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ASH 2023 Comes to You!

January 29, 2024

1:00 PM PT, 2:00 PM MT
3:00 PM CT, 4:00 PM ET

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Speakers

Speaker
Nicole Lamanna, MD
Associate Professor of Clinical Medicine, Department of Medicine, Division of Hematology Oncology
Columbia University Medical College

Moderator and Speaker
Brian Koffman, MDCM (retired), MS Ed
Executive Vice President and Chief Medical Officer
CLL Society

Welcome
Robyn Brumble, MSN, RN
Director of Scientific Affairs and Research
CLL Society

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ASH 2023

Dr. Brian Koffman

January 29, 2024

First-in-Human Phase 1 Trial of NX-2127

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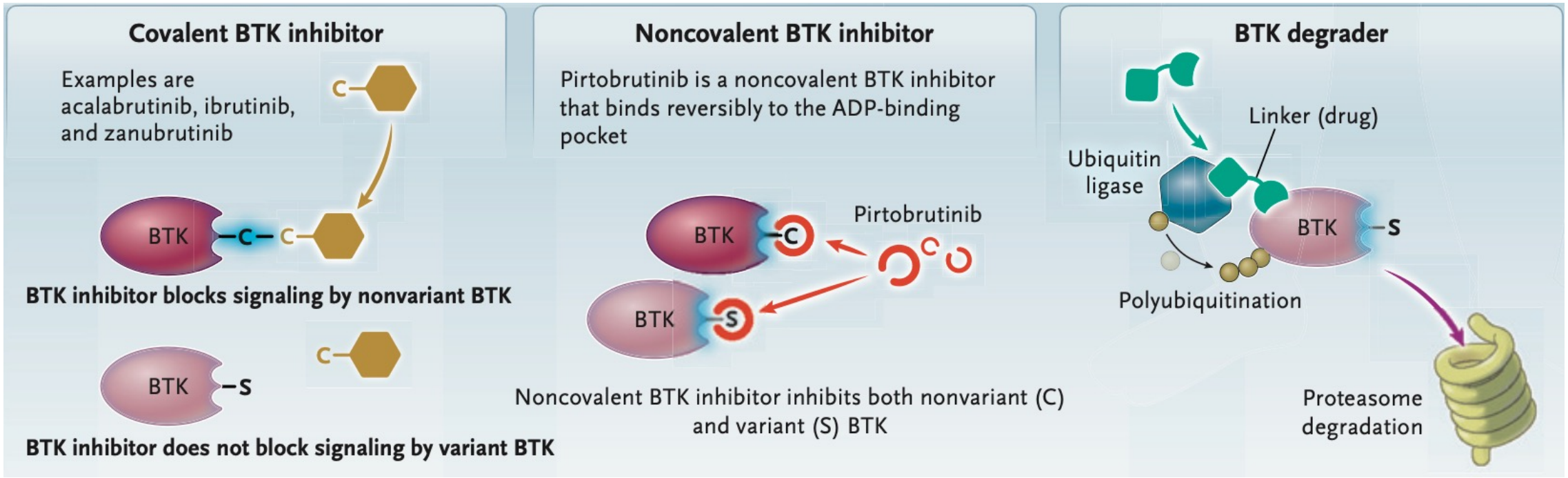
First-in-Human Phase 1 Trial of NX-2127, a First-in-Class Bruton's Tyrosine Kinase (BTK) Dual-Targeted Protein Degrader with Immunomodulatory Activity, in Patients with Relapsed/Refractory B Cell Malignancies (Dr. Alexey Danilov)

- BTK inhibitors (BTKi) have revolutionized the treatment of CLL, but emerging BTK resistance mutations as well as the importance of scaffolding function of BTK, present a need for new approaches
- NX-2127 is an oral, first-in-class, dual-function small molecule degrader that combines BTK degradation with the immunomodulatory activity

First-in-Human Phase 1 Trial of NX-2127

How BTKi and Degraders Work



n engl j med 389;1 nejm.org July 6, 2023

First-in-Human Phase 1 Trial of NX-2127

- 47 patients were treated with NX-2127 at once-daily doses of 100 mg (n=28), 200 mg (n=10), and 300 mg (n=9)
- 66% were male. Median age of 74 (range 50–92) years
- 29 patients were treated for CLL/SLL
- Heavily pretreated CLL/ SLL with median of 5 prior therapies
  - 100% prior BTKi, 76% BCL2i, most resistant to BTKi

Adverse events:

- Fatigue (48.9%) low neutrophils (38.3%), hypertension (14.9%), anemia (12.8%), confusion (17.7%), atrial fibrillation (12.8%)

First-in-Human Phase 1 Trial of NX-2127

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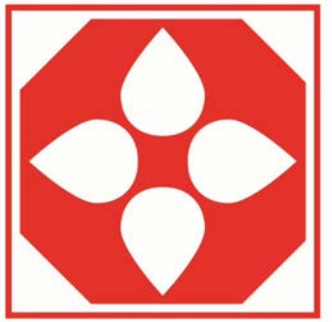
CLL Results:

- 9 partial remissions, 11 stable disease and 4 progressive disease

Conclusions:

- Go forward dose is 100mg for CLL and 300 mg for MCL & DLBCL.
- Promising in a difficult to treat population, but trial is on a partial hold now not due to safety but due to manufacturing issues
- NX-5948 is a similar degrader in open trials with only BTK activity that now has FDA fast track designation for CLL/SLL

Clinical Outcomes with Venetoclax-Based Treatment Regimens in CLL



Clinical Outcomes with Venetoclax-Based Treatment Regimens in Patients with Chronic Lymphocytic Leukemia (CLL) (Dr. Paul Hempel)

- Goal was to identify factors that impact outcomes of venetoclax for patients with CLL treated at a tertiary center (Mayo Clinic)
- Studied:
  - Frontline use
  - Relapsed with no prior BTKi exposure
  - Relapsed with prior BTKi exposure

Clinical Outcomes with Venetoclax-Based Treatment Regimens in CLL

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Results:

- 155 patients were identified between 2012 and 2023 at Mayo:
  - 55 front line therapy (in combination with obinutuzumab)
  - 100 relapsed CLL
    - 17 had relapsed/BTKi-naïve CLL
    - 83 had previously received BTKi, 55 with progression after BTKi, relapsed/BTKi-exposed
- The median treatment free survival (TFS) for the overall cohort was 39.0 months. The median overall survival (OS) was 54.6 months.
- Among patients treated with venetoclax as first-line therapy (n=55), the 2-year TFS and 2-year OS rates were both 91%
- MRD testing was performed in 28 patients and was uMRD in 23 (82%) patients (only PB assessed, n=7; only BM assessed, n=2; PB and BM assessed, n=14)

Clinical Outcomes with Venetoclax-Based Treatment Regimens in CLL

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Results:

- Patients treated with venetoclax in the relapsed/BTKi-naïve setting (n=17), the 2-year TFS rate was 73% and the 2-year OS rate was 100%. MRD testing was performed in 7 patients and was uMRD in all 7
- Among relapsed/BTKi-exposed venetoclax-treated patients (n=83), the median TFS was 26.9 months and the median OS was 39.4 months
- The median TFS for patients with (n=55) and without (n=28) prior disease progression on prior BTKi were 22.3 and 42.3 months, respectively. Median TFS with venetoclax monotherapy (n=30) was 24.0 months, venetoclax in combination with rituximab (n=37) was 26.9 months, and venetoclax in combination with obinutuzumab (n=16) was 39.0 months

Clinical Outcomes with Venetoclax-Based Treatment Regimens in CLL

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Results:

- TP53 disruption, unmutated IGHV genes, older age, complex karyotype (CK; defined as more than 3 chromosomal aberrations on CpG stimulated karyotype), and disease progression on prior BTKi were associated with shorter TFS in the overall cohort. TP53 disruption, older age, CK, and disease progression on prior BTKi were associated with shorter OS in the overall cohort.

Conclusions:

- Patients with BTKi-exposed CLL, particularly those with prior disease progression on BTKi, had worse outcomes. CK as one of the most important baseline predictors of adverse TFS and OS.

CAR-T for Richter's Transformation: A Retrospective Study

Anti-CD19 Chimeric Antigen Receptor T-Cell Therapy for Richter's Transformation: An International Multicenter Retrospective Study (Dr. Adam S Kittai)

- CAR-T has drastically improved outcomes for patients with diffuse large B-cell lymphoma (DLBCL), but Richter's Transformation (RT) has been mostly excluded from trials
- RT is when CLL transforms into a more aggressive lymphoma, usually DLBCL

CAR-T for Richter's Transformation: A Retrospective Study

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Results:

- 62 patients were included. Median age was 65
- Median prior therapies for both CLL and RT was 2 each
- 84% had received a prior BTKi or a BCL2i (venetoclax)
- Ki-67 was 80% which means the cancer was growing very fast
- Medium SUV was 15: this is a high measure of metabolic activity seen on PET scan. Median lymph node size was 3.8 cm
- Median wait from apheresis (special blood draw to get the T cells) to receiving CD19 CART infusion was 33 days
- 84% had "bridging therapy" or treatment to control CLL while waiting

CAR-T for Richter's Transformation: A Retrospective Study

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Results:

- Overall response rate was 65%, with 29 (47%) and 11 (18%) pts attaining complete response (CR) and partial response (PR), respectively
- After a median follow up of 24.1 months (mos) from CD19 CART infusion, the median progression free survival (PFS) was 4.7 mos and median overall survival (OS) was 8.5 mos
- Median duration of response was 14.5 mos with a median not reached (NR) for pts who achieved a complete remission (CR), but only 2.3 mos for pts who achieved a partial remission (PR)

CAR-T for Richter's Transformation: A Retrospective Study

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Results and Adverse Events:

- 39 pts died:
  - 28 (72%) died due to progression of disease (PD)
  - 11 (28%) died for other reasons including
    - 8 infections (4 COVID)
    - 1 septic shock
    - 1 stroke
    - 1 respiratory failure
- 3 pts in a CR underwent allogeneic stem cell (bone marrow transplant from someone else (ASCT), 2 were alive at last known follow up, 1 died post transplant of progressive disease
- 55 (89%) pts had CRS, with 9 (15%) grade ≥3 events. 43 (69%) pts had neurotoxicities (ICANS), with 23 (38%) grade ≥3 events

CAR-T for Richter's Transformation: A Retrospective Study

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Conclusions:

- Largest cohort studied with RT who received CD19 CART
- Earlier use of CD19 CART in the RT might yield better results
- Follow-up with transplant seems to improve outcomes
- CART combinations with novel agents are in trials now
- RT remains a major unmet need, though these results are better than historical results with chemoimmunotherapy

Pirtobrutinib in Richter Transformation

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Pirtobrutinib in Richter Transformation: Updated Efficacy and Safety Results with 18-Month Median Survival Follow-up from the Phase 1/2 BRUIN Study (Dr. William G. Wierda)

- Richter transformation (RT) occurs in up to 10% of CLL patients
- Poor prognosis with no standard of care so often a clinical trial is the best option
- Updated data from the Bruin trial on use of pirtobrutinib in RT

Pirtobrutinib in Richter Transformation

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Results:

- Among all pts with RT (N=82) the median age was 67 and the median total number of lines of prior therapy was 4
- Overall response rate (ORR) was 50.0% including complete (13.4%, n=11) and partial (36.6%, n=30) responses
- For 61 pts who received prior covalent BTKi (cBTKi) such as ibrutinib, acalabrutinib, and zanubrutinib), the ORR was 45.9%
- At median follow-up time of 9.7 months, the median duration of response (DoR) for all 82 RT pts was 7.4 months
- Eight pts stopped pirtobrutinib to pursue a ASCT (bone marrow transplant from someone else) with the intent to cure

Pirtobrutinib in Richter Transformation

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Adverse Events:

- Low neutrophil count (29.3%, n=24), fatigue (24.4%, n=20) and diarrhea, shortness of breath, low platelet count, and fever (18.3% each, n=15)
- Only 3 had hypertension and 1 had atrial fibrillation
- No one stopped pirtobrutinib due to an adverse event

Conclusions:

- Pirtobrutinib is well tolerated and has some activity in RT
- Better treatments for RT are needed

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Nicole Lamanna, MD

January 29, 2024

Abstracts:

- 202 Extended Follow-up of ALPINE Randomized Phase 3 Study Confirms Sustained Superior Progression-Free Survival of Zanubrutinib Versus Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma (R/R CLL/SLL). *Brown JR, Eichhorst B, Lamanna N, et al.*
- 325 Pirtobrutinib in Post-cBTKi CLL/SLL: ~30 Months Follow-up and Subgroup Analysis With/Without Prior BCL2i from the Phase 1/2 BRUIN Study. *Woyach J, et al.*
- 631 FLAIR: Improved Outcomes With MRD-Directed Ibrutinib-Venetoclax Over FCR in Untreated CLL. *Hillmen P, et al.*

Targeted Therapy: FDA Approvals

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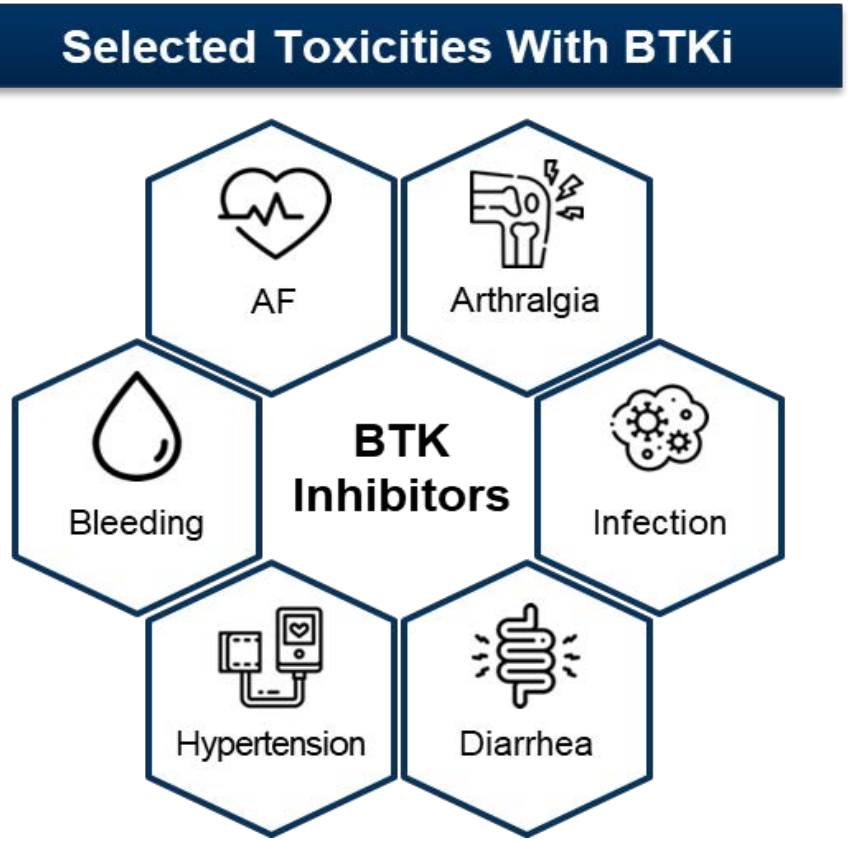
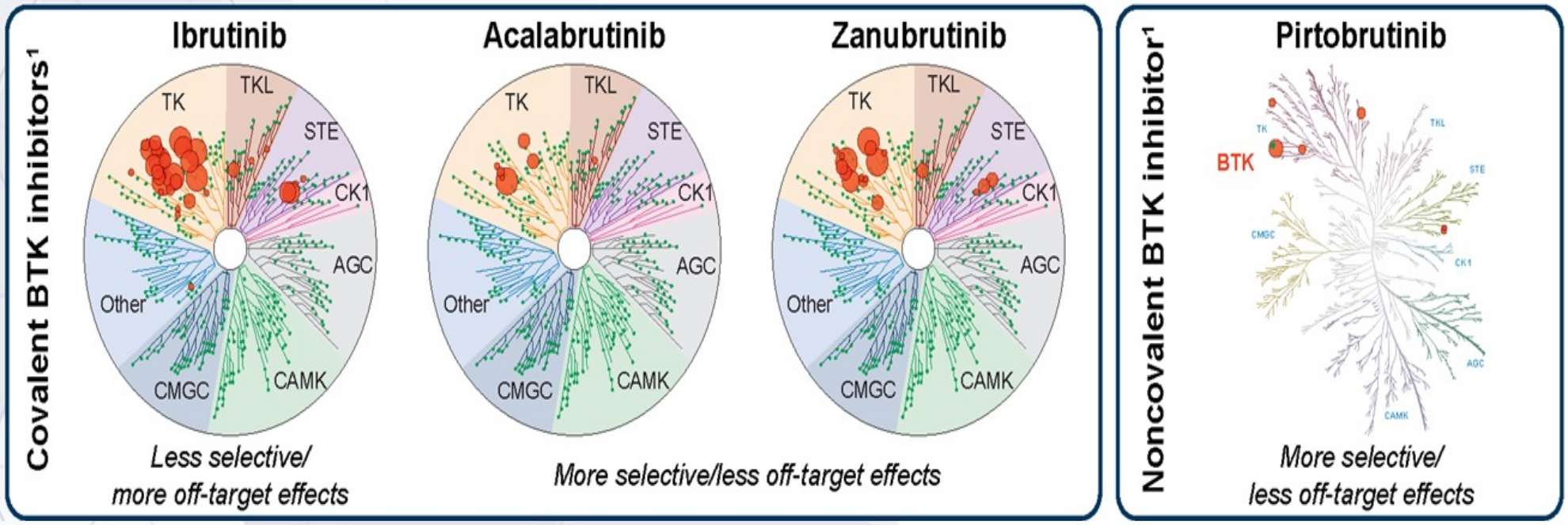
Agent	Target	Status in CLL/SLL
Ibrutinib[1]	BTK (covalent)	Approved
Acalabrutinib[2]		Approved
Zanubrutinib[3]		Approved
Venetoclax[4]	BCL2	Approved
Pirtobrutinib[5]	BTK (noncovalent)	December 2023: Approved for patients receiving ≥prior lines of therapy, including a BTKi and a BCL2i

Summarizing the Safety Experience With BTKi



1. Lipsky A, Lamanna N. *Hematology Am Soc Hematol Educ Program.* 2020;1:336-345

What Are the Implications of Covalent and Noncovalent BTKi Selectivity for Off-Target Effects?



Less selective BTK inhibitors (eg, ibrutinib) have more off-target effects, which contribute to more toxicity compared with more selective agents[2]

Potential off-target effects include:

Abstract 202: Alpine Follow-Up Zanubrutinib

ALPINE Study Design

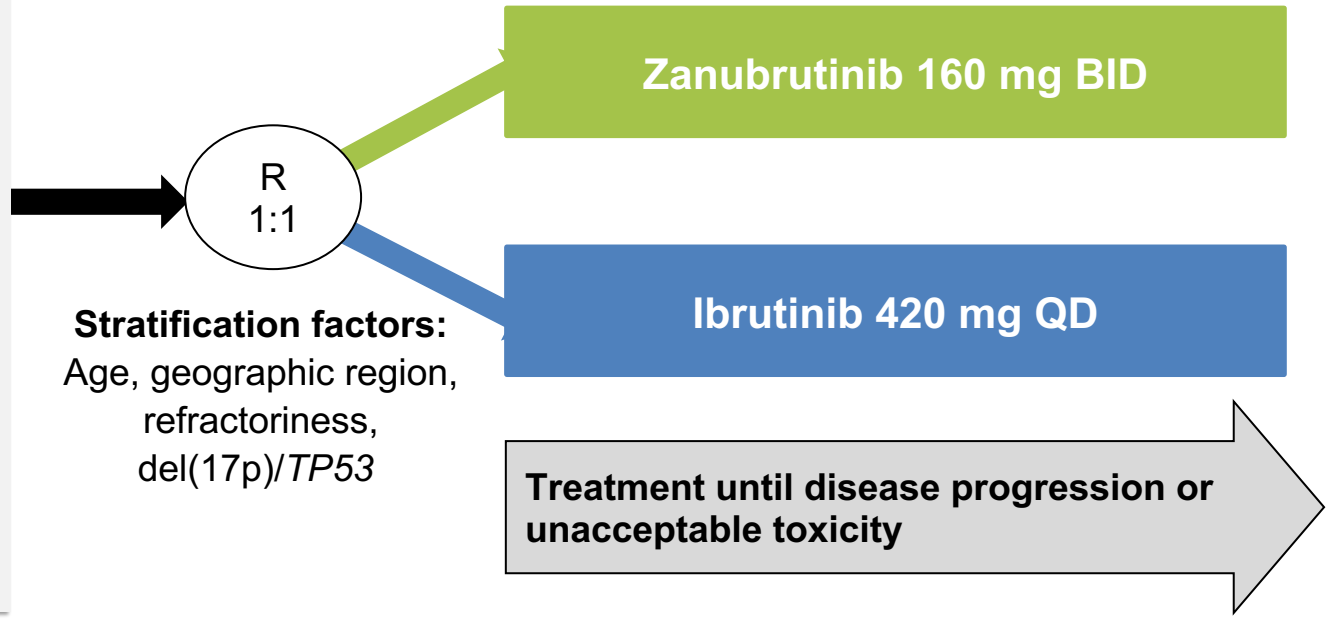
R/R CLL/SLL with ≥1 prior treatment
(N=652)

Key Inclusion Criteria

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

Key Exclusion Criteria

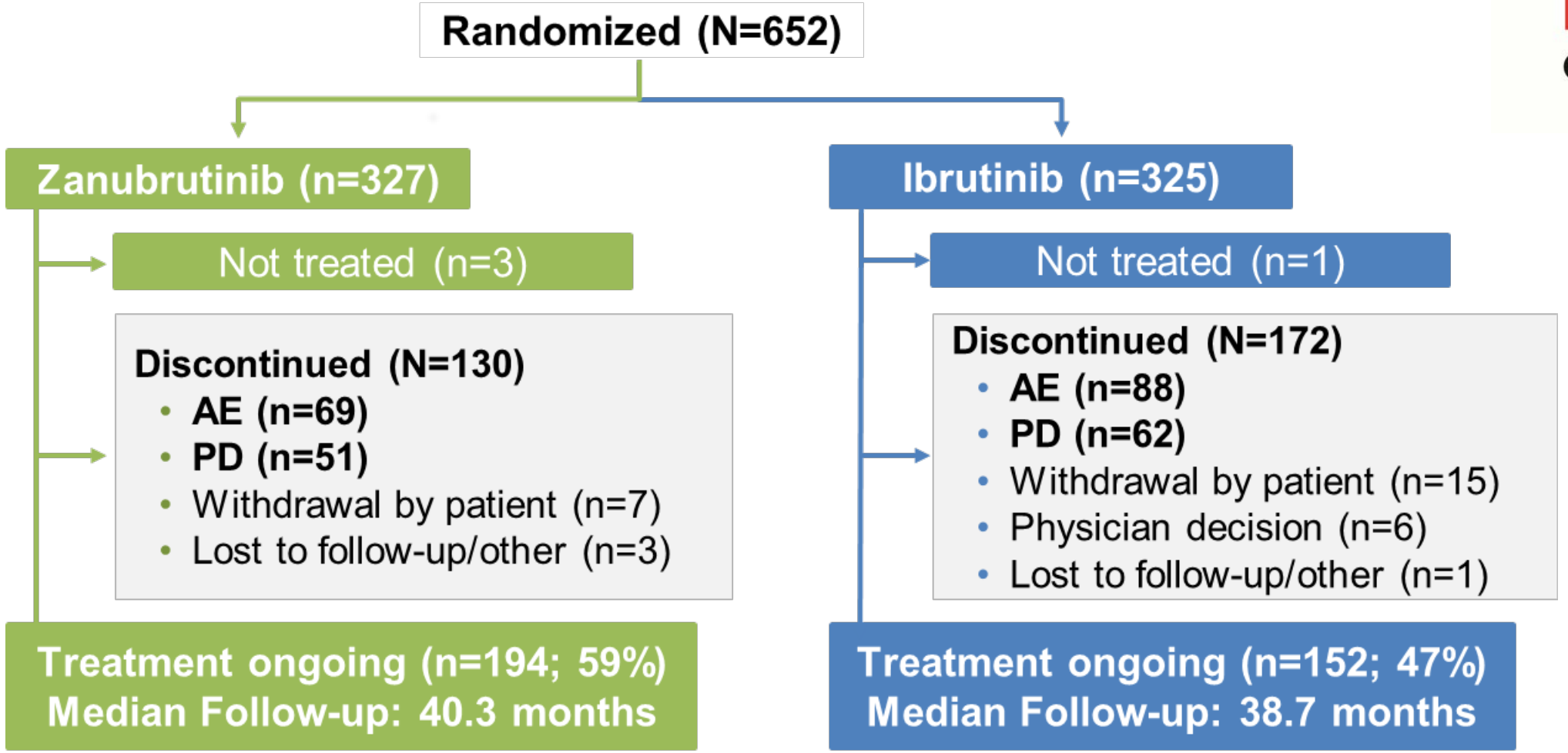
- Prior BTK inhibitor therapy
- Treatment with warfarin or other vitamin K antagonists



Brown JR, Eichhorst B, Hillmen P, et al. *N Engl J Med*. 2023;388:319-332.

Abbreviations: BID, twice daily; CT, computed tomography; MRI, magnetic resonance imaging; QD, once daily; R, randomized.

Patient Disposition At Extended Follow-Up



AE= Adverse Events
PD = Progressive Disease

Brown J, et al. ASH Annual Meeting. 2023: Abstract 202.

Zanubrutinib Demonstrates Sustained PFS Benefit Over Ibrutinib

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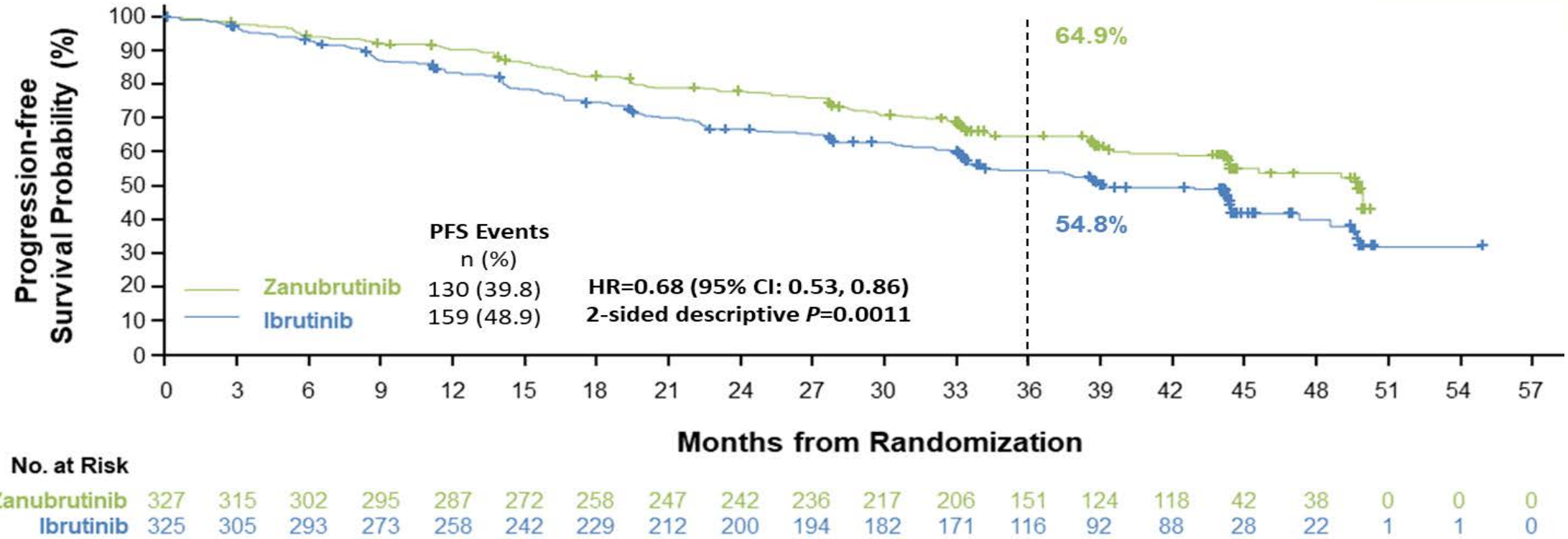
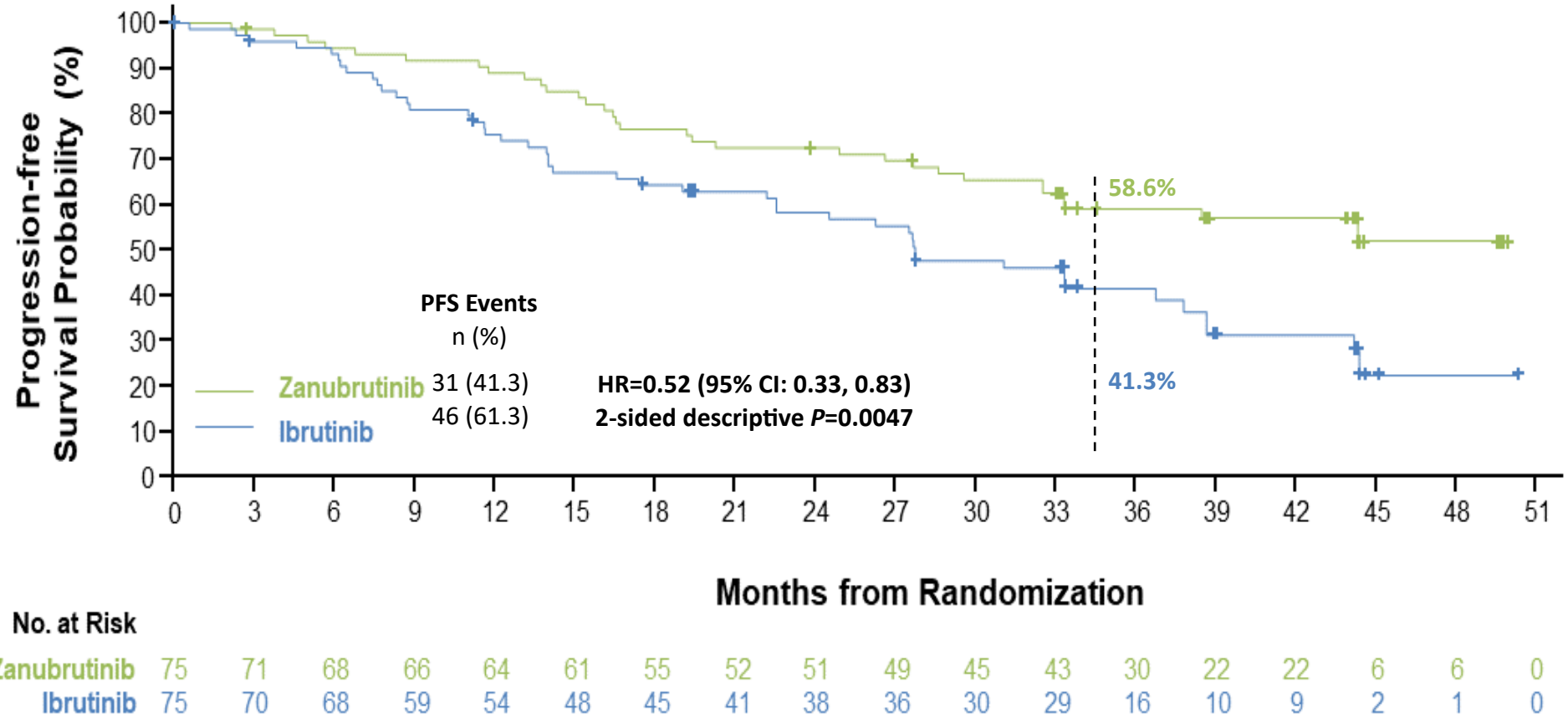
Across arms, median study follow-up was 39 months



Progression Free Survival (PFS): refers to the time from randomization or initiation of treatment to the occurrence of disease progression or death.

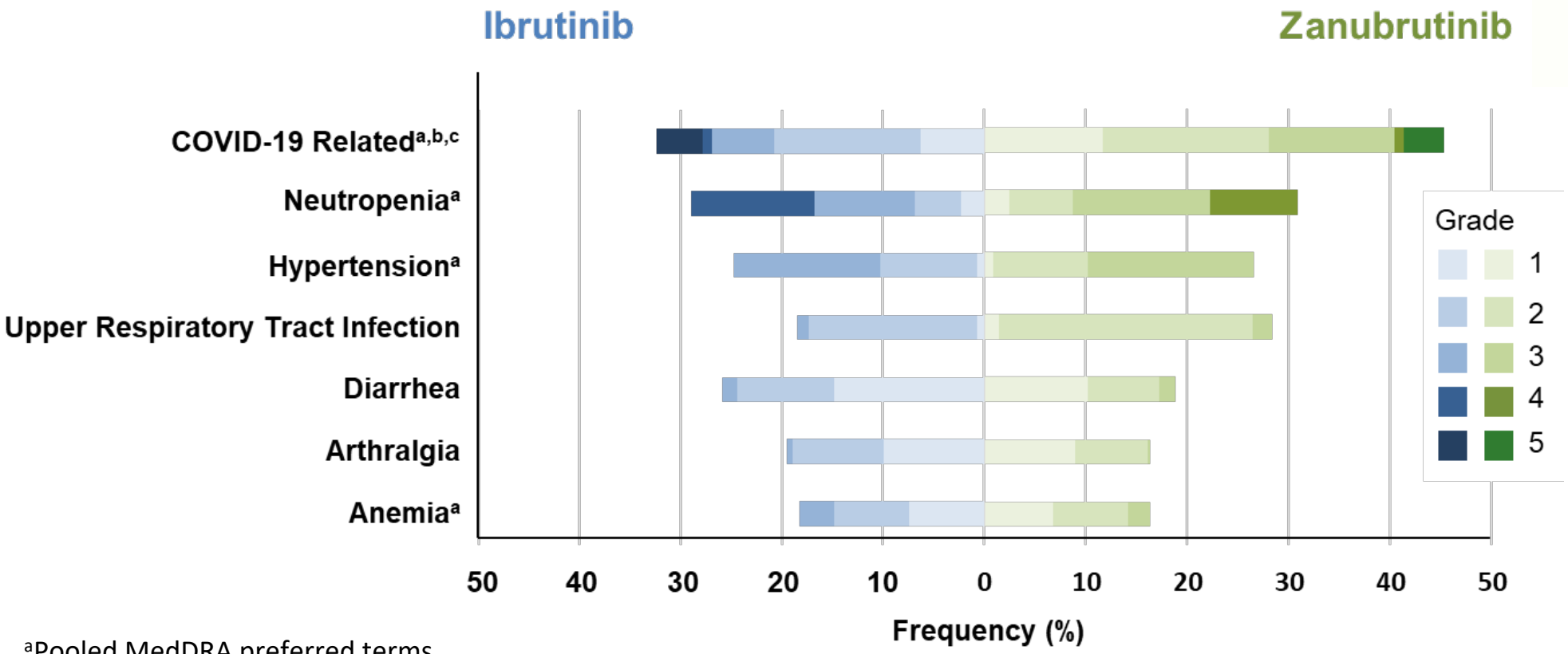
Brown J, et al. ASH Annual Meeting. 2023: Abstract 202.

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



Brown J, et al. ASH Annual Meeting. 2023: Abstract 202.

Most Common Adverse Events (AE)



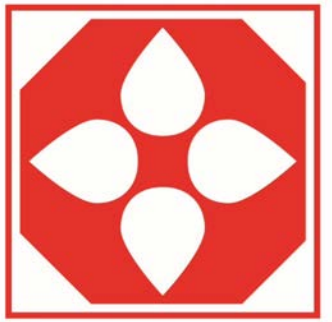
[a]Pooled MedDRA preferred terms

[b]Includes preferred terms of COVID-19, COVID-19 pneumonia, and suspected COVID-19.

[c]**COVID-related deaths** (grade 5 AE): 13 (4.0%) with zanubrutinib and 15 (4.6%) with ibrutinib.

Brown J, et al. ASH Annual Meeting. 2023: Abstract 202.

Zanubrutinib Continues to Demonstrate a Favorable Cardiac Safety Profile



- Serious cardiac adverse events were lower with zanubrutinib vs ibrutinib
  - Atrial fibrillation/flutter (3 vs 13)
  - Ventricular fibrillation/ supraventricular tachycardia (0 vs 4)
  - MI/ACS (2 vs 3)
- **Fatal cardiac events:**
  - **Zanubrutinib, n=0 (0%)**
  - **Ibrutinib, n=6 (1.9%)**

	Zanubrutinib (n=324)	Ibrutinib (n=324)
Cardiac adverse events	**80 (24.7)**	**112 (34.6)**
Serious cardiac adverse events	**11 (3.4)**	**31 (9.6)**
Cardiac adverse events leading to treatment discontinuation	**3 (0.9)**	**15 (4.6)**
Ventricular extrasystoles	1 (0.3)	0
Atrial fibrillation/flutter	1 (0.3)	6 (1.9)
Cardiac failure	1 (0.3)	2 (0.6)
Cardiac arrest	0	2 (0.6)[a]
Cardiac failure acute	0	1 (0.3)[a]
Congestive cardiomyopathy	0	1 (0.3)[a]
Myocardial infarction	0	1 (0.3)[a]
Palpitations	0	1 (0.3)
Ventricular fibrillation	0	1 (0.3)

[a]Cardiac death; 1 death not listed due to myocardial infarction with ibrutinib discontinuation due to diarrhea 14 days prior to the fatal event.

Abbreviations: ACS, acute coronary syndrome; CHF, congestive heart failure; MI, myocardial infarction.

Brown J, et al. ASH Annual Meeting. 2023: Abstract 202.

Conclusions:

- Zanubrutinib continues to demonstrate sustained progression free survival (PFS) superiority over ibrutinib in patients with R/R CLL/SLL with over 39 mos of follow-up
- This advantage also seen in patients with 17p del/TP53 mut
- Although similar rates of hypertension between zanubrutinib and ibrutinib, there was still lower rates of other serious adverse events and fewer adverse events leading to treatment discontinuation or dose reduction
- Similar to ELEVATE-RR study (acalabrutinib vs ibrutinib), less cardiac issues and likely that most patients initiating a BTKi for first time will likely be started on one of these newer BTKis over ibrutinib

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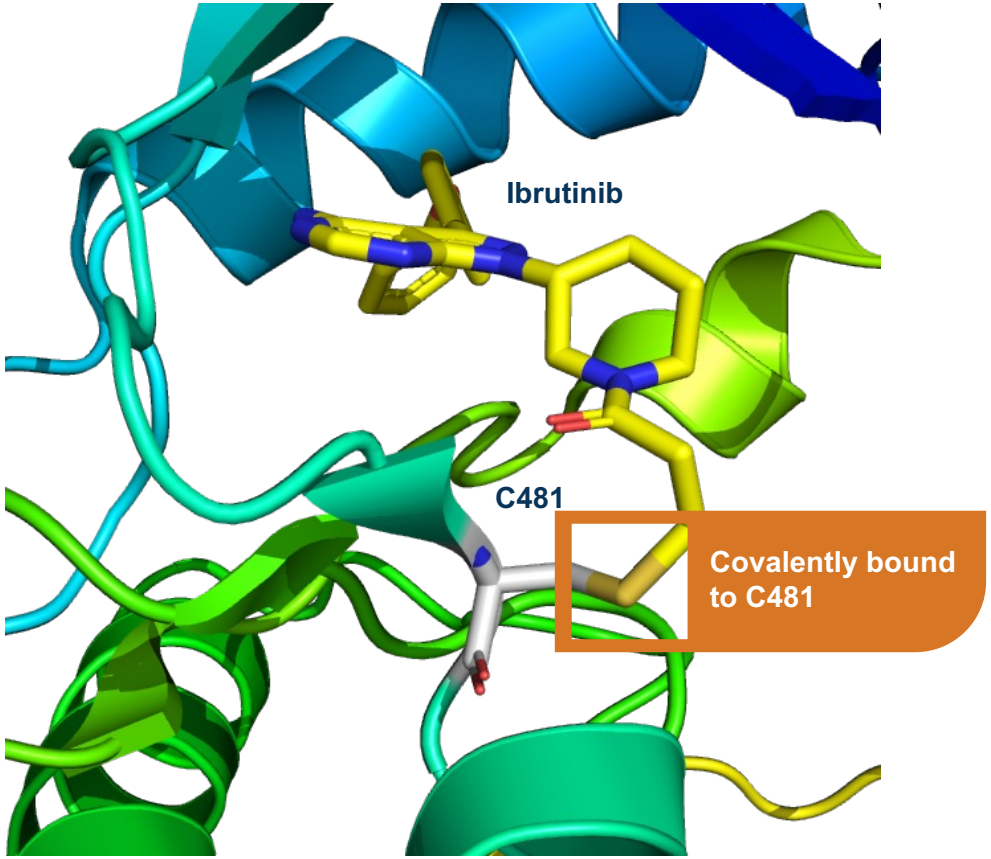
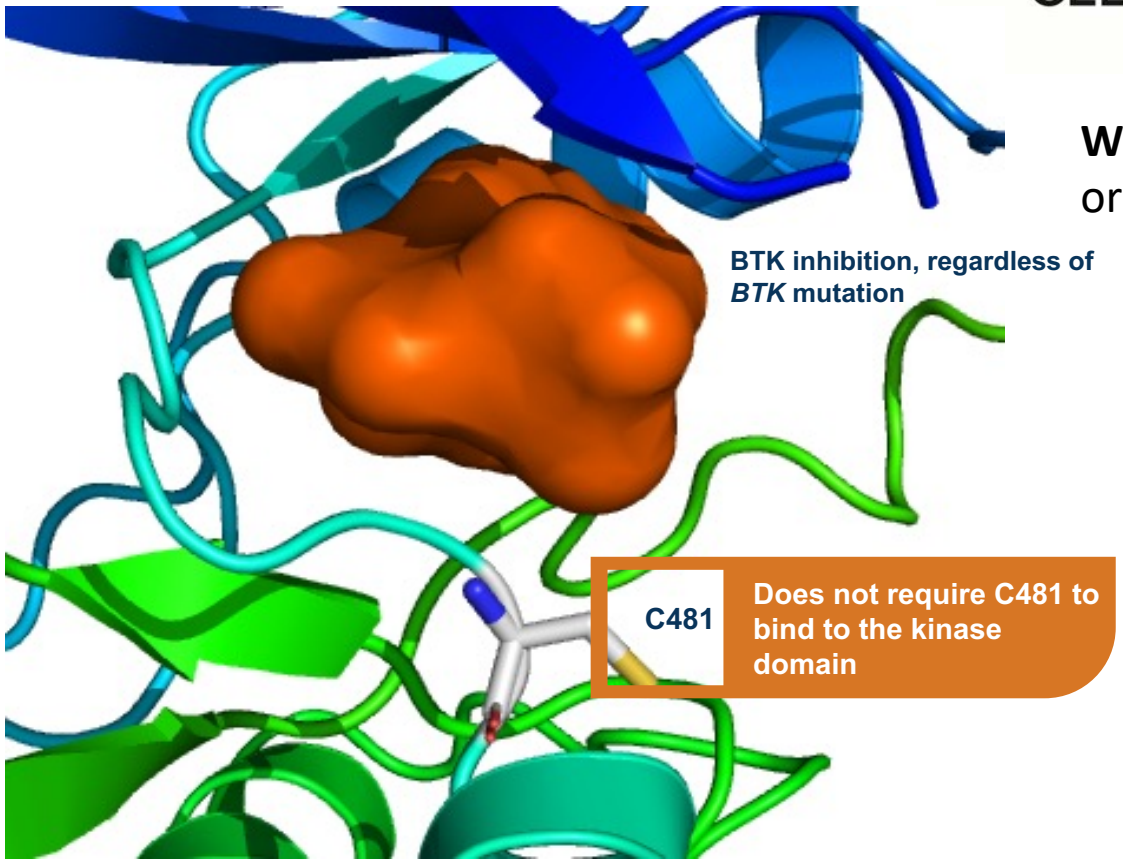
How Noncovalent BTK Inhibitors Overcome Resistance

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



Noncovalent BTK Inhibitors (Pirtobrutinib/Nemtabrutinib) Are Potent Against Both WT and C481-Mutated *BTK*



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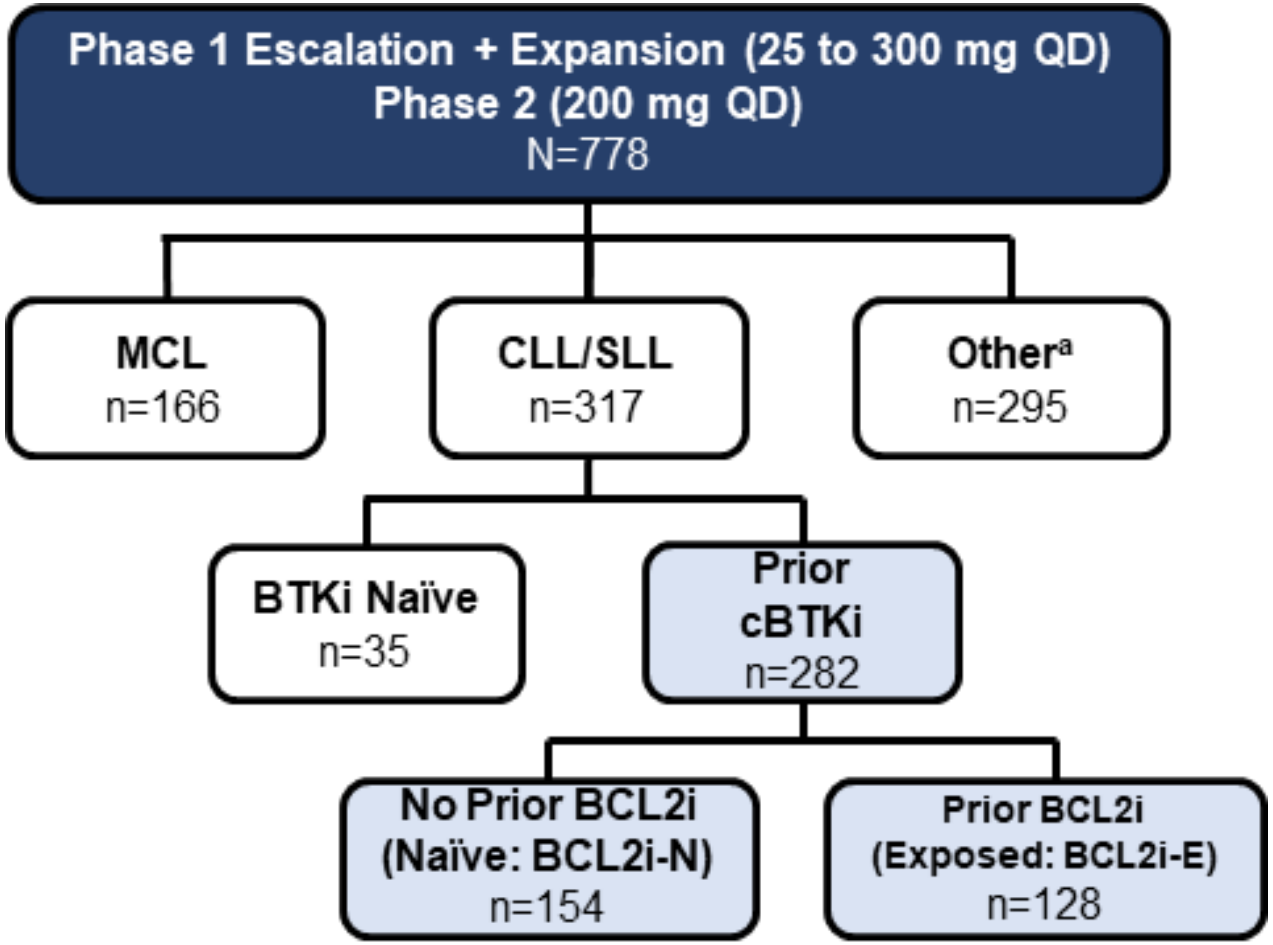
WT = wild type or no mutations

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



MCL = mantle cell lymphoma
cBTKi = covalently binding BTKi (ibrutinib, acalabrutinib and zanubrutinib
BCL2i (only venetoclax now)

BRUIN: Longer (~30 Month) Follow-Up Demonstrates Durable Efficacy of Pirtobrutinib After cBTKi Therapy

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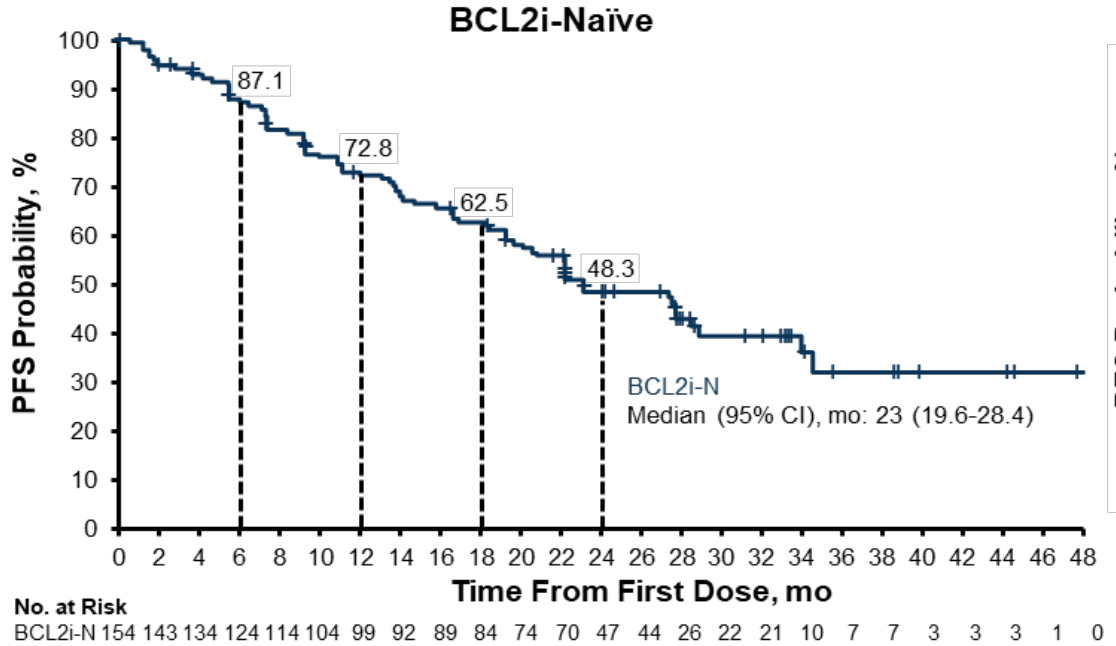
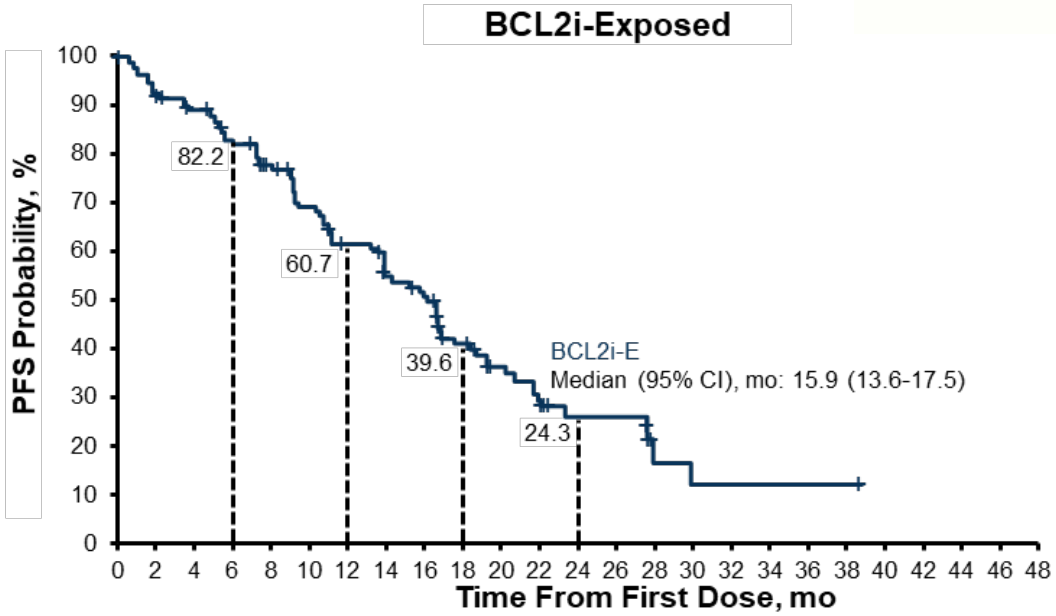
… regardless of prior BCL2i status

ORR for all post-cBTKi patients: 72%





ORR of 83.1% for BCL2i-N patients

Median follow-up 22 months

ORR of 79.7% for BCL2i-E patients

Median follow-up 15.9 months

ORR = overall response rate

Woyach J, et al. ASH Annual Meeting. 2023: Abstract 325.

Pirtobrutinib PFS with Prior cBTKi, with or without Prior BCL2i

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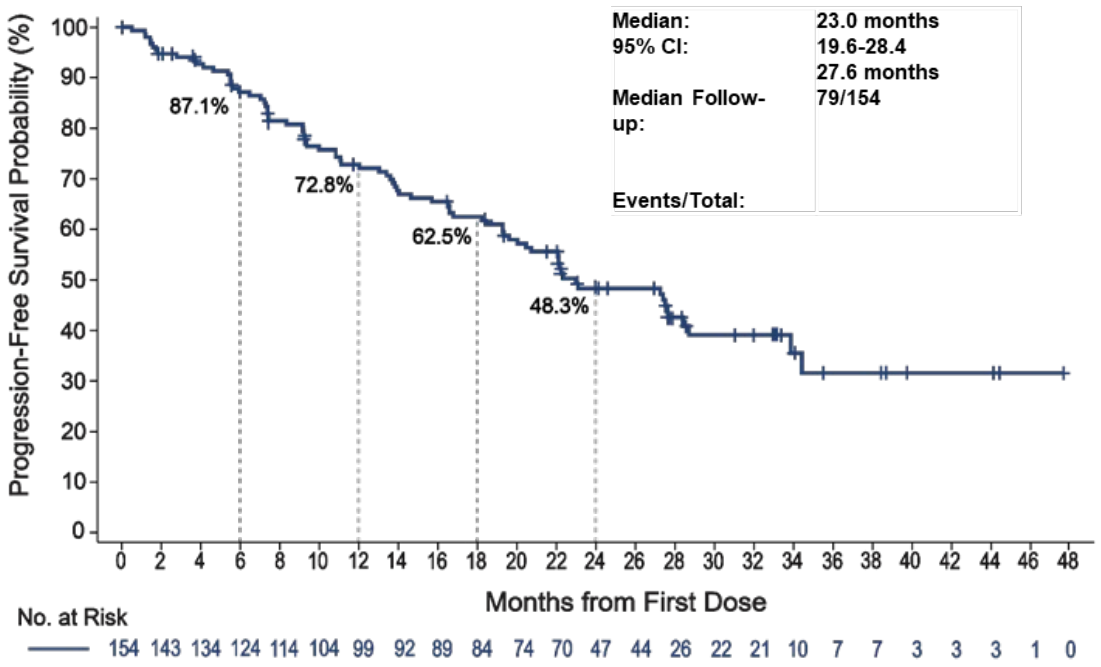
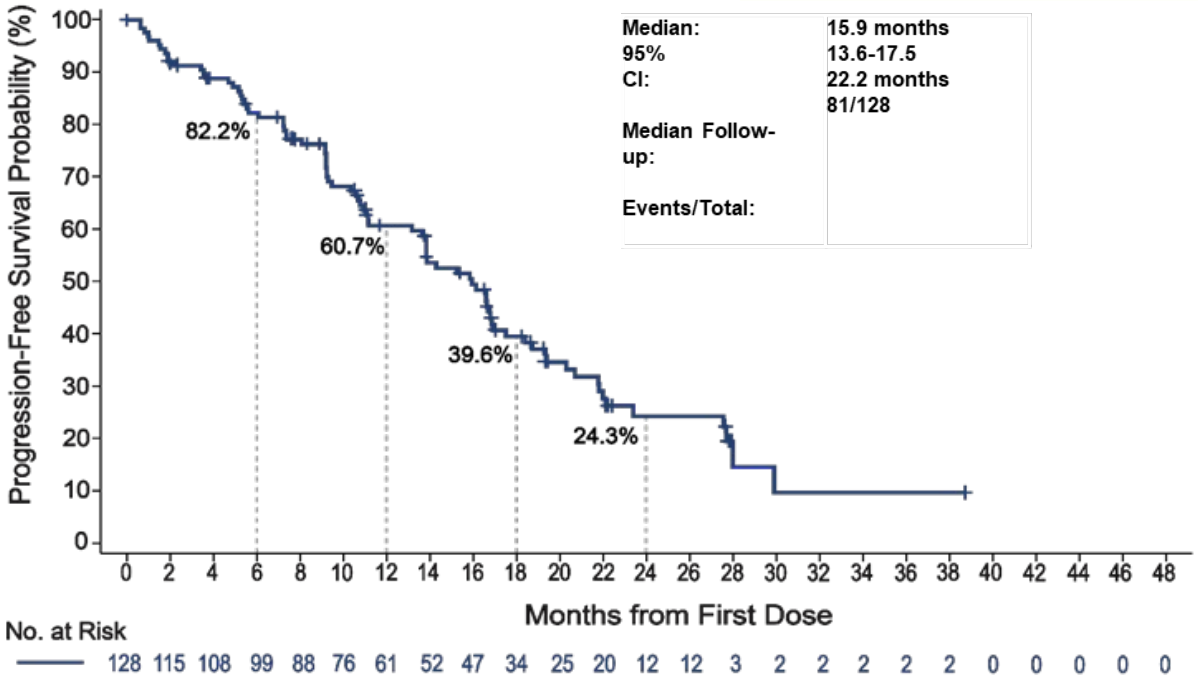
BCL2i-N (naïve)



BCL2i-E (exposed)



Woyach J, et al. ASH Annual Meeting. 2023: Abstract 325.

Conclusions:

- Pirtobrutinib is a very active agent in patients previously exposed to prior covalent BTK inhibitors
- Efficacy also seen in patients who received *both* covalent BTK inhibitors as well as BCL2 inhibitors
- Now FDA approved for this indication
- Very well tolerated with longer follow-up with low rates of cardiac events
- New studies combining pirtobrutinib with BCL2 inhibitors and CD20-monoclonal antibody combinations and in earlier lines of therapy are ongoing

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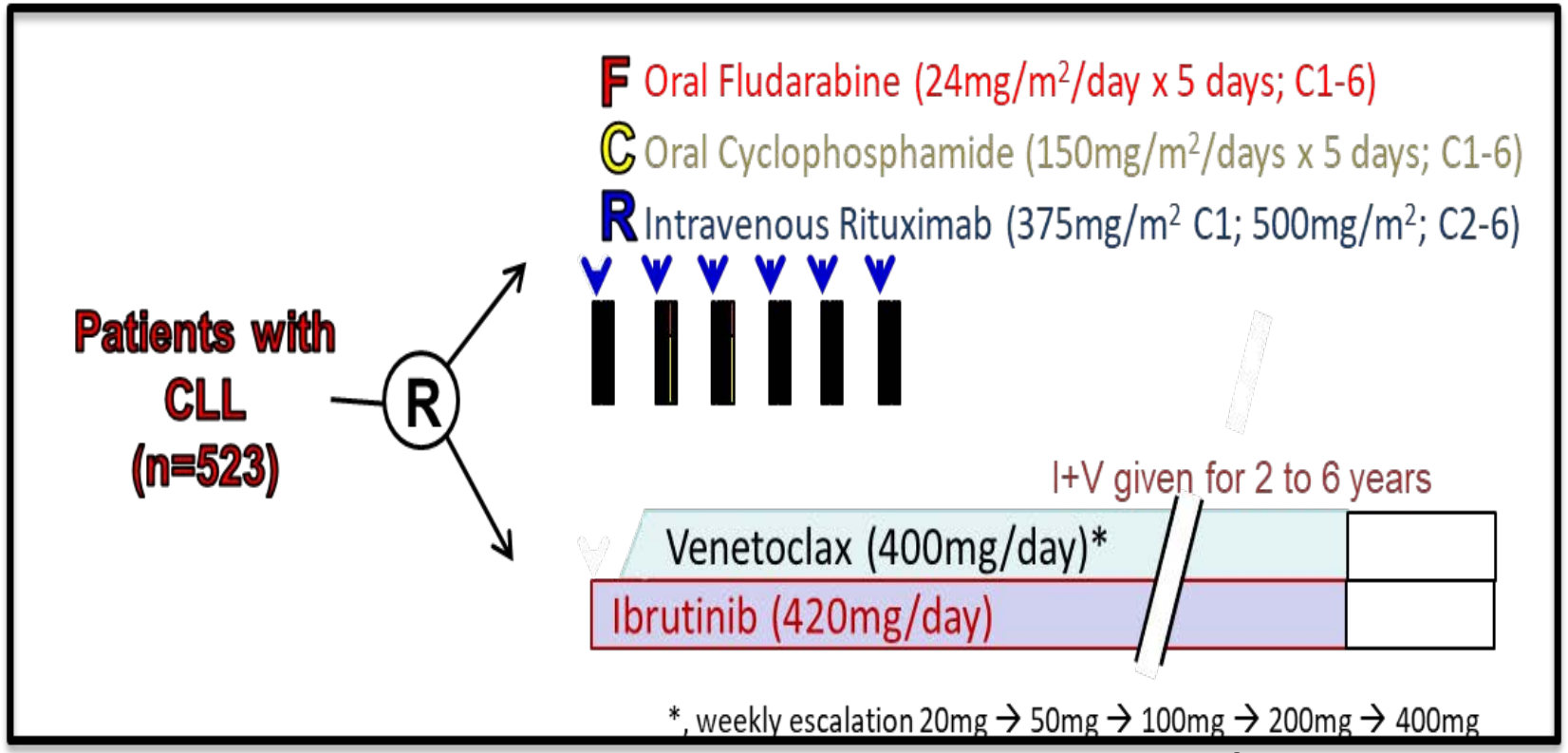
FLAIR: FCR vs I+V: Trial Design



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Primary end-point:
To assess whether I+V is superior to FCR in terms of PFS

Key secondary end-points:
Overall survival (OS)
Response incl. MRD
Safety and toxicity

Key Inclusion Criteria:

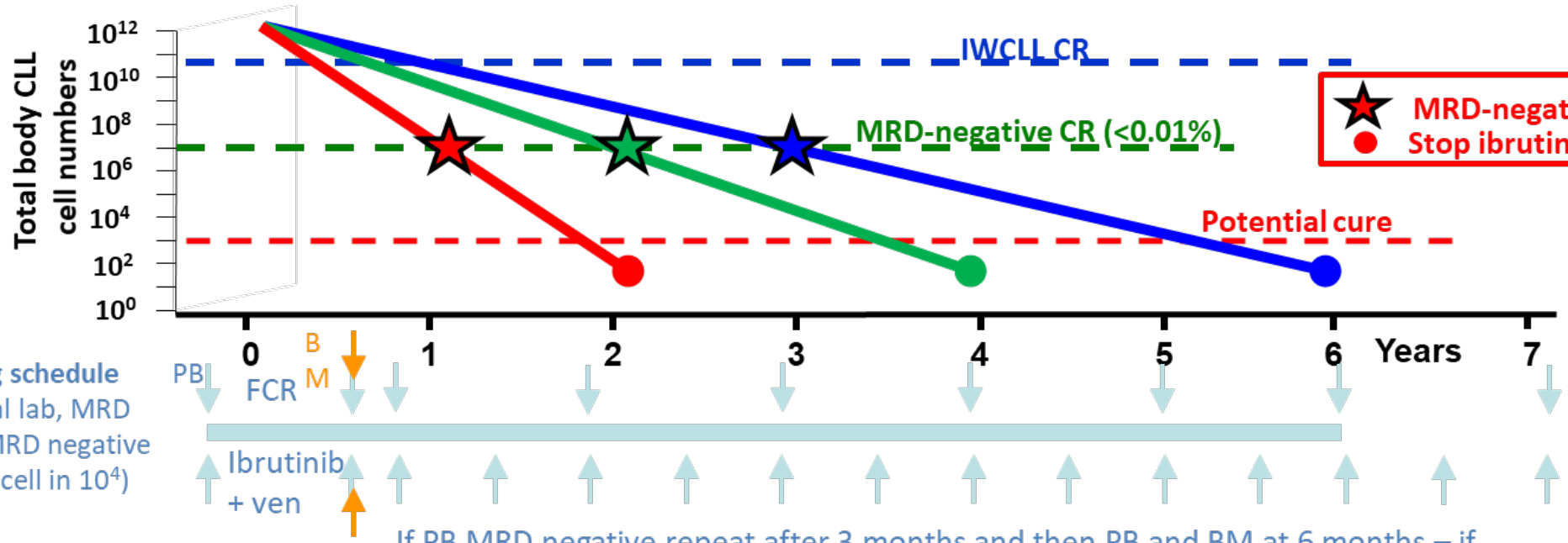
- Previously untreated CLL requiring therapy by IWCLL criteria
- Considered fit for FCR
- ≤75 years old

Key Exclusion Criteria:

- Prior therapy for CLL; History of Richter's transformation;
- >20% TP53 deletion by FISH; Concomitant warfarin (or equivalent)
- Symptomatic cardiac failure or angina

Hillmen P, et al. ASH 2023, Abstract #631

Stopping Rules for Ibrutinib + Venetoclax



Testing schedule
(Central lab, MRD flow, MRD negative <1 CLL cell in 10^4)

If PB MRD negative repeat after 3 months and then PB and BM at 6 months – if all MRD negative then first PB MRD negative result is time to MRD negativity

Defining treatment duration
2 to 6 years Ibrutinib
or both ibr+venetoclax
Double time after MRD negative

Restart ibrutinib + venetoclax if becomes MRD positive prior to Year 6

Hillmen P, et al. ASH 2023, Abstract #631

FLAIR: Improved Outcomes With MRD-Directed Ibrutinib-Venetoclax Over FCR in Untreated CLL

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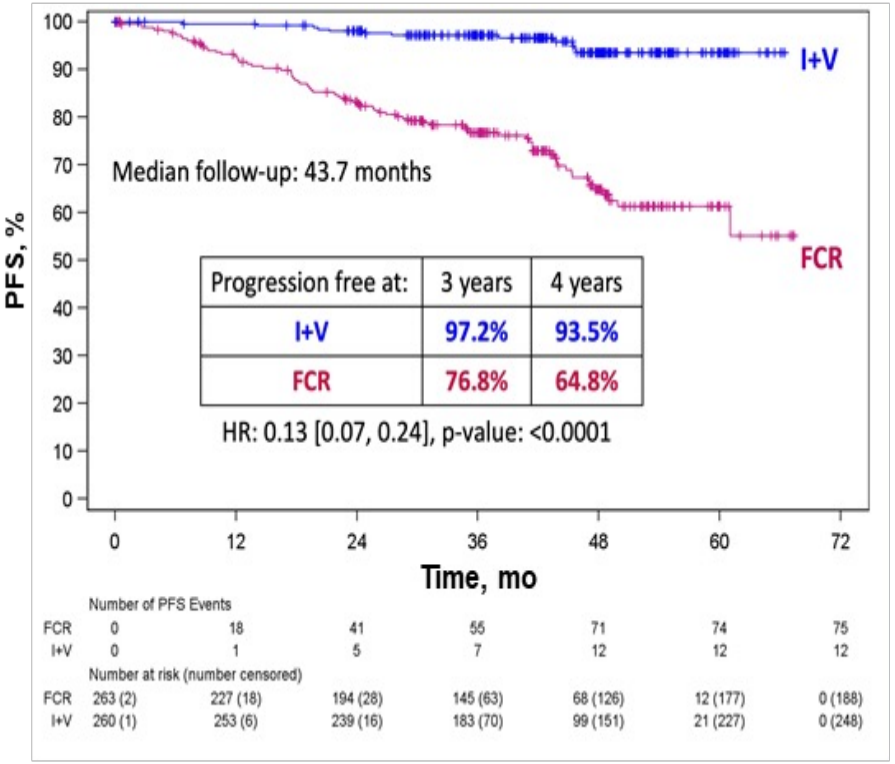
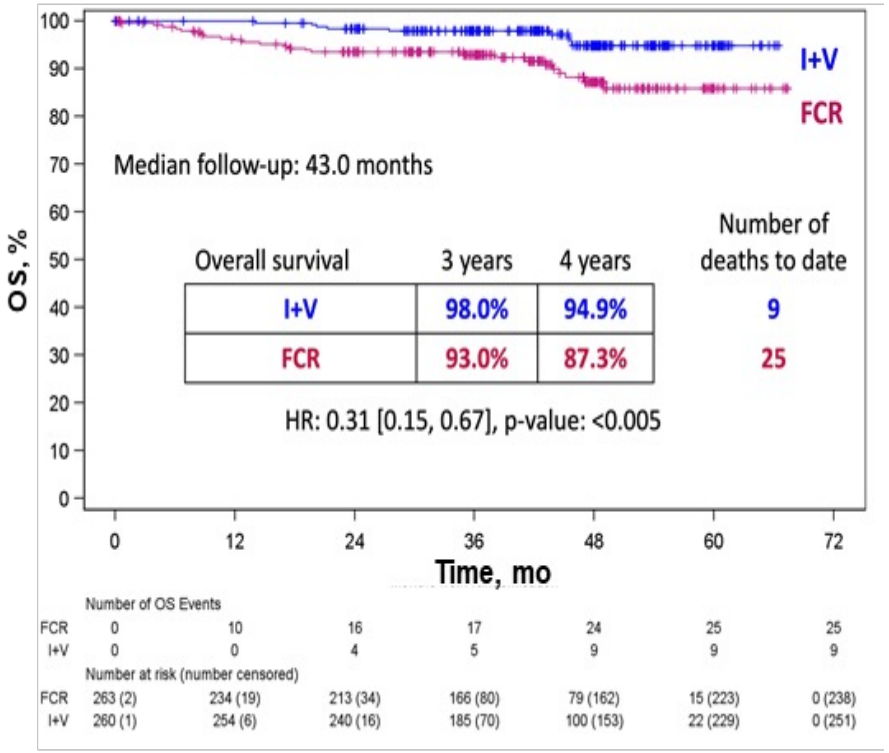
Ibrutinib Plus Venetoclax Significantly Improved PFS and OS Compared With FCR in Untreated CLL[1]

Primary Analysis of PFS in FCR vs I + V



- In I + V after 2 mo of I, V was added with a 4-week dose escalation and then I + V was given for up to 6 years; duration of I + V was defined by MRD (<1 CLL cell in 10,000 using flow)
- PB MRD was assessed regularly[a]
- If all were MRD negative, then the duration of I + V was double the time between start of I + V and the initial MRD-negative PB (I + V duration: 2 to 6 years)

OS in FCR vs I + V



- Using MRD to direct the duration of I + V maximizes outcome with a PFS of 97.2% at 3 years

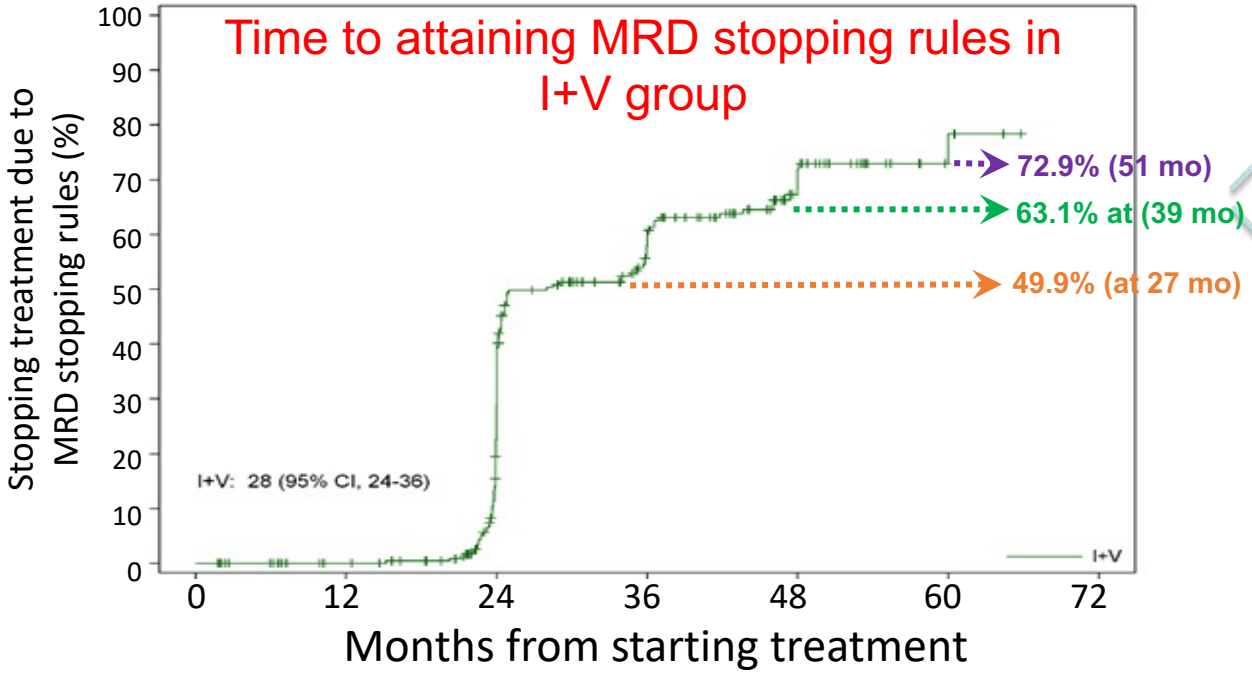
[a] At 12 months and then 6 monthly and if negative, was repeated at 3 mo and 6 mo in PB and BM.

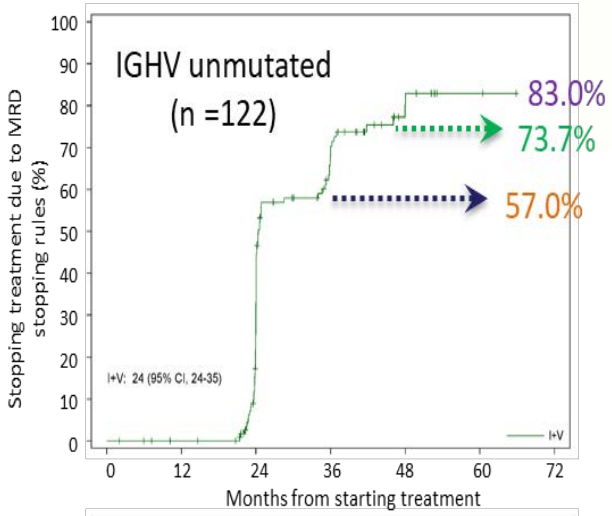
1. Hillmen P et al. ASH 2023. Abstract 631.

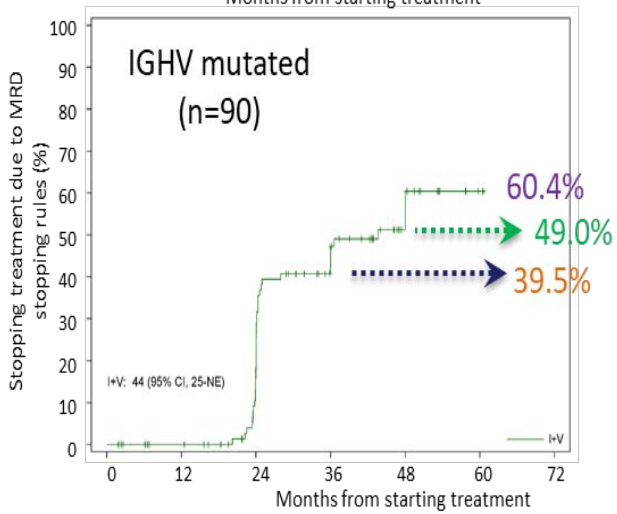
iwCLL Response and MRD Stopping Rules

iwCLL Responses

	Complete Response/CRi		Overall Response		BM uMRD
	9 months	Anytime	9 months	Anytime	Anytime
FCR	49%	71.5%	76.4%	83.7%	40.3%
I+V	59.2%	92.3%	86.5%	95.4%	61.9%







Kaplan–Meier estimates of the percentage of patients who had stopped treatment by specific time points are as follows:
by 24 months, 28.9%
by 36 months, 58.0%
by 60 months, 78.4%.

Five patients restarted ibrutinib–venetoclax and were alive and progression-free at the last follow-up.

Hillmen P, et al. ASH 2023, Abstract #631

Conclusions:

- MRD-guided ibrutinib–venetoclax was superior to FCR with respect to progression-free survival (97.2% vs. 76.8% at 3 years)
- Overall survival also favored ibrutinib–venetoclax over FCR (98.0% vs. 93.0% at 3 years)
- These results appear better than those in previous studies of ibrutinib monotherapy or venetoclax, as monotherapy or in combination with anti-CD20
- This study raises more questions about what is “time-limited” when utilizing MRD guided approaches to individualize patient care/outcomes. More work to be done….

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