BEYOND THE CONGRESS

Key Conversations from the
2021 Hematology Annual Meeting™

FRIDAY, FEBRUARY 4, 2022

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Dana-Farber Cancer Institute | BWH BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

DANA-FARBER/BRIGHAM AND WOMEN'S CANCER CENTER

Updates in Management of Relapsed and Refractory CLL/SLL

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February 4, 2022

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 AEs
  - Progressed during therapy
- Patients relapsing after venetoclax (or PI3Ki)
- Patients relapsing after BTKi and BCL-2

Kinome Selectivity Among Covalent BTKis

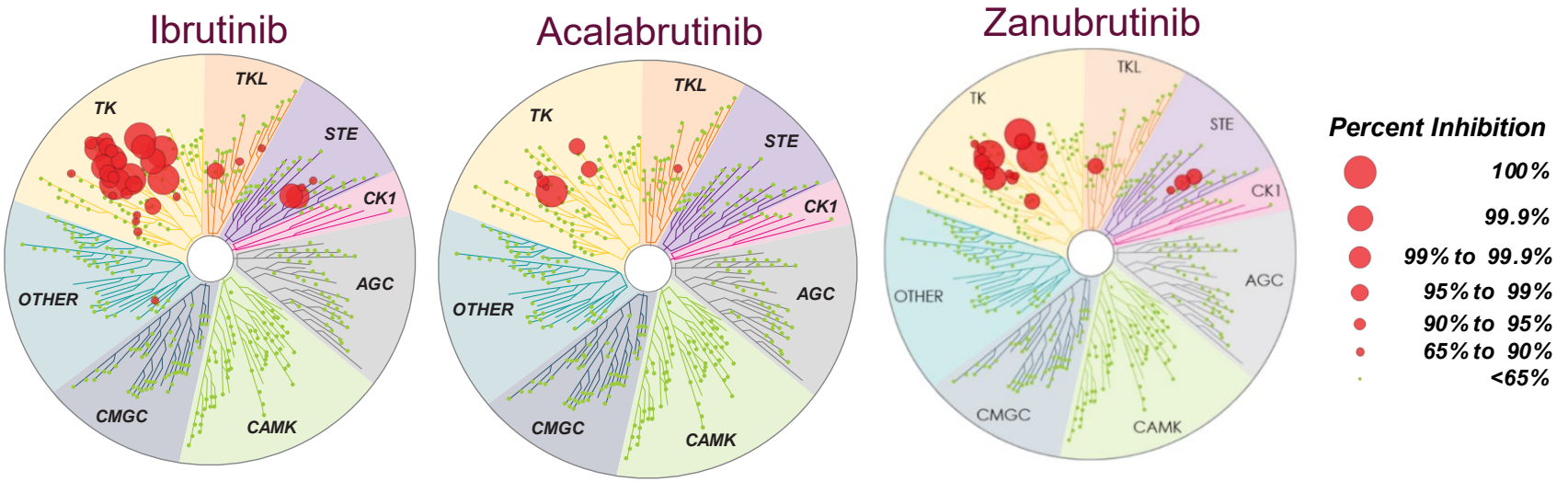
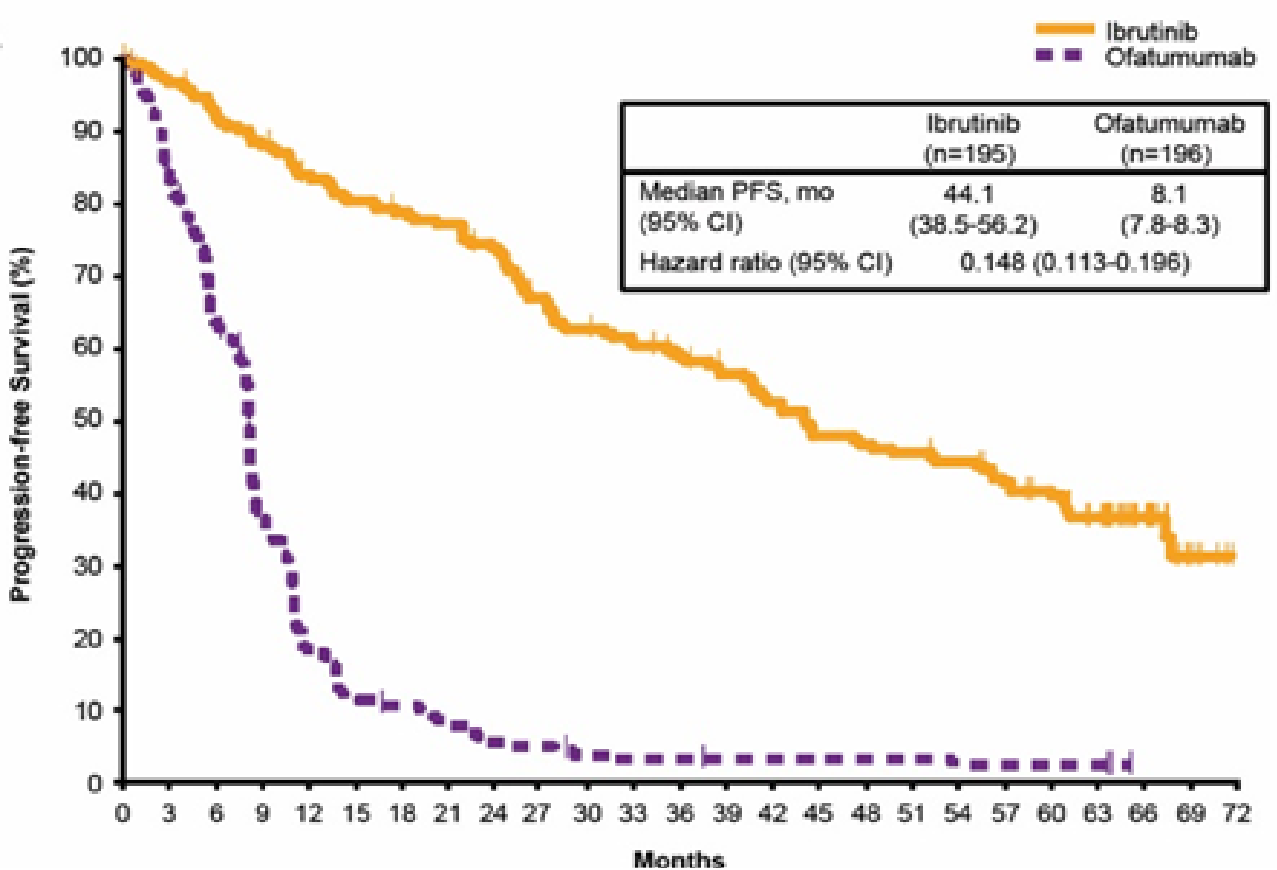


Figure 1. Kinome profiling at a single dose of 1 μM (KINOMEscan, Eurofins DiscoverX)

Final Analysis of RESONATE
Median 65 Mo F/U

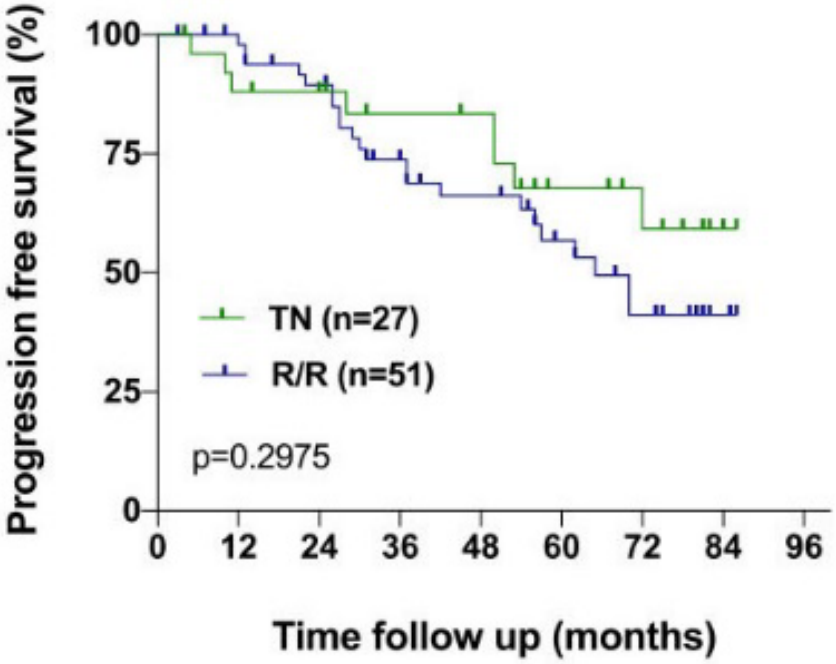


	Ibrutinib (n=195)	Ofatumumab (n=196)
Median PFS, mo (95% CI)	44.1 (38.5-56.2)	8.1 (7.8-8.3)
Hazard ratio (95% CI)	0.148 (0.113-0.196)	

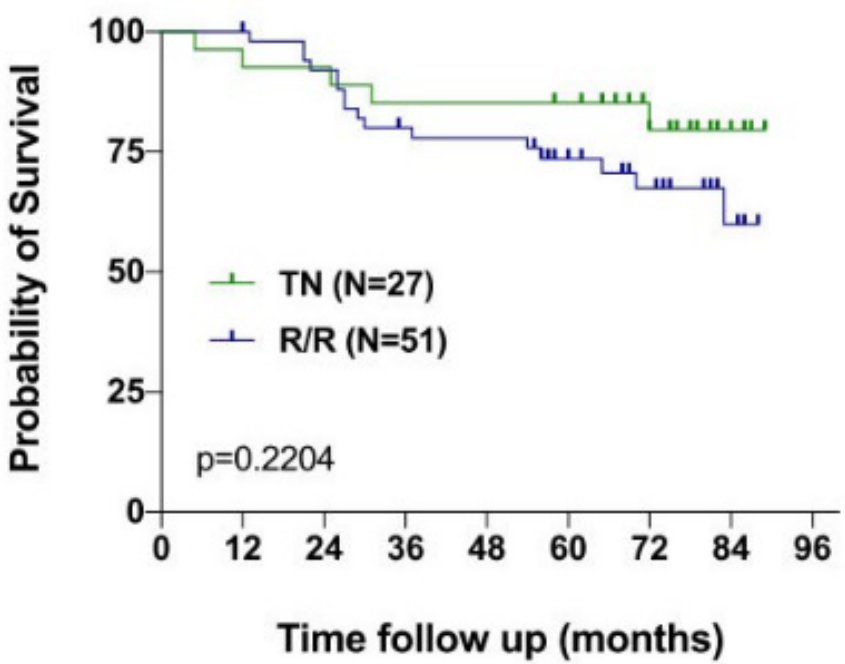
Munir et al. submitted

PFS and OS in Patients with CLL and *TP53* Aberrations
Ibrutinib +/- Rituximab

PFS



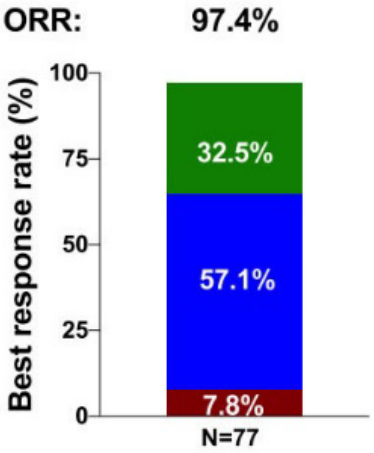
OS

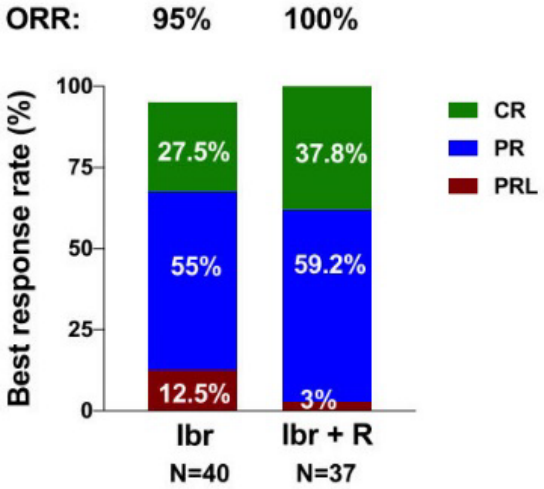


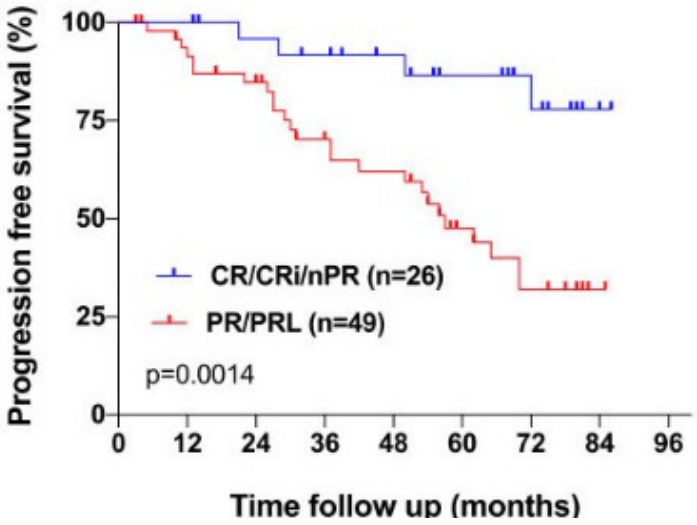
Five Year Follow-up from a Phase 2 Study

Burger, JA et al. ASH 2021. Abstract 2218

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







Five Year Follow-up from a Phase 2 Study

Burger, JA et al. ASH 2021. Abstract 2218

MDACC Venetoclax Consolidation

Primary endpoint: U-MRD4* in bone marrow after 12 months of combination

*MRD testing performed using standardized 4 color flow cytometry, sensitivity 1 in 10^4

Response assessment pre-venetoclax and q6m CT and bone marrow with MRD4 analysis

Eligibility:
- **CLL/SLL, treated with ibrutinib for ≥ 12 months with measurable MRD AND no clinical disease progression**
- **≥1 high risk feature*:**
- **del(17p) or *TP53*mut**
- **del(11q)**
- **Complex karyotype**
- **Elevated B2M**

*1st 45 patients – high risk defined as above. 2nd 45 patients – high risk will be del(17P)/TP53 mutated/CKT only. Del(11q) and Elevated B2M will not be inclusion criteria for 2nd 45 patients

Continue ibrutinib at current dose.

Venetoclax standard weekly dose escalation x28 days, followed by 400mg/d, for max. 24 cycles total*

*Each cycle 28 days. MRD-directed therapy: patients who achieve CR with U-MRD4 on two consecutive occasions, 6 months apart, will stop venetoclax

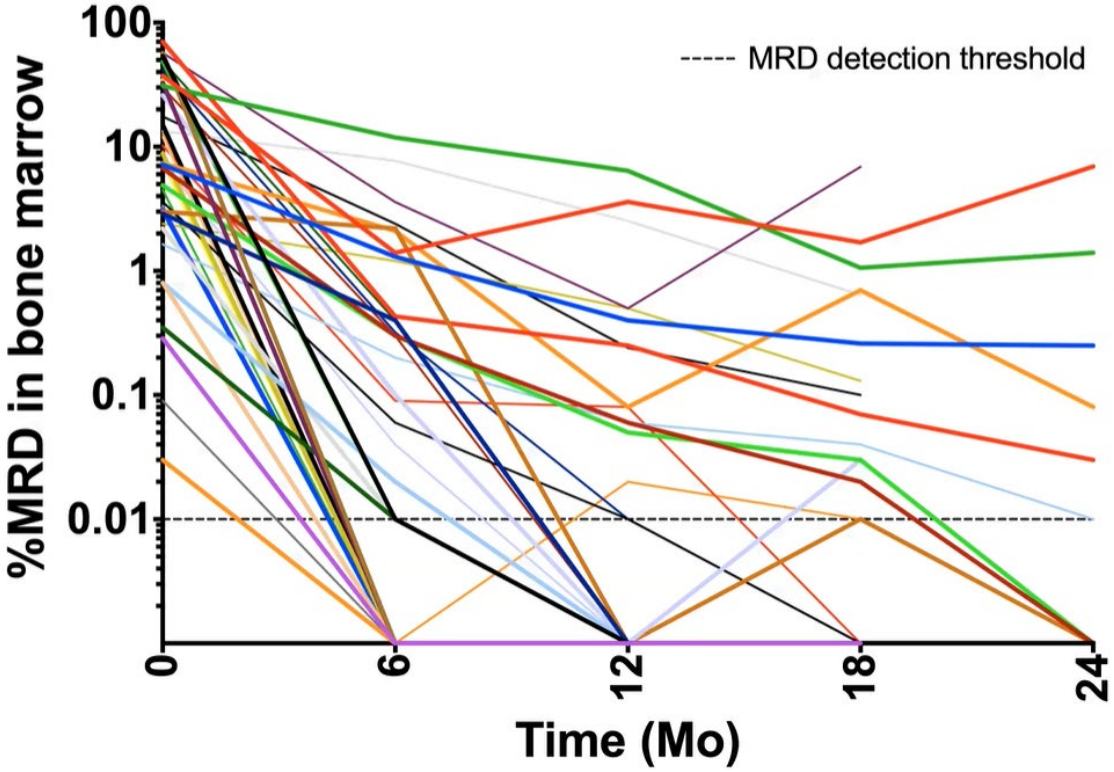
MRD q6m in PB during maintenance/observation

MRD+ → **Ibrutinib maintenance**

MRD- → **Stop therapy or Ibrutinib maintenance (Physician's choice)**

Abstract 3723, Thompson et al.

MRD Results



ITT Analysis of MRD:

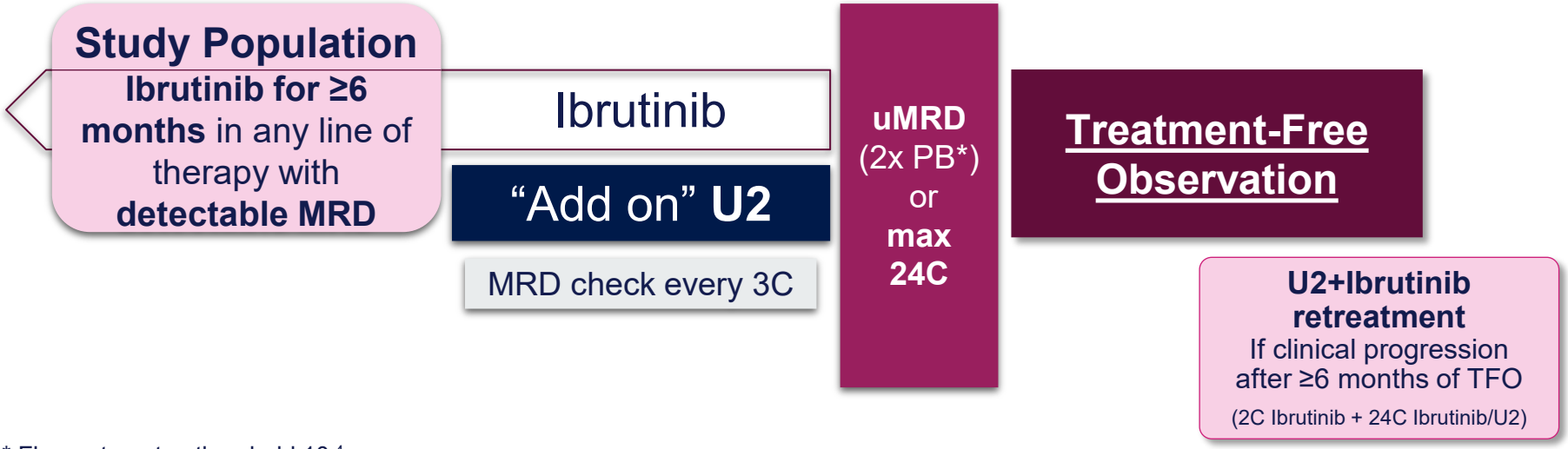
1. 38% U-MRD4 at C6
2. 57% U-MRD4 at C12
3. Best Cumulative U-MRD4: 73%

ITT Analysis CR/CRi:

- 2/45 (4%) were in CR at baseline
- 23/43 (53%) improved to CR/CRi during ven

Abstract 3723, Thompson et al.

MSKCC: Add U2 to Ibrutinib



* Flow cytometry, threshold 10^{-4}

Treatment Regimen

- Umbralisib 800mg PO QD
- Ublituximab 900mg IV C1 D1/2, 8, 15 C2-6 D1, and D1 every 3C
- Ibrutinib (previously tolerated dose)

Primary Endpoint:

- Rate of uMRD

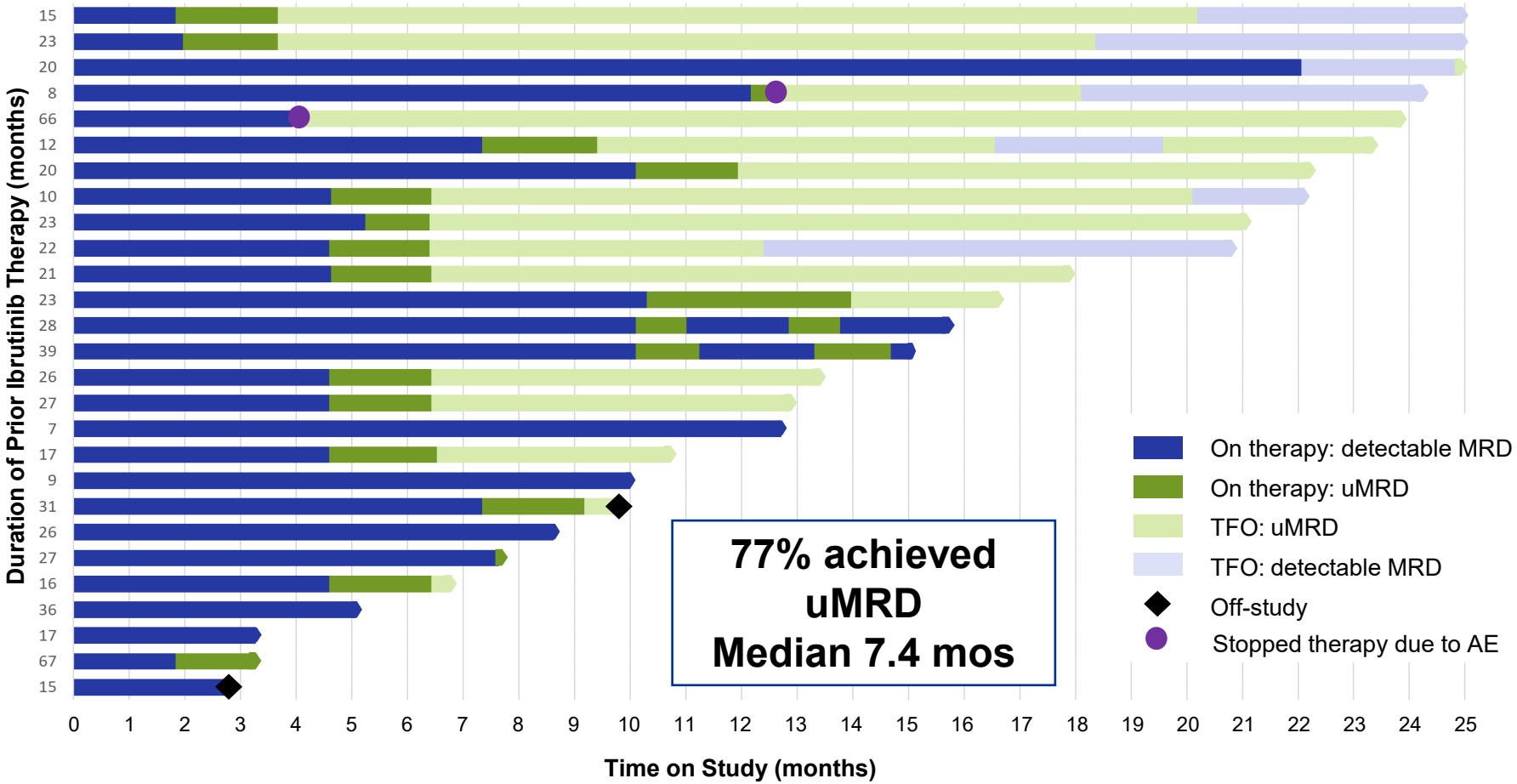
Sample size based on uMRD target ≥25%

Key Secondary Endpoints:

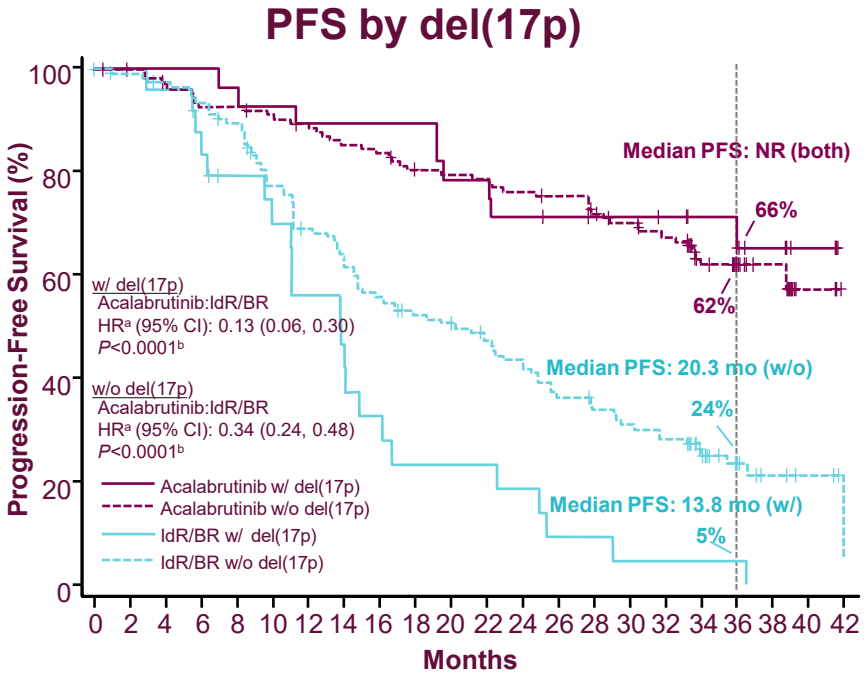
- Safety, time to uMRD, PFS, TTP, OS, response to retreatment

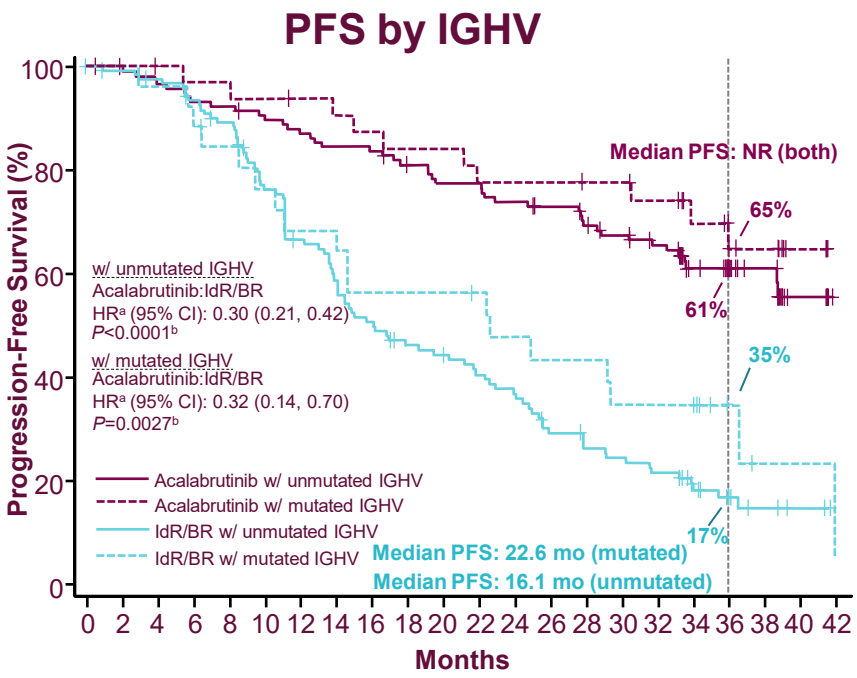
Abstract 395, Roeker et al.

Duration on Therapy



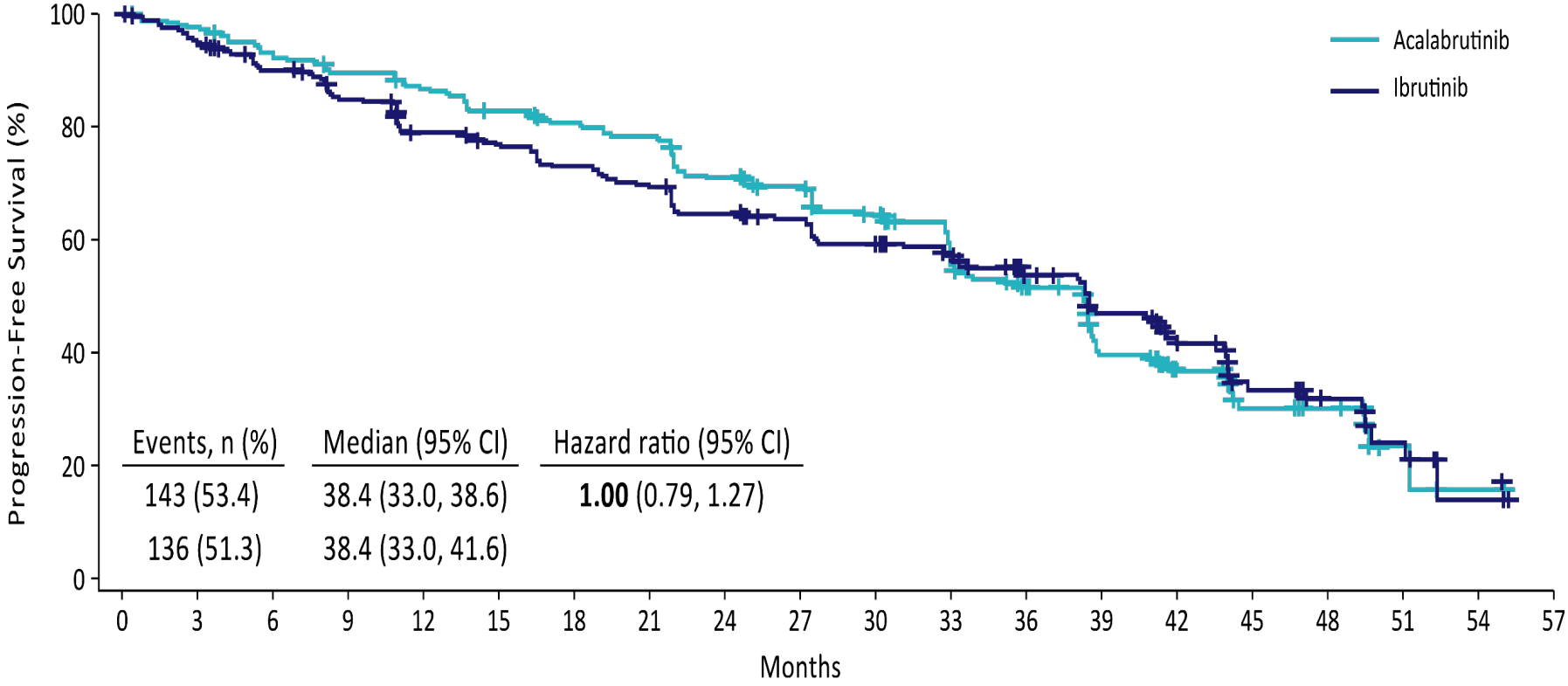
ASCEND: Investigator-Assessed PFS in Patients with High-Risk Features





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

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

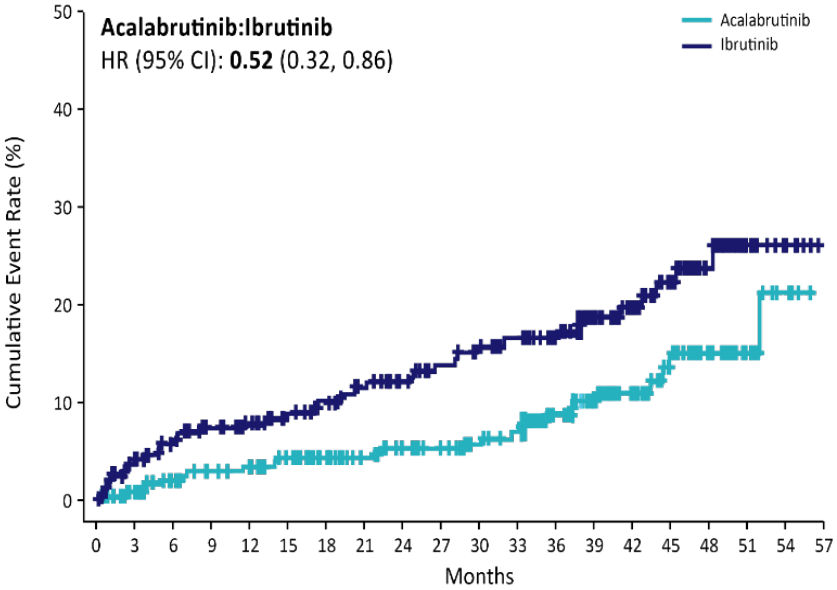


Median follow-up: 40.9 months (range, 0.0–59.1).

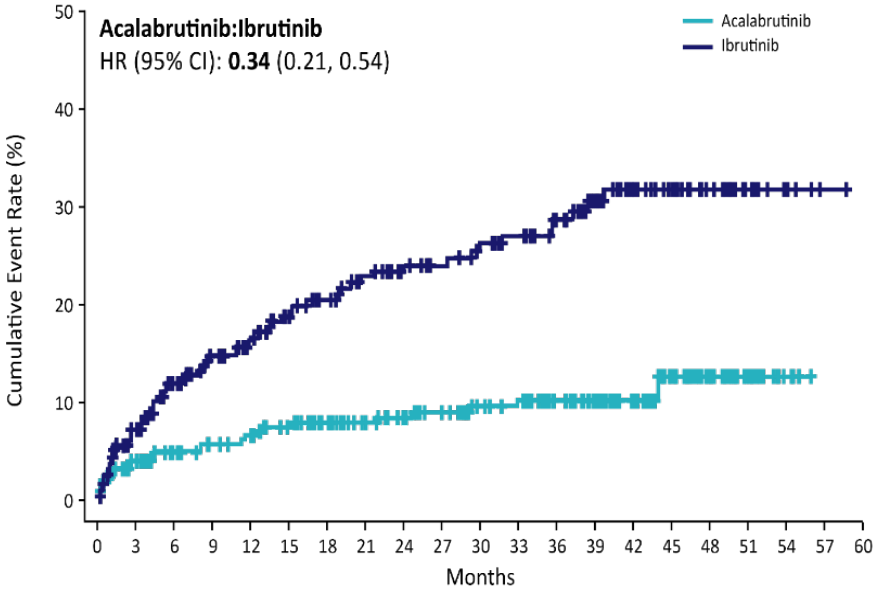
Hillmen *et al.* ELEVATE-RR, S145, EHA 2021.

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

Afib/Flutter, Any Grade



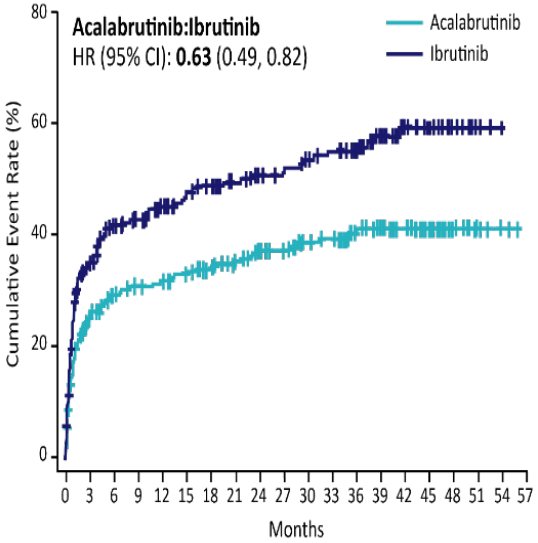
Hypertension, Any Grade



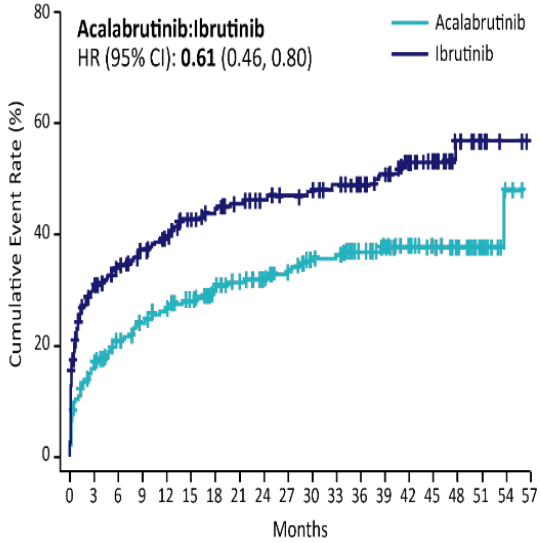
Hillmen *et al.* ELEVATE-RR, S145, EHA 2021.

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

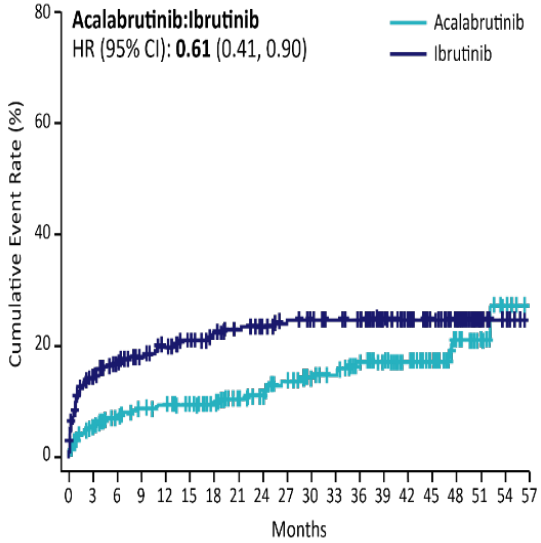
Bleeding Events



Diarrhea



Arthralgia



Hillmen *et al.* ELEVATE-RR, S145, EHA 2021.

ALPINE: Phase 3, Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory CLL or SLL

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
- Current or past Richter's transformation
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists

R 1:1

Arm A
Zanubrutinib 160 mg BID

Arm B
Ibrutinib 420 mg QD

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

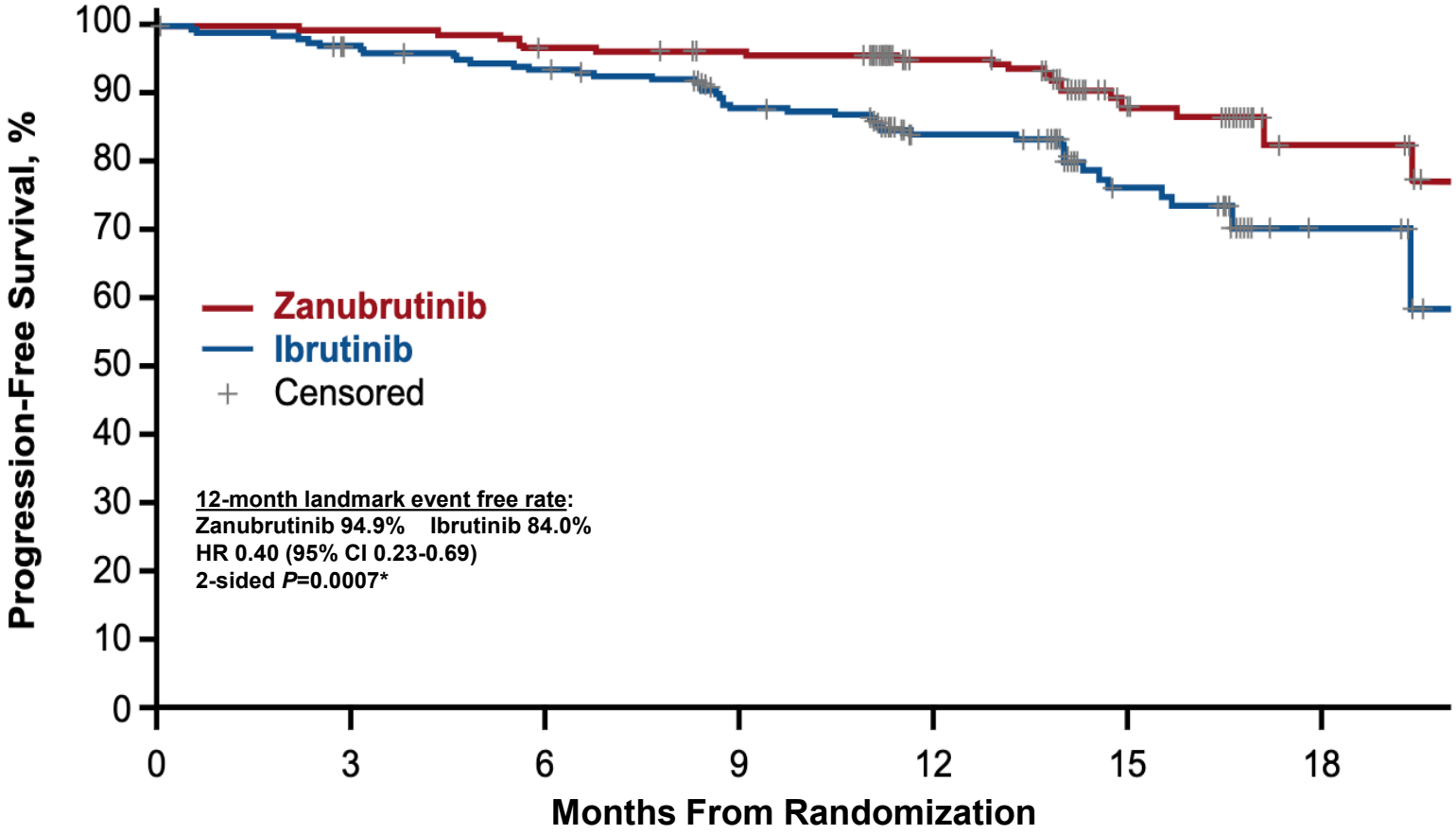
ALPINE study. Hillmen et al. LB1900 EHA 2021.

ORR by Investigator Assessment

	Zanubrutinib (n=207), n (%)	Ibrutinib (n=208), n (%)
Primary endpoint: ORR (PR+CR)	162 (78.3) 95% CI: 72.0, 83.7	130 (62.5) 95% CI: 55.5, 69.1
	Superiority 2-sided *P*=0.0006 compared with pre-specified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
ORR (PR-L+PR+CR)	*183 (88.4)*	*169 (81.3)*
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to 1st assessment	6 (2.9)	9 (4.3)
	del(17p) (n=24), n (%)	del(17p) (n=26), n (%)
ORR (PR+CR)	20 (83.3)	14 (53.8)

ALPINE study. Hillmen et al. LB1900 EHA 2021.

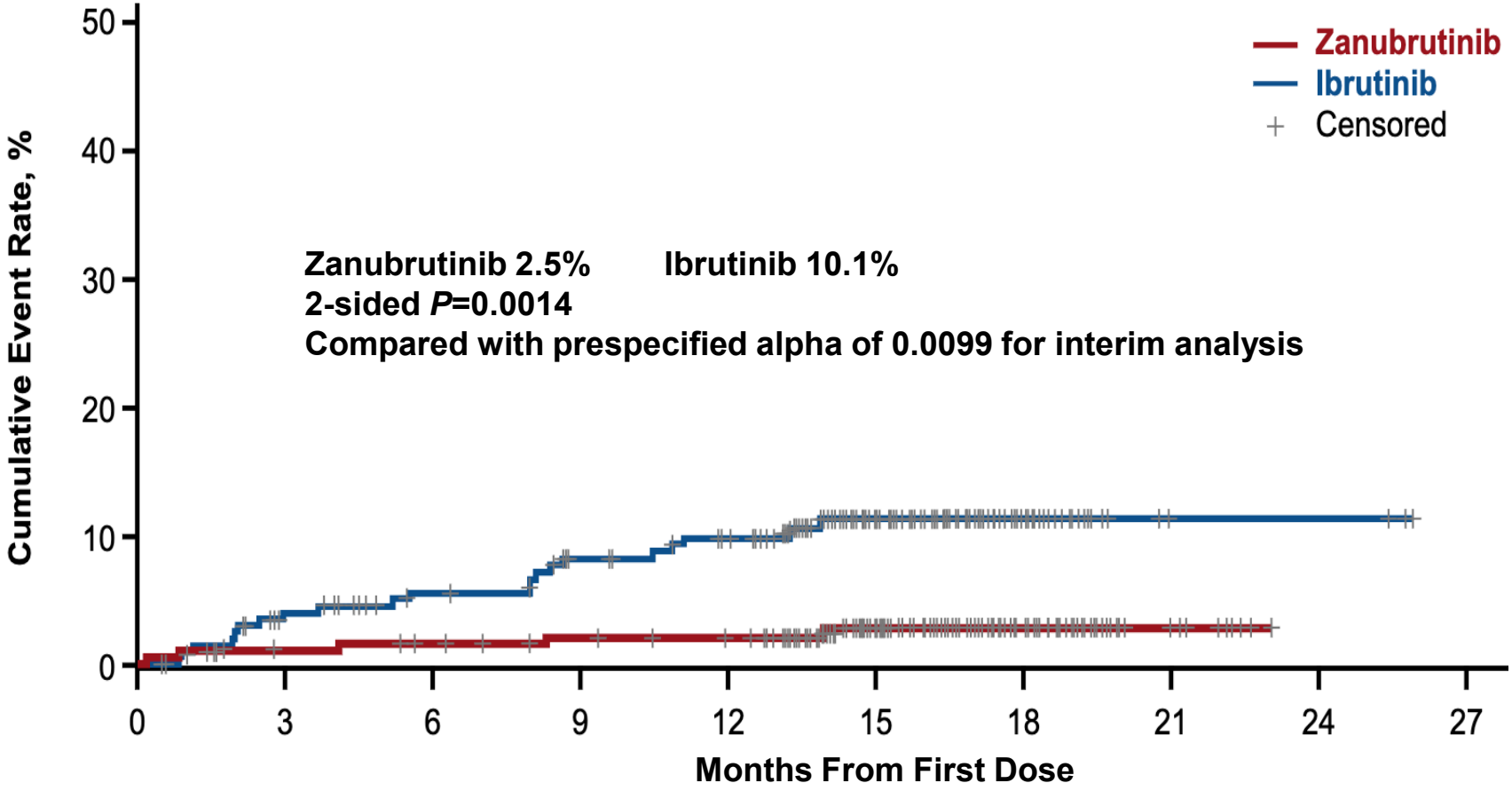
ALPINE: PFS by Investigator Assessment



*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.

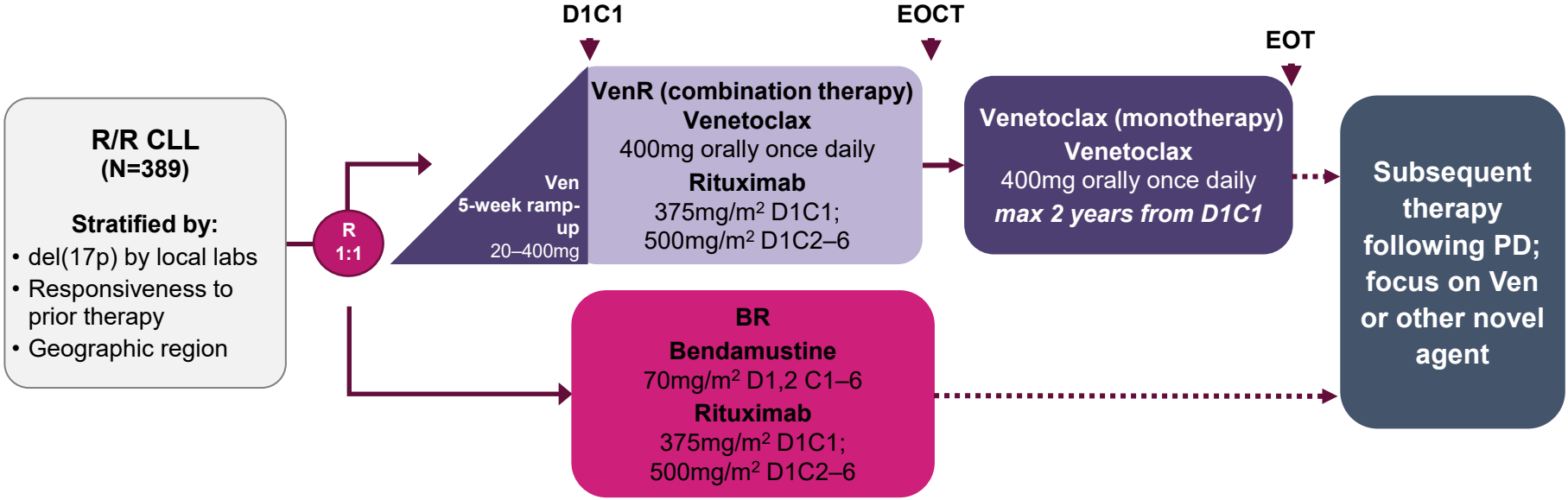
ALPINE study. Hillmen et al. LB1900 EHA 2021.

Atrial Fibrillation/Flutter



ALPINE study. Hillmen et al. LB1900 EHA 2021.

MURANO Study Design

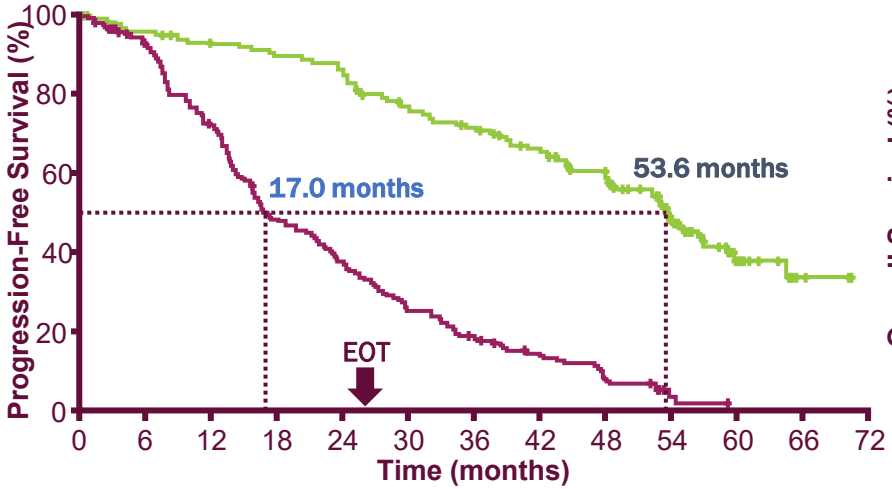


- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoint:** rates of clearance of MRD
- Clinical response and MRD* in PB during Ven monotherapy and follow-up visits were assessed every 3 months for 3 years, then every 6 months thereafter, or until PD

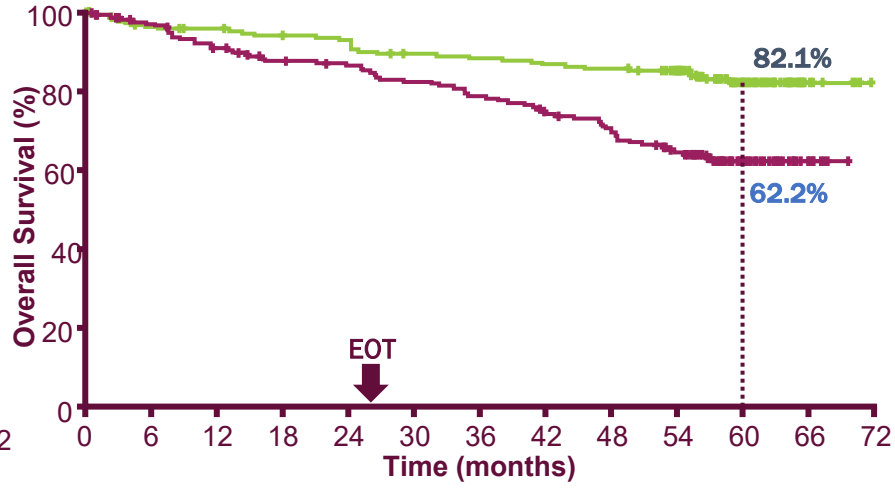
Kater AP et al. ASH 2020. Paper 125

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



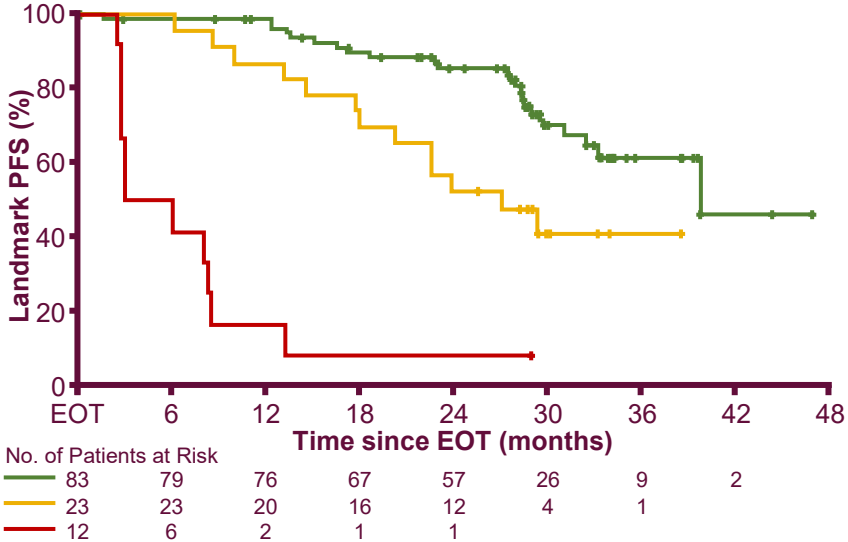
- With this 5-year update we can now accurately define the median PFS of VenR-treated patients
- No new safety signals were identified 3 years after EOT with longer follow up and patients are outside of the adverse event reporting window

uMRD at EOT is Associated with Improved PFS

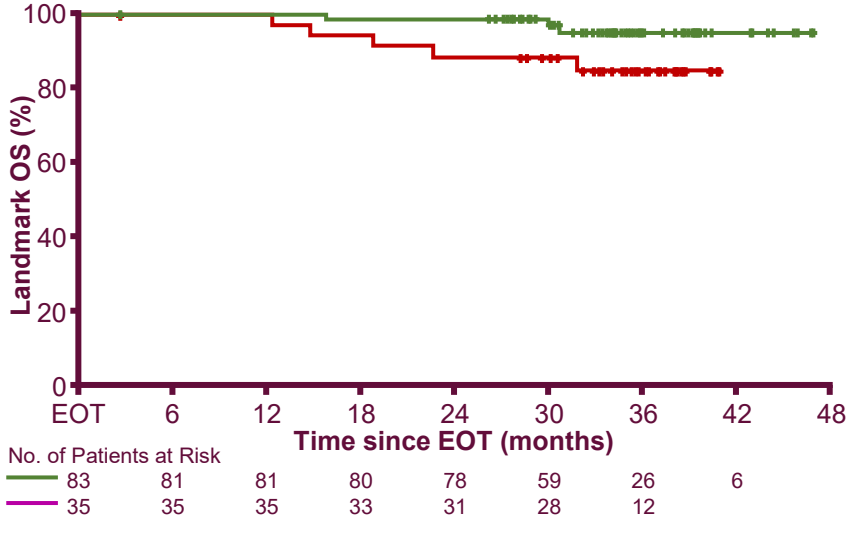
	PFS (95% CI) since EOT	
Category	24 month	36 month
uMRD ($<10^{-4}$)* (N=83)	85.4% (77.4, 93.4)	61.3% (47.3, 75.2)
Low-MRD+ (10^{-4}–10^{-2}) (N=23)	52.2% (31.8, 72.6)	40.7% (19.2, 62.2)
High-MRD+ ($>10^{-2}$) (N=12)	8.3% (0.0, 24.0)	NE
	HR (95% CI)	P-value
uMRD vs Low-MRD+	0.40 (0.18, 0.91)	0.0246
uMRD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

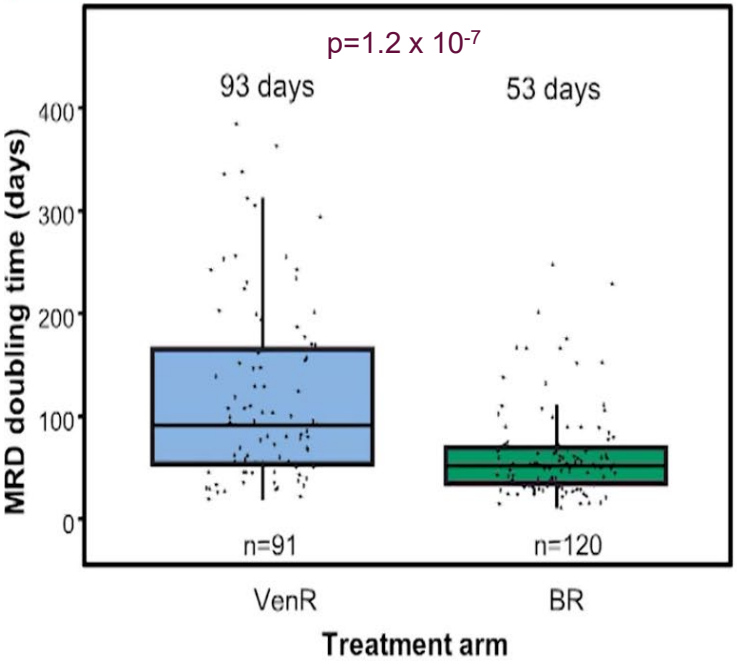


OS post-EOT

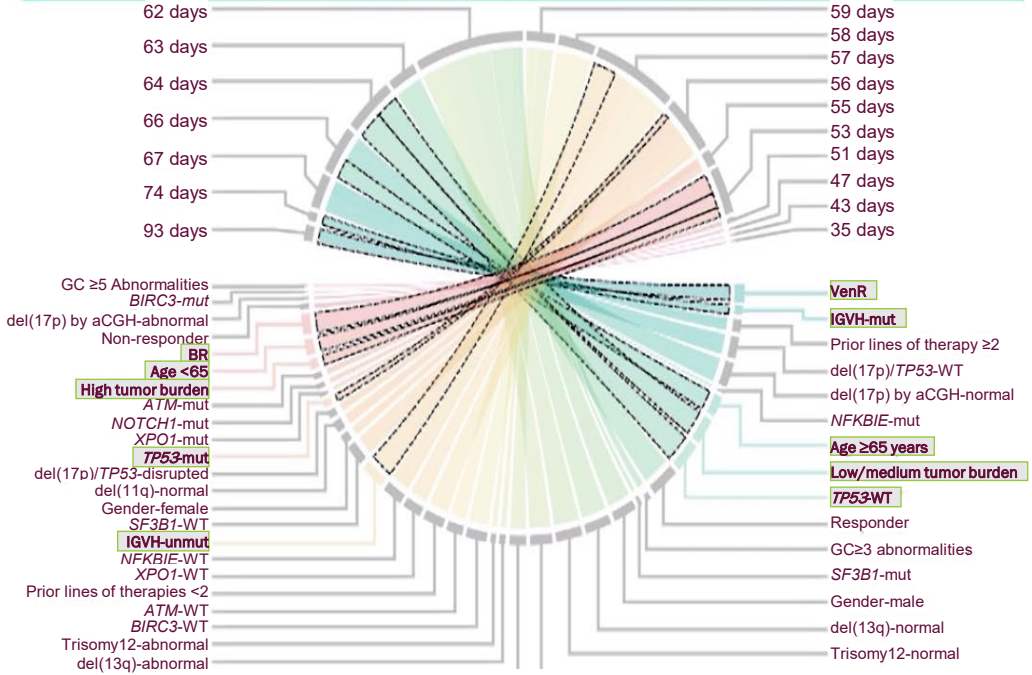


CLL Clonal Growth Rate

Median MRD doubling time, was significantly longer with VenR (93 days) vs BR (53 days)



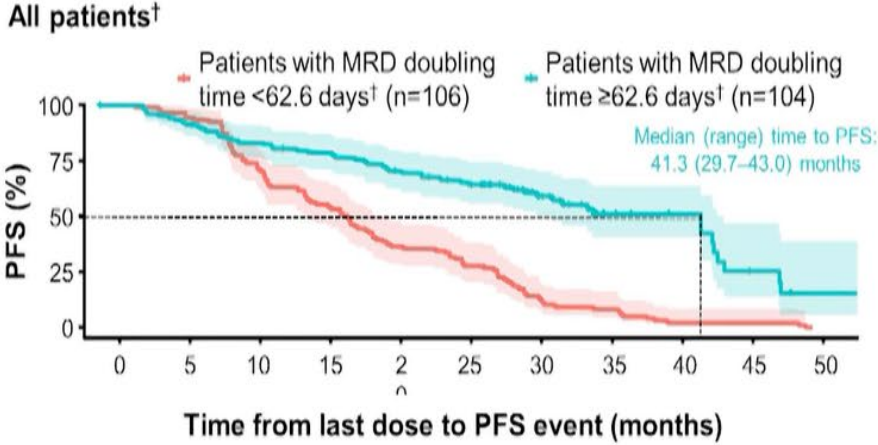
Covariate screening showed treatment type, age, IGHV and *TP53* mutation status, and tumor burden at study initiation to significantly impact MRD growth rate



Abstract 1551; Kater et al.

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)

Abstract 1551; Kater et al.

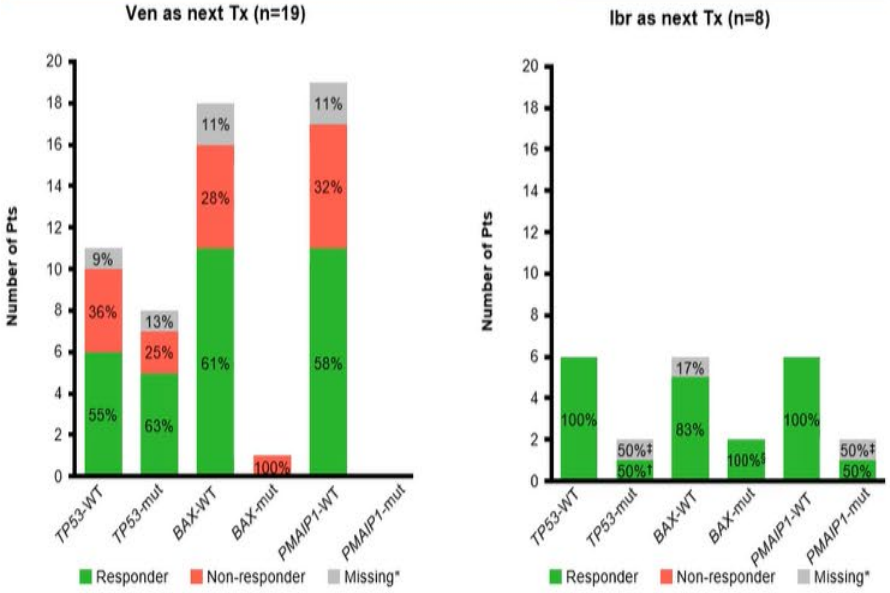
Acquired Mutations in MURANO

	*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]

Abstract 1548, Seymour et al.

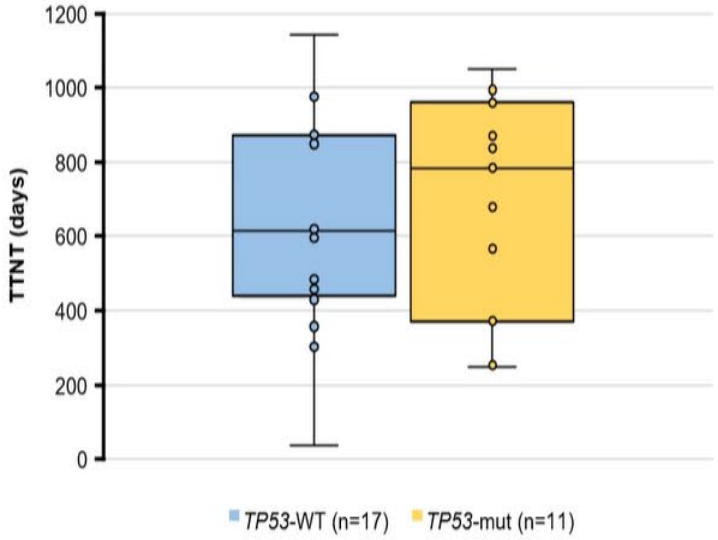
Acquired Mutations and TTNT

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

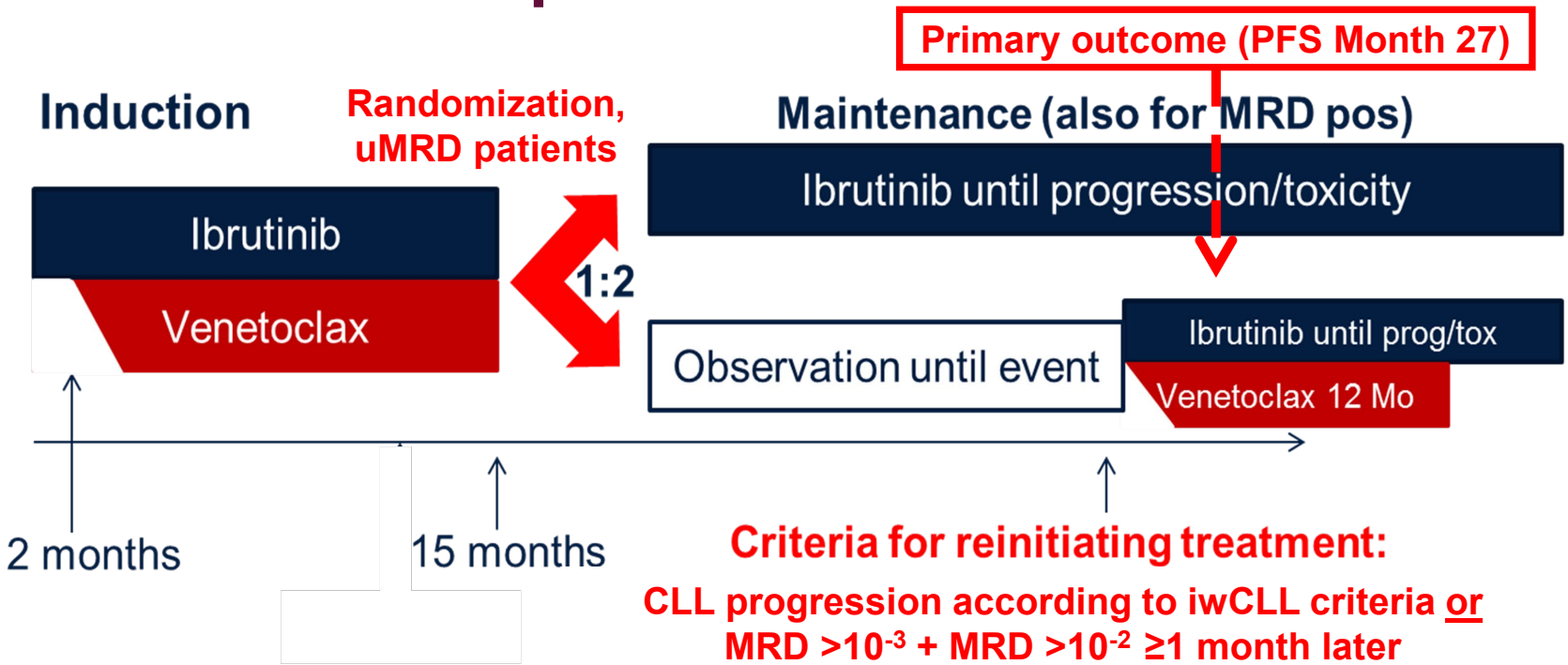
TTNT per *TP53* mutations in VenR-treated Pts who were MRD+ post-Tx cessation



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

Abstract 1551; Kater et al.

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

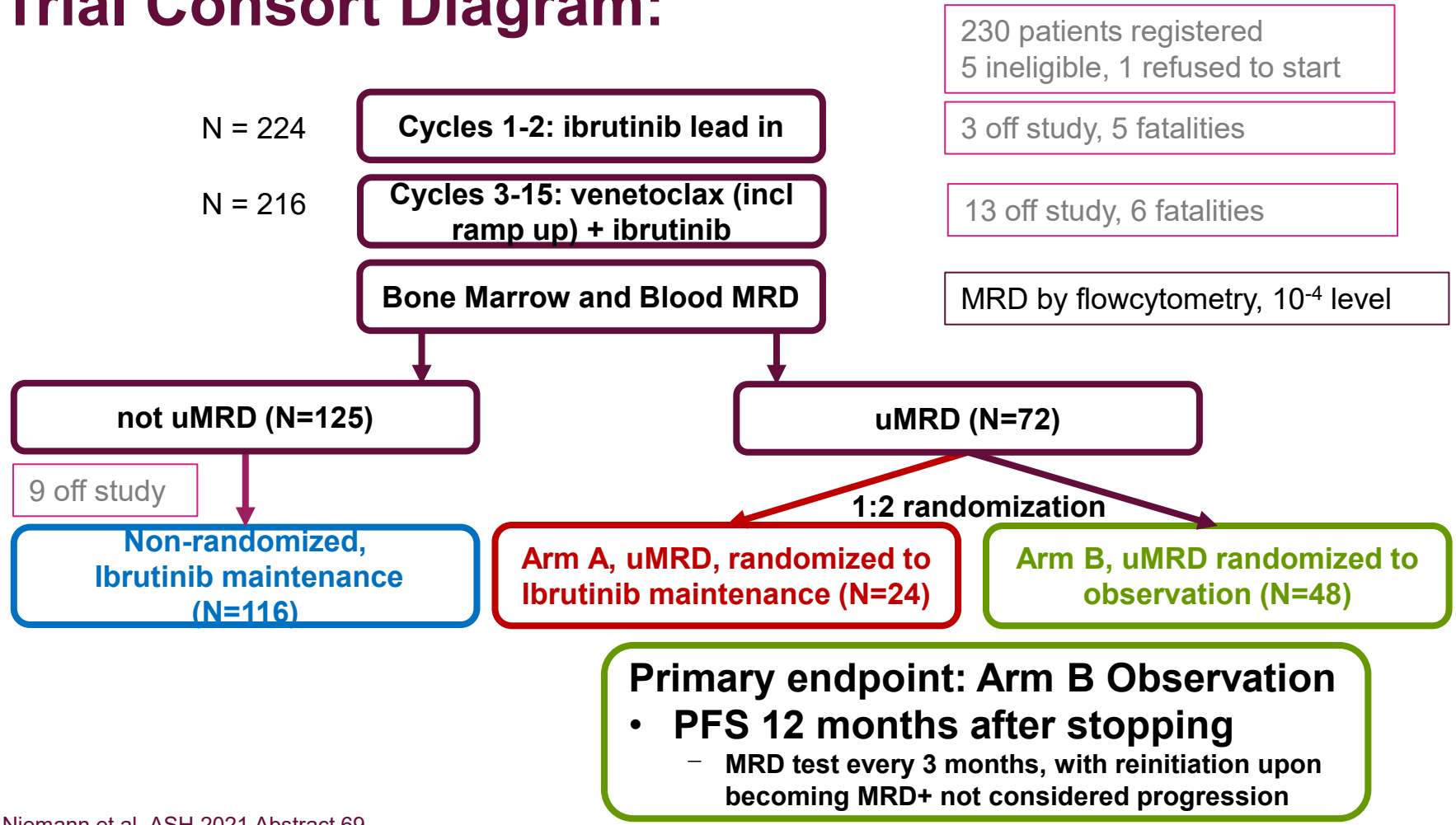


Main Inclusion / Exclusion Criteria:

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

Niemann et al. ASH 2021 Abstract 69

Trial Consort Diagram:

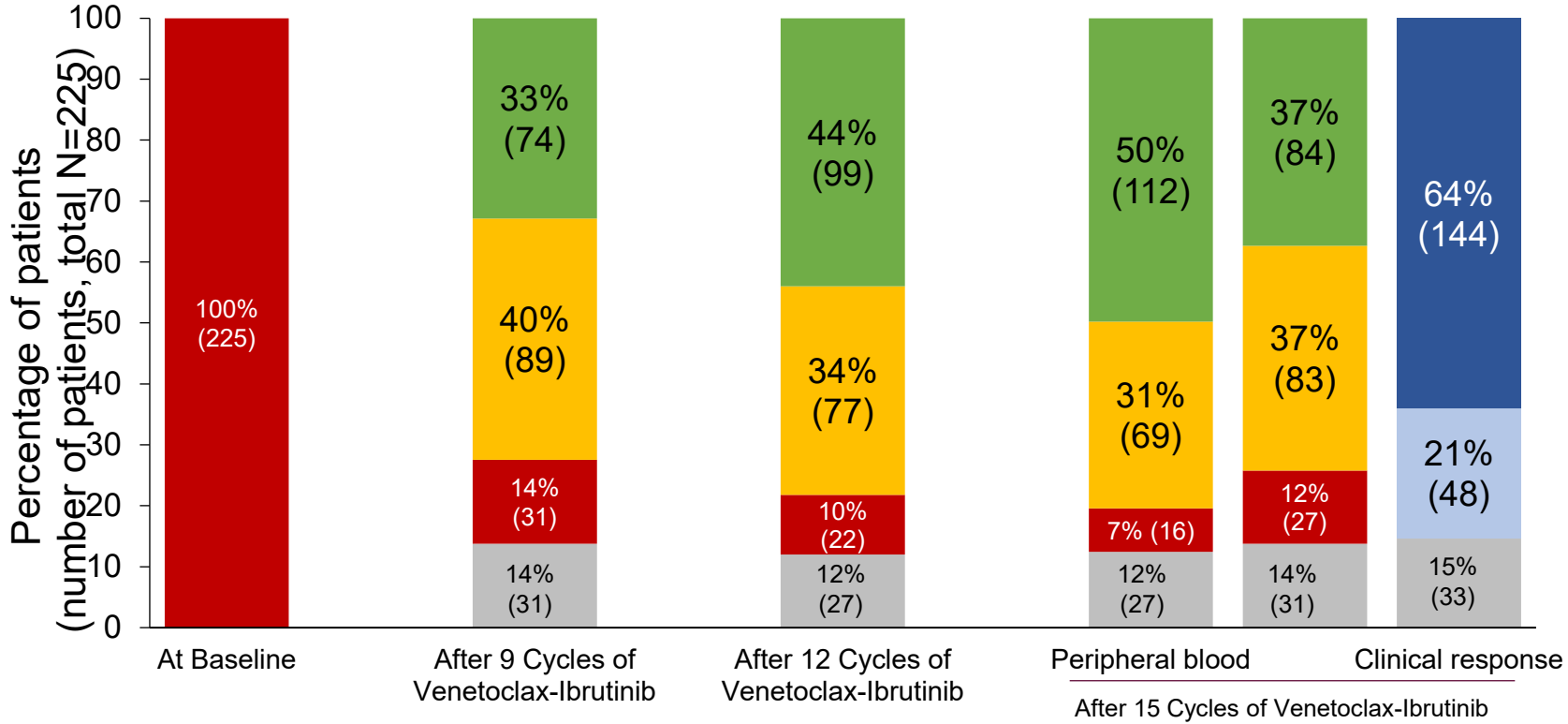


Primary endpoint: Arm B Observation

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

Niemann et al. ASH 2021 Abstract 69

MRD and Response, 15 Cycles Ibrutinib-Venetoclax Induction:



Undetectable MRD ($<10^{-4}$)
Low MRD Positive ($\geq 10^{-4}$ and $<10^{-2}$)
High MRD Positive ($\geq 10^{-2}$)
Complete remission (with or without normal blood count recovery)
Partial remission
Not available

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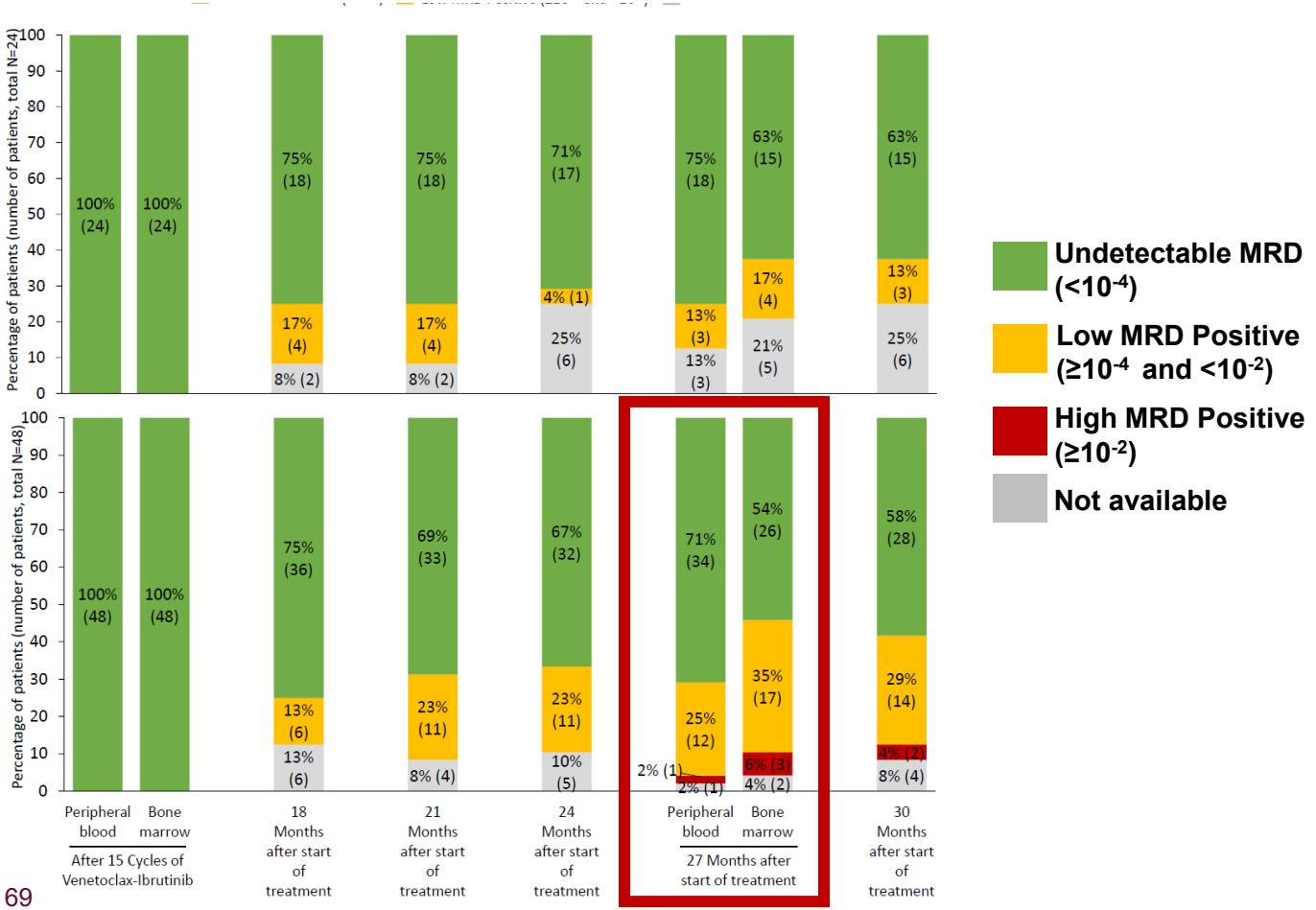
MRD Over Time from C15, Arm A, Ibrutinib and Arm B, Observation:

Arm A, Ibrutinib

Arm B, Observation
Primary Endpoint



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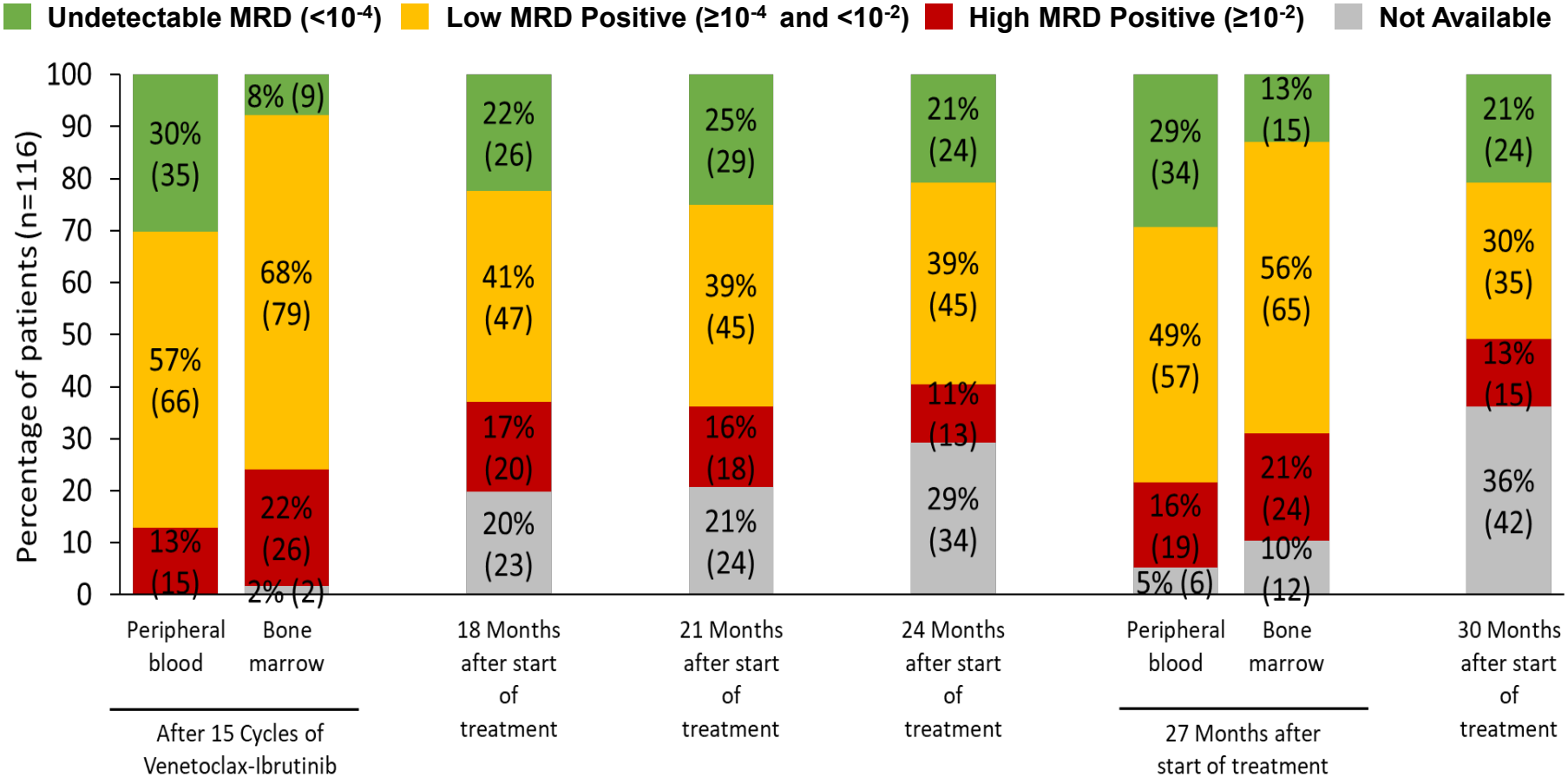
MRD Over Time from C15, Non-Randomized, Ibrutinib Maintenance:



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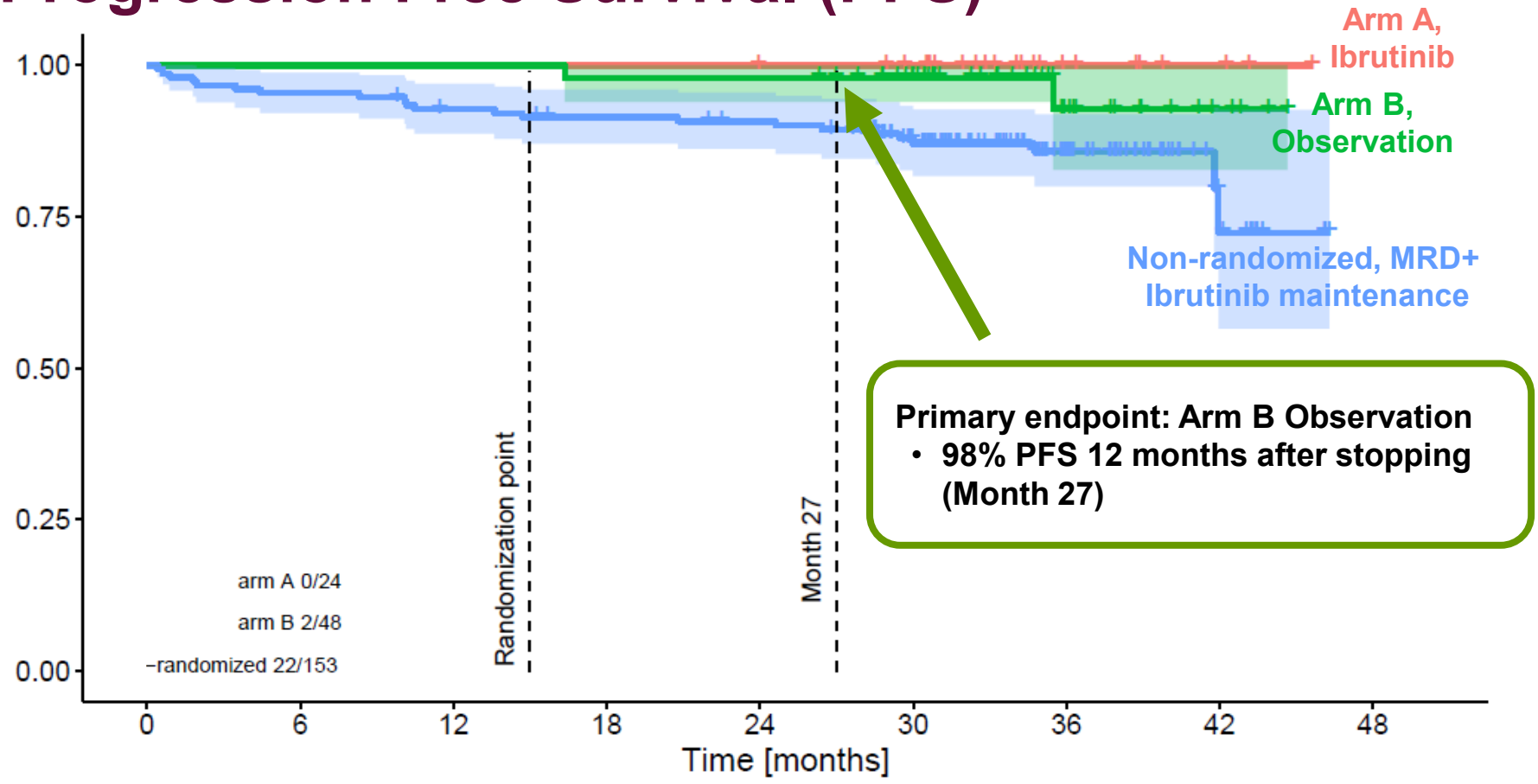
Progression Free Survival (PFS)



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

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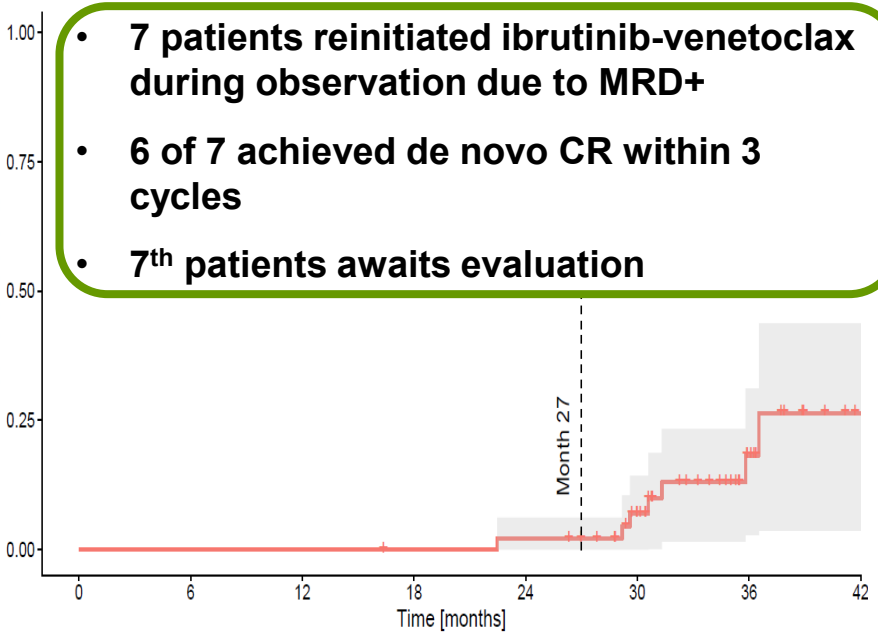
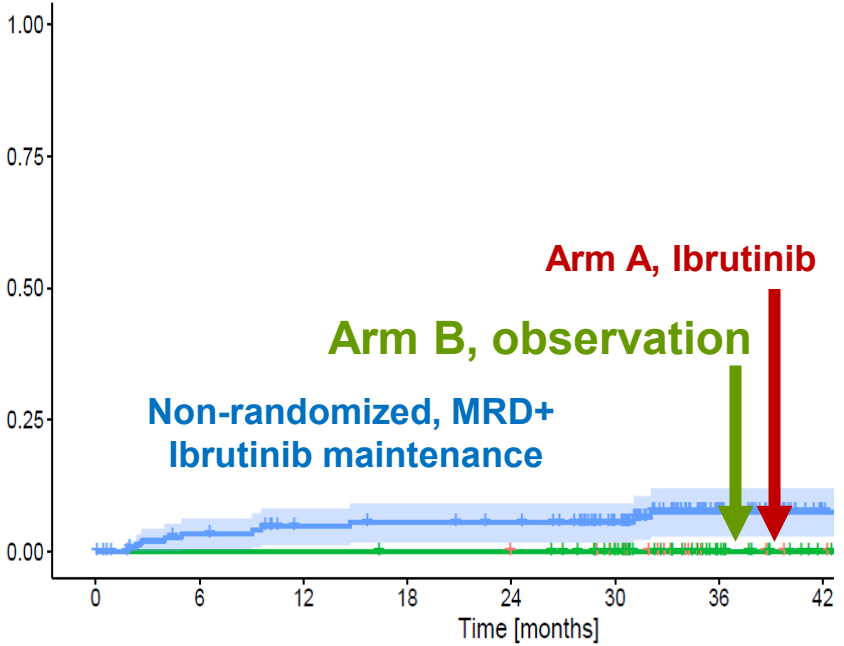
Reinitiation, Arm B: observation and Time To Next Treatment

- 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

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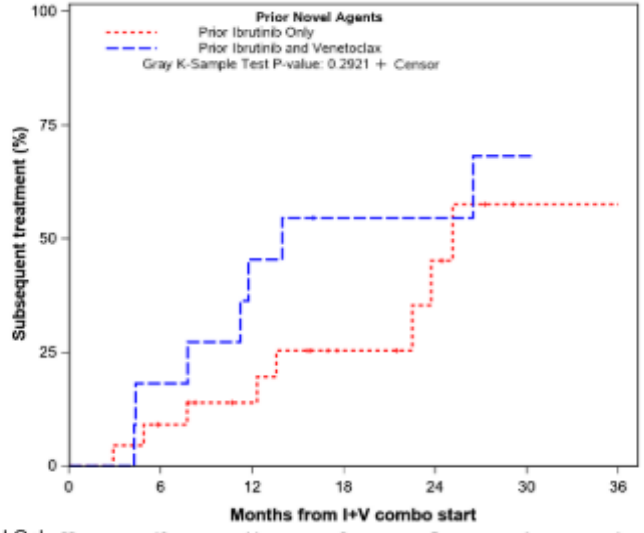
Outcomes of I+V Given for CLL Progression

Time to Next Therapy from I+V Start

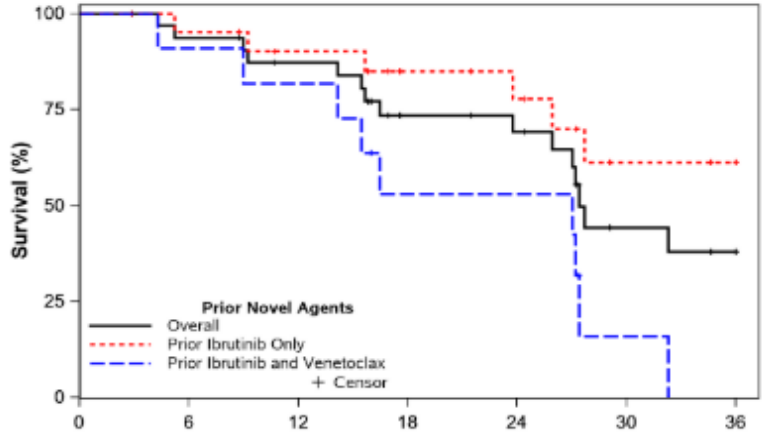


Prior I Only	22	19	14	8	5	1	1
Prior I and V	11	8	4	2	2	1	0

	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

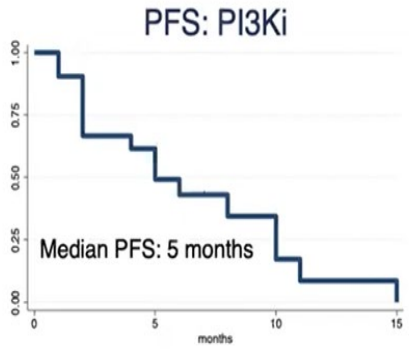
	Event/Total	Median (95% CI)[1]	Survival Estimates (95% CI)[1]
Overall	16/33	27.4 (25.9-NE)	12 Months: 87.3 (76.4-99.7%) 24 Months: 69.2 (54.1-88.5%)
Prior Ibrutinib Only	7/22	47.1 (27.7-NE)	12 Months: 90.2 (78.2-100.0%) 24 Months: 77.8 (60.5-100.0%)
Prior Ibrutinib and Venetoclax	9/11	27.0 (15.5-NE)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

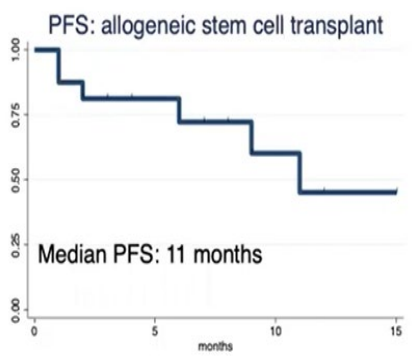
[1]Kaplan-Meier method

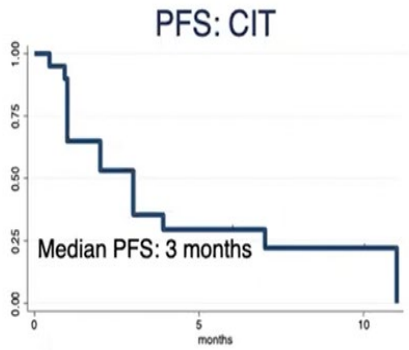
ASH Abstract 1560, Hampel et al.

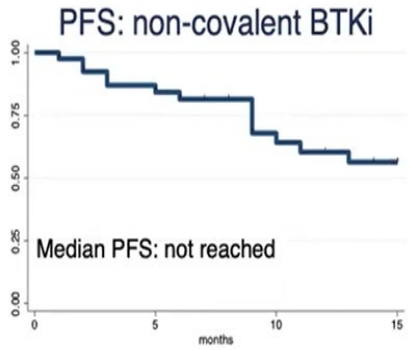
Real-World Outcomes of Patients with Prior Exposure to cBTKi and Ven

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









Abstract 2628 Thompson et al.

Summary: CLL

- Comparative data suggest similar efficacy and improved tolerability for the 2nd generation cBTKis acalabrutinib and zanubrutinib
- Adding either venetoclax or U2 in patients already on ibrutinib leads to high rates of uMRD
- Clonal regrowth rates after ven R are lower than after BR and associate with PFS
  - Known poor prognostic features are associated with higher regrowth rates
- Acquired TP53 mutations, but not BCL-2 mutations, were detected in relapsing MURANO patients
- Time-limited I+V is effective in patients relapsed after CIT or ibrutinib
- Relapse after both cBTKi and venetoclax is a major new unmet need
  - ?Non covalent BTKi