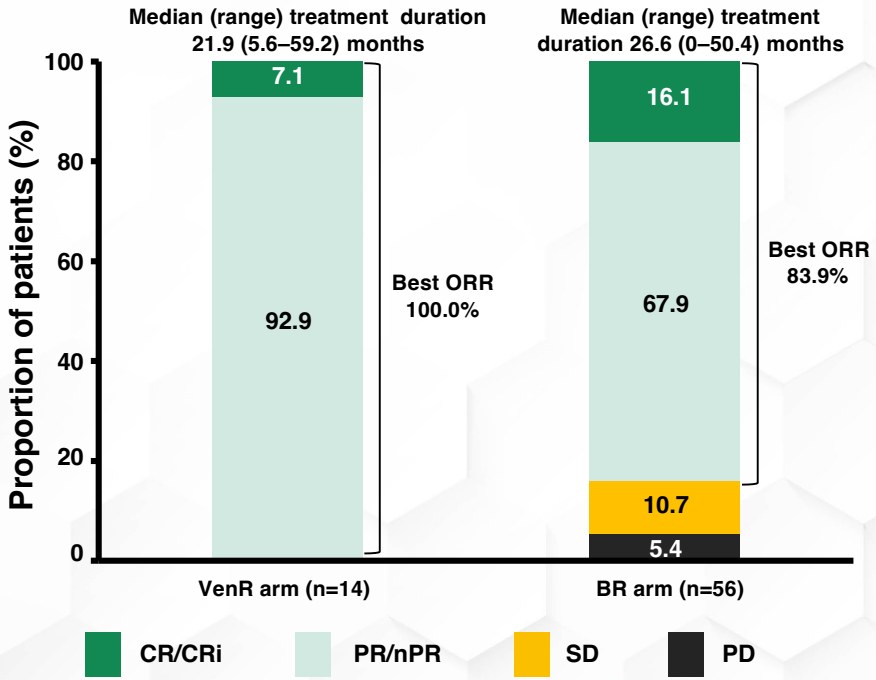
Lin VS, et al. *Blood.* 2020;135(25):2266-2270.

MURANO: Response Rates to Subsequent BTKi-Based Therapy Were High

Subsequent therapy (ITT)

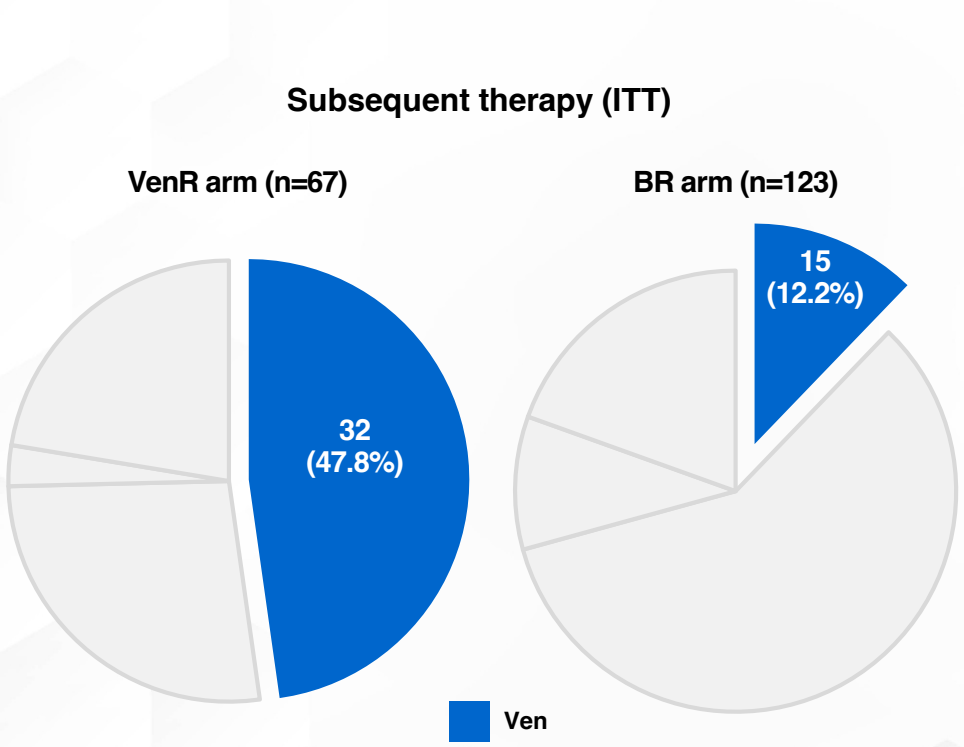


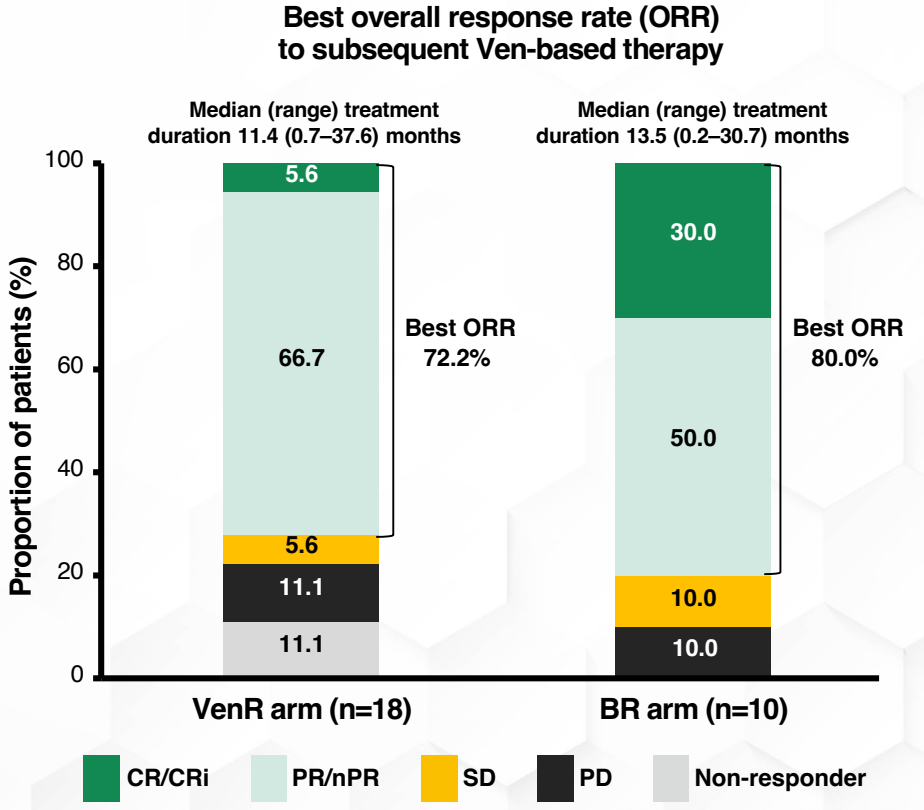
Best overall response rate (ORR) to subsequent BTKi-based therapy



Harrup RA, et al. *Blood.* 2020;136(Suppl 1):44–45.

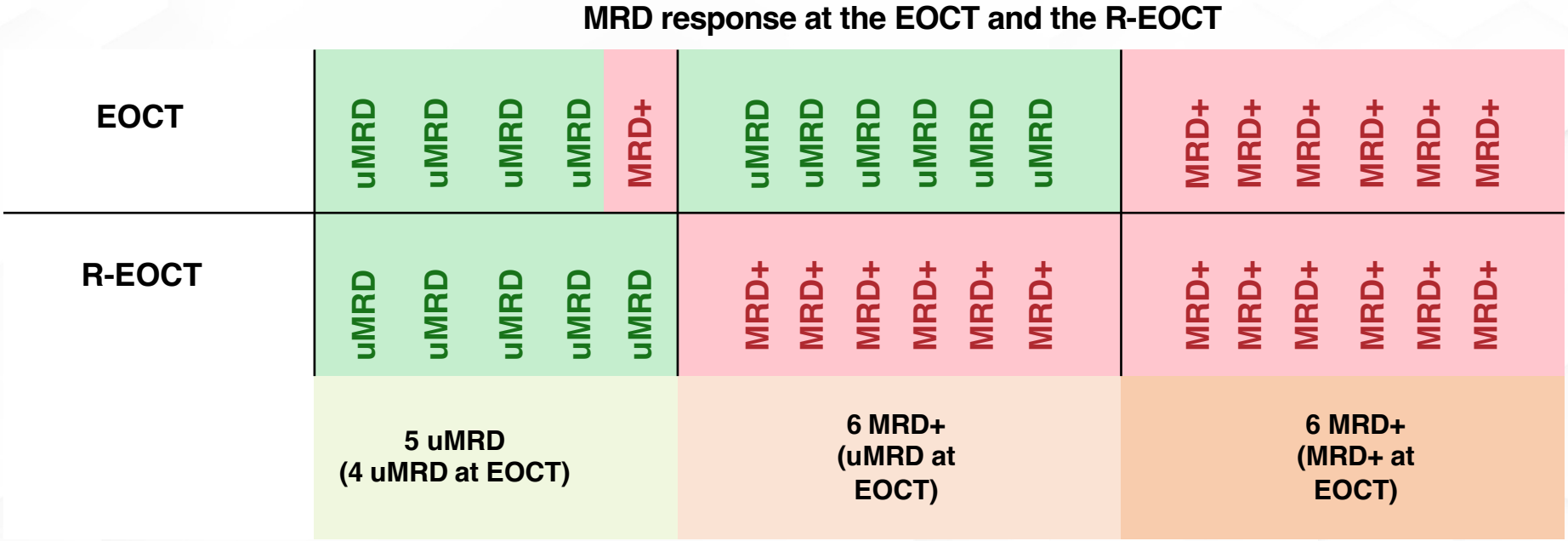
MURANO: Response Rates to Subsequent Ven-Based Therapy Were High





Harrup RA, et al. *Blood.* 2020;136(Suppl 1):44-45.

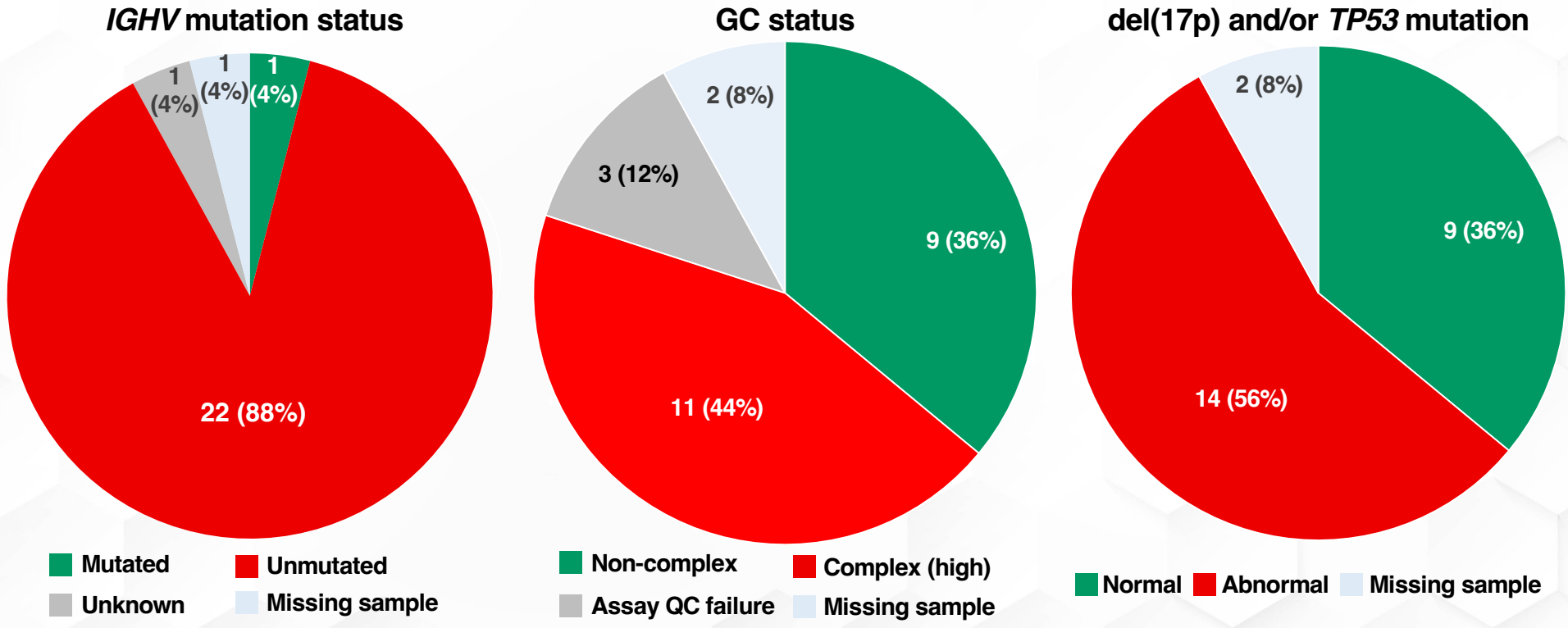
MURANO: Deep MRD Responses Were Less Frequent But Occurred Following Retreatment



- 17/25 patients retreated with VenR had a valid MRD assessment at the R-EOCT; 5/17 achieved uMRD and 12/17 were MRD+

Qun Wu J, et al. Presented at: EHA;2021. Poster EP599.

Unfavorable Genetic Characteristics of Patients in the Retreatment Cohort (n=25) at BL-1

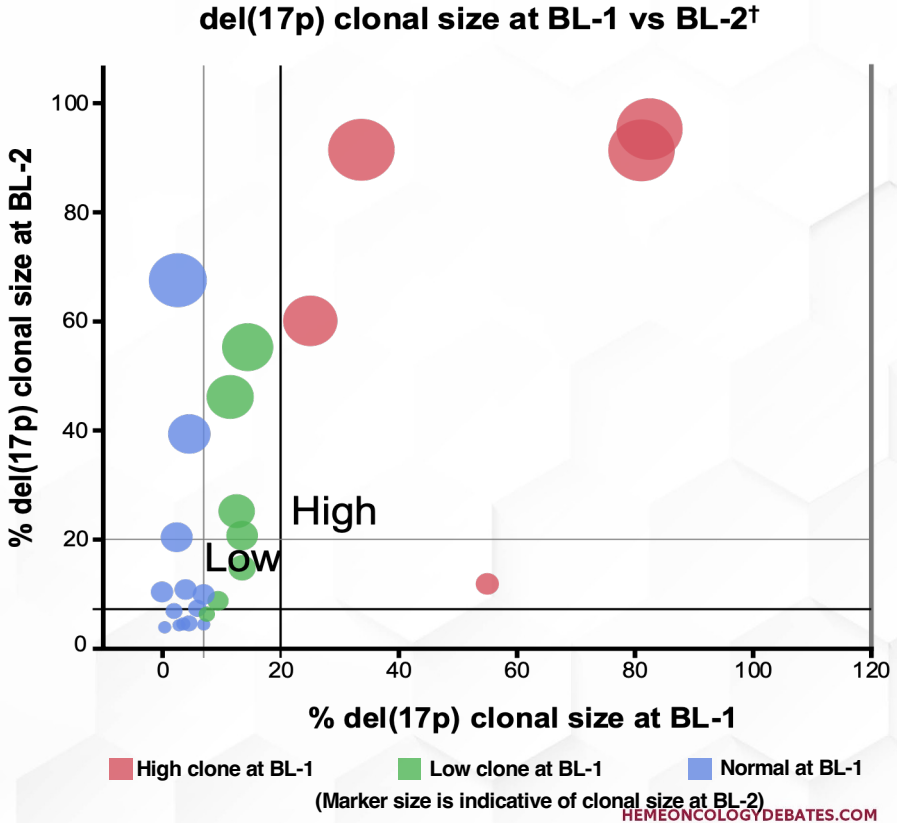


Qun Wu J, et al. Presented at: EHA;2021. Poster EP599.

Higher Prevalence of del(17p) Was Seen at BL-2, Including Acquired Clonal Shift from BL-1

Del(17p)*	BL-1 (n=20)	BL-2 (n=20)
Total (% of BEP)	10 (50.0)	13 (65.0)
High clone, ≥20%	3 (30.0)	10 (76.9)
Low clone, 7–20%	7 (70.0)	3 (23.1)
Median (range) clone size of del(17p)	14 (7.5–82.5)	25 (8.5–95.5)

- 13/20 evaluable patients had del(17p) at BL-2, including 10 high clones, with 3 newly acquired and 4 who shifted from low to high clone

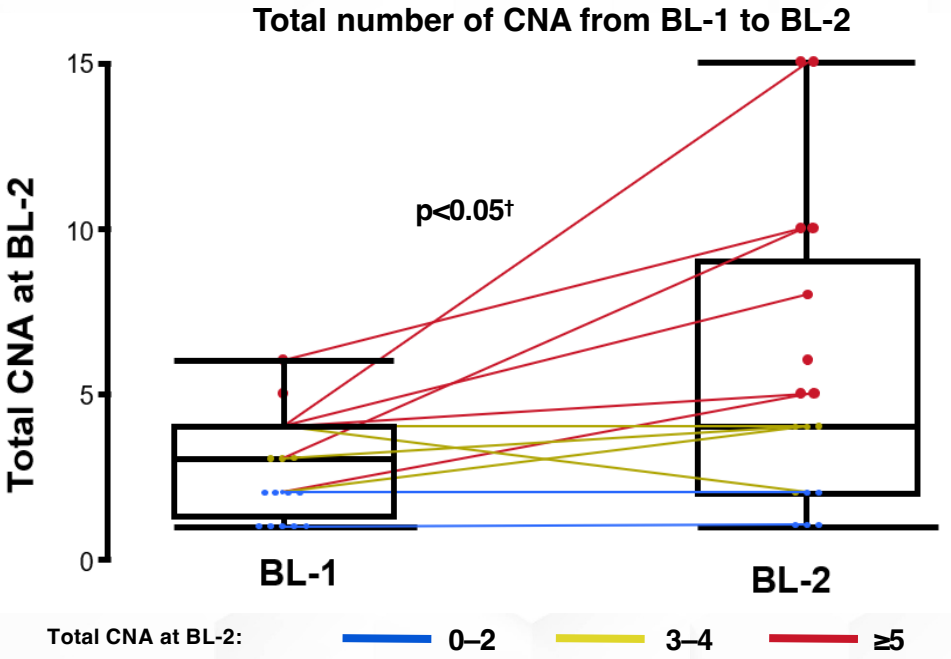


*Analyzed in the BEP by FISH. †Patients from the BEP who had del(17p) at both BL-1 and BL-2 (n=13).

Qun Wu J, et al. Presented at: EHA;2021. Poster EP599.

Number of CNAs and Prevalence of High GC Increased from BL-1 to BL-2

GC*	BL-1 (n=14)	BL-2 (n=14)
Median (range) CNA	2.5 (1–6)	4 (1–15)
No GC, 0–2 CNA	6 (42.9)	5 (35.7)
Low GC, 3–4 CNA	7 (50.0)	3 (21.4)
High GC, ≥5 CNA	1 (7.1)	6 (42.9)



- Median (range) number of CNA was 2.5 (1–6) at BL-1 and 4 (1–15) at BL-2
- 9/14 patients had GC at BL-2, 6 (42.9%) of whom had high GC

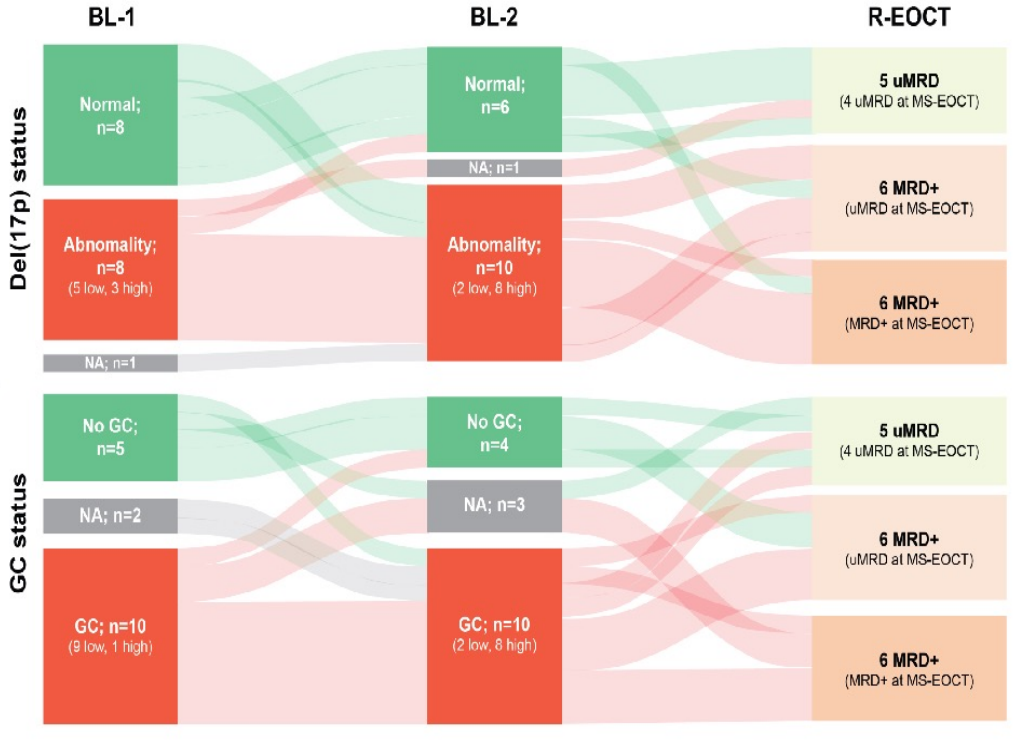
*Analyzed in the BEP. †p value determined by a Student's t-test.

Qun Wu J, et al. Presented at: EHA;2021. Poster EP599.

Increased del(17p) Clone Size and GC Negatively Impacted MRD Response at the R-EOCT

Shift of del(17p) clone size and GC status from BL-1 to BL-2, and impact on MRD response at the R-EOCT

- Of 6 patients without del(17p) at BL-2, 4 attained uMRD at the R-EOCT and 2 were MRD+
- All 10 patients with del(17p) at BL-2 were MRD+ at the R-EOCT
  - 4/10 had new del(17p) from BL-1 or had evolved from low clone to high clone
- Among the 6 patients with uMRD at the EOCT who didn't reattain uMRD status after VenR retreatment, 5/6 had del(17p) at BL-2 (3/5 newly evolved from BL-1) vs 2/5 at BL-1
- Of 4 patients without GC at BL-2, 2 attained uMRD at the R-EOCT
- Of 10 patients with GC at BL-2, 8 were MRD+ and 2 had uMRD at the R-EOCT
  - 5/10 pts with GC at BL-2 had new or increased GC from BL-1



Qun Wu J, et al. Presented at: EHA;2021. Poster EP599.

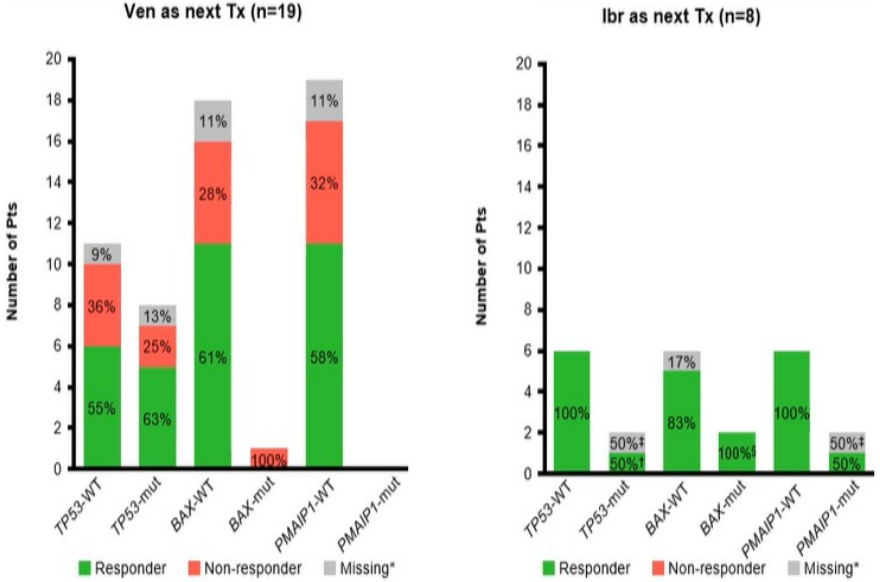
Acquired Mutations in MURANO

	*TP53**		*BAX*		*PMAIMP1*	
Treatment arm	VenR, n=42	BR, n=28	VenR, n=42	BR, n=28	VenR, n=42	BR, n=28
Pts with mutation, n (%)	15 (35.7)	9 (32.1)	4 (9.5)	0 (0)	2 (4.8)	0 (0)
Total no. of mutations	19	15	4	0	2	0
Present at baseline	10 [7]	2 [2]	0 [0]	0 [0]	0 [0]	0 [0]
Newly acquired	9 [9]	13 [8]	4 [4]	0 [0]	2 [2]	0 [0]

Seymour JF, et al. *Blood*. 2021;138(Suppl 1):1548.

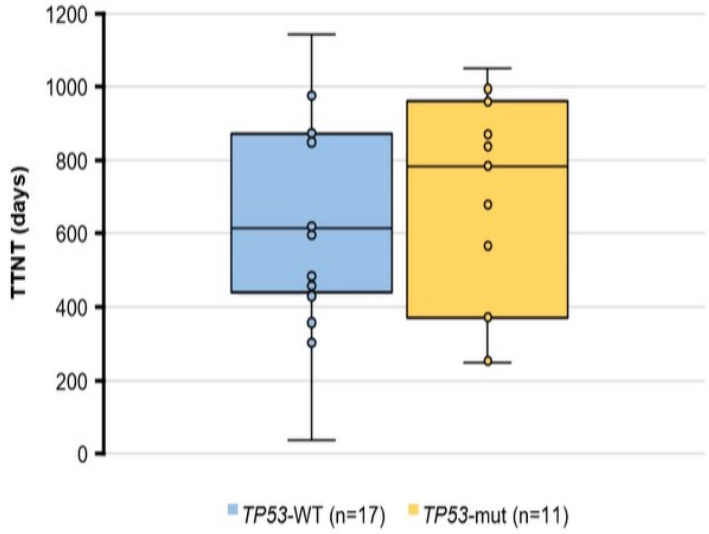
Acquired Mutations and TTNT

Response to next line of Tx per acquired mutations in VenR-treated Pts who were MRD+ post-Tx cessation



By the data cutoff, 28/42 (66.7%) Pts had received an additional anti-CLL therapy after VenR Tx

TTNT per *TP53* mutations in VenR-treated Pts who were MRD+ post-Tx cessation



There was no apparent association between *TP53*-mut and TTNT; median (range) TTNT 784 days (248–1051) in *TP53*-mut compared with 614 days (38–1142) in *TP53*-WT Pts

Seymour JF, et al. *Blood*. 2021;138(Suppl 1):1548.

The Changing Landscape of Relapsed CLL

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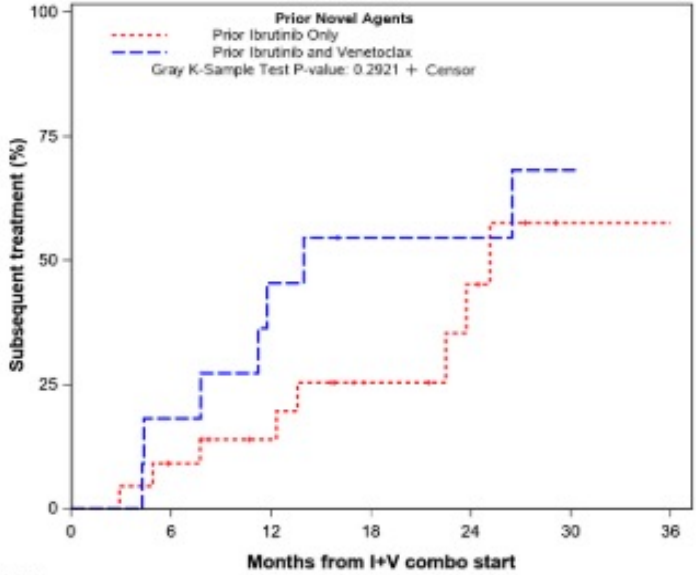
- Patients relapsing after effective CIT
- Patients exposed to ibrutinib:
  - Off for adverse events
  - Progressed during ibrutinib therapy
- Patients relapsing after frontline venetoclax
- Patients relapsing after BTKi and BCL-2

Outcomes of I+V Given for CLL Progression

Time to Next Therapy from I+V Start

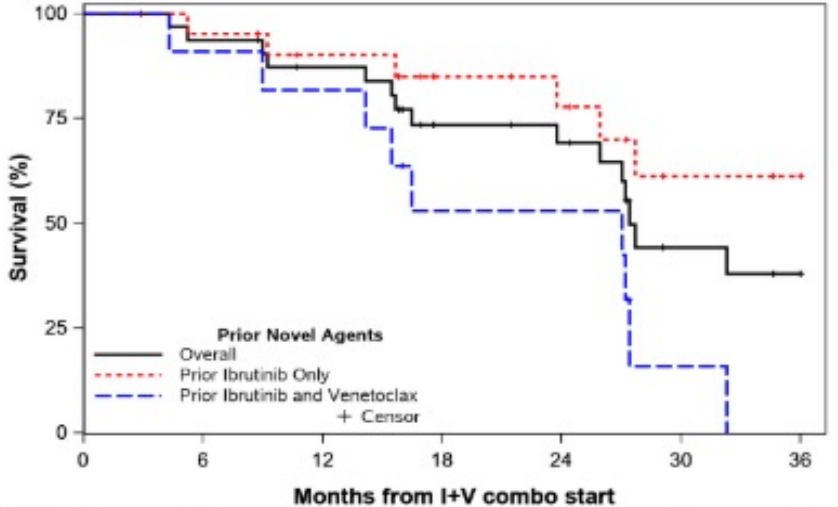


Prior I Only	22	19	14	8	5	1	1
Prior I and V	11	8	4	2	2	1	0

	Event/Total	Median (95% CI)[1]	Survival Estimates (95% CI)[1]
Prior Ibrutinib Only	9/22	25.1 (13.6-NE)	12 Months: 13.9 (4.7-40.8%) 24 Months: 45.2 (23.6-86.6%)
Prior Ibrutinib and Venetoclax	7/11	14.0 (4.2-NE)	12 Months: 45.5 (22.5-91.7%) 24 Months: 54.5 (30.1-98.8%)

[1]Cumulative incidence method

Overall Survival from I+V Start



Overall	33	30	26	18	16	7	5
Prior I Only	22	20	17	13	11	6	5
Prior I and V	11	10	9	5	5	1	0

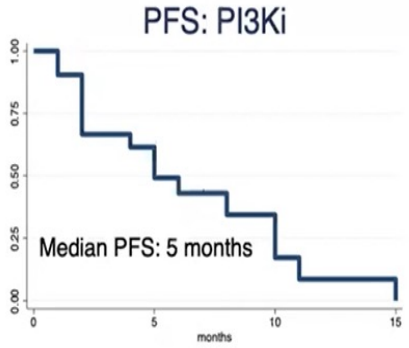
	Event/Total	Median (95% CI)[1]	Survival Estimates (95% CI)[1]
Overall	16/33	27.4 (25.9-NE)	12 Months: 87.3 (76.4-99.7%) 24 Months: 69.2 (54.1-88.5%)
Prior Ibrutinib Only	7/22	47.1 (27.7-NE)	12 Months: 90.2 (78.2-100.0%) 24 Months: 77.8 (60.5-100.0%)
Prior Ibrutinib and Venetoclax	9/11	27.0 (15.5-NE)	12 Months: 81.8 (61.9-100.0%) 24 Months: 53.0 (29.9-94.0%)

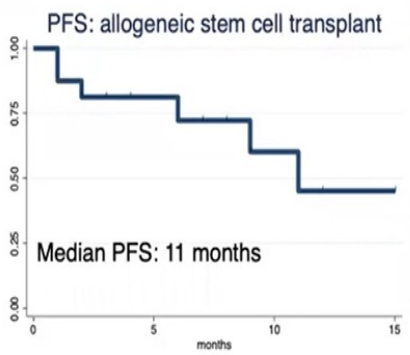
[1]Kaplan-Meier method

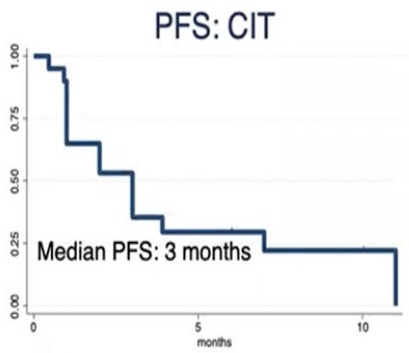
Hampel PJ, et al. *Blood.* 2021;138(Suppl 1):1560.

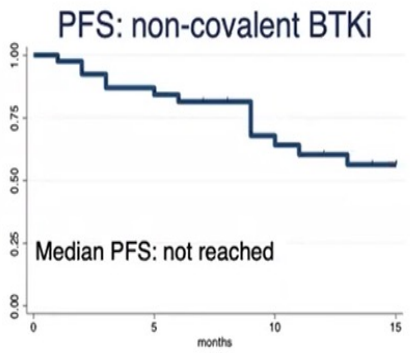
Real-World Outcomes of Patients with Prior Exposure to cBTKi and Ven

SUBSEQUENT THERAPY	CAR-T	AlloSCT	ncBTKi	PI3Ki	CIT
Patients treated	9	17	45	24	23
ORR	85.7% n=7	76.5% n=17	75.0% n=43	40.9% n=22	31.8% n=22
Median PFS (months)	4 n=9	11 n=16	Not reached n=40	5 n=21	3 n=20
Median follow-up (months)	3	6.5	9	4	2





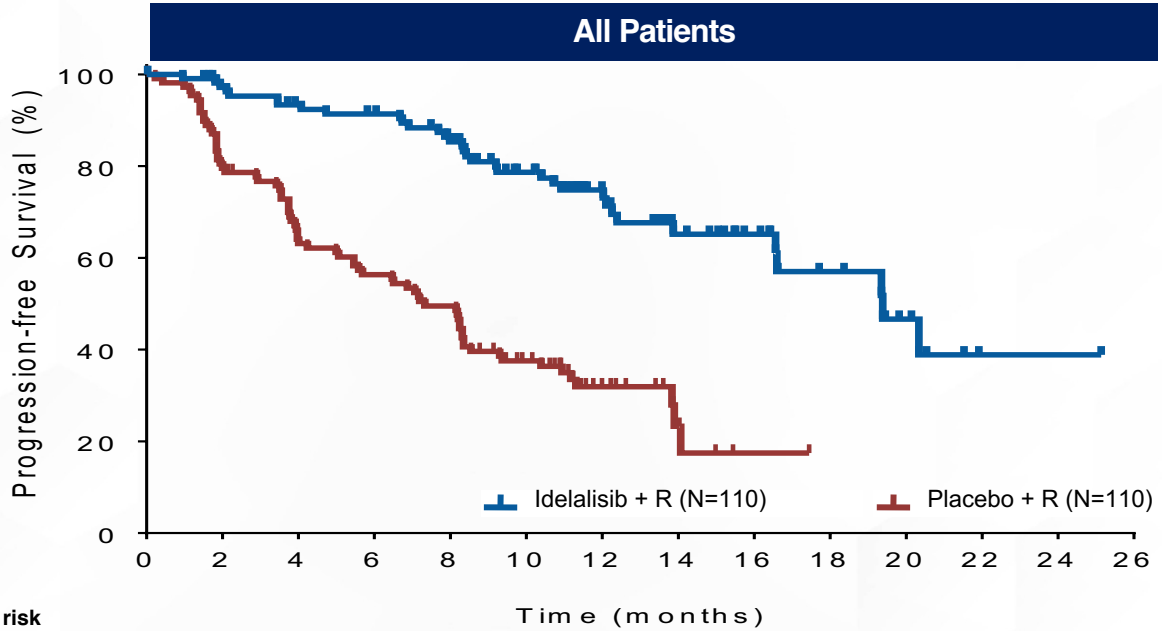




Thompson MC, et al. *Blood.* 2021;138(Suppl 1):2628.

GILEAD 116: PFS, Including Extension Study*

Idelalisib + R vs Placebo + R



N at risk														
IDELA + R	110	102	95	92	83	64	43	26	19	12	7	1	1	0
PBO + R	110	86	66	58	51	33	15	5	1	0	-	-	-	-

	Median PFS (95% CI)	HR (95% CI)	p-value
IDELA + R	19.4 mo (16.6, -)	0.25 (0.16, 0.39)	<0.0001
PBO + R	7.3 mo (5.5, 8.5)		

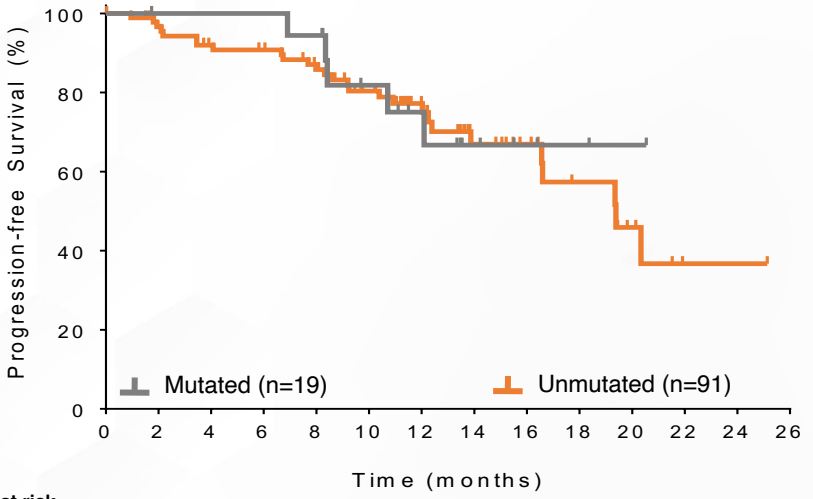
*Placebo + R includes those patients who received open-label idelalisib after unblinding without prior progression (n=42).

Sharman JP, et al. *Blood* .2014' 124 (21):330.

PFS Subgroup Analysis*

Idelalisib + R (N=110)

IGHV: Unmutated vs Mutated



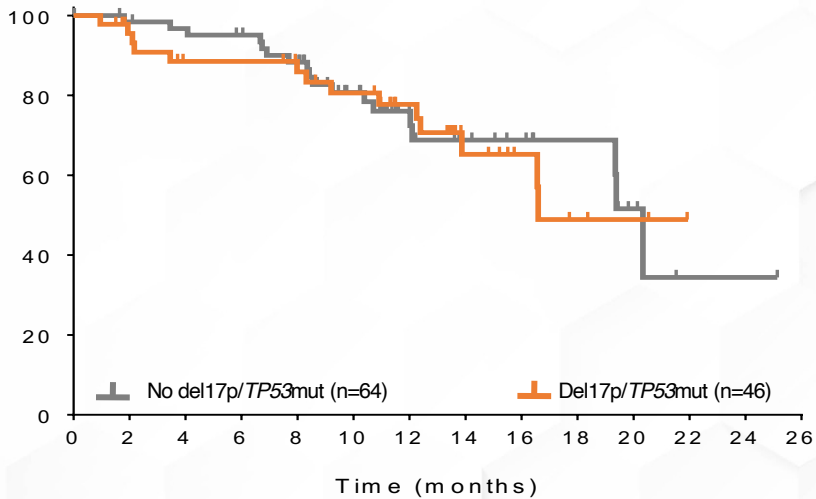
N at risk

Mutated	19	18	18	18	17	12	9	5	3	2	1	0	
Unmut	91	84	77	75	68	54	34	21	16	10	6	1	1	0

	Median PFS (95% CI)	p-value
Mut	NR (10.7, -)	0.75
Unmut	19.4 mo (16.6, -)	

*Including extension study

Del17p/TP53mut: Present vs Not Present



No del	64	61	59	59	52	37	21	14	11	8	4	1	1	1
Del	46	41	36	36	33	30	22	12	8	4	3	0		

	Median PFS (95% CI)	p-value
No del	20.3 mo (19.4, -)	0.94
Del	16.6 mo (13.9, -)	

Sharman JP, et al. *Blood* .2014' 124 (21):330.

Idelalisib Discontinuation

n (%)	Study 116/117 IDELA+R/IDELA n=110	Study 116/117 PBO+R (PD)/IDELA[a] n=42	Study 116/117 PBO+R/IDELA[a] n=44	Study 119 IDELA+O n=173	Total N=369
Median duration of idelalisib exposure (range), months	16.2 (0.3-39.9)	5.7 (0.4-26.2)	9.2 (0.2, 22.1)	13.9 (0.2-28.5)	–
Patients with ongoing idelalisib treatment	20 (18.2%)	5 (11.9)	12 (27.3)	46 (26.6)	83 (22.5)
Patients who discontinued idelalisib treatment	90 (81.8)	37 (88.1)	32 (72.7)	127 (73.4)	286 (77.5)
Due to disease progression	18 (16.4)	5 (11.9)	3 (6.8)	31 (17.9)	57 (15.4)
CLL progression	16 (14.5)	4 (9.5)	2 (4.5)	27 (15.6)	49 (13.3)
Richter's transformation	2 (1.8)	1 (2.4)	1 (2.3)	4 (2.3)	8 (2.2)[b]
Due to adverse events	47 (42.7)	20 (47.6)	21 (47.7)	62 (35.8)	150 (40.7)
Due to other reasons	25 (22.7)	12 (28.6)	8 (18.2)	34 (19.7)	79 (21.4)
Withdrawal by patient	12 (10.9)	6 (14.3)	3 (6.9)	12 (6.9)	33 (8.9)
Physician's decision	7 (6.4)	4 (9.5)	2 (4.5)	14 (8.1)	27 (7.3)
Death	2 (1.8)	2 (4.8)	2 (4.5)	8 (4.6)	14 (3.8)
Other	4 (3.6)	0	1 (2.3)	0	5 (1.4)

Brown JR, et al.
Presented at: EHA;2015.
Abstract P215.

PI3K Inhibitors: When To Use

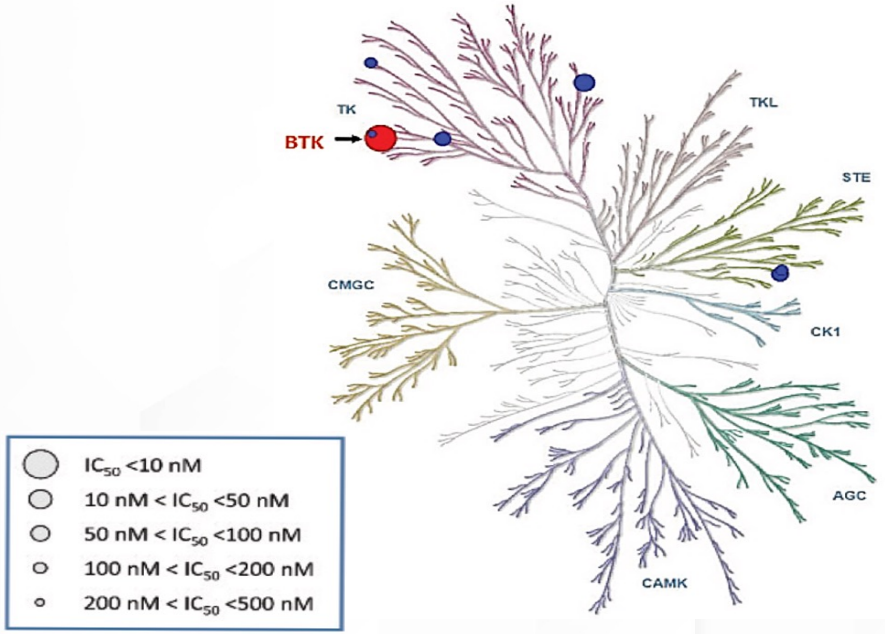
- Patients not developing autoimmune tox or infection have few side effects
- Registration trial enrolled patients with a high level of comorbidities:
  - Not contra-indicated in cardiac or renal disease

- *Predictors of tox:* no prior therapy, younger age, and mutated IGHV
  - *Use In: older, pretreated patients preferably with unmut IGVH*
  - *With significant comorbidities that impact BTK inhibitor (cardiac) or VEN tolerability (renal)*

  - Previously exposed to BTK inhibitors or VEN (activity not established)

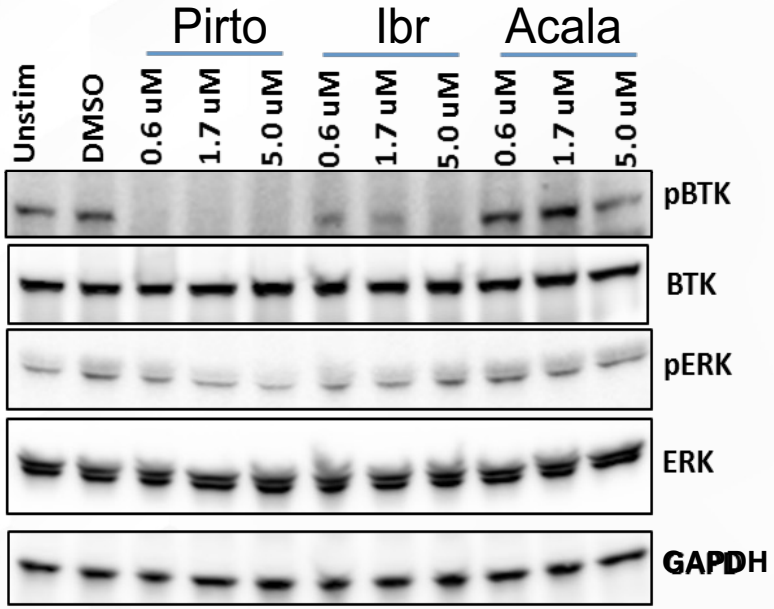
Pirtobrutinib Is Highly Selective with Minimal Activity against Non-BTK Kinases

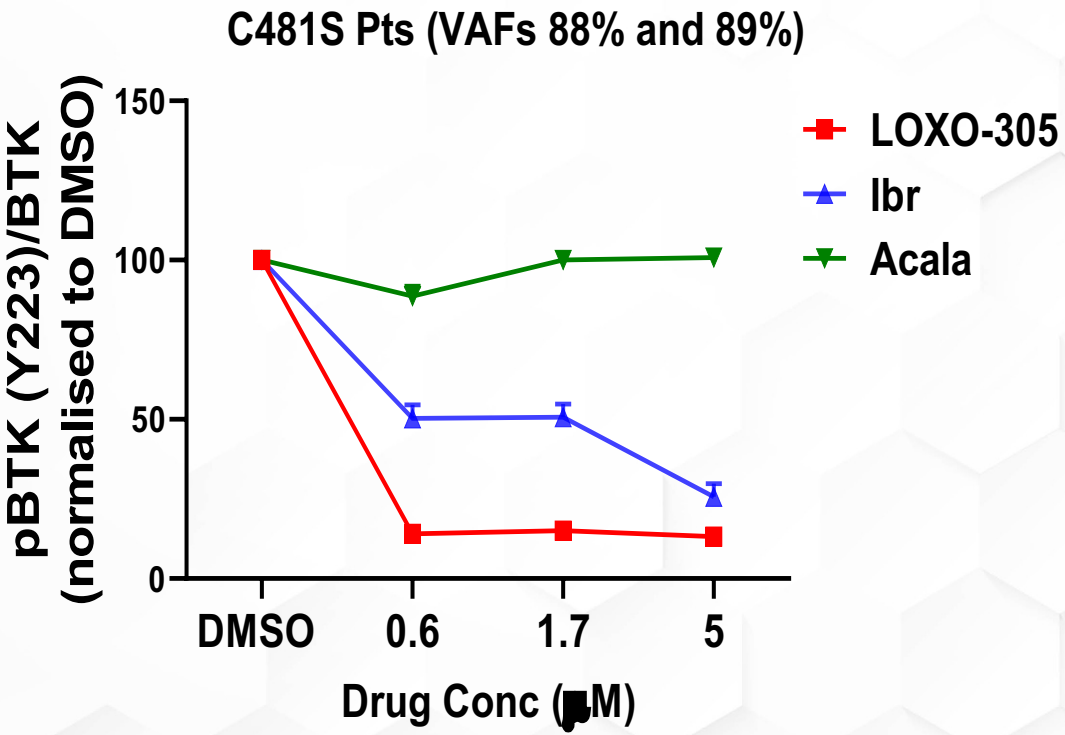
Kinase	Percent of control @ 1 μM LOXO-305, [ATP] = K_M (%)	IC_{50} [ATP] = K_M (nM)	Fold selectivity over BTK
BTK C481S	ND	1.42	0.5 X
BTK	1.8	3.15	1.0 X
ERBB4	2.6	13.3	4.2 X
BRK	10.3	54.3	17 X
MEK2	7.6	82.7	26 X
MEK1	12.2	147	47 X
YES1	38.6	157	50 X
TXK	19.6	209	66 X
BMX	70.2	1155	367 X
TEC	64.6	1234	392 X
BLK	72.8	4100	1302 X
EGFR	60.6	>1000	>317 X
ITK	103	>5000	>1587 X
SRC	90.5	>5000	>1587 X
JAK1	96.4	>30000	>9524 X
JAK2	94.5	ND	ND
JAK3	97	ND	ND



Brandhuber B, et al. Presented at: SOHO;2018. Abstract CLL-200.

Pirtobrutinib: Potent and Selective Non-Covalent Inhibitor of WT & C481-Mutant BTK





Naeem A, et al. *Blood Adv*. 2023)7(9):1929–1943.

BTK Pre-treated 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)	12 (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, n (%)	
Progressive disease	190 (77)
Toxicity/Other	57 (23)

ECOG PS, Eastern Cooperative Oncology Group Performance Score; 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.

Naeem A, et al. *Blood Adv*. 2023)7(9):1929–1943.

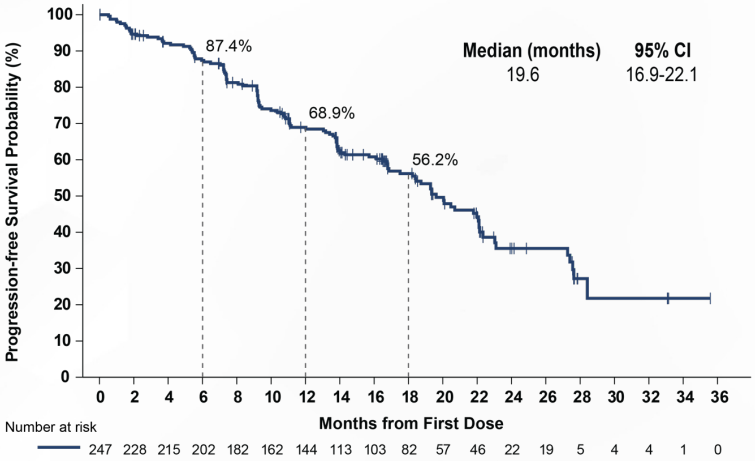
Pirtobrutinib Safety Profile

	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	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest							
Bruising	20%	2%	-	-	22%	-	15%
Rash	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter	-	1%	<1%	<1%	2%[h]	-	<1%

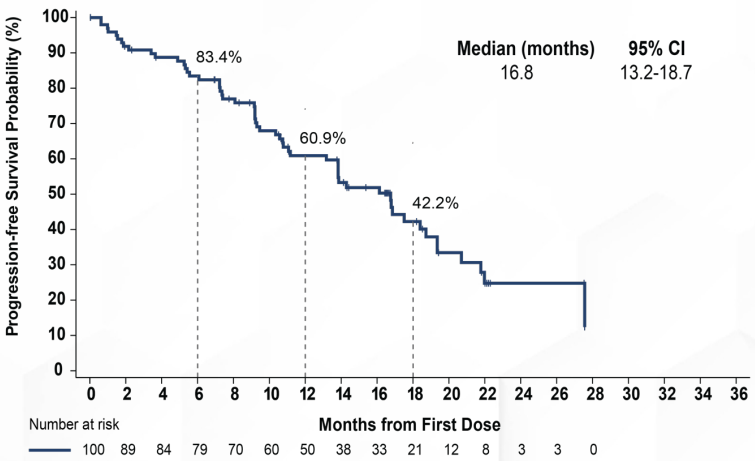
No DLTs reported and MTD not reached; 96% of patients received ≥1 pirtobrutinib dose at or above RP2D of 200 mg daily; 1% (n=6) of patients permanently discontinued due to treatment-related AEs

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

BTKi pre-treated patients
Median prior lines = 3



BTKi and BCL2i pre-treated patients
Median prior lines = 5



- **44.1% (109/247) of BTKi pre-treated patients remain on pirtobrutinib**
- **Median follow-up of 19.4 months for BTK pre-treated patients**

Data cutoff date of 29 July 2022. Response status per iwCLL 2018 according to independent review committee assessment.

Summary:

Treating CLL in Subsequent Lines of Therapy

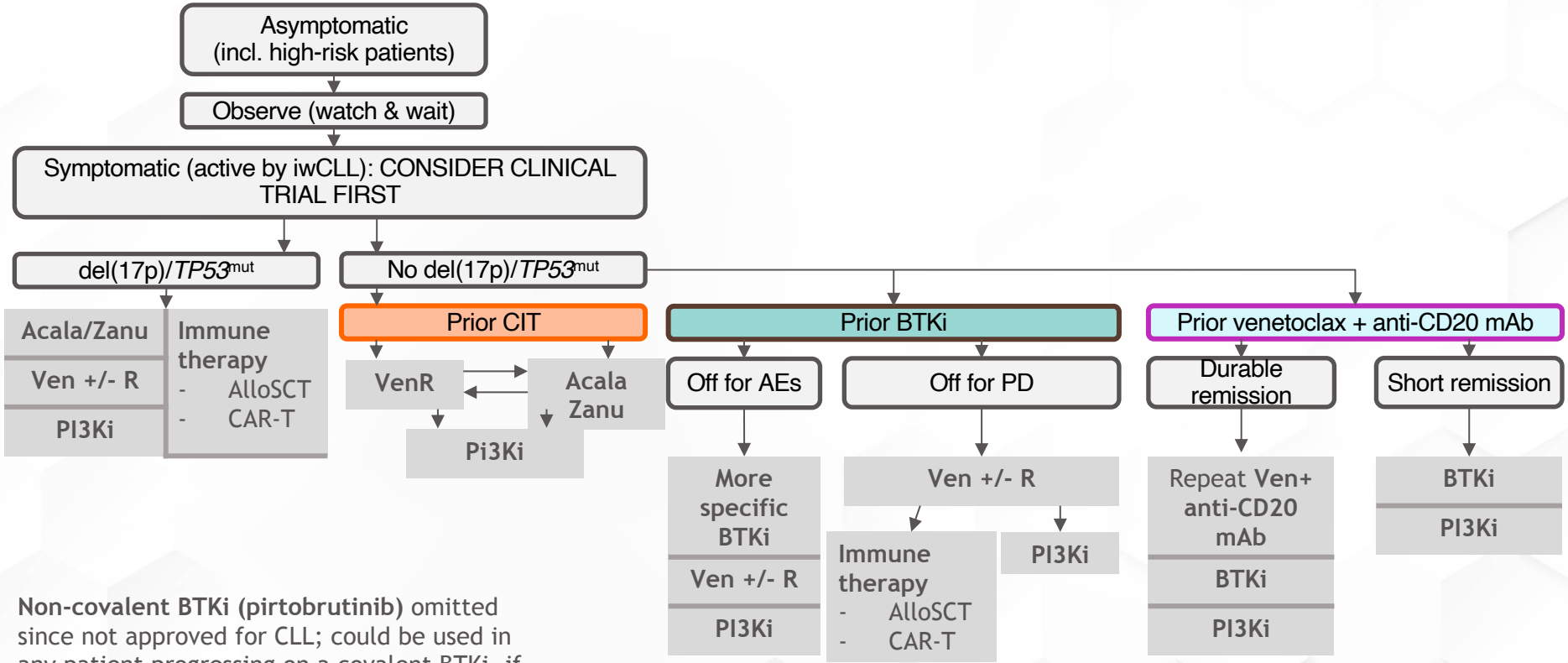
- **Patients with disease progression on BTK inhibitor or continuous venetoclax are best treated with the other agent**
  - **Prospective data are limited but support venetoclax after prior BTKi progression**

- **Patients who stop a BTKi for an AE can receive a next generation cBTKi (or venetoclax)**
- **Patients with disease progression on ibrutinib should NOT be treated with another covalent BTKi (but can receive a noncovalent BTKi if available)**

- **Patients who received time-limited venetoclax +/- anti-CD20 antibody can be re-treated with the same regimen – the longer the prior remission the better, at least 2 yrs preferred**

- **Disease progression on both BTKi and venetoclax represents a major new unmet need, with no clear standard of care**
  - **Non-covalent BTKis are promising**
  - **No data with PI3K inhibitors, anecdotal experience suggests limited durability of response**
  - **Supports efforts to use time-limited therapy or clinical trials BEFORE "using up" both classes of highly effective therapies**

2023 Sequencing Algorithm for R/R CLL



Non-covalent BTKi (pirtobrutinib) omitted since not approved for CLL; could be used in any patient progressing on a covalent BTKi, if available

Great Debates & Updates Hematologic Malignancies

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Q&A Session