Fred Hutch Cancer Center

Chronic Lymphocytic Leukemia and Hairy Cell Leukemia

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Fred Hutchinson Cancer Center and University of Washington

Hematology/Oncology Fellows Core Lecture Series
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Disclosures

Consulting, advisory boards, steering committees or data safety monitoring committees: Abbvie, Genentech, AstraZeneca, Genmab, Janssen, Beigene, Bristol Myers Squibb, Morphosys/Incyte, Kite Pharma, Eli Lilly, Fate therapeutics, Nurix and Merck.

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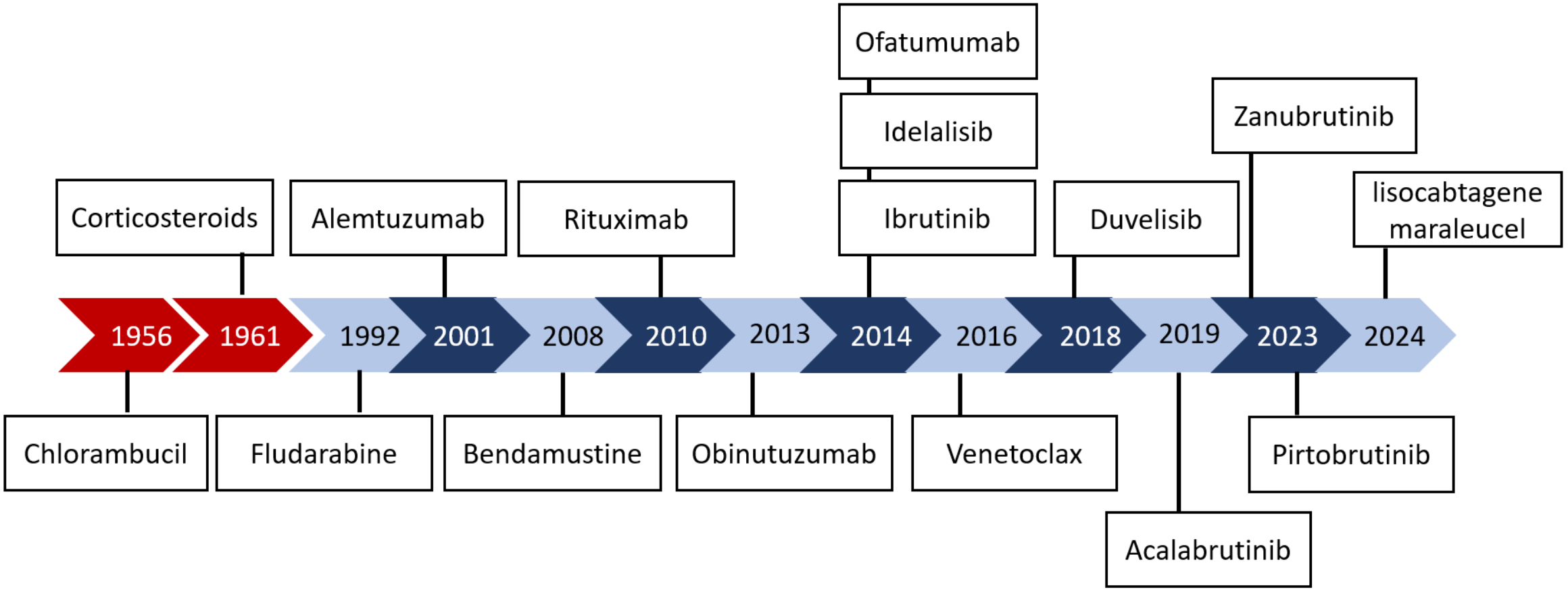
Stock options: Koi Biotherapeutics.

CLL/SLL

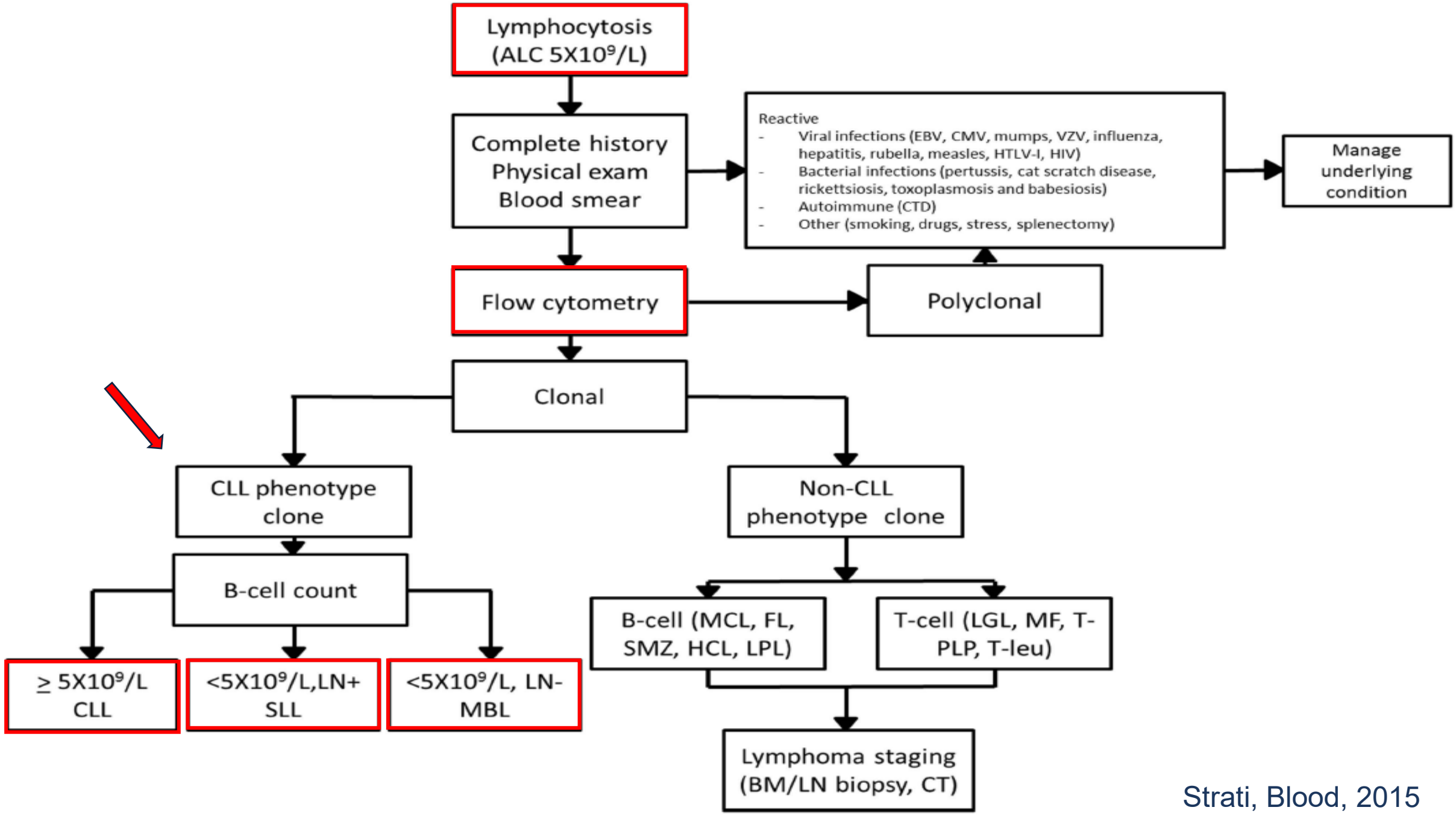
Treatment Options for CLL/SLL



Epidemiology

- CLL/SLL is the most common leukemia in adults in western countries
  - 4.5 cases per 100,000
- Median age ~ 70 years
- Slight male predominance (1.7:1)
- Familial risk (7-8 fold)
- Caucasians > African Americans > Asian Pacific Islanders
- Genetic > Environmental

Initial diagnosis and appropriate work-up



Strati, Blood, 2015

Immunophenotypic Features

	CD5	CD10	CD23	CD103	BCL6	CD20	Cyclin D1
CLL/SLL	+	-	+	-	-	+ (weak)	-

Immunophenotypic Features

	CD5	CD10	CD23	CD103	BCL6	CD20	Cyclin D1
CLL/SLL	+	-	+	-	-	+ (weak)	-
MCL	+	-	-	-	-	+	+
LPL	-	-	-	-	-	+	-
sMZL	-	-	-	-	-	+	-
FL	-	+/-	-/+	-	+	+	-
HCL	-	-	-	+	-	+	+/-

	CD23	Cyclin D1	t(11,14)
CLL/SLL	+	-	-
MCL	-	+	+

MBL (monoclonal B cell lymphocytosis)

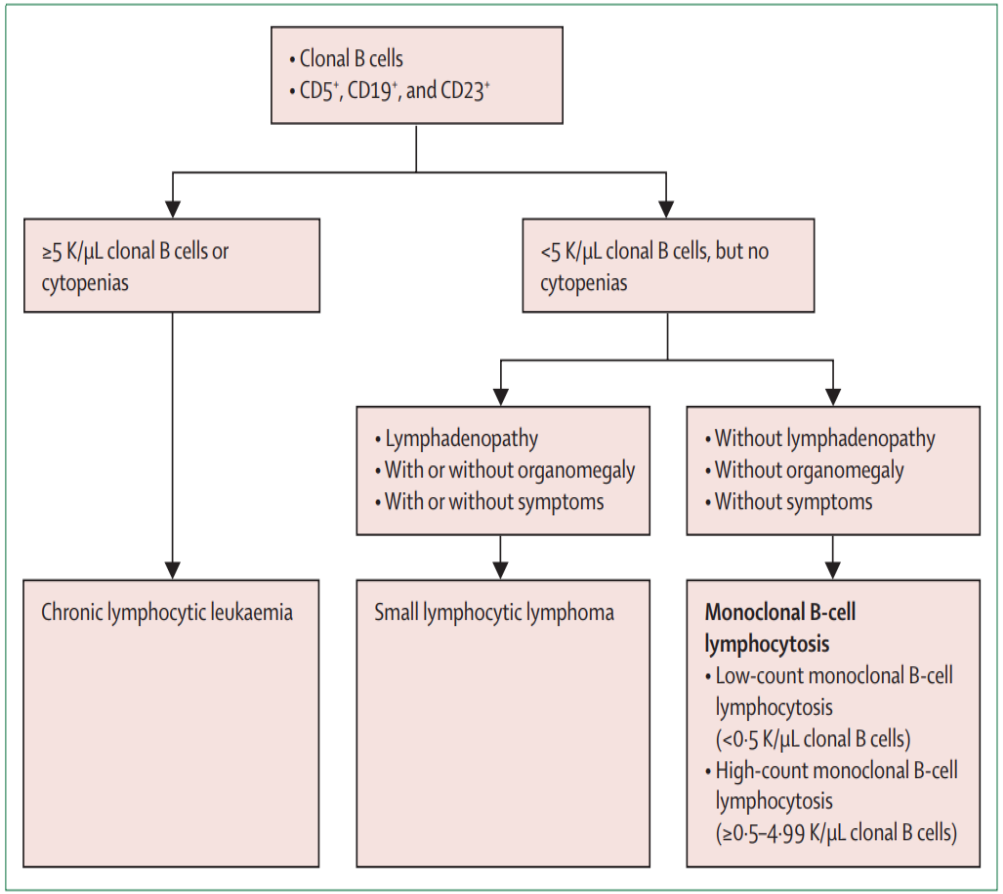
- < 5x 10^9/L monoclonal B- cells in the PB AND no lymphadenopathy

- Almost all cases of CLL are preceded by MBL but only a small percentage of persons with MBL will ultimately develop CLL

- **Low-count MBL (< 0.5x 10^9/L) ➔ rarely progresses to CLL**
  - No need for hematology follow-up
  - Higher risk for serious infections
  - OS similar to general population
- **High-count MBL (0.5-4.9 x 10^9/L) ➔ progresses to CLL at a rate of 1-2% /year**
  - CLL-IPI can predict the risk
  - Higher risk for serious infections and secondary malignancies
  - OS similar to general population

- Up to 17 percent of first-degree family members of patients with CLL were found by flow cytometry to have MBL

- **Screening of family members is NOT recommended**



Jain, Lancet, 2024

WHO-HAEM5 Terminology

- **Monoclonal B-cell lymphocytosis (MBL)**
  - **Low-count MBL or clonal B-cell expansion**: clonal CLL/SLL phenotype B-cell count <0.5 x 10^9 /L with no other features diagnostic of B-lymphoproliferative disorder
  - **CLL/SLL-type MBL**: monoclonal CLL/SLL-phenotype B-cell count ≥0.5 x 10^9 /L and total B-cell count less than 5 x 10^9 /L with no other features diagnostic of CLL/SLL
  - **Non-CLL/SLL-type MBL**: ANY monoclonal non-CLL/SLL phenotype B-cell expansion with no symptoms or features diagnostic of another mature B-cell neoplasm (majority of cases have features consistent with MZL)
- **Chronic lymphocytic leukemia (CLL)**:
  - Monoclonal CLL/SLL-phenotype B-cell count ≥5 x 10^9 /L
  - Cytopenias with marrow infiltration even if monoclonal CLL/SLL-phenotype B-cell count <5 x 10^9 /L
- **Small lymphocytic lymphoma (SLL)**: Monoclonal CLL/SLL-phenotype B-cell count < 5 x 10^9 /L but with evidence of lymphadenopathy
- **B-prolymphocytic leukemia (B-PLL)** is no longer recognized in WHO-HAEM5 in view of its heterogeneous nature.
- **Richter Transformation**: CLL ➔NHL or CLL➔ HL. The term is recommended over “Richter Syndrome”

Alaggio, Leukemia, 2022

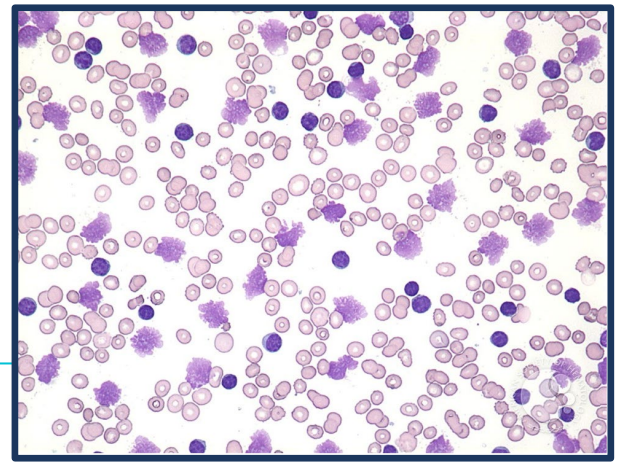
Diagnosis

- **Flow cytometry** of **blood** is **essential and adequate** to make the diagnosis
- Biopsy may be needed if PB flow cytometry is not conclusive
- Cytogenetic and molecular studies are informative for prognostic and/or therapy determination .
- Baseline CT scan (or PET) is **NOT** required for asymptomatic patients

  (The ASH "Choosing Wisely" List)

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

American Board of Internal Medicine



Prognostic and predictive markers

Staging for CLL

Rai staging			Binet staging	
Stage	Risk category	Findings	Stage	Findings
0	Low	Lymphocytosis[a]	A	No cytopenia and ≤2 lymphoid area involvement
1	Intermediate	Lymphadenopathy[b]	B	No cytopenia and >3 lymphoid area involvement
2	Intermediate	Hepatosplenomegaly[b]	C	Presence of anemia or thrombocytopenia
3	High	Anemia[c]		
4	High	Thrombocytopenia[d]		

[a] Lymphocyte count greater than 5×10^9/L.

[b] On physical examination.

[c] Hemoglobin level less than 11 g/dL.

[d] Platelet count less than 100 000/μL

Use Ann Arbor staging for SLL

Molecular Biomarkers for CLL

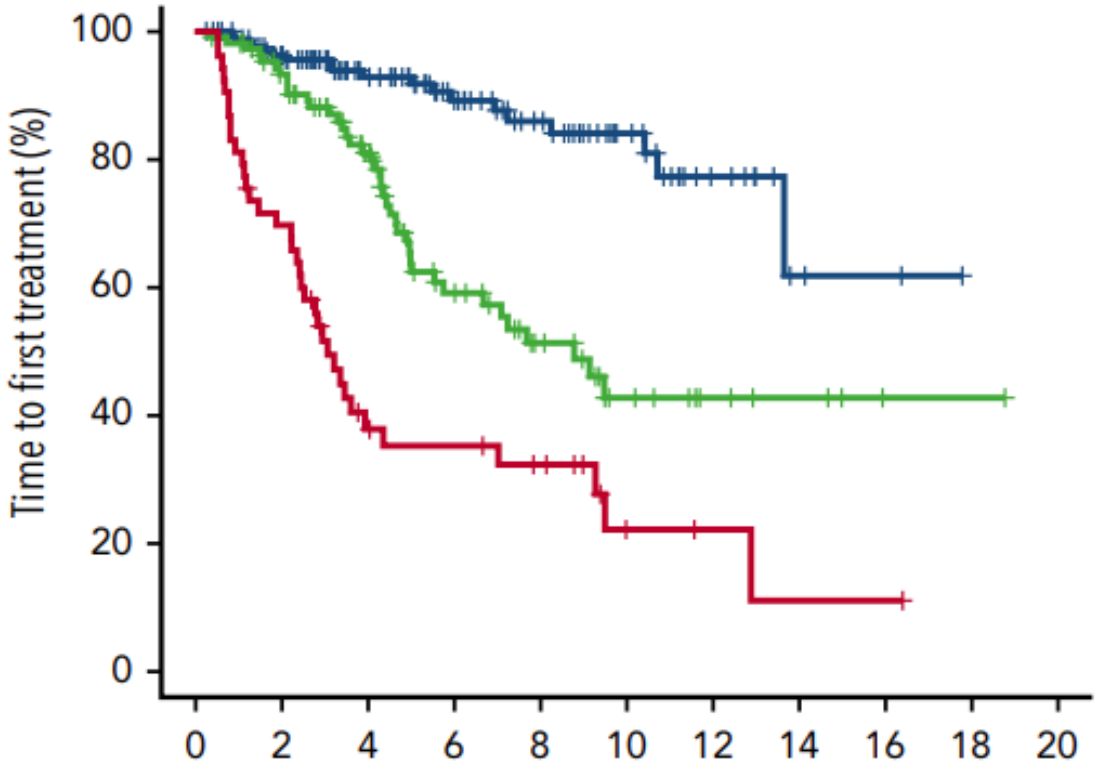
	FISH	Karyotype	Mutations
Unfavorable	del (17p) del (11q)	Complex (>3 abnormalities) (> 5?)	TP53 unmutated IGHV (≤ 2%) * NOTCH-1 SF3B1 BIRC3 ATM
Neutral	Normal +12		
Favorable	del (13q) (sole abnormality)		mutated IGVH (>2%)

* If chemotherapy is used

Time to first treatment (TTFT): IPS-ES

Variable	Point
Unmutated IGHV	1
ALC > 15 x 10^9/L	1
Palpable lymph node	1

Risk category	Score	5-year cumulative risk for treatment start
Low risk	0	8.4%
Intermediate risk	1	28.4%
High risk	2-3	61.2%



Condoluci, Blood, 2020

Impact of Recurrent Gene Mutations on Time to First Treatment

Predictors of shorter time from diagnosis to first treatment

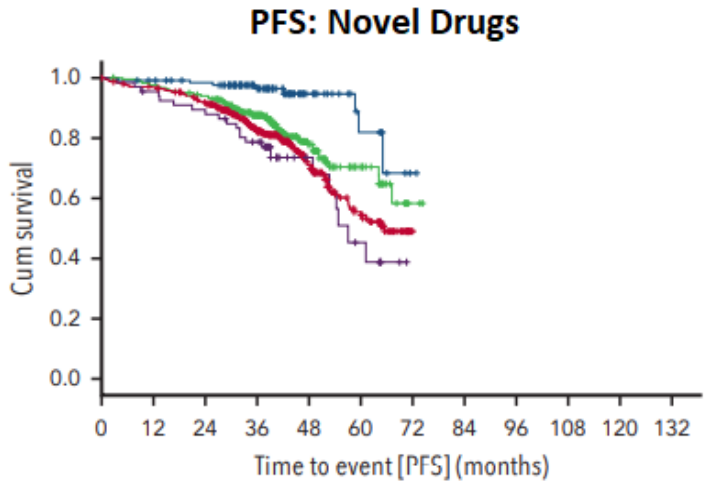
	SF3B1	XPO1	NOTCH1	NFKBIE	TP53	BIRC3	EGR2
Mutated IGHV	X	X	X	X			
Unmutated IGHV	X	X			X	X	X

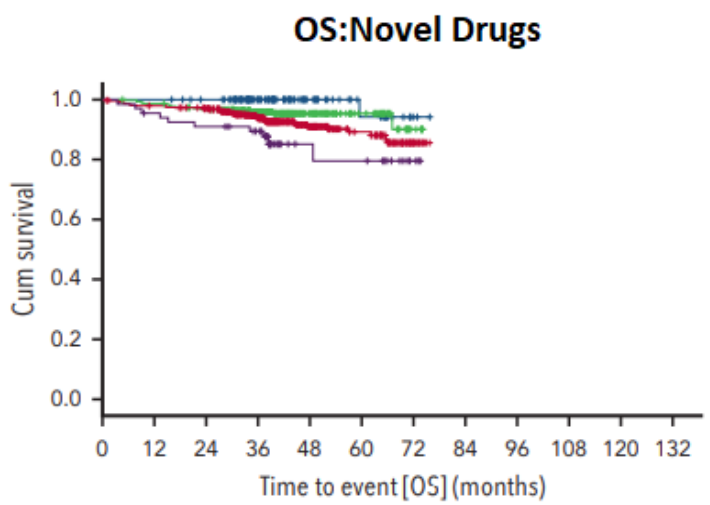
Mansouri, Leukemia,2023

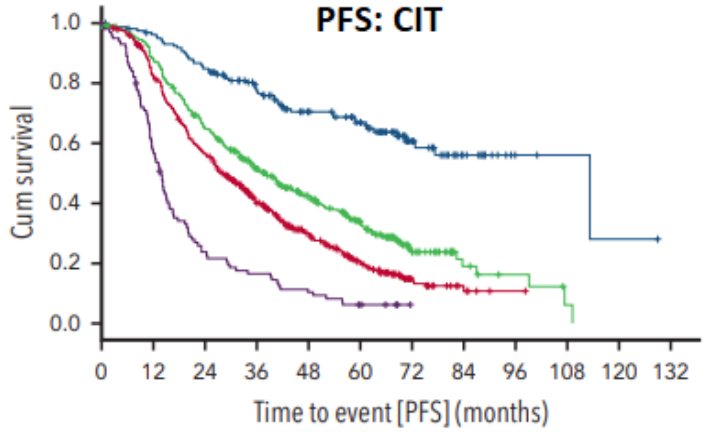
Prognostic Models: CLL-IPI

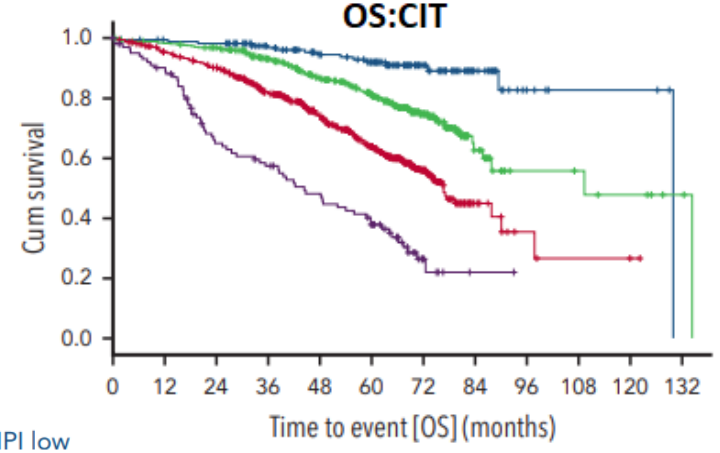
Characteristic	Points
Del(17p) or TP53 mutation	4
Serum beta-2-macroglobulin ≥ 3.5mg/L	2
Un-mutated IgVH	2
Rai Stage I-IV	1
Age > 65 years	1

Points	Risk Group	5-y OS (%)	10-yr OS (%)
0-1	Low	93	79
2-3	Int	79	39
4-6	High	63	22
7-10	Very High	23	4









CLL-IPI low
CLL-IPI intermediate
CLL-IPI high
CLL-IPI very high

Langerbeins, Blood, 2024

Supportive Care

Supportive Care Recommendations

- Avoid live vaccines
- Patients should receive annual influenza vaccine and recombinant zoster vaccine
- The 20-valent pneumococcal conjugate vaccine (PCV20) is recommended in previously unvaccinated patients or those with prior receipt of 23-valent pneumococcal polysaccharide vaccine (PPSV23), 1 year apart
- Patients should be informed that their immune response to vaccinations is lower than that of the general population For COVID-19 vaccination, follow the Centers for Disease Control and Prevention recommendations for patients with moderate and severe immunocompromised state, and protective measures should be continued in high-risk conditions such as viral pandemics
- Consider monoclonal antibodies against COVID-19 (pemivibart, sepivibart)
- Patients with frequent sinus or lung infections who have hypogammaglobulinemia (IgG level <500 mg/dL) benefit from intravenous immunoglobulin infusions every 6 to 8 weeks if the levels remain low
- Age-specific cancer screening guidelines should be followed in patients with CLL
- Patients with CLL have a higher risk for recurrence of basal cell carcinoma and squamous cell carcinoma of skin compared with those without CLL; routine examinations and skin protection measures are recommended
- There is no indication for screening or genetic testing in family members

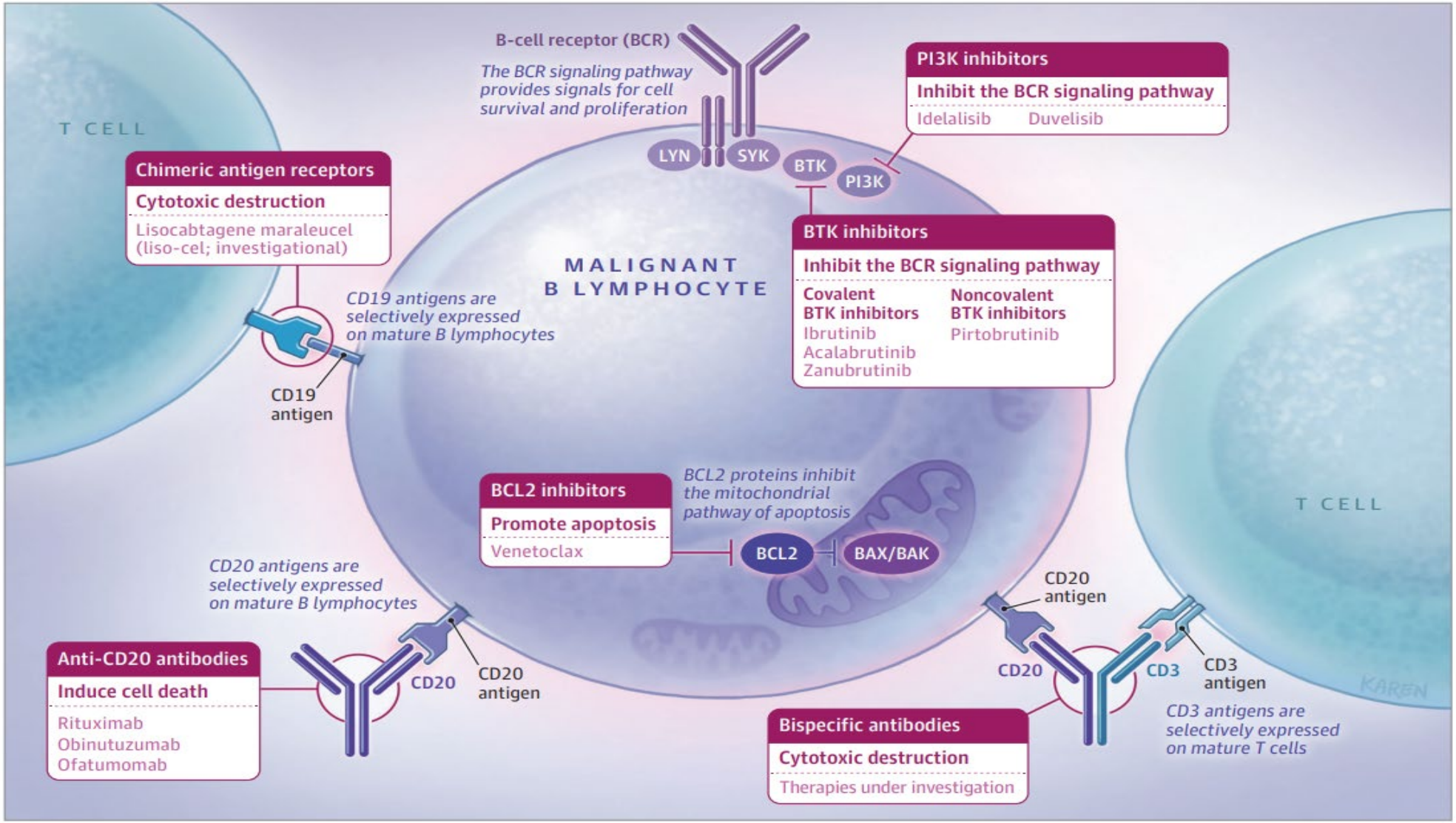
Important therapeutic agents for CLL

What are the approved treatment options?

Chemotherapy	anti-CD20 Abs	BCR inhibitors	BCL-2 inhibitor	CAR-T therapy

• fludarabine
• cyclophosphamide
• bendamustine
• chlorambucil
	• rituximab
	• ofatumumab
	• obinutuzumab
		• **BTK inhibitors**
		• Covalent
		  • acalabrutinib
		  • zanubrutinib
		  • Ibrutinib
		• Non-covalent
		  • pirtobrutinib
		• **PI3K inhibitors**
		  • idelalisib
		  • duvelisib
			• venetoclax	• lisocabtagene maraleucel

Therapeutic Agents for CLL



Fred H

Shadman, JAMA,2023

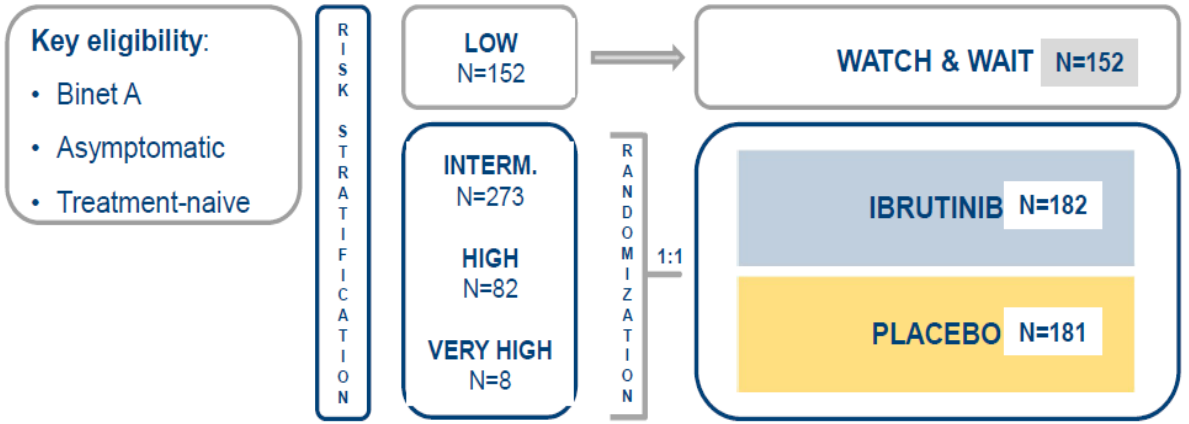
Who needs to be treated?

Indications for treatment

- Progressive marrow failure
- Massive , progressive or symptomatic lymphadenopathy or organomegaly
- Constitutional symptoms
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- ~~Lymphocyte doubling time~~

Is there a role for early intervention in “high-risk” patients?

CLL-12 Study – Early intervention with Ibrutinib



Phase 3, placebo-controlled, double-blind, multicenter trial

Primary endpoint EFS: time from randomization until symptomtatic PD, new treatment, death

Secondary endpoints: survival, PFS, TFS, TTNT, ORR, safety

π_2 **:** median EFS from 24 to 48 months with ibrutinib (superiority test)

- **EFS, PFS, and TTNT :** Improved with ibrutinib
- **OS**: No difference (HR, 0.791; 95% CI, 0.358-1.748; *P* = .562)

Early intervention with ibrutinib is NOT recommended

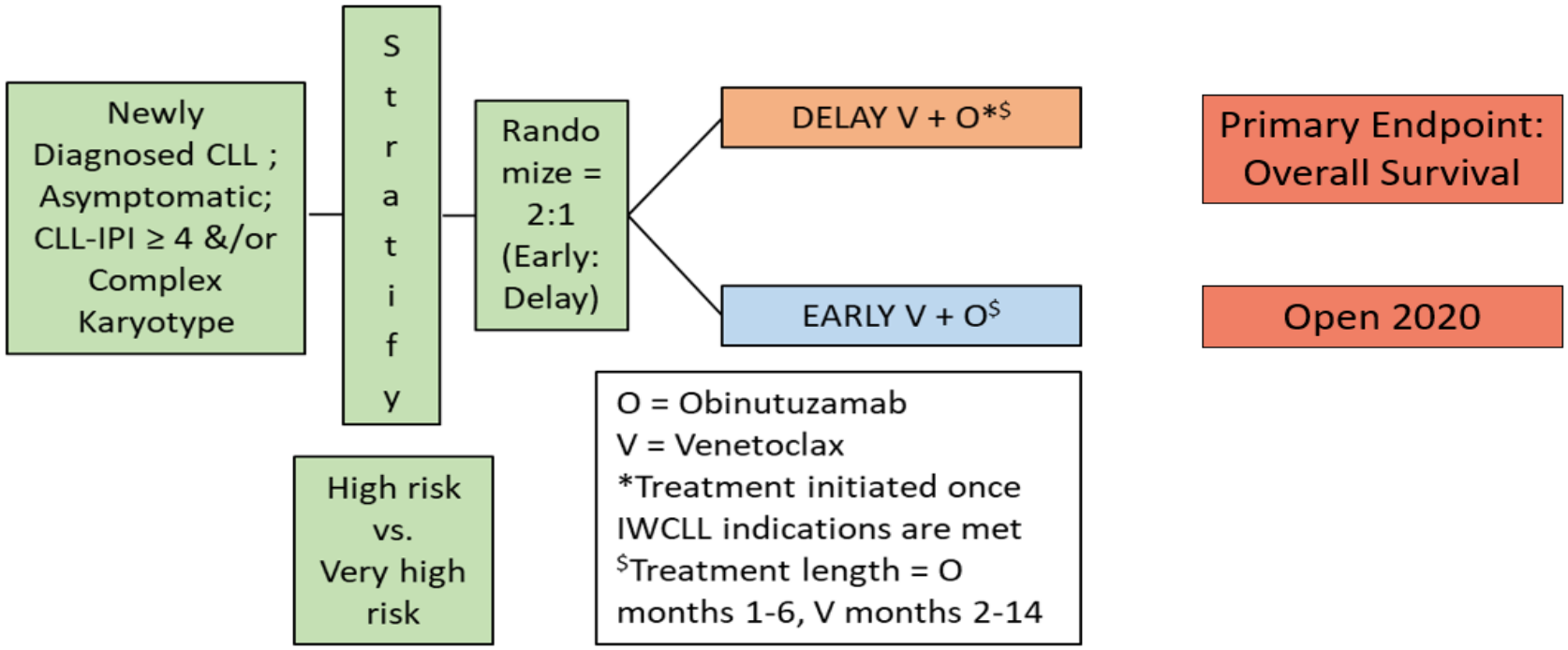
Langerbeins, Lugano (17-ICML) meeting , 2023

Ongoing US Intergroups Early Intervention Trial

CLL-IPI

Characteristic	Points
Del(17p) or TP53 mutation	4
Serum beta-2-macroglobulin ≥ 3.5mg/L	2
Un-mutated IgVH	2
Rai Stage I-IV	1
Age > 65 years	1

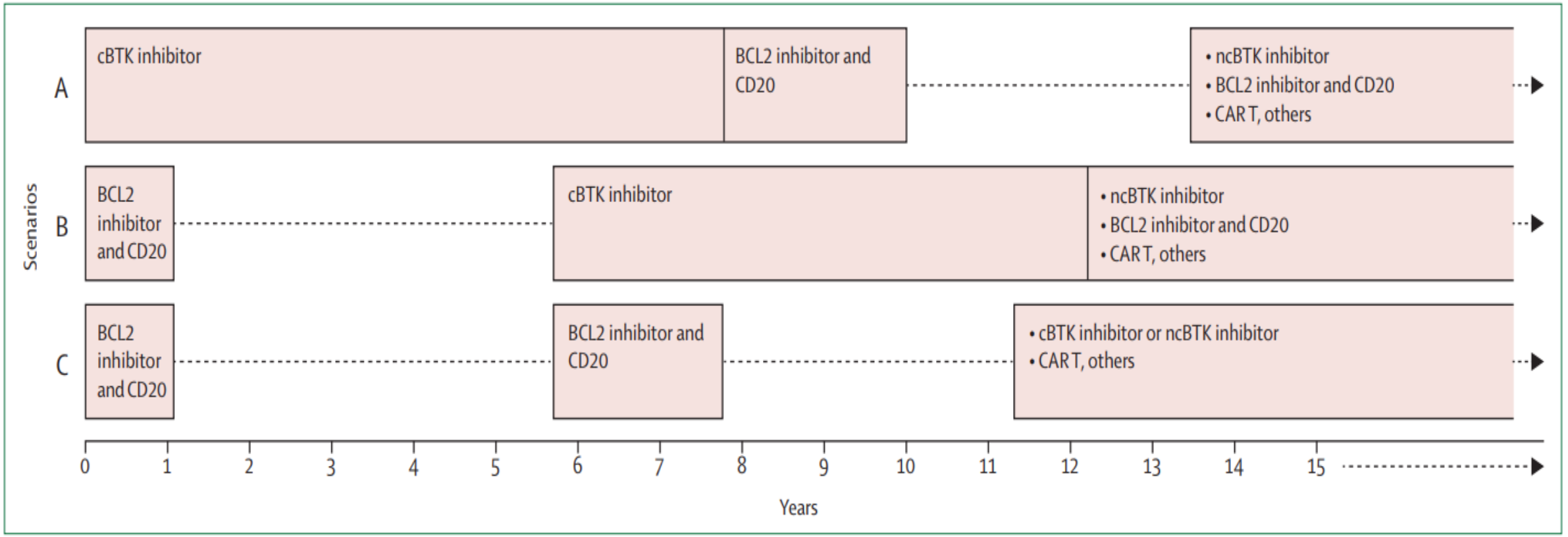
Points	Risk Group
0-1	Low
2-3	Int
4-6	High
7-10	Very High



Courtesy: Dr. Deborah Stephens (study PI)

Treatment Strategy and Recommendations for treatment-naïve patients

Treatment Strategies in CLL/SLL



Jain, Lancet, 2024

First line treatment: for patients with normal TP53

Preferred BTKis

Acalabrutinib ± G
Or
Zanubrutinib

OR

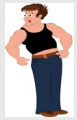
Venetoclax + G

Alternative BTKi

Ibrutinib

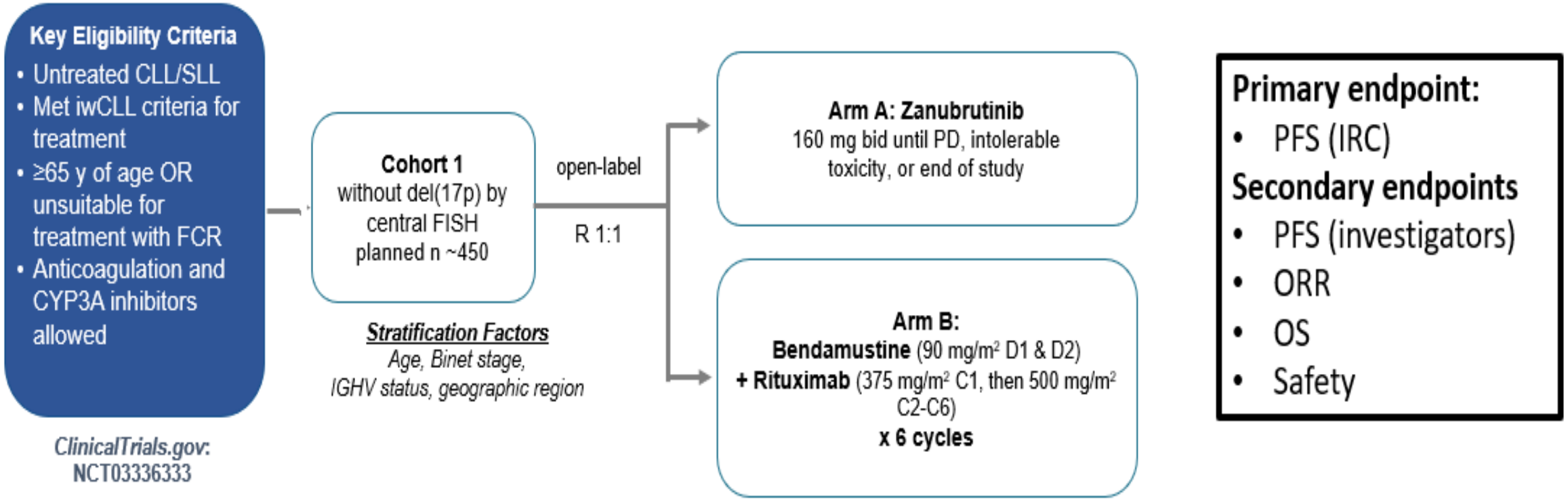
G = Gazyva = obinutuzumab

Novel agents are superior to CIT in first line

Patients	Study	Investigational arm	Control arm	Primary endpoint	Winner
	E1912	Ibrutinib + R	FCR	PFS	Ibrutinib + R
	A041202	Ibrutinib ± R	BR	PFS	Ibrutinib ± R
	Sequoia	Zanubrutinib	BR	PFS	Zanubrutinib
	Illuminate	Ibrutinib + G	CHL+G	PFS	Ibrutinib + G
	Elevate TN	Acalabrutinib ± G	CHL+G	PFS	Acalabrutinib ± G
	CLL14	Venetoclax + G	CHL+G	PFS	Venetoclax + G
	Glow	Venetoclax + Ibrutinib	CHL+G	PFS	Venetoclax + Ibrutinib

CIT=chemoimmunotherapy ; G = Obinutuzumab; R = rituximab

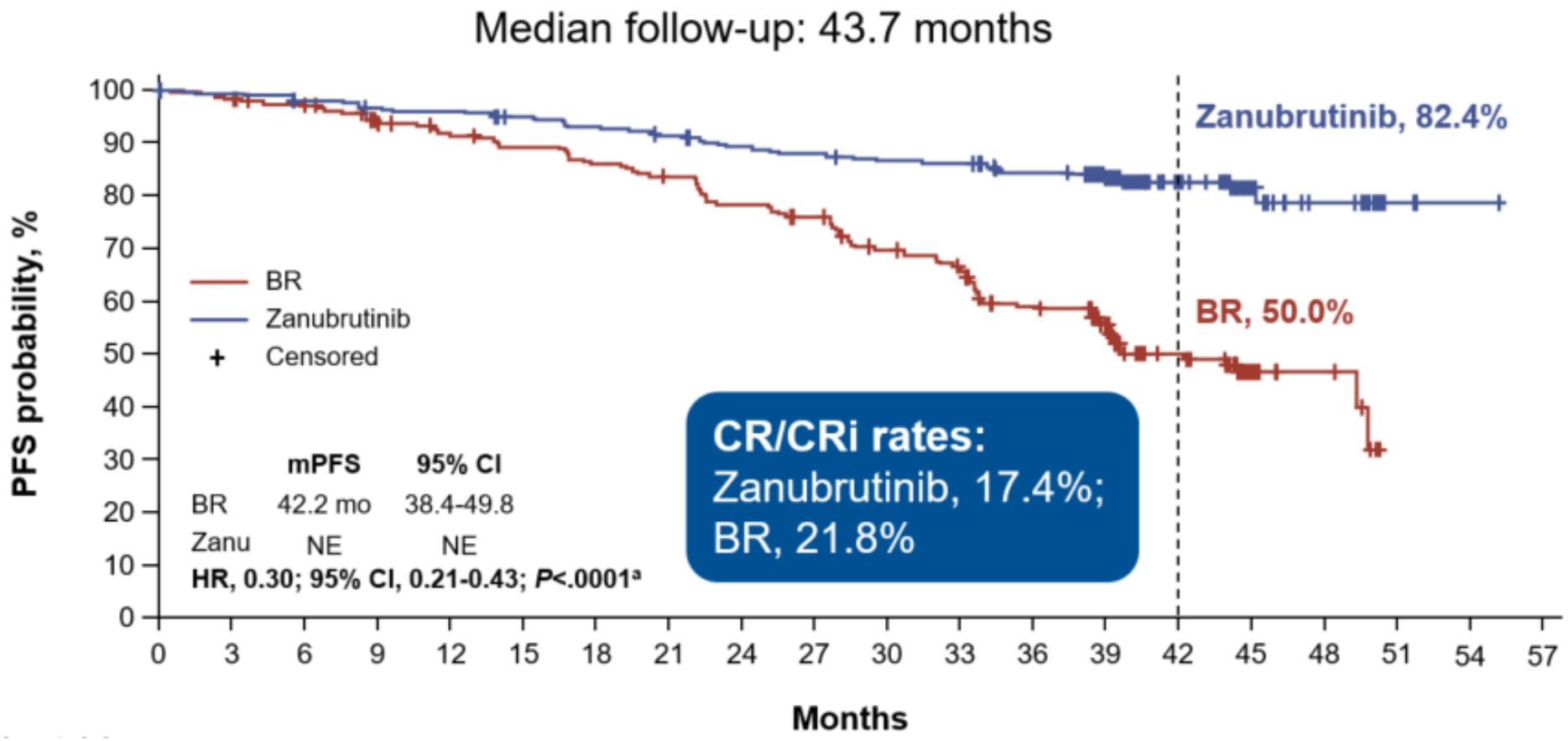
BR vs. Zanubrutinib (SEQUOIA)



Shadman, 17-ICML, 2023

BR vs. Zanubrutinib (SEQUOIA)

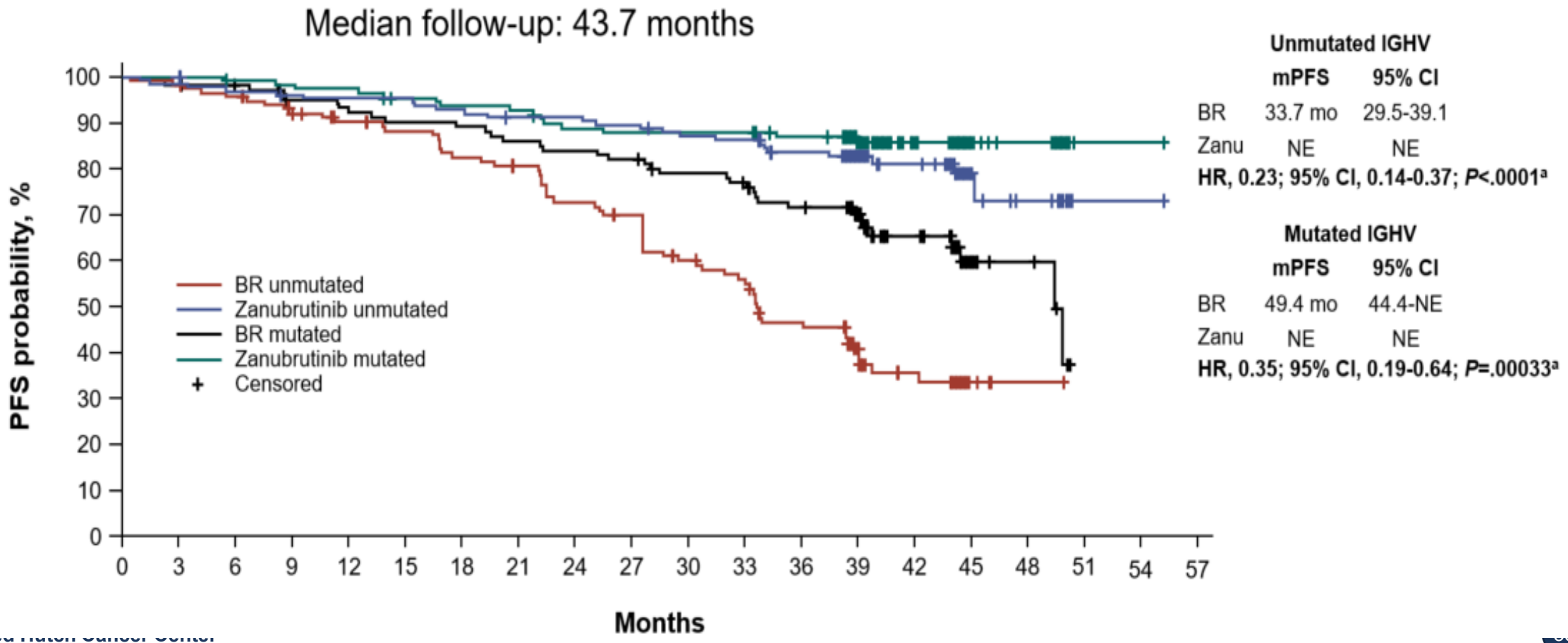
Progression-free Survival



Shadman, 17-ICML,2023

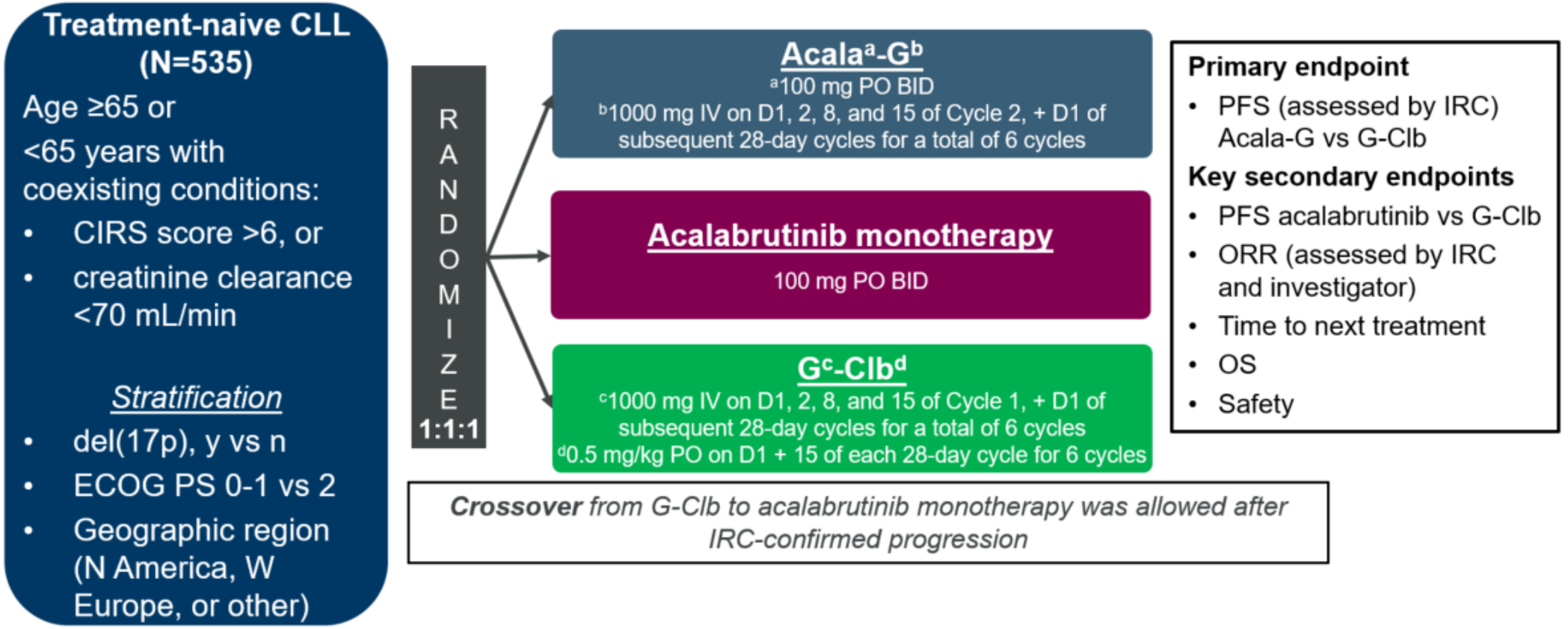
BR vs. Zanubrutinib (SEQUOIA)

Progression-free Survival (by IGHV)



Shadman, 17-ICML,2023

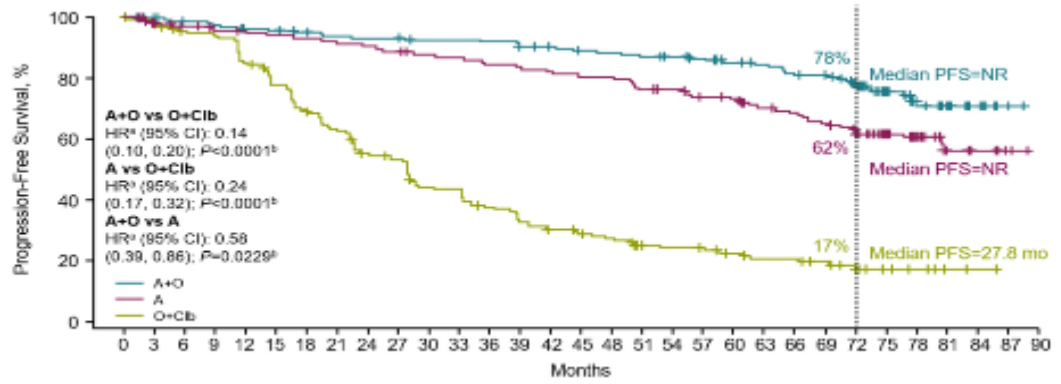
Acalabrutinib ± G vs. CHL+G:(ELEVATE TN)



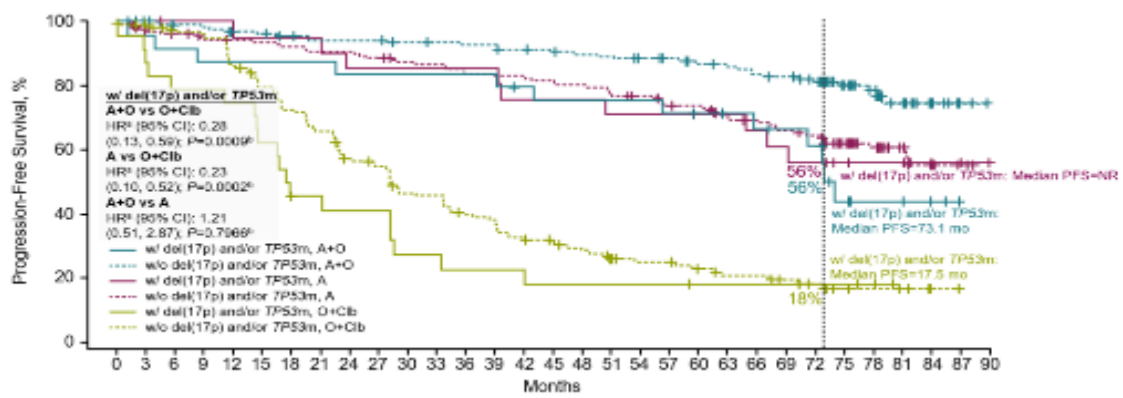
Sharman, Lancet, 2020

Acalabrutinib ± G vs Clb + G: ELEVATE-TN – 6-Year Update

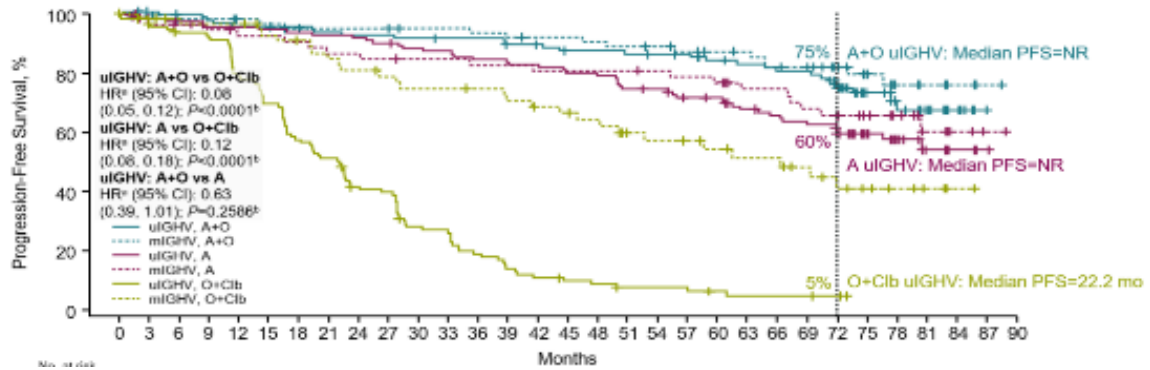
INV-Assessed PFS (median follow-up: 74.5 months)



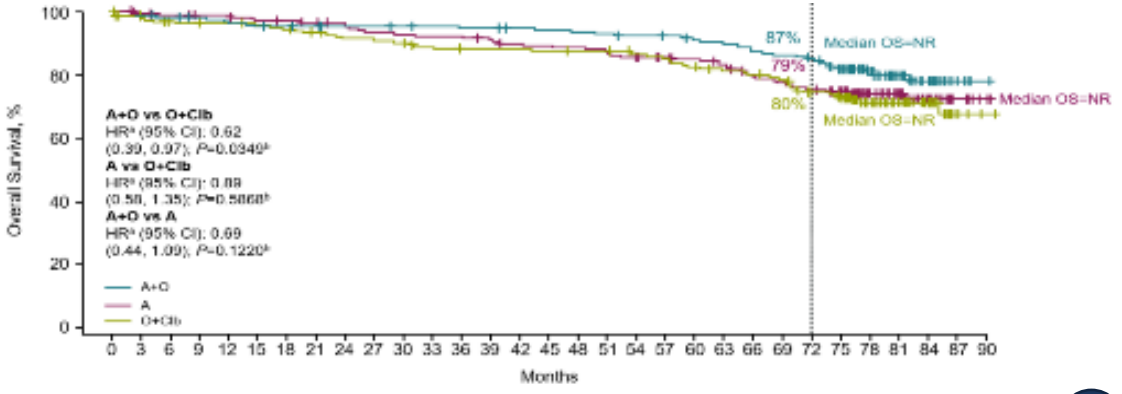
INV-Assessed PFS in Del(17p) and/or *TP53* Mutated



INV-Assessed PFS in Unmutated *IGHV*

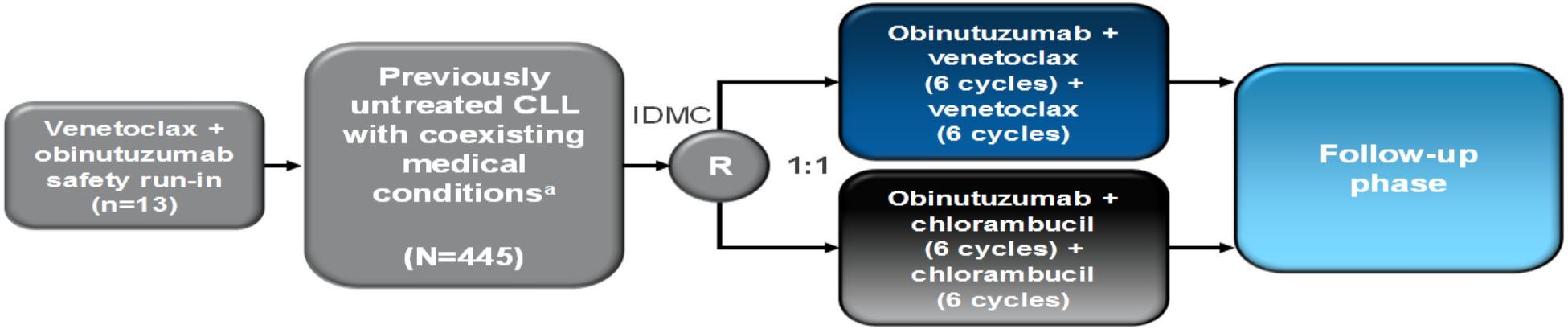


Overall Survival



Sharman JP, et al. ASH 2023. Abstract 636.

Venetoclax + G vs CHL + G: (CLL-14)



Primary endpoint:

- PFS as assessed by investigator[3]

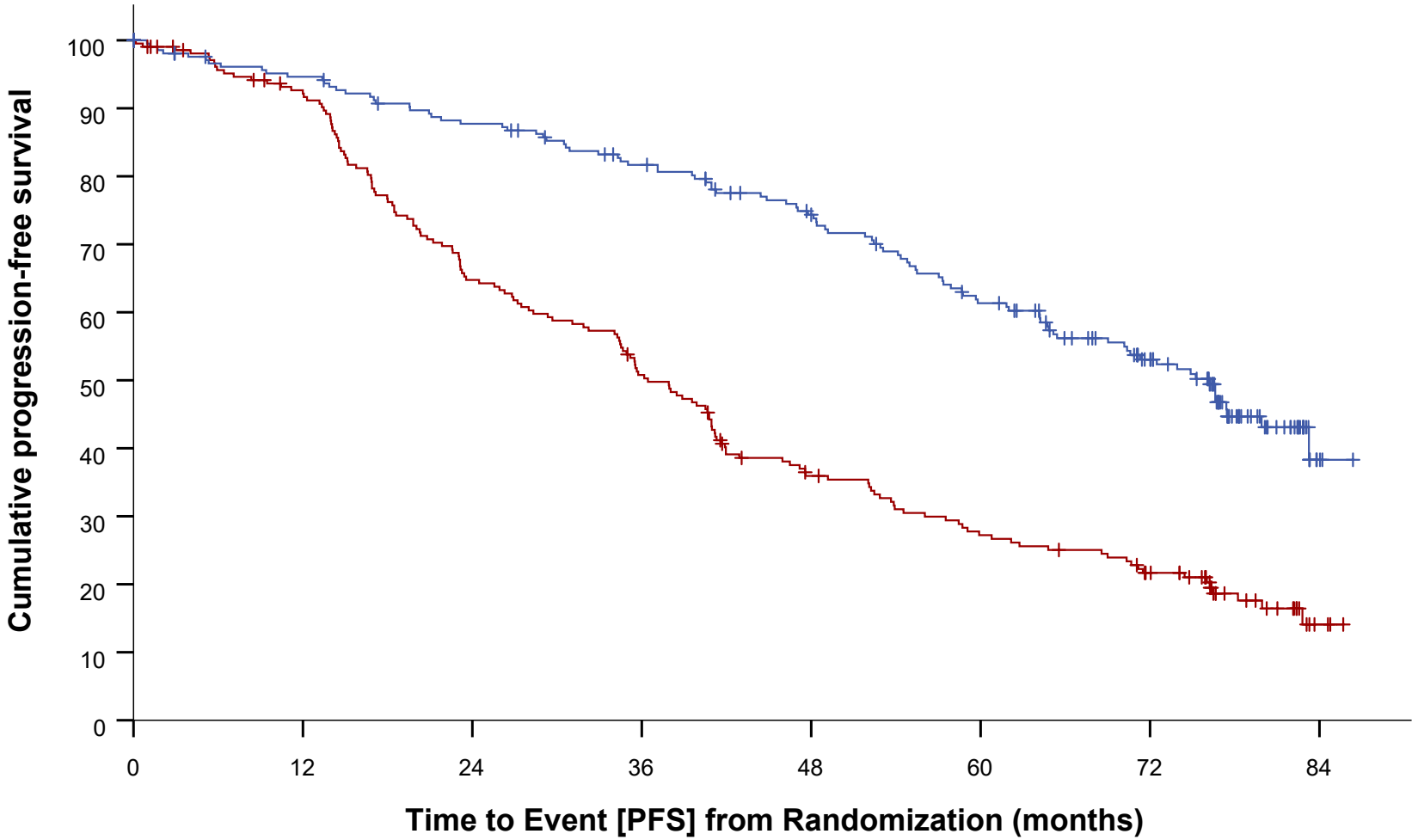
Secondary endpoints[3]:

- PFS as assessed by IRC
- MRD
- ORR
- CR rate
- DOR
- EFS
- OS
- TTNT
- Safety

[a]CIRS >6 and/or CrCl <70 mL/min

Al-Sawaf, EHA,2023

Venetoclax + G vs Clb + G: CLL-14 – 6-Year Follow-Up



Median PFS
Ven-Obi: 76.2 months
Clb-Obi: 36.4 months

6-year PFS rate
Ven-Obi: 53.1%
Clb-Obi: 21.7%

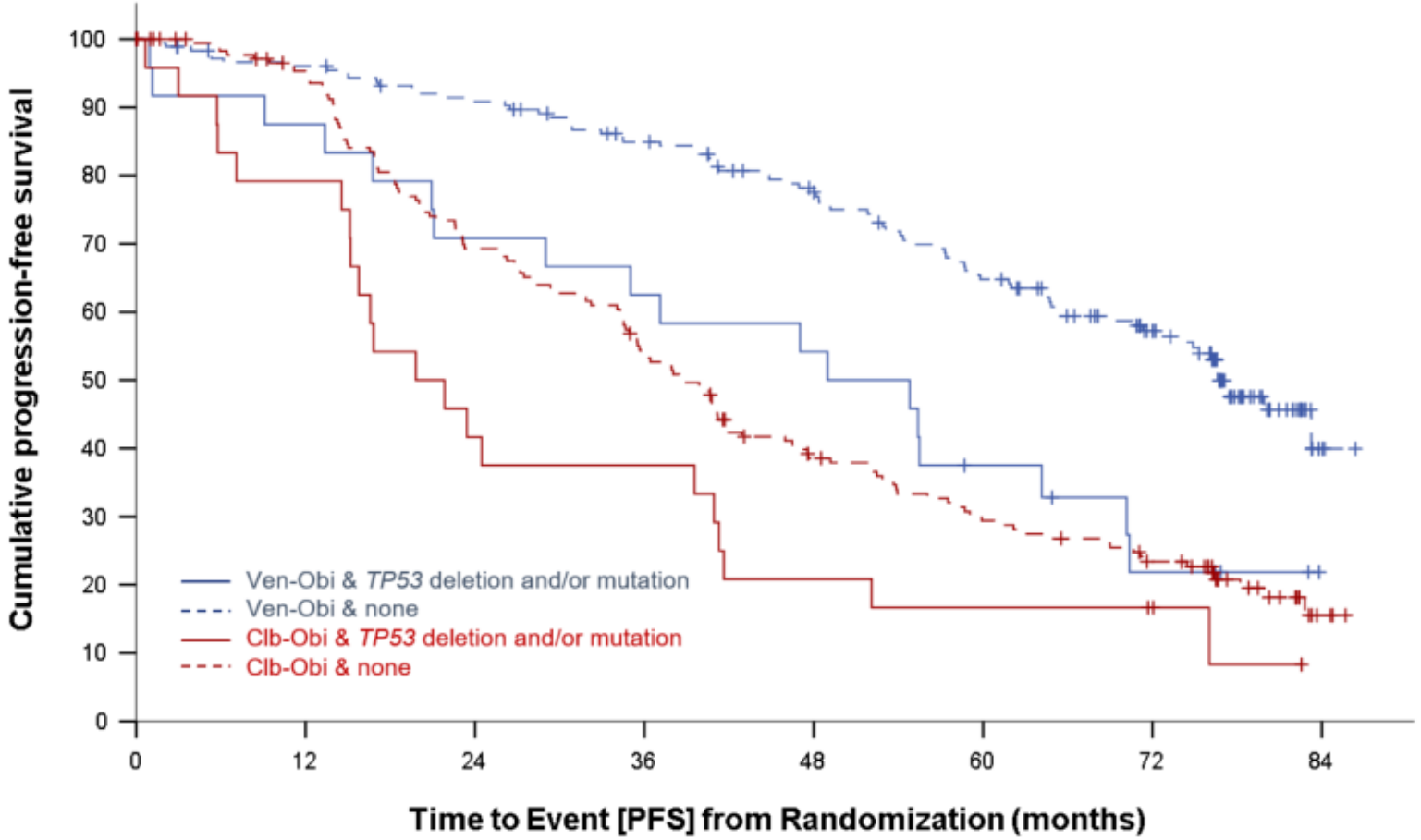
HR 0.40, 95% CI (0.31–0.52)
P <.0001

Al-Sawaf O, et al. EHA 2023. Abstract S145.

Venetoclax + G vs Clb + G: CLL-14 – 6-Year Follow-Up

PROGRESSION-FREE SURVIVAL – *TP53* status

Median observation time 76.4 months



Median PFS

Ven-Obi & no *TP53*del/mut: 76.6 m

Ven-Obi & *TP53*del/mut: 51.9 m

HR 2.29, 95% CI [1.37-3.83], p=0.001

Clb-Obi & no *TP53*del/mut: 38.9 m

Clb-Obi & *TP53*del/mut: 20.8 m

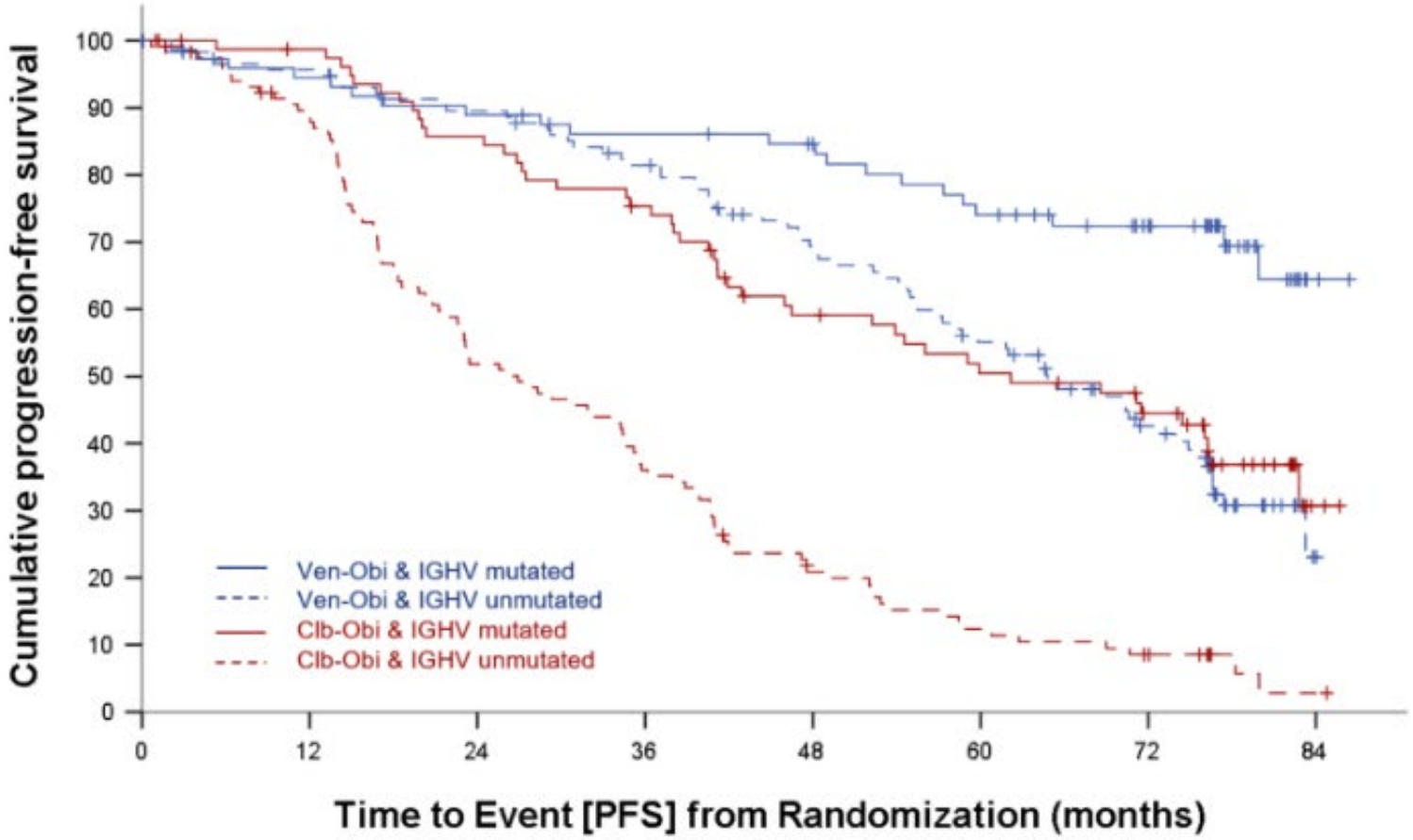
HR 1.66, 95% CI [1.05-2.63], p=0.03

Al-Sawaf O, et al. EHA 2023. Abstract S145.

Venetoclax + G vs Clb + G: CLL-14 – 6-Year Follow-Up

PROGRESSION-FREE SURVIVAL – IGHV status

Median observation time 76.4 months



Median PFS

Ven-Obi & IGHVmut: NR

Ven-Obi & IGHVunmut: 64.8 m

HR 0.38, 95%CI [0.23-0.61], p<0.001

Clb-Obi & IGHVmut: 62.2 m

Clb-Obi & IGHVunmut: 26.9 m

HR 0.33, 95% CI [0.23-0.47], p<0.001

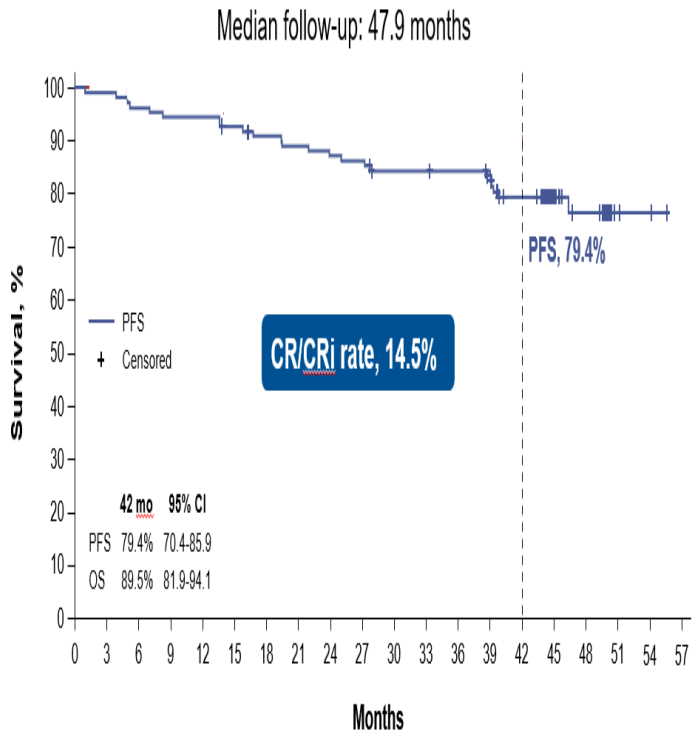
Al-Sawaf O, et al. EHA 2023. Abstract S145.

BTKis and TN CLL with abnormal TP53

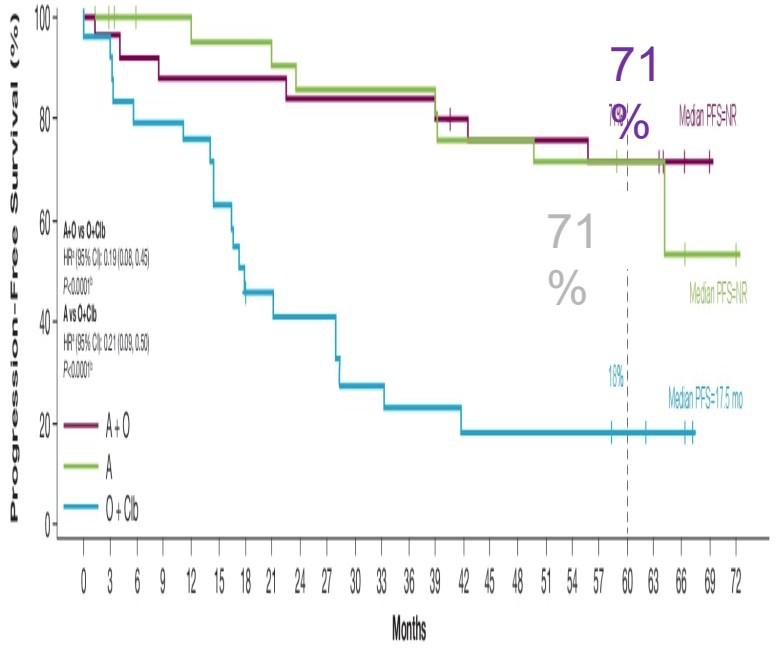
	ibrutinib	acalabrutinib	zanubrutinib
Study	Pooled analysis	ELEVATE TN	SEQUOIA
N	89	48	109
Median follow-up	49.8 months	46.9	48
Anti-CD20	44/89	23/48	0
Del17p	53%	68%, 69%	100%
Mutated TP53	59%	84% , 83%	Not reported
PFS	79% (48-months)	74.8% and 76.2% (mono) (48-months)	79.4 (42 months)
Reference	Allan, BJH, 2021	Sharman, Leukemia,2021	Shadman,17-ICML,2023

BTKis for abnormal TP53

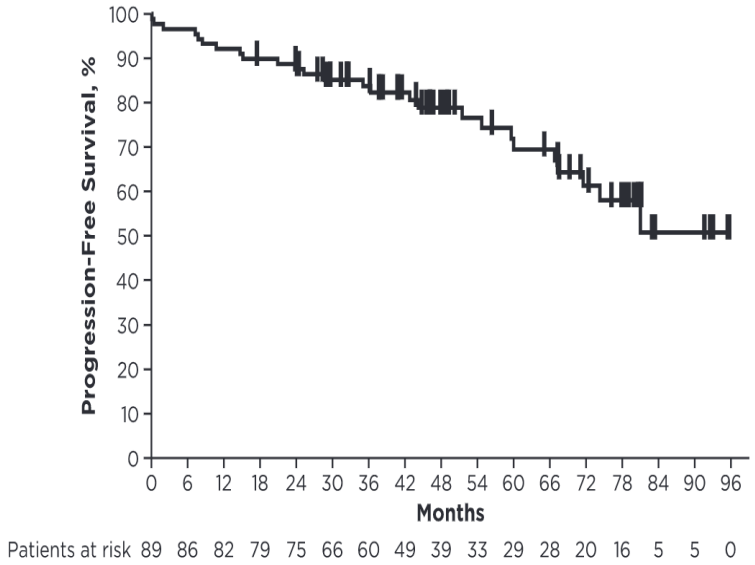
Zanubrutinib



Acalabrutinib



Ibrutinib



Shadman, 17-ICML,2023

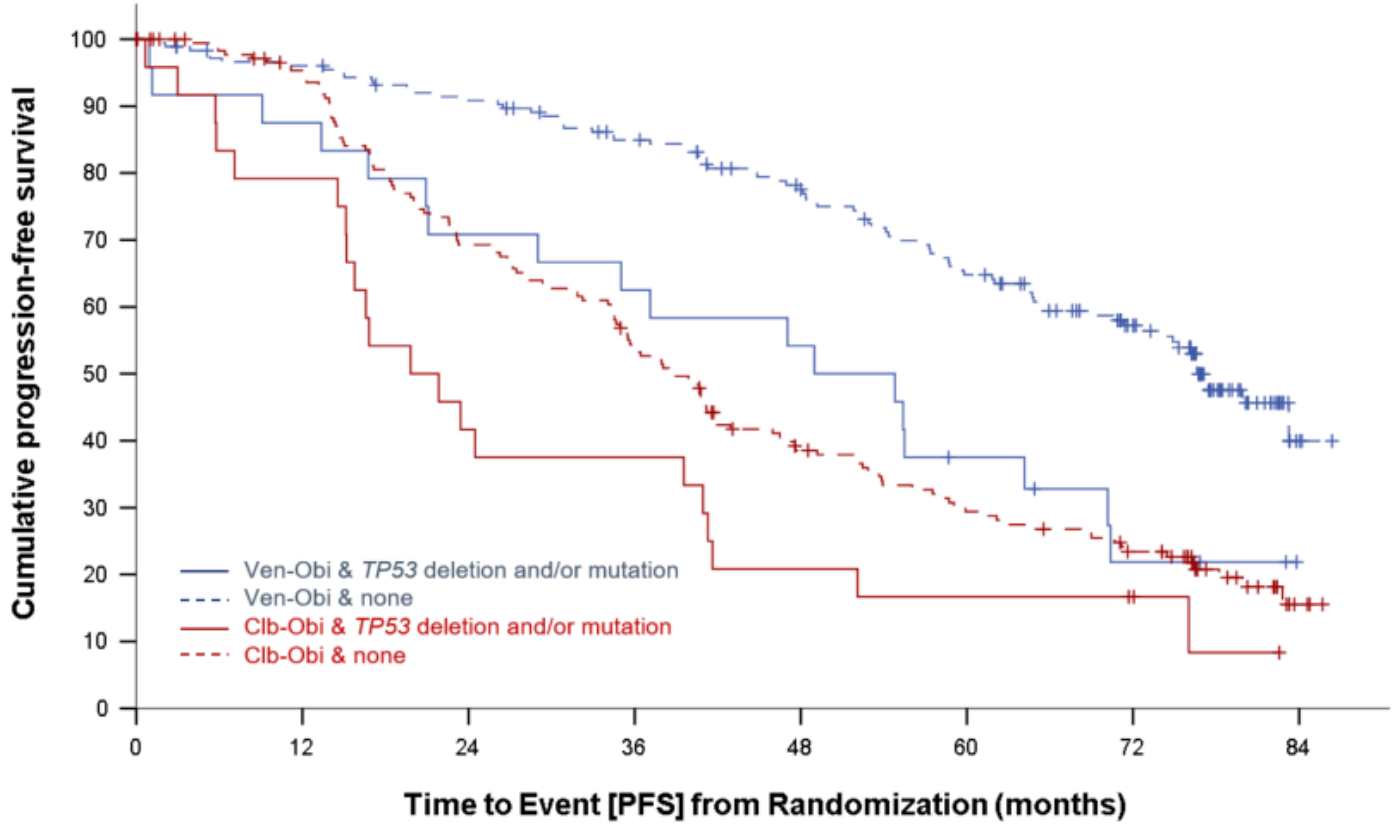
Sharman, EHA, 2022

Allan, Br. J Haematology,2022

Venetoclax and TN CLL with abnormal TP53

PROGRESSION-FREE SURVIVAL – *TP53* status

Median observation time 76.4 months



Median PFS

Ven-Obi & no *TP53*del/mut: 76.6 m

Ven-Obi & *TP53*del/mut: 51.9 m

HR 2.29, 95% CI [1.37-3.83], p=0.001

Clb-Obi & no *TP53*del/mut: 38.9 m

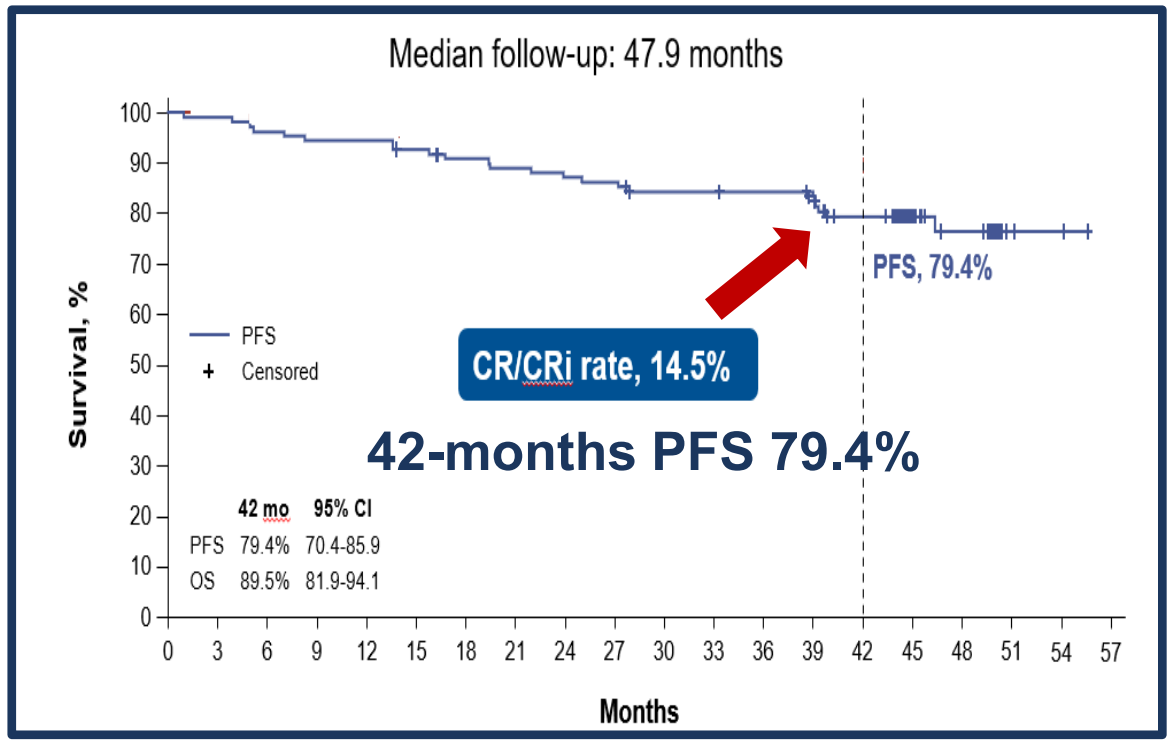
Clb-Obi & *TP53*del/mut: 20.8 m

HR 1.66, 95% CI [1.05-2.63], p=0.03

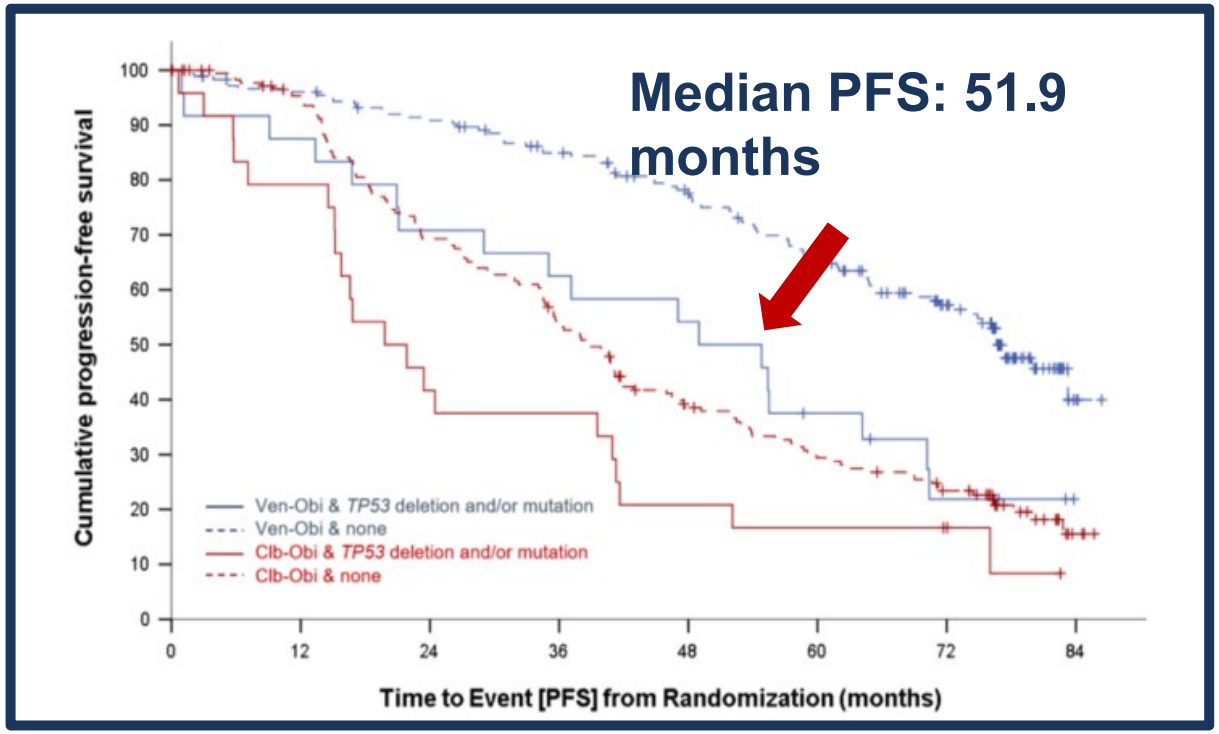
Al-Sawaf, EHA, 2023

Ibrutinib vs. Ven-G for first-line treatment in CLL patients with abnormal TP53

Zanubrutinib



Venetoclax + Obinutuzumab



Shadman, 17-ICML,2023

Al-Sawaf, EHA, 2023

BTKis vs. Ven-O

Class	BTKis (Acalabrutinib/Zanubrutinib/Ibrutinib)	Ven-Obino
Duration	Indefinite therapy	Time-limited
Deep responses	Not expected / Not relevant	High CR and uMRD rate
Convenience	Easy to start	Frequent visits initially
Not preferred if:	• Significant cardiac history (structural, HTN, arrythmia) • Major bleeding issues	
TP53 abnormal	Not a predictors of response	Shorter PFS; discuss with the pt
unmutated IGHV	Not a predictors of response	Shorter PFS ; discuss with the pt
Sequencing	Can be used after Ven	Can be used after BTKi

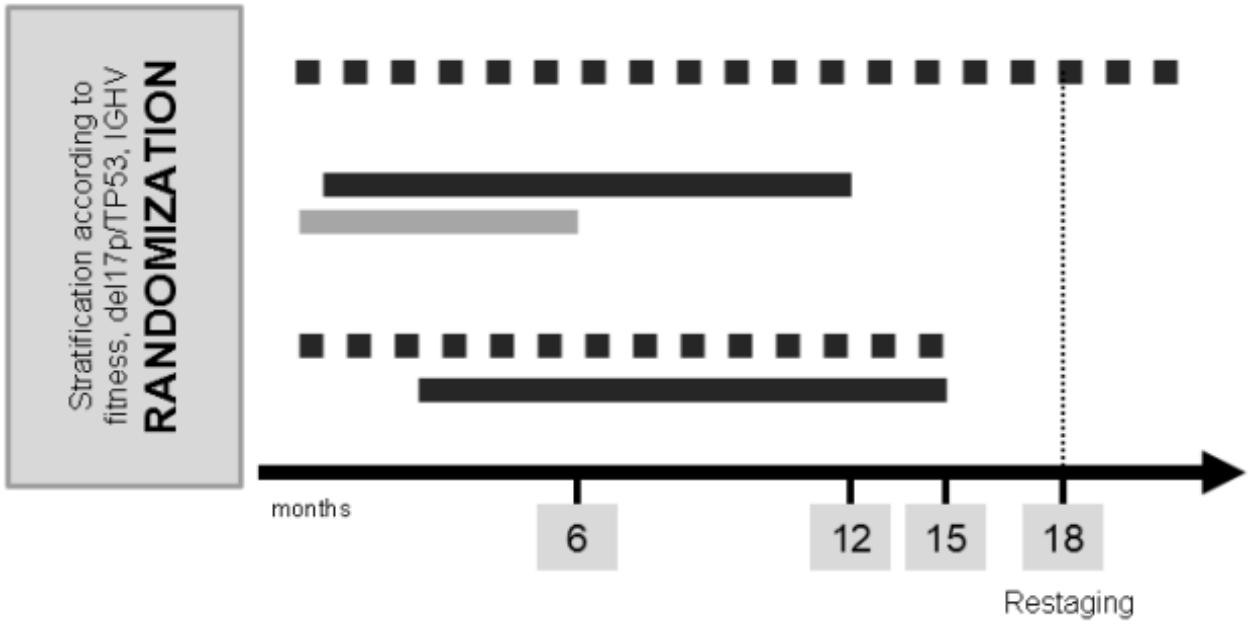
- **No head-to-head comparison**
- **Both are reasonable options**
- **Consider patient and disease factors**
- **Look at pros and cons for each**

BTKi + BCL2i Combination for CLL

- Ibrutinib + Venetoclax is superior to Chlorambucil + Obinutuzumab (GLOW study) and FCR (UK Flair study) and is approved in Europe and Canada but approval in US in not expected

- Awaiting results for combination of second generation cBTKis with venetoclax and new BCL2is

GCLLSG: CLL17 Trial



Ibrutinib d1 420 mg po daily until PD or intolerance

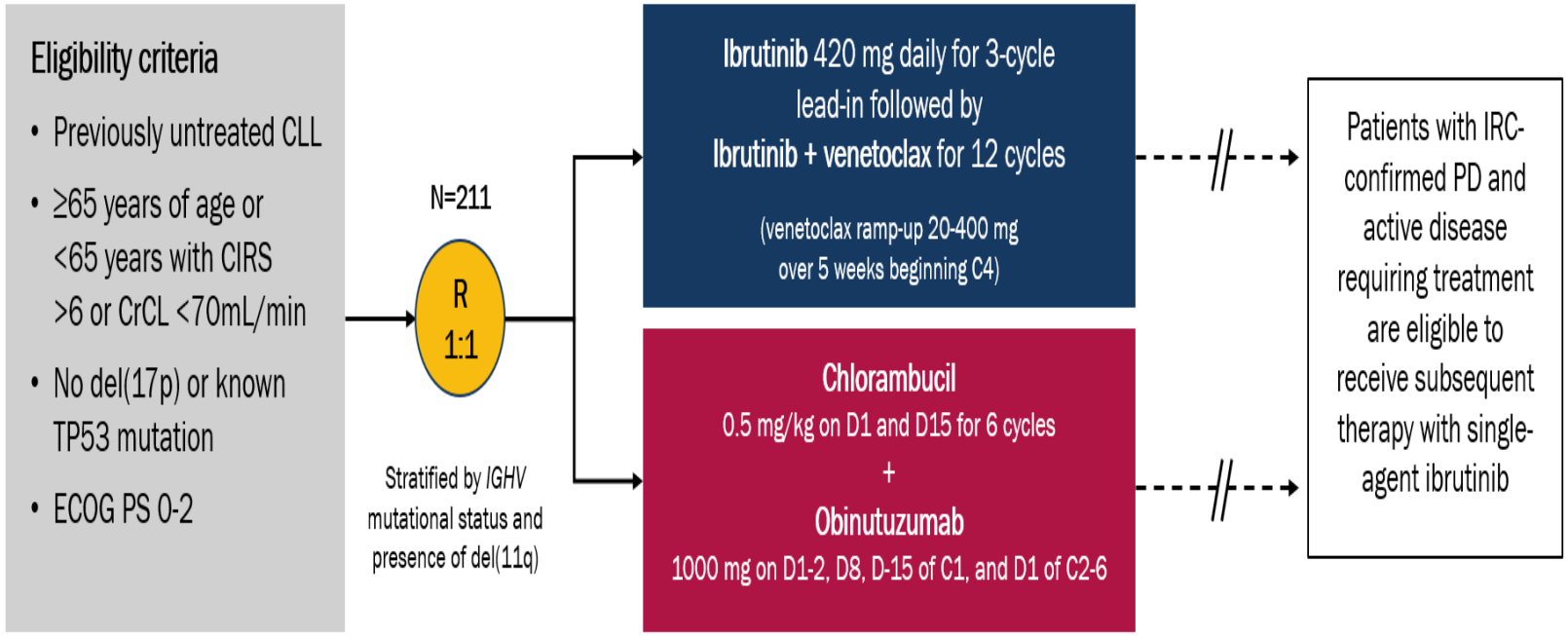
Venetoclax 400 mg po daily (c1 d22 – c12 d28)
Obinutuzumab 1000 mg iv (c1 d1(2)/8/15, c 2-6 d1)

Ibrutinib 420 mg po daily (c1 d1 – c15 d28)
Venetoclax 400 mg po daily (c4 d1 – c15 d28)

DEUTSCHE STUDIENGRUPPE

University of Cologne

Venetoclax + Ibrutinib vs CHL + G (GLOW)



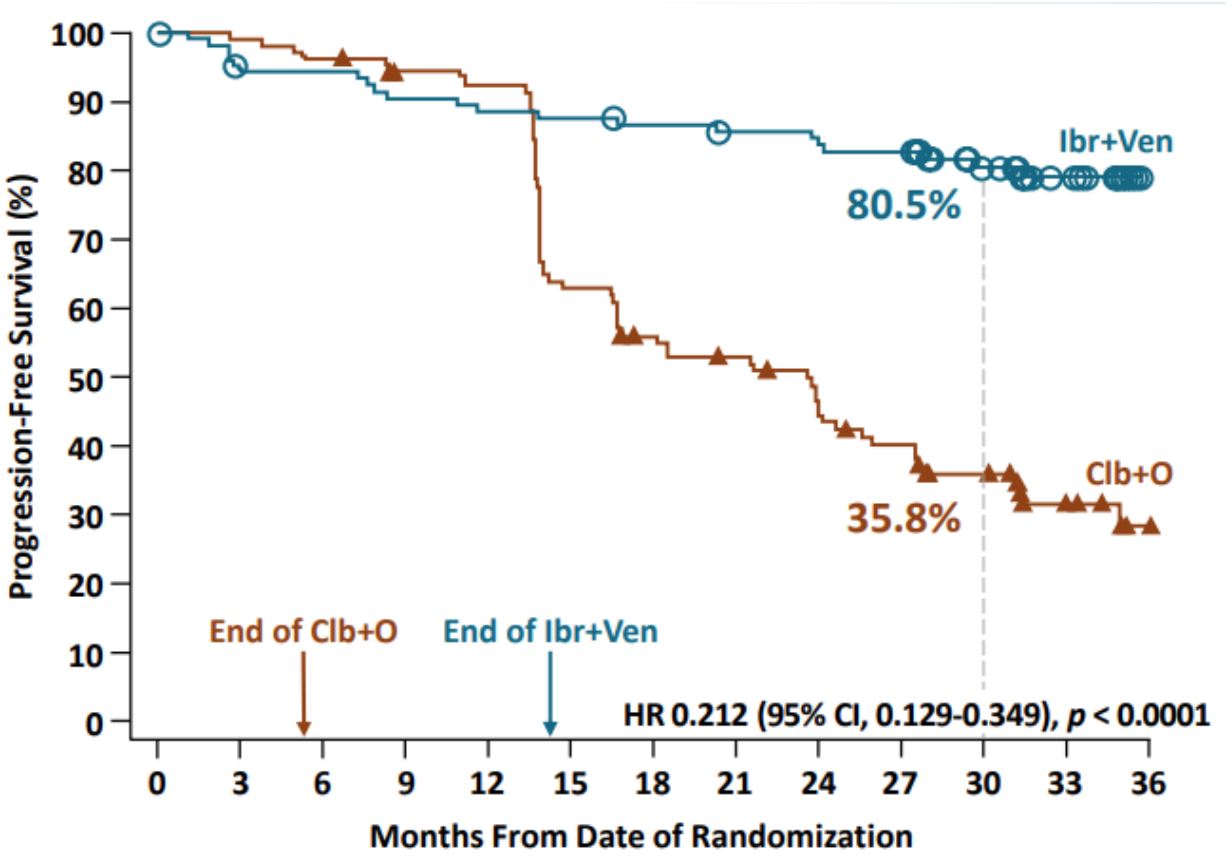
Primary endpoint:
PFS by IRC

Key secondary endpoints:

- uMRD in BM
- CR rate (IRC)
- ORR (IRC)
- OS
- Safety

Kater, NEJM Evidence, 2022

Venetoclax + Ibrutinib vs CHL + G (GLOW)



Safety Analysis of an Elderly Comorbid Population[1]:

- Most common grade ≥3 TEAEs were:
  - neutropenia (34.9%)
  - diarrhea (10.4%)
  - hypertension (7.5%) for Ibr+Ven
  - Grade 5 AEs occurred in 7 patients on Ibr+Ven and 2 patients on Clb+O

* Combination is not FDA approved for CLL as of September 2022

Munir, ASH,2021; Kater, NEJM Evidence, 2022

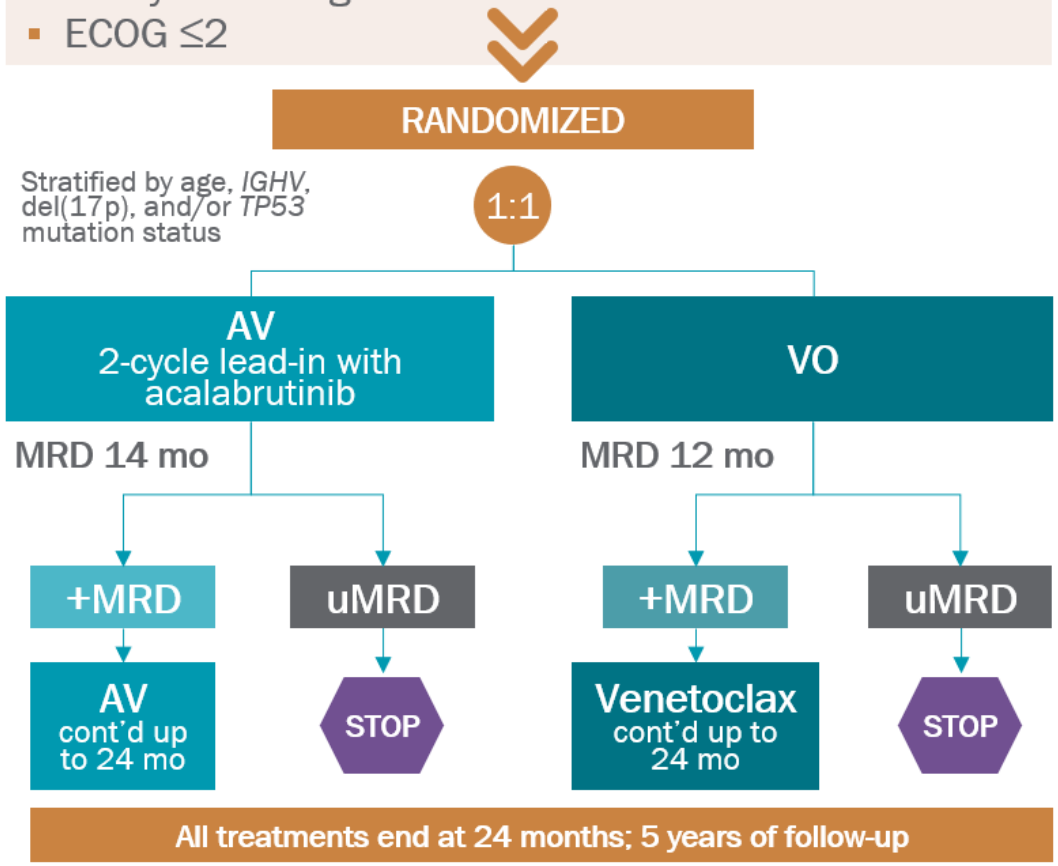
Fixed-duration Calquence plus venetoclax, with or without obinutuzumab, significantly improved progression-free survival in 1st-line chronic lymphocytic leukaemia in AMPLIFY Phase III trial

PUBLISHED
29 July 2024

MAJIC: Phase 3 Study of Acalabrutinib + Venetoclax (AV) vs Venetoclax + Obinutuzumab (VO) – Study Design

Key Eligibility Criteria

- Previously untreated CLL
- ≥18 years of age
- ECOG ≤2



Primary endpoint

- INV-assessed PFS

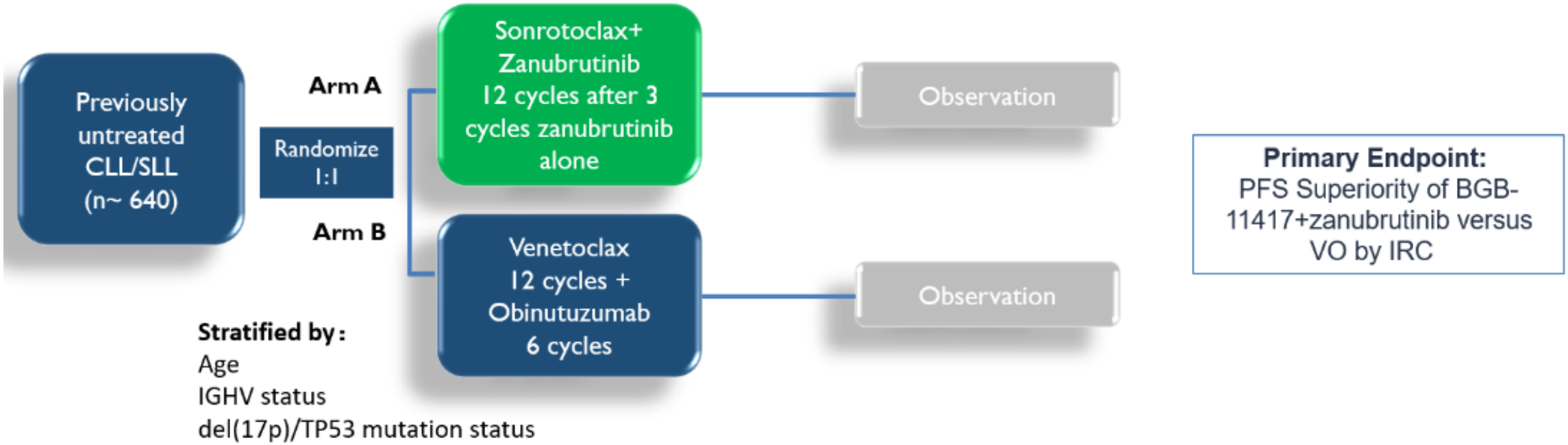
Key secondary endpoints

- uMRD rates at sequential timepoints (after 6 and 12 cycles of V and yearly thereafter [key timepoint: after 12 cycles of V])
- OS
- EFS
- ORR
- CR rate (per uMRD)
- Quality of life/patient-reported outcomes
- Safety and tolerability

CELESTIAL-CLLTN: Sonrotoclax + Zanubrutinib

BGB-11417-301: 2-arm fixed duration study design

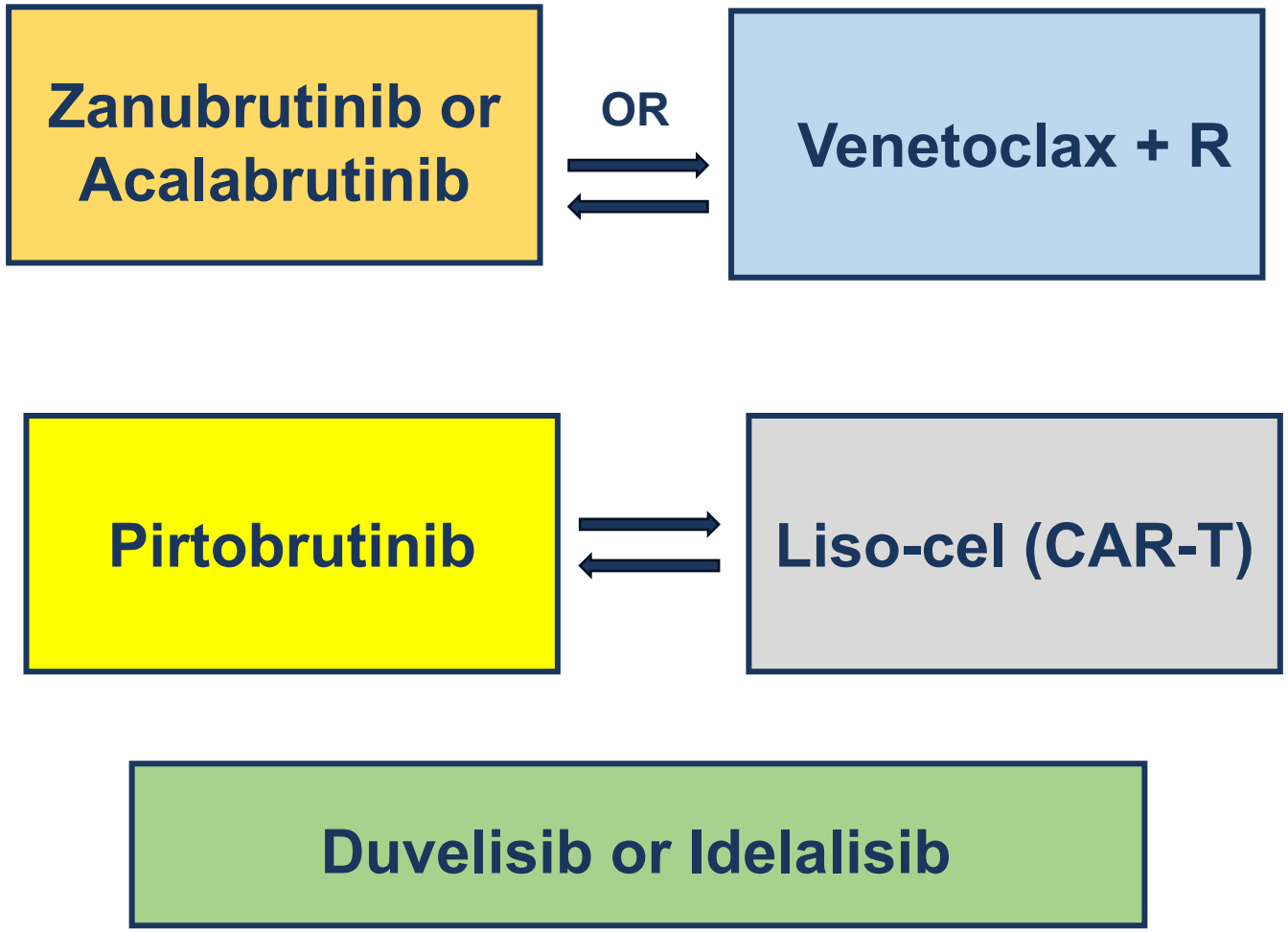
Phase 3 registrational trial



Treatment options for previously treated patients

Previously Treated CLL Summary

Preferred BTKis

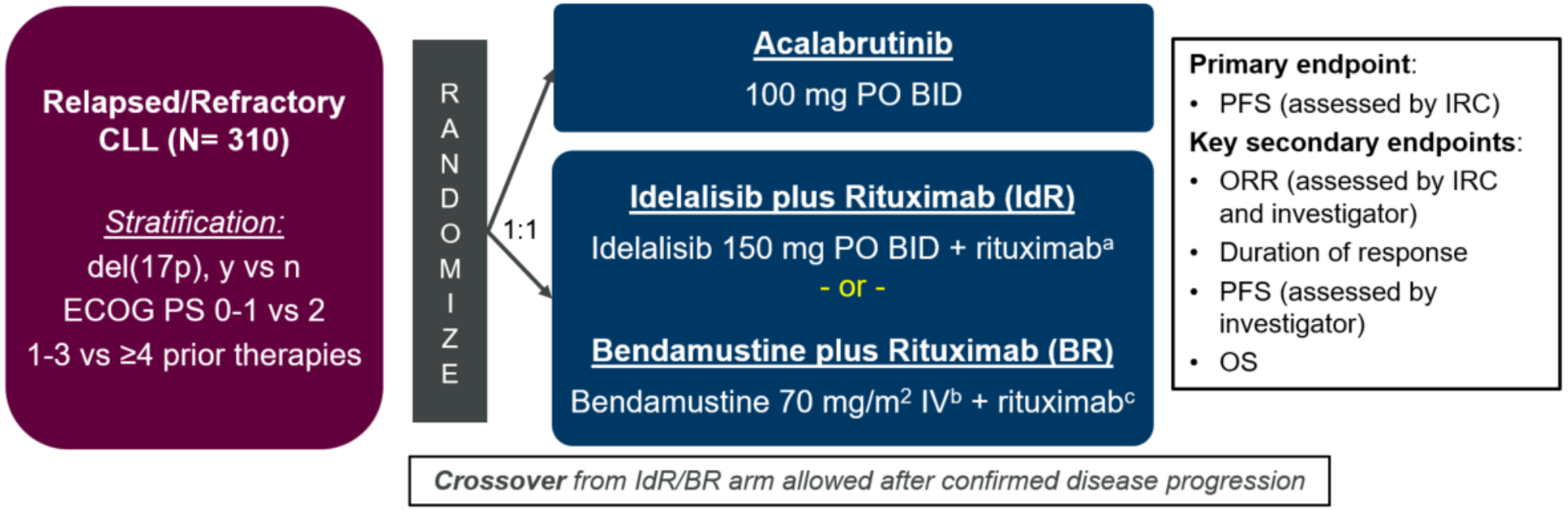


R = rituximab

Previously treated CLL : Principles

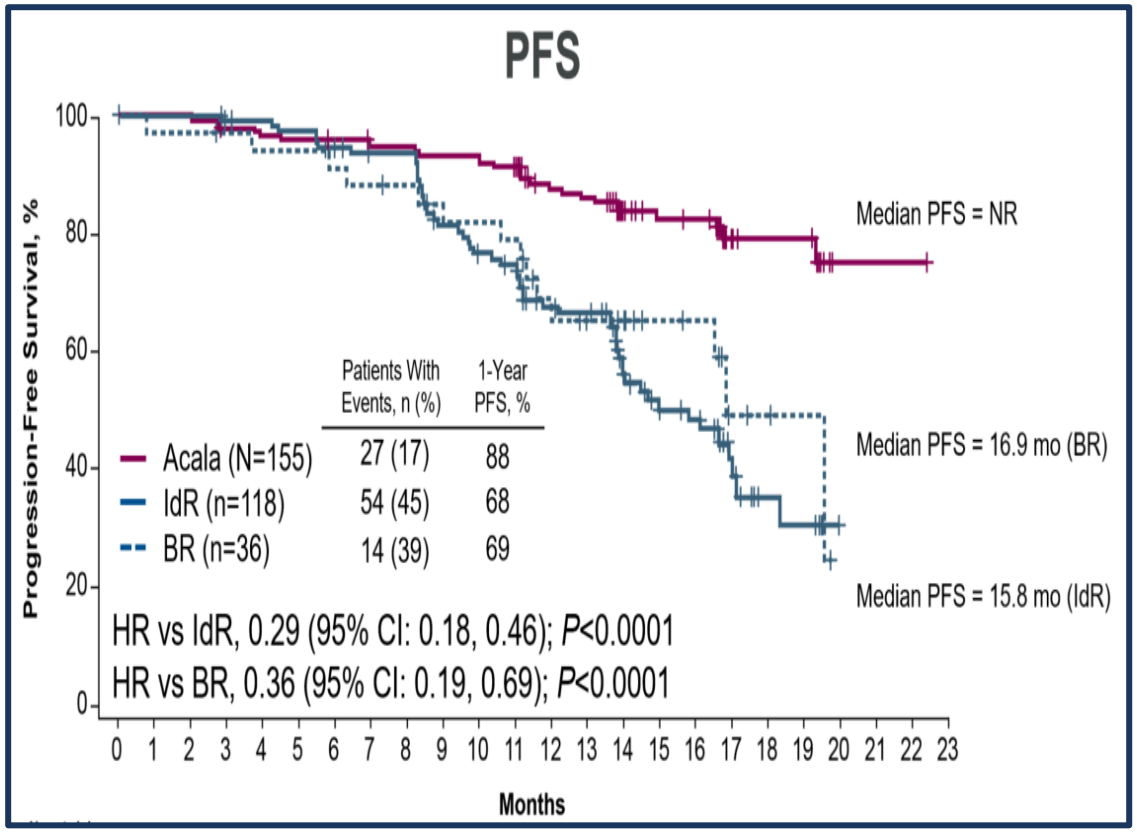
1. **Repeat FISH panel - look for del (17p) or TP53 mutation**
2. Bone marrow needs to be repeated to assess for MDS if prior FCR
3. Very limited role for chemoimmuntherapy (almost never)

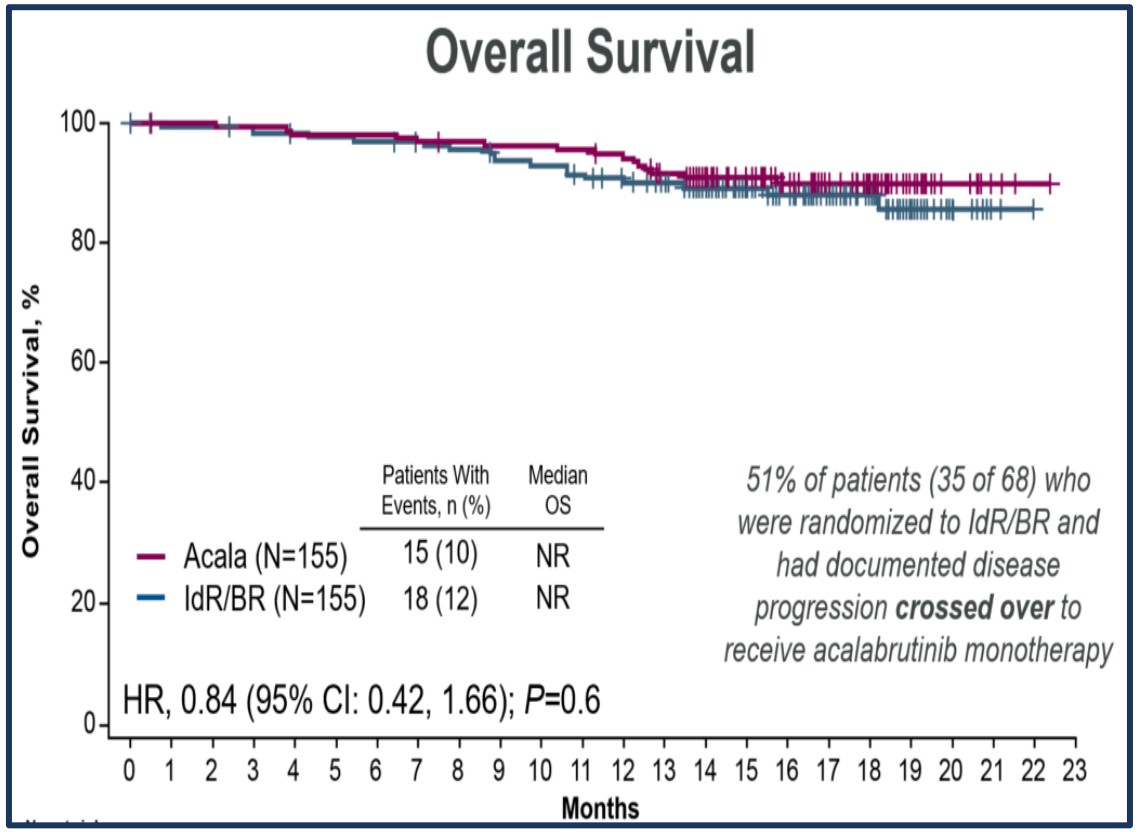
Acalabrutinib vs. Investigator choice for relapsed CLL: (ASCEND Study)



Ghia,JCO,2020

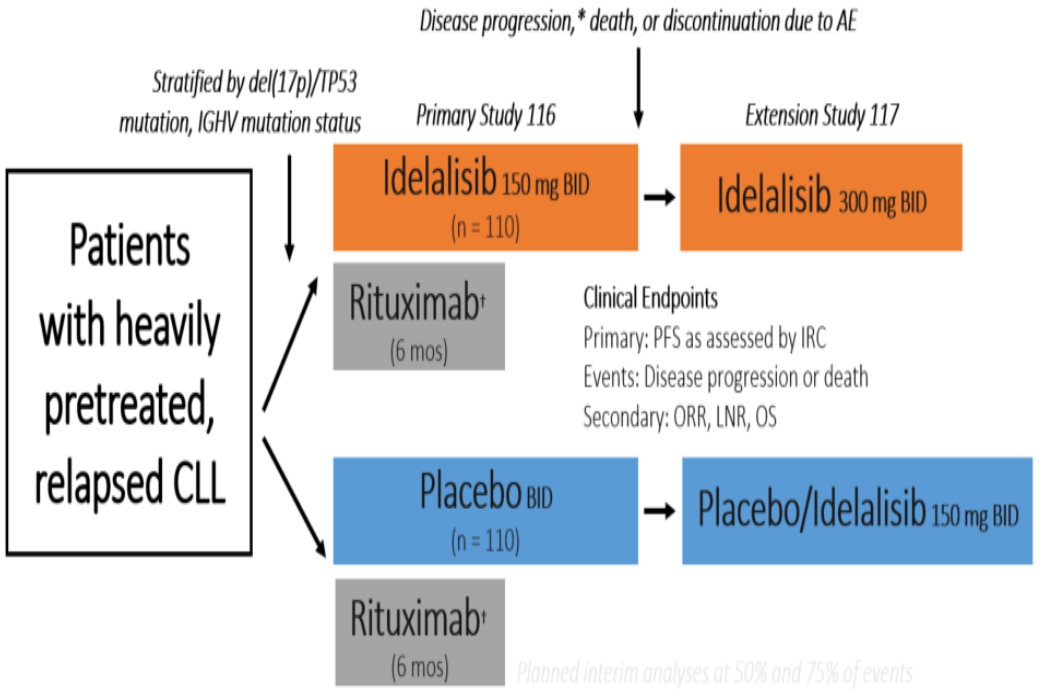
Acalabrutinib vs. Investigator choice for relapsed CLL: (ASCEND Study)

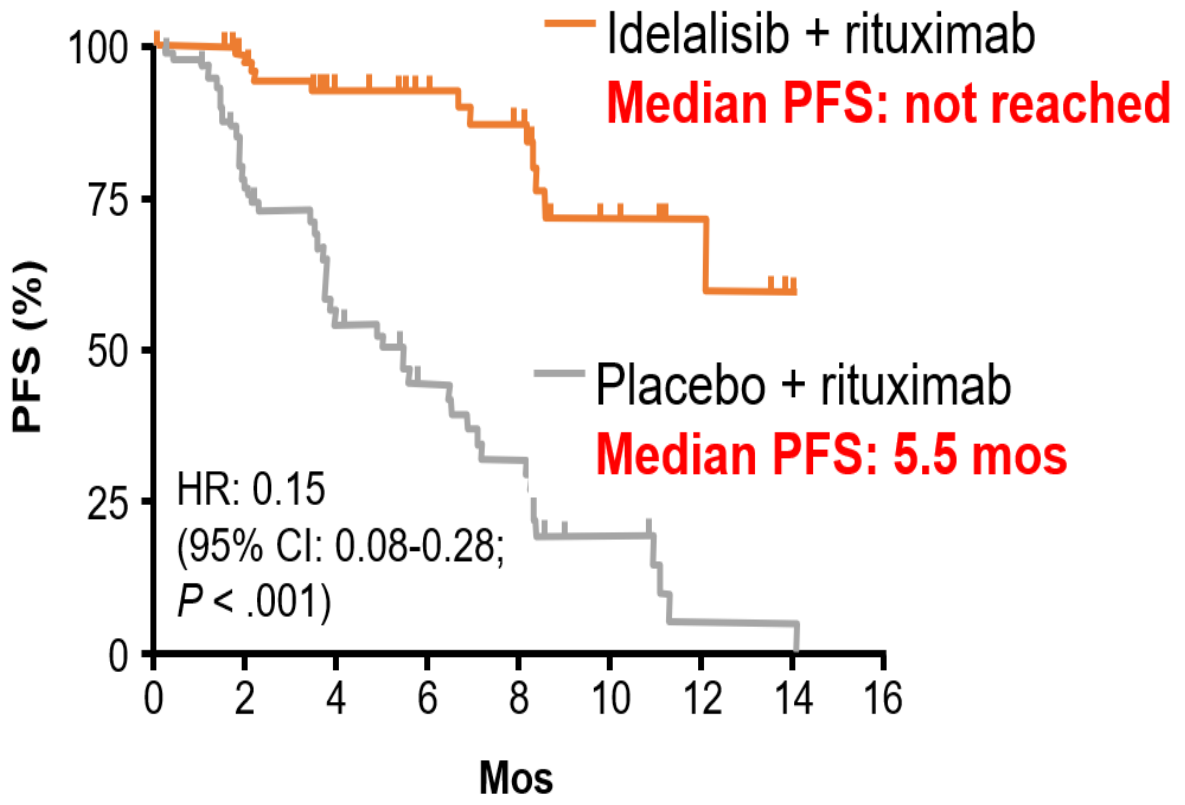




Ghia, JCO, 2020

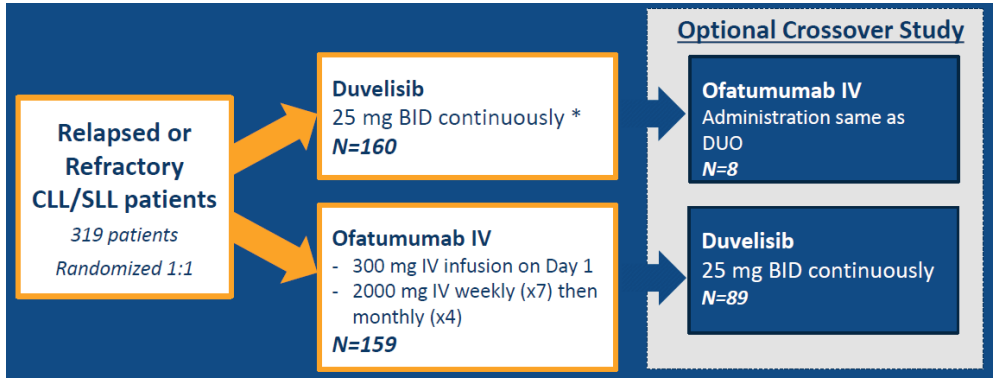
Idelalisib and Rituximab for Previously Treated Patients





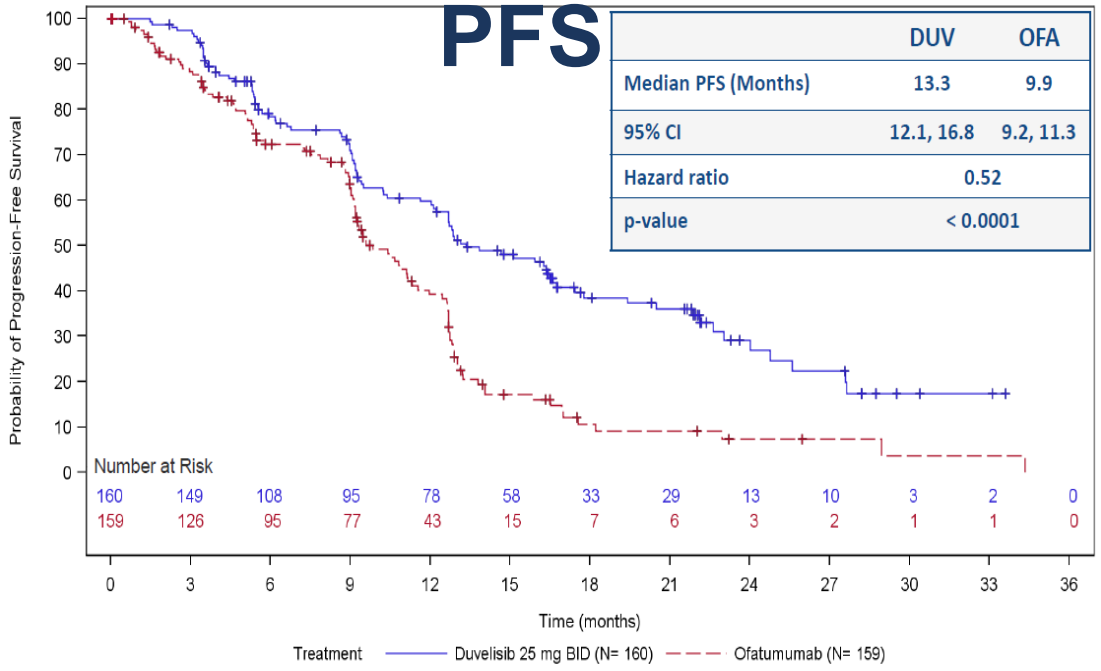
Furman, NEJM,2014

Duvelisib vs Ofatumumab (DUO trial) - Relapsed/Refractory



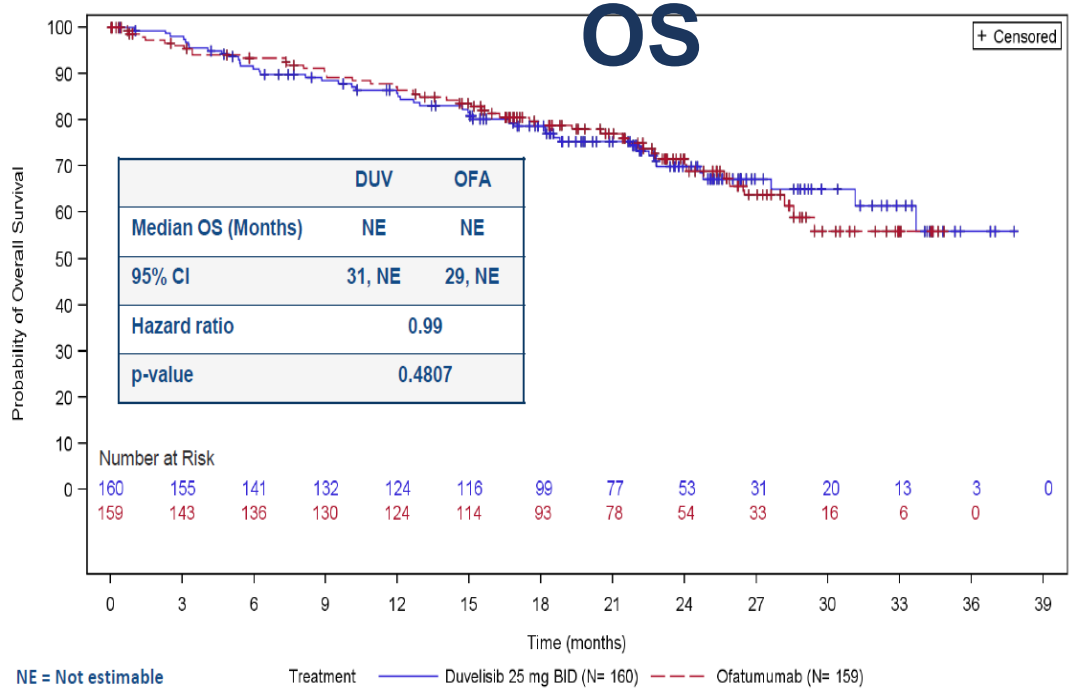
PFS

	DUV	OFA
Median PFS (Months)	13.3	9.9
95% CI	12.1, 16.8	9.2, 11.3
Hazard ratio	0.52	
p-value	< 0.0001	



OS

	DUV	OFA
Median OS (Months)	NE	NE
95% CI	31, NE	29, NE
Hazard ratio	0.99	
p-value	0.4807	



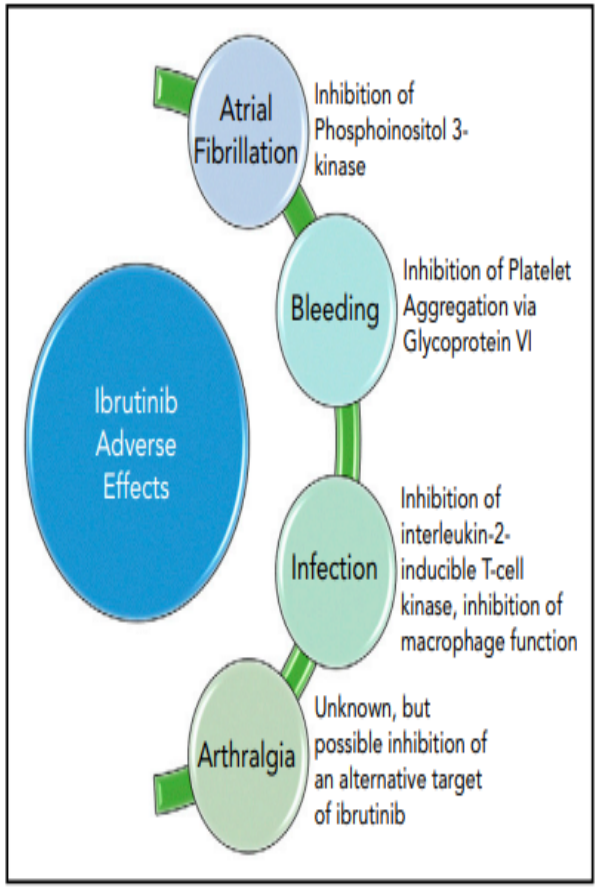
NE = Not estimable

Flinn, Blood, 2018

Novel Agents for R/R setting

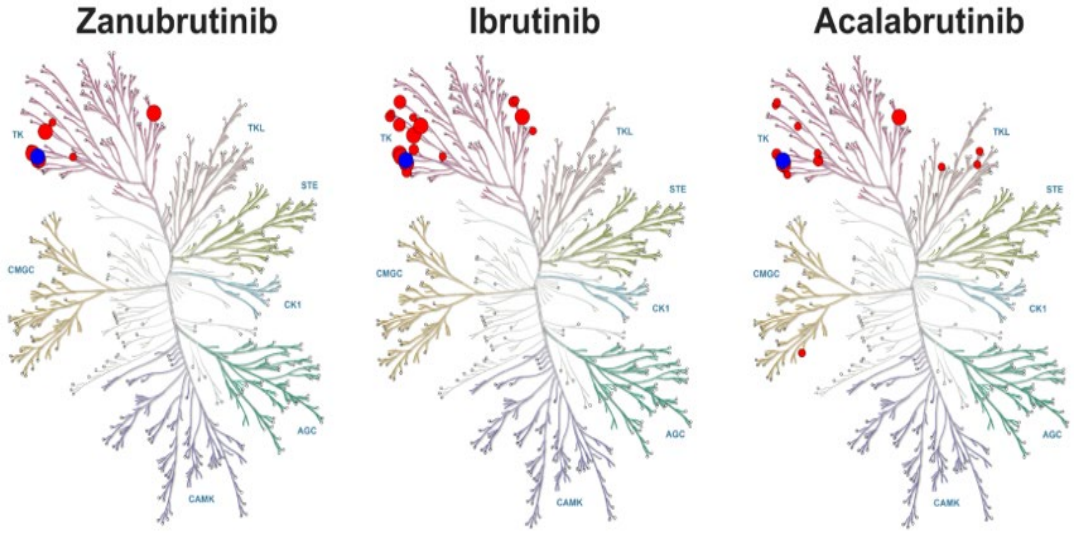
	BTKis	Venetoclax	Pi3Kis
Target	BTK	BCL-2	PI3K delta+gamma / delta
Duration	Indefinite	2-years	Indefinite
Addition of Anti CD20 Ab	No major benefit Faster “response”	Recommended	Idelalisib + R Duvelisib monotherapy
Major side effect (concern)	Bleeding (anticoagulation) Cardiac in pts with past hx	TLS (initially)	Colitis (diarrhea) Infections (FDA alert)
Other side effects	• Body pain • Fatigue • Hypertension • A fib	• Neutropenia	• Pneumonitis • Transaminitis (mainly idela) • PJP • CMV
FDA label for CLL	All settings	All settings	Relapsed

Choice of BTKi



Treatment discontinuation rates due to toxicity

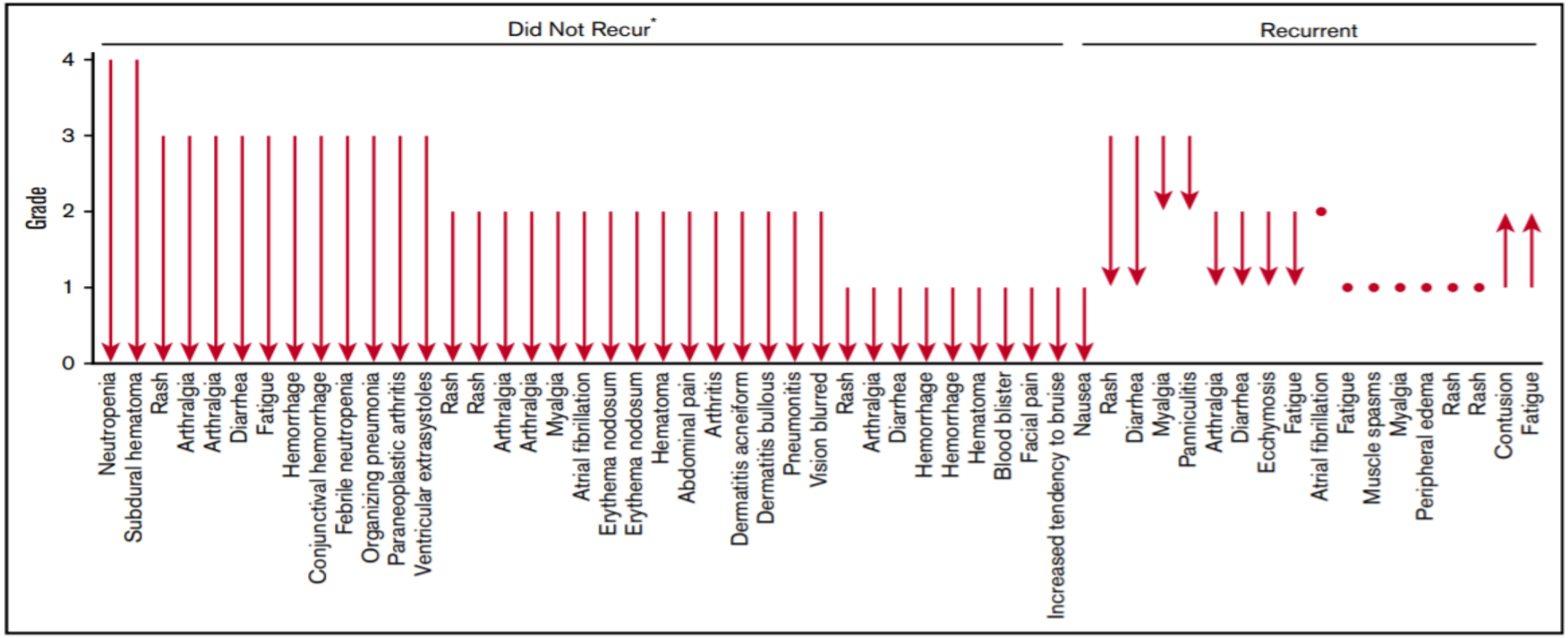
Ibrutinib	Frontline: 15% Relapsed: 22%
Acalabrutinib	Frontline: no data Relapsed: 12%



Assayed by Reaction Biology Corp. at 100X of IC_{50} (against BTK) concentration with IC_{50} (BTK)s of 0.71±0.09, 0.32±0.09, 24±9.2, 63±28 and 15±5.5 nM (n=3), for zanubrutinib, ibrutinib, acalabrutinib, M27, and orelabrutinib, respectively.

Mato, Haematologica, 2018 ; Yazdi,ASH,2019; Roeker, Clin Cancer Research, 2019 ;Shadman, ASH,2019; Stephens, Blood, 2019

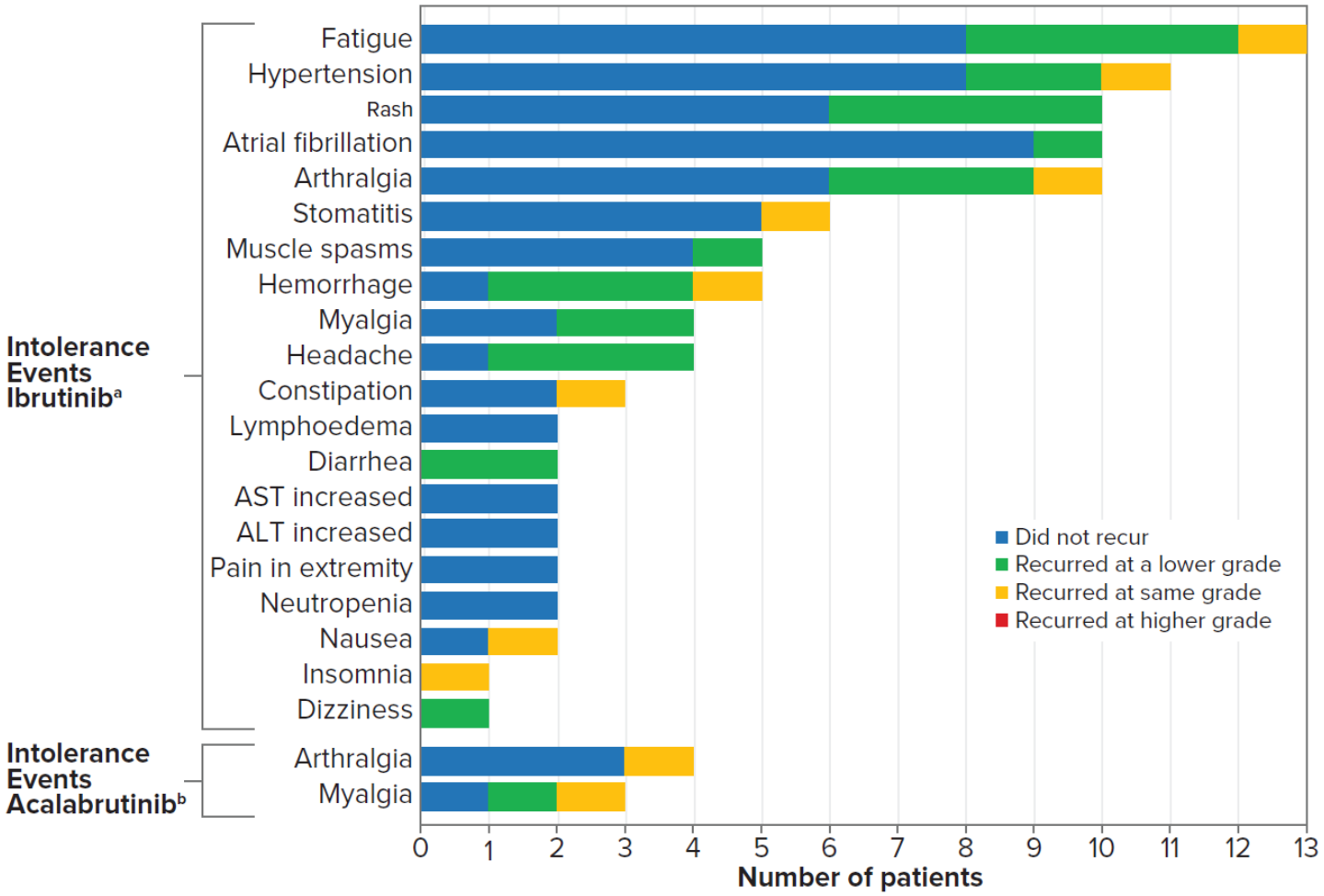
Acalabrutinib in Ibrutinib intolerant patients



of 61 ibrutinib-related AEs associated with intolerance, 72% did not recur and 13% recurred at a lower grade with acalabrutinib

Awan, Blood Adv, 2019

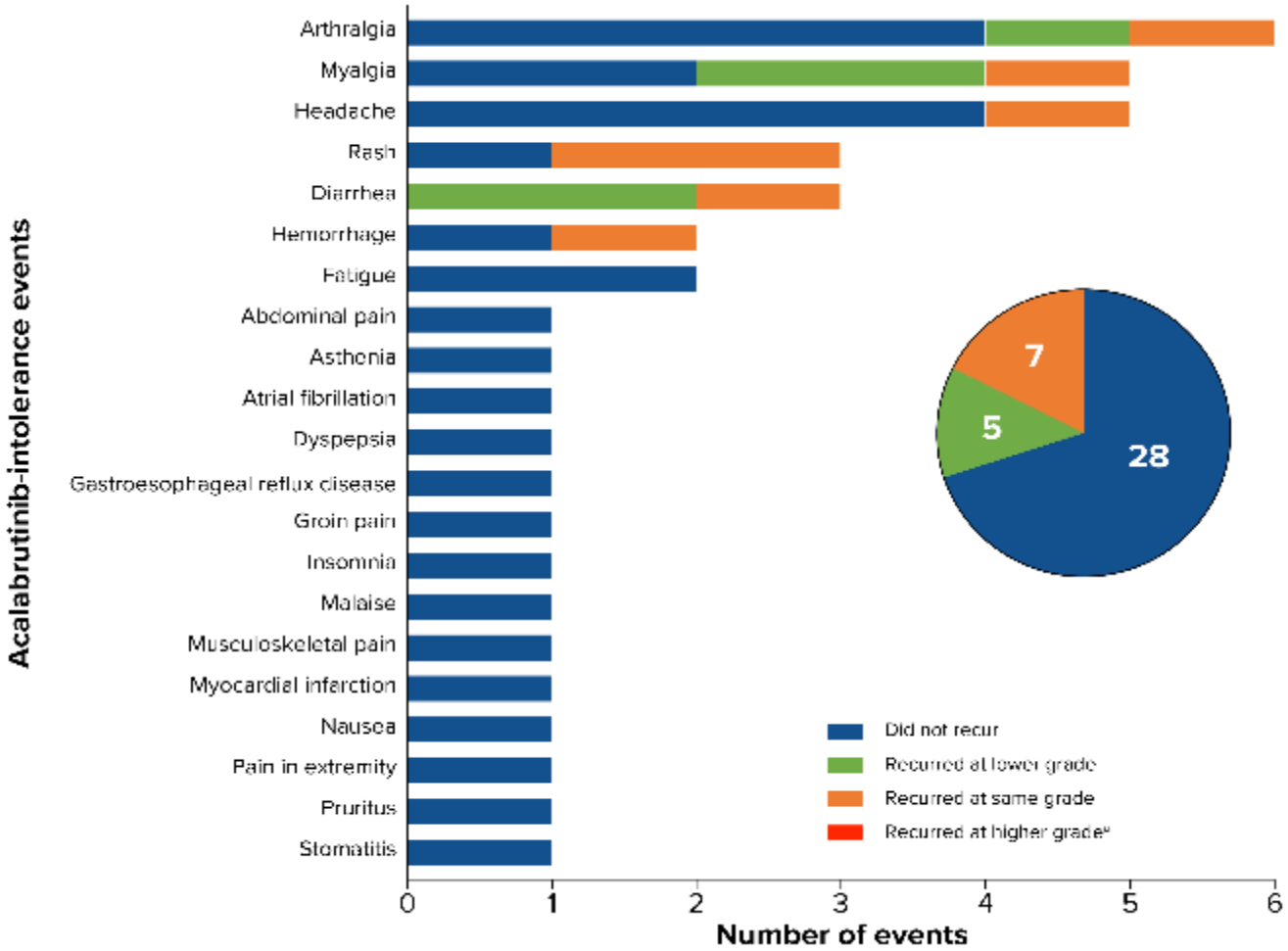
Zanubrutinib in Acalabrutinib/Ibrutinib intolerant patients



- 34/57 (59.6%) of patients who took ibrutinib and 7/10 (70.0%) of patients who took acalabrutinib did not have recurrence of any intolerance event
- No ibrutinib or acalabrutinib intolerance events recurred at a higher severity
- 81/115 (70.4%) ibrutinib intolerance events and 15/18 (83.3%) acalabrutinib intolerance events did not recur
- 25/38 (65.8%) grade 3 ibrutinib intolerance events and 3/4 (75.0%) grade 3 acalabrutinib intolerance events did not recur while on zanubrutinib
- All grade 4 intolerance events (neutropenia [n=2], ALT increase [n=1], AST increase [n=1]) did not recur on zanubrutinib
- 1 patient (1.5%) discontinued zanubrutinib due to recurrence of a prior intolerant event (myalgia; acalabrutinib)

Shadman, Lancet Haematology, 2023

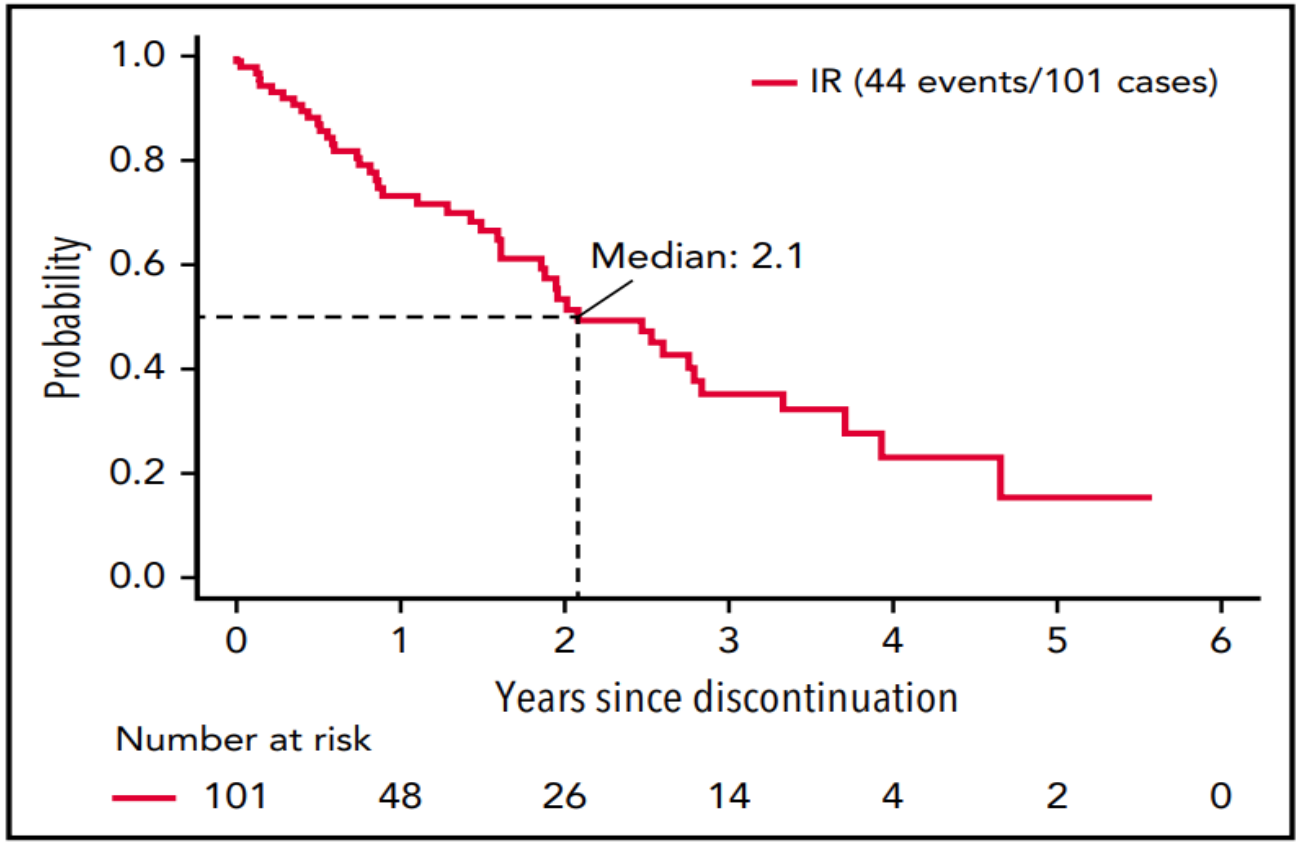
Zanubrutinib in Acalabrutinib-Intolerant Patients



- 40 acalabrutinib-intolerance events were reported by 27 patients
- Most (70%) of acalabrutinib-intolerance events did not recur at any grade with zanubrutinib treatment, and of the 12 events that did recur, none recurred at a higher severity, 7 recurred at the same grade, and 5 recurred at a lower grade
- 63% of patients did not experience any recurrence of their prior acalabrutinib-intolerance events

Shadman M, et al. ASH 2023. Abstract 3279.

PFS from discontinuation of ibrutinib: (off treatment)

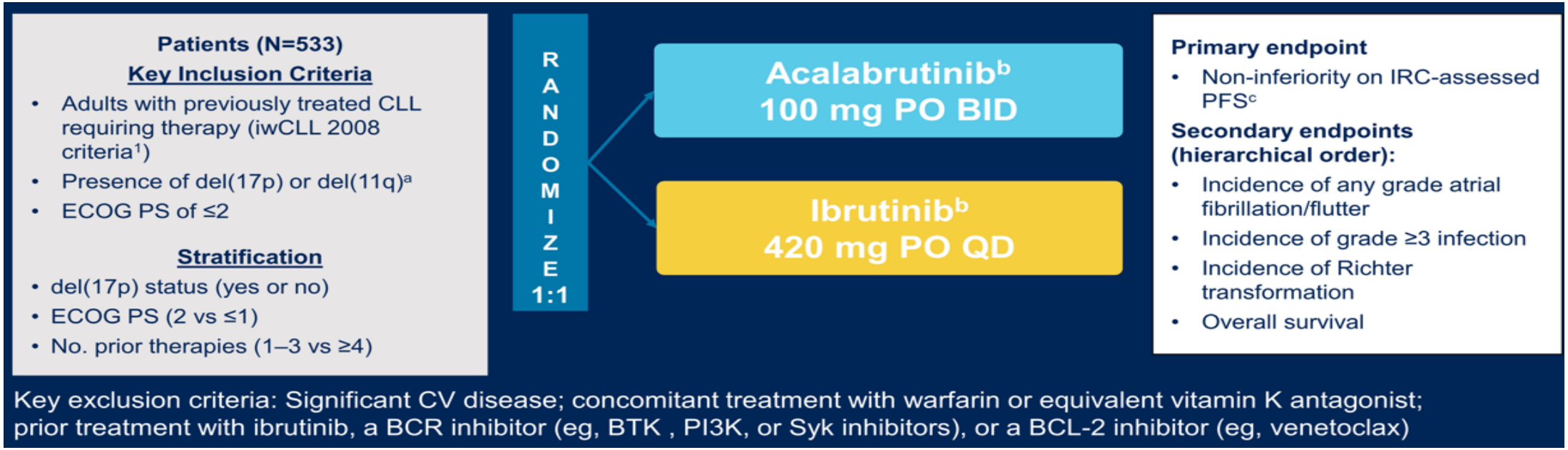


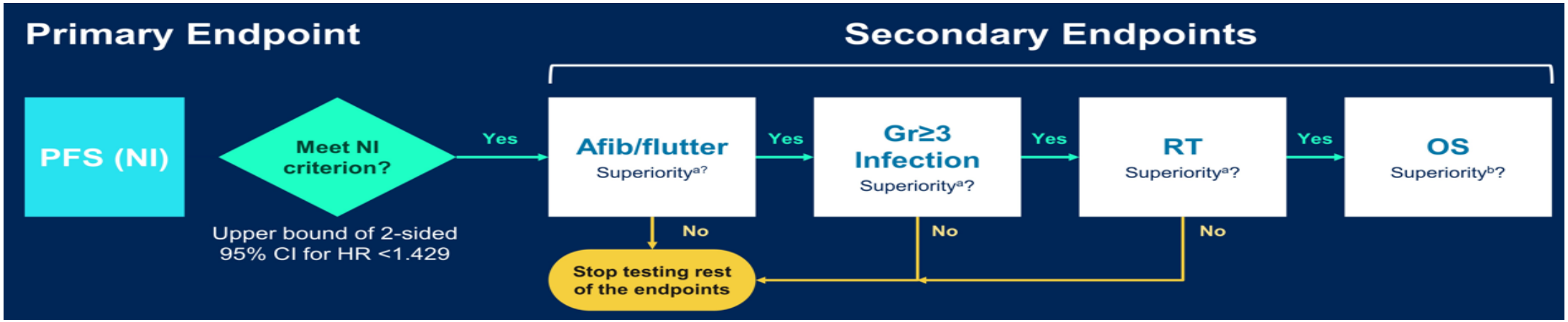
- Consider “watch and wait” strategy in patients who stop BTKis after more than 2 years for intolerance

The median time on ibrutinib was 25.9 months (range, 0.2-82.0 months)

Shanafelt, Blood, 2022

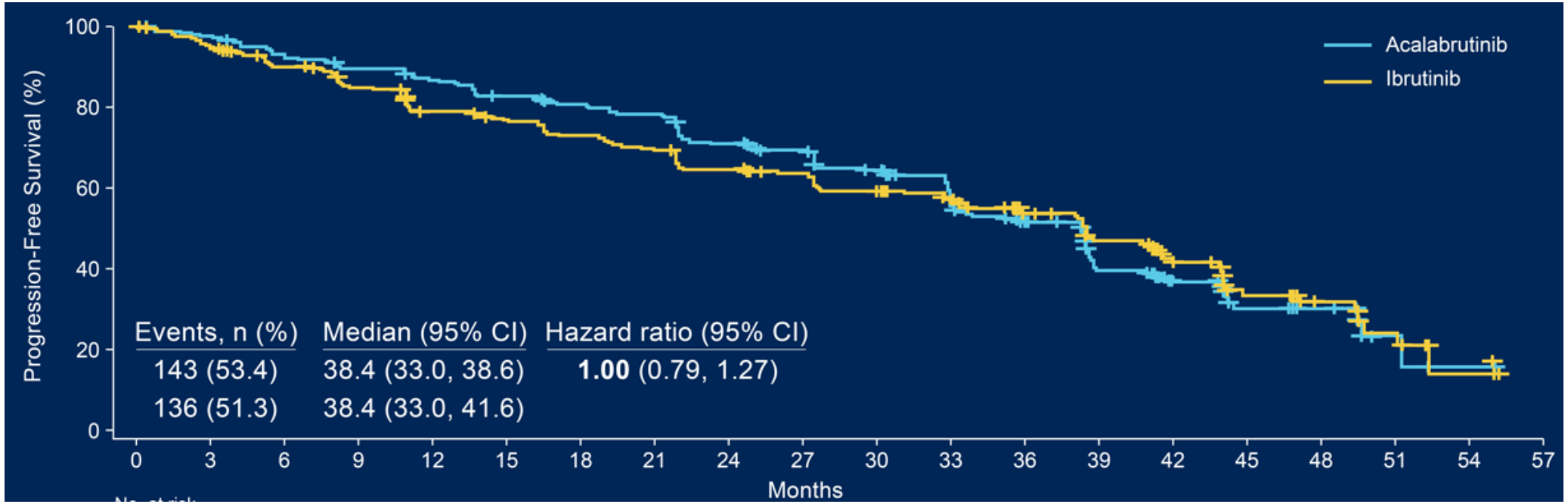
Ibrutinib vs. Acalabrutinib (ELEVATE-RR)





Byrd, ASCO, 2021

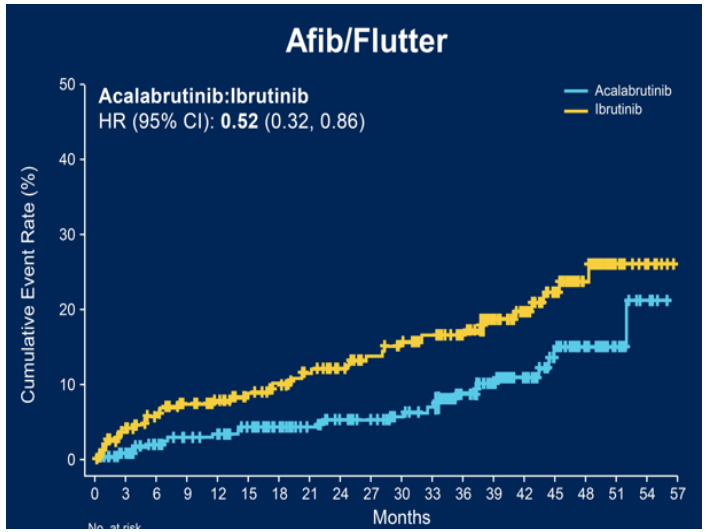
Ibrutinib vs. Acalabrutinib (ELEVATE-RR)

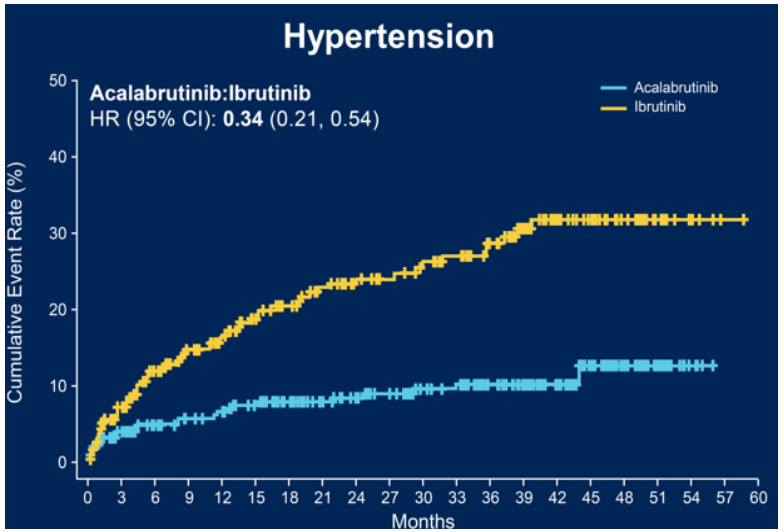


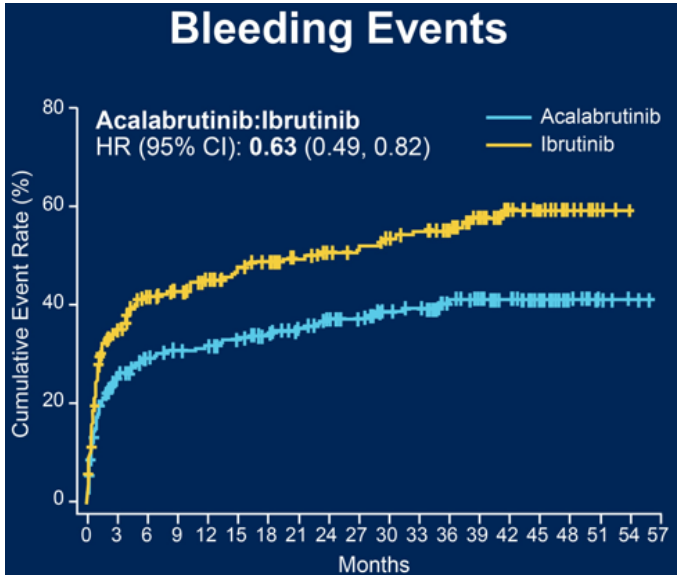
- High-risk patients only:
  - Del 17p: 45%
  - TP53 mutated 37-42%
  - Unmutated IGVH 82-89%
- Stopped because of adverse events:
  - 14.9% in acalabrutinib and 22.3% in ibrutinib group

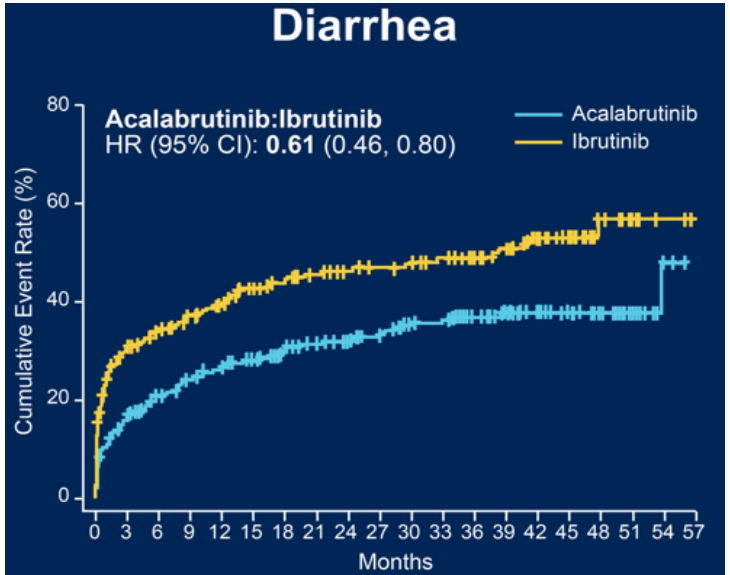
Byrd, ASCO, 2021

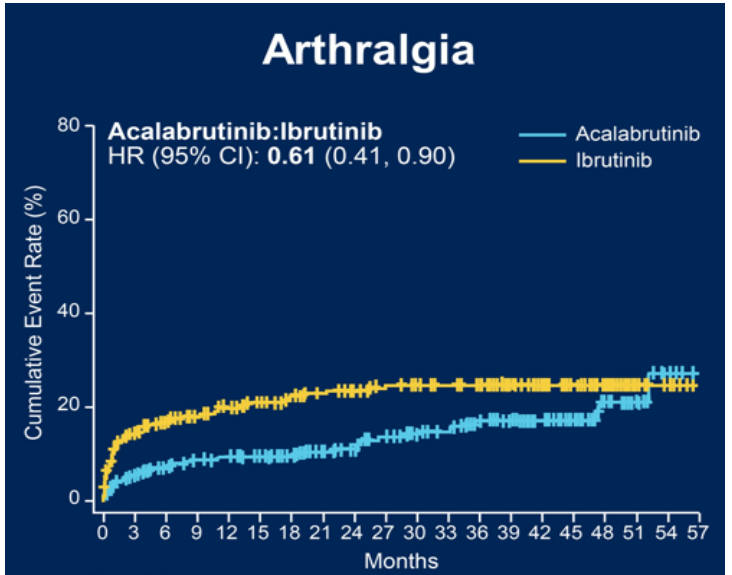
Ibrutinib vs. Acalabrutinib (ELEVATE-RR)











Zanubrutinib vs Ibrutinib in r/r CLL (ALPINE)

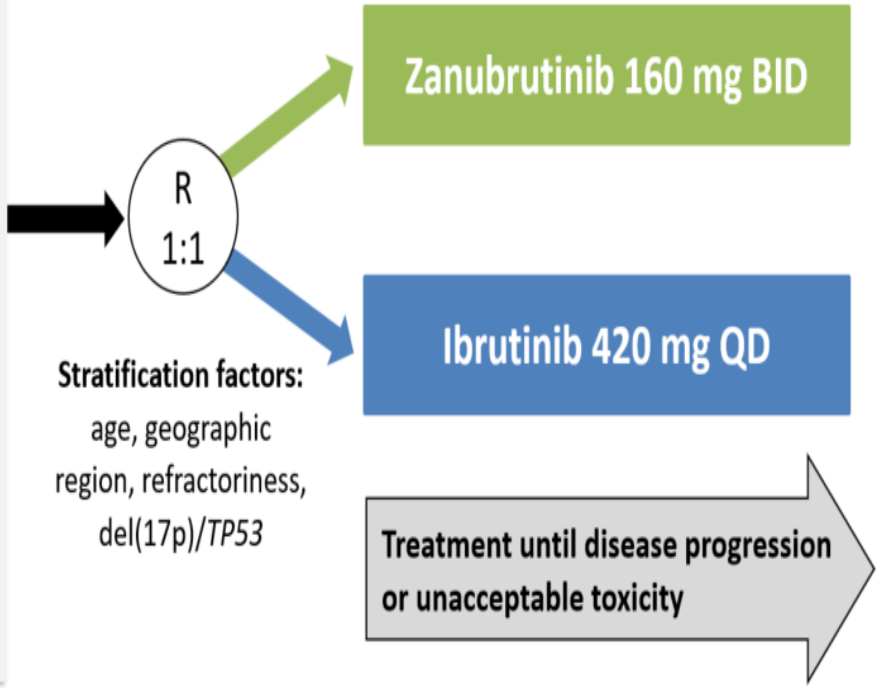
R/R CLL/SLL with ≥ 1 prior treatment
(Planned N=600, Actual N=652)

Key Inclusion Criteria

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

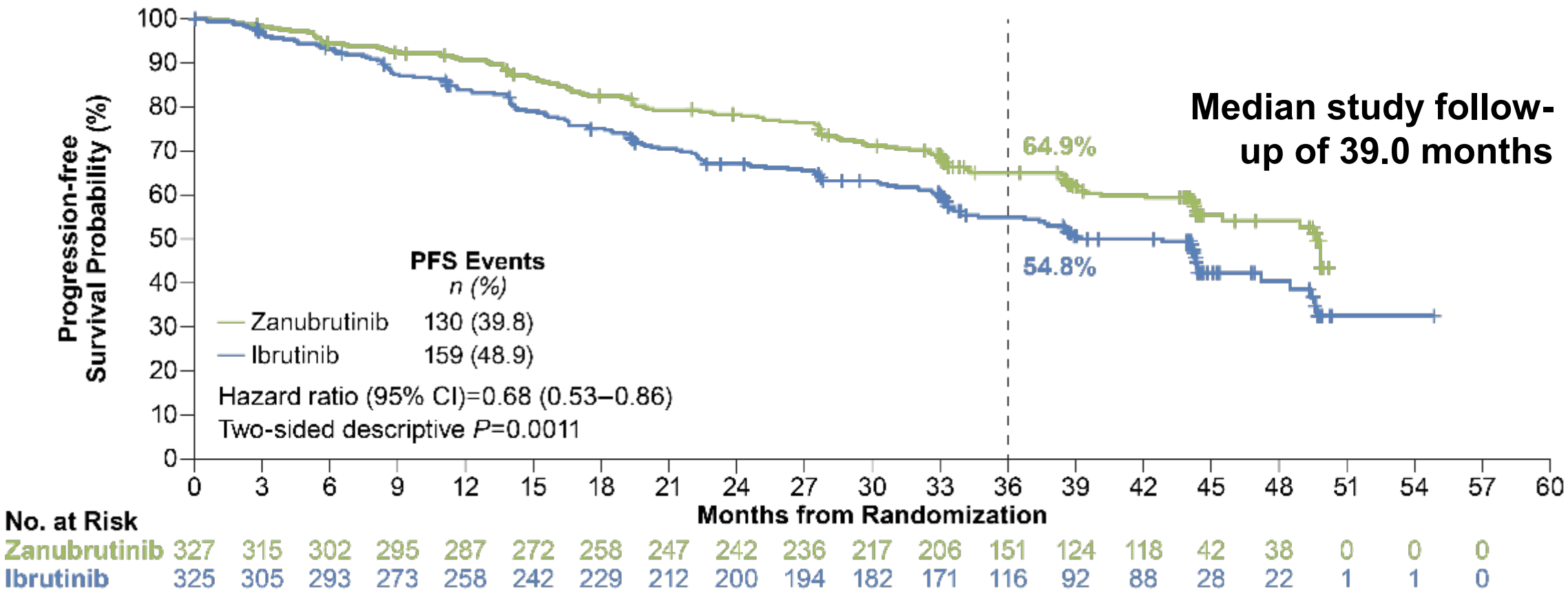
Key Exclusion Criteria

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



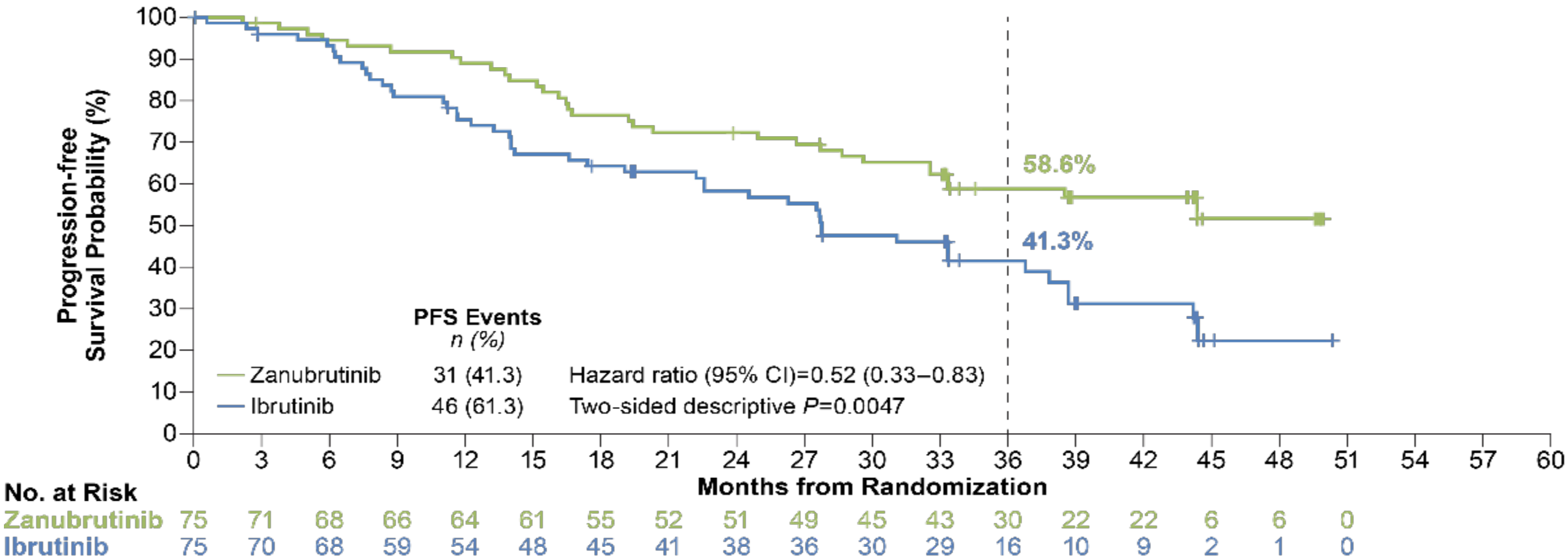
Brown, NEJM,2023

ALPINE Efficacy: PFS Extended Follow-Up



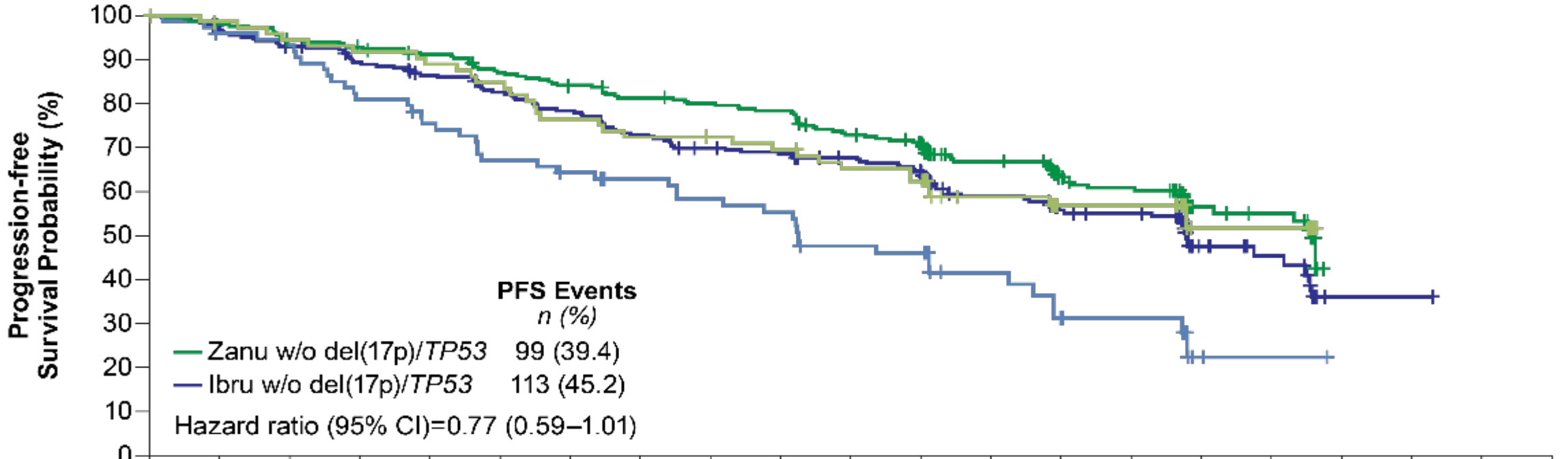
Brown JR, et al. *N Engl J Med.* 2023; 388:319-332; Brown JR, et al. ASH 2023. Abstract 202. Brown JR, Blood, *in press*

ALPINE Efficacy: PFS in Del(17p)/*TP53*^{mut} Extended Follow-Up



Brown JR, et al. *N Engl J Med.* 2023; 388:319-332; Brown JR, et al. ASH 2023. Abstract 202. Brown JR, Blood, *in press*

ALPINE: Zanubrutinib Demonstrated Robust PFS Benefit Independent of Del(17p)/*TP53* Mutation Status

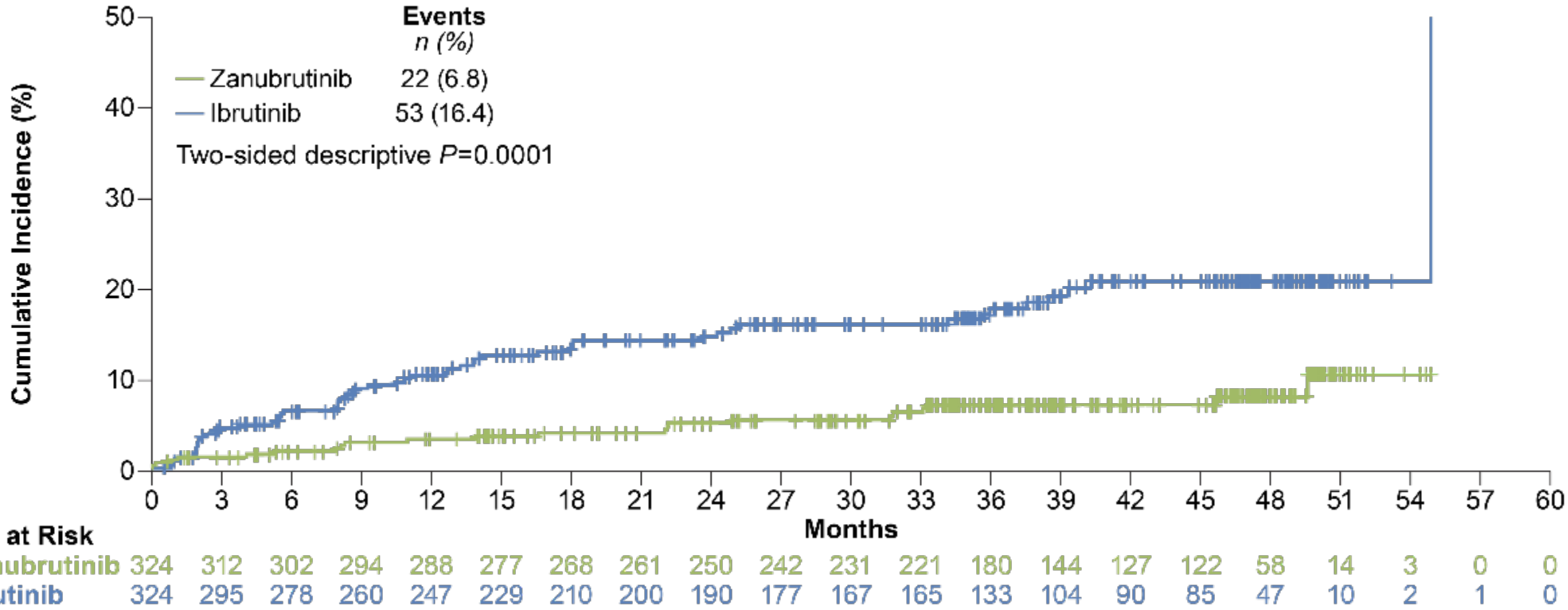


No. at Risk

Zanu with del(17p)/*TP53*	75	71	68	66	64	61	55	52	51	49	45	43	30	22	22	6	6	0	0	0
Ibru with del(17p)/*TP53*	75	70	68	59	54	48	45	41	38	36	30	29	16	10	9	2	1	0	0	0
Zanu w/o del(17p)/*TP53*	251	243	233	228	222	211	203	195	191	187	172	163	121	102	96	36	32	0	0	0
Ibru w/o del(17p)/*TP53*	250	235	225	214	204	194	184	171	162	158	152	142	100	82	79	26	21	1	1	0

Brown JR, et al. *N Engl J Med.* 2023; 388:319-332; Brown JR, et al. ASH 2023. Abstract 202. Brown JR, Blood, *in press*

ALPINE: Atrial Fibrillation/Flutter Events



Brown JR, et al. *N Engl J Med.* 2023; 388:319-332; Brown JR, et al. ASH 2023. Abstract 202. Brown JR, Blood, *in press*

BTKi inhibitors

Drug	Binding to BTK	Reversibility	BTKi generation	Use after progression after a 1st or 2nd gen BTKI?	Selectivity for BTK	Use after intolerance to other BTKis?
Ibrutinib	Covalent	Irreversible	First	No	No	Yes, but unlikely to be helpful
Acalabrutinib	Covalent	Irreversible	Second	No	Yes	Yes
Zanubrutinib	Covalent	Irreversible	Second	No	Yes	Yes
Pirtobrutinib	Non-Covalent	Reversible	Third	yes	Yes	Yes
Nemtabrutinib*	Non-Covalent	Reversible	Third	Potentially	Maybe	Need more data
BGB-16673*	Degrader		Fourth			
NX-5948*	Degrader		Fourth			

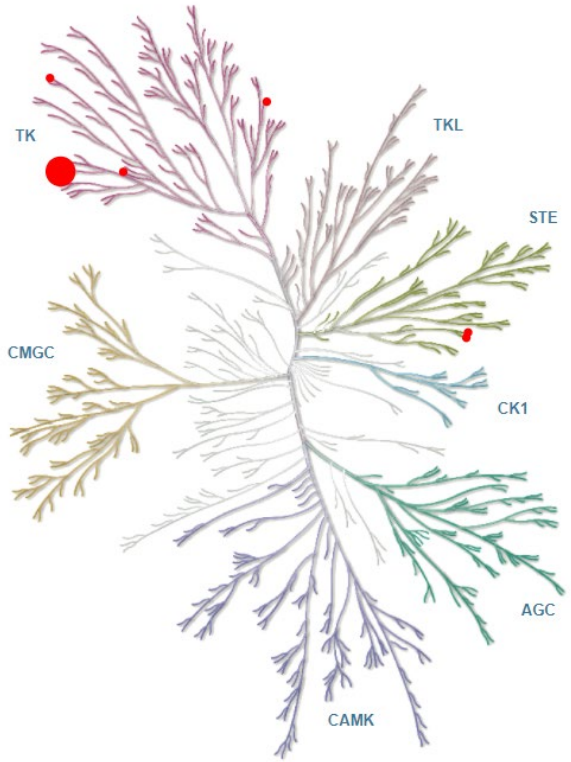
* Not FDA approved for CLL as of September 2024

Pirtobrutinib for r/r CLL

- A third generation BTKi
- Reversible (non-covalent) BTKi
- High selectivity for BTK
- Potency against WT & C481-mutant BTK in cell and enzyme assays

- **Phase 1/2 study included high-risk patients (n=261):**
  - Prior BTKi 100% ; BTKi PD 77%
  - Prior Venetoclax 41%
  - Prior CAR-T 6%
  - BTK C481 mutant 38%
  - PLCG2 mutant 8%
  - Abnormal TP53 46% ; both del and mut 28%
  - Unmutated IGHV 84%

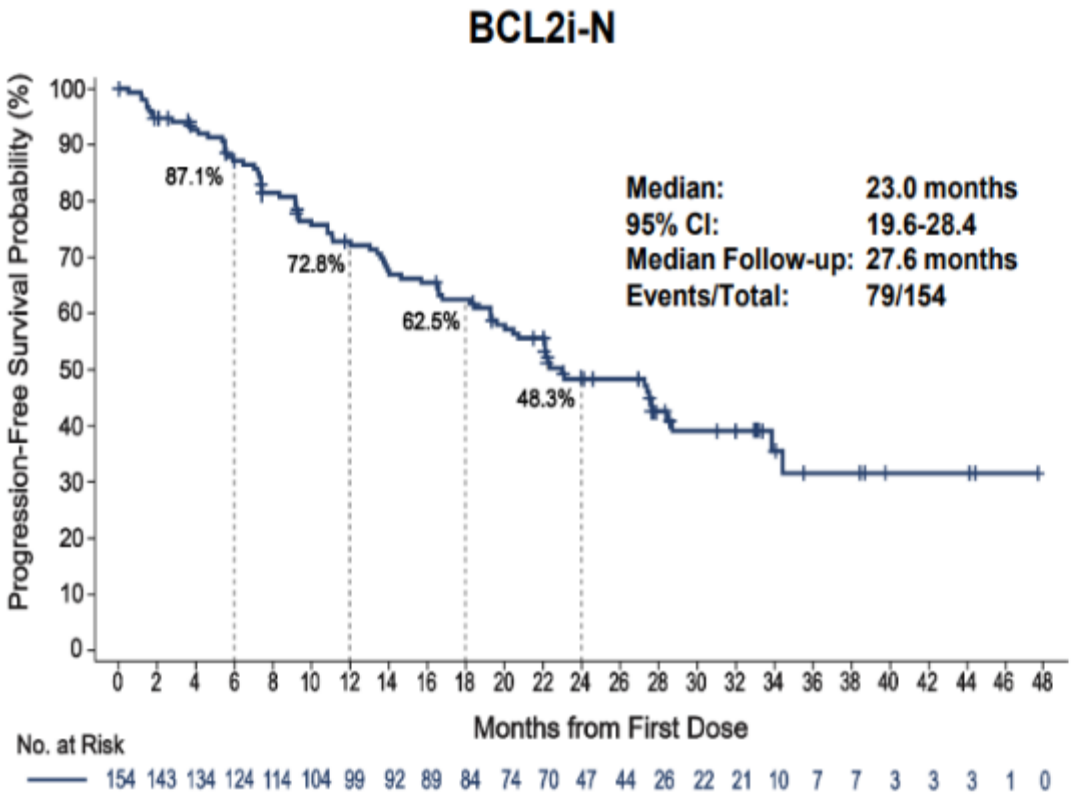
Kinome selectivity
Highly selective for BTK

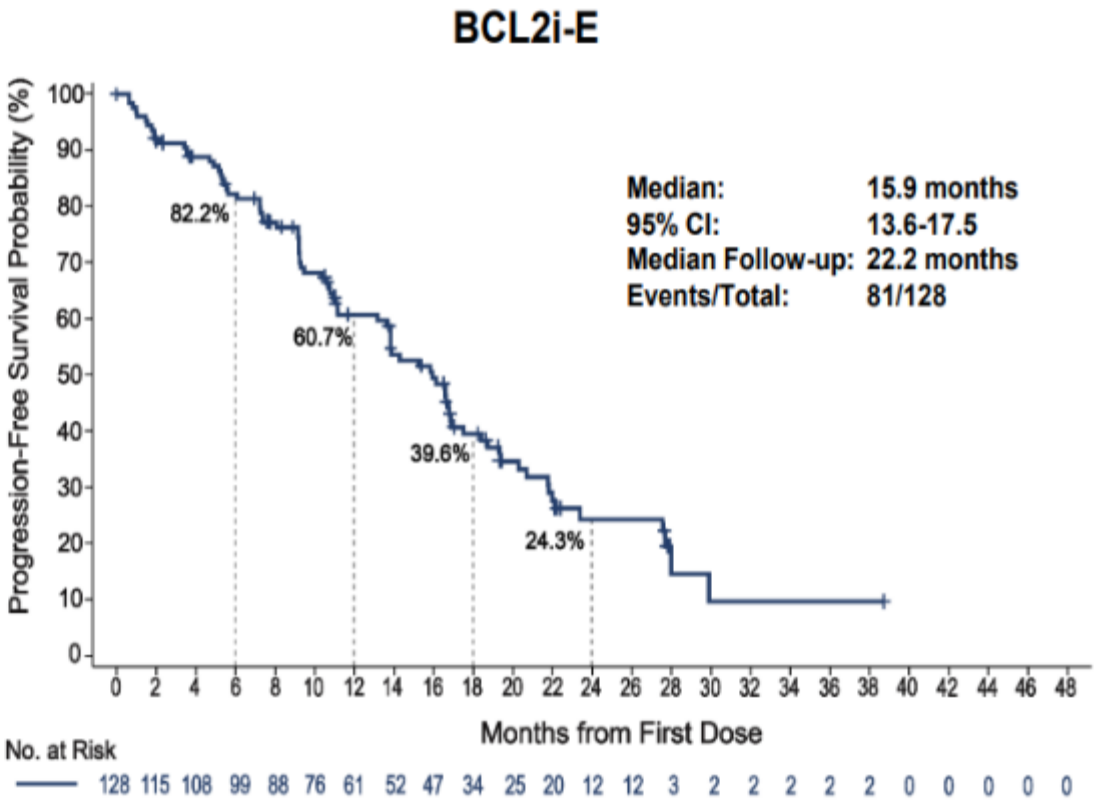


Mato, NEJM, 2023

Pirtobrutinib for r/r CLL

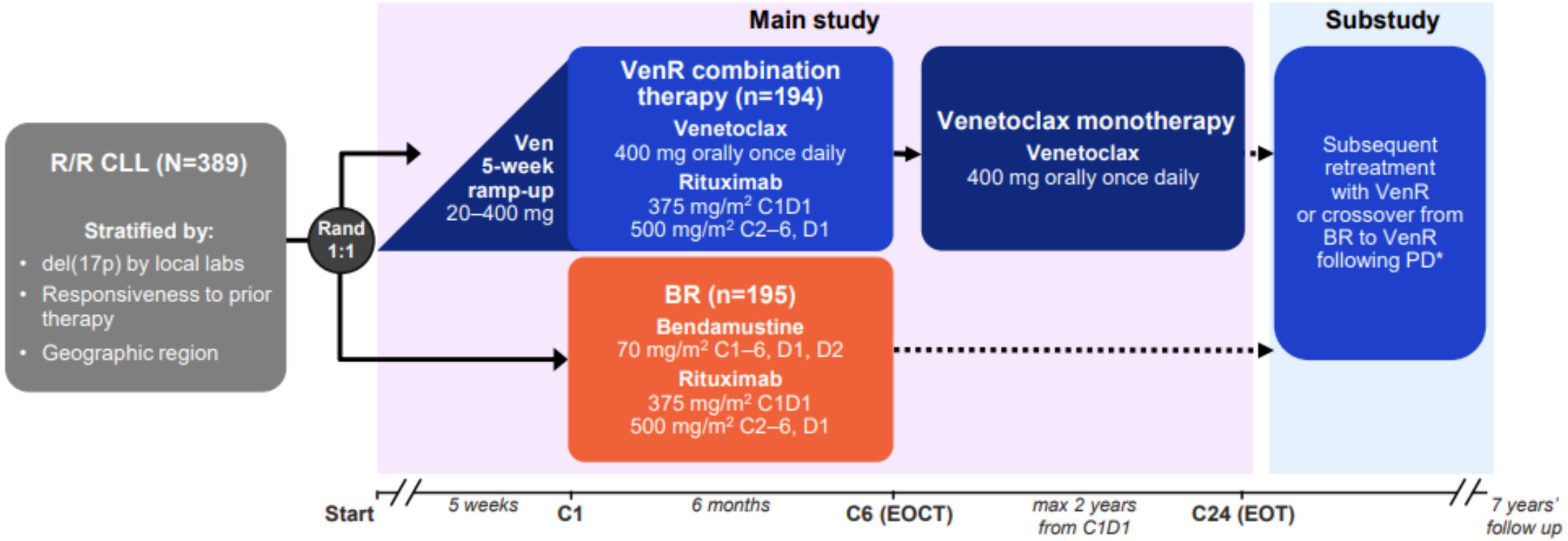
Pirtobrutinib Progression-free Survival With Prior cBTKi, With or Without Prior BCL2i





Mato, NEJM,2023; Woyach JA, et al. ASH 2023. Abstract 325.

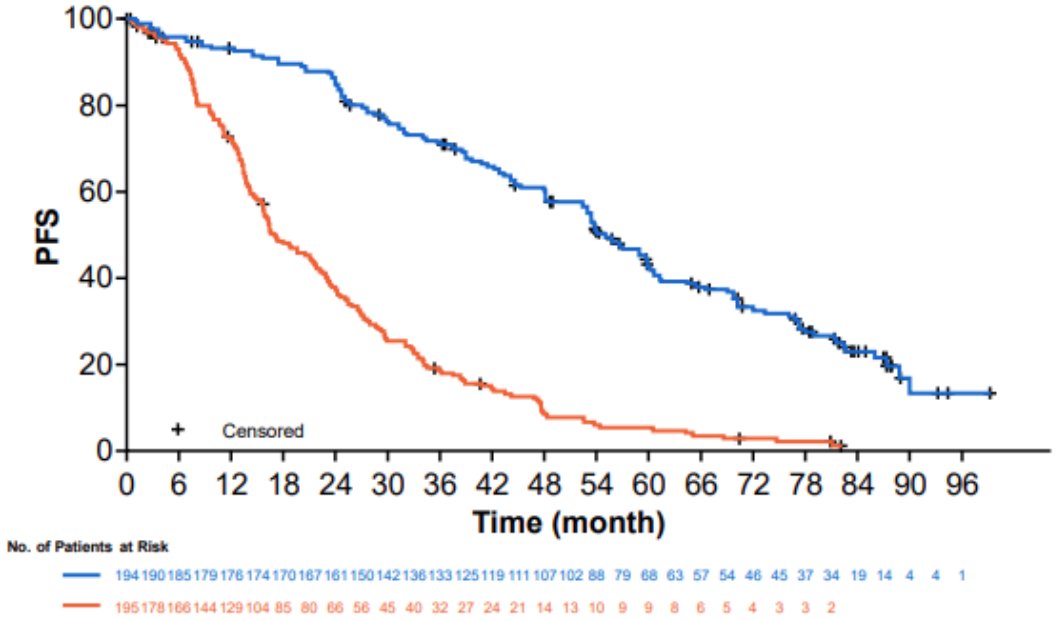
Ven-R vs. BR in R/R CLL (MURANO Study)



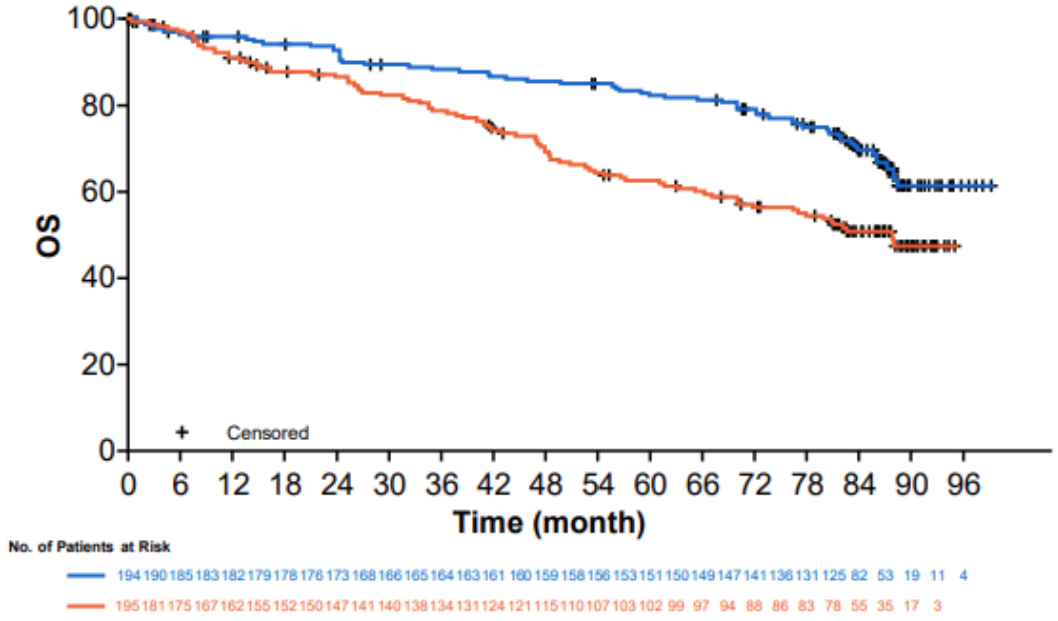
Kater, 17-ICML,

Ven-R vs. BR in R/R CLL (MURANO Study): 7-year follow-up

	Median PFS (95% CI), months	HR* (95% CI)	7-year PFS (%)
VenR (n=194)	54.7 (52.3–59.9)	0.23 (0.18–0.29) Stratified P-value <0.0001†	23.0
BR (n=195)	17.0 (15.5–21.7)		NE



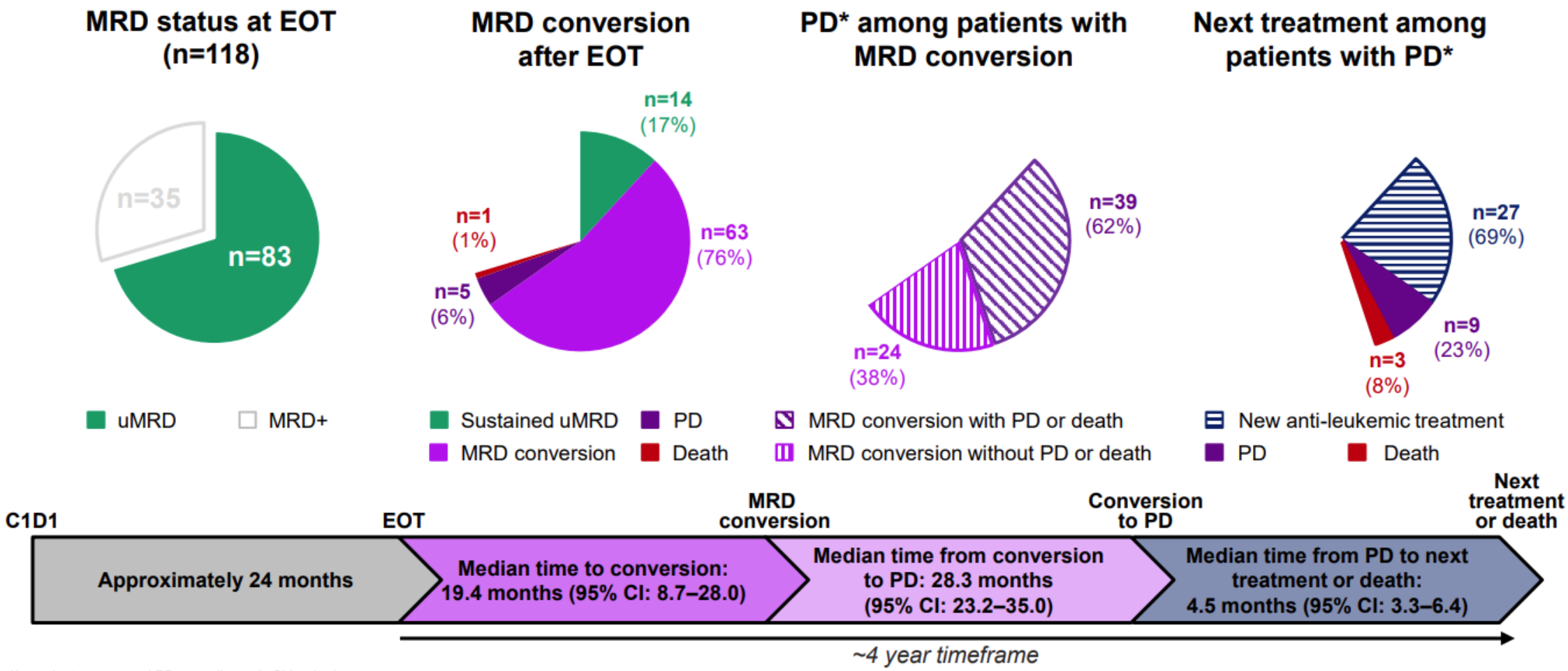
	Median OS (95% CI), months	HR‡ (95% CI)	7-year OS (%)
VenR (n=194)	NE	0.53 (0.37–0.74) Stratified P-value <0.0002†	69.6
BR (n=195)	87.8 (70.1–NE)		51.0



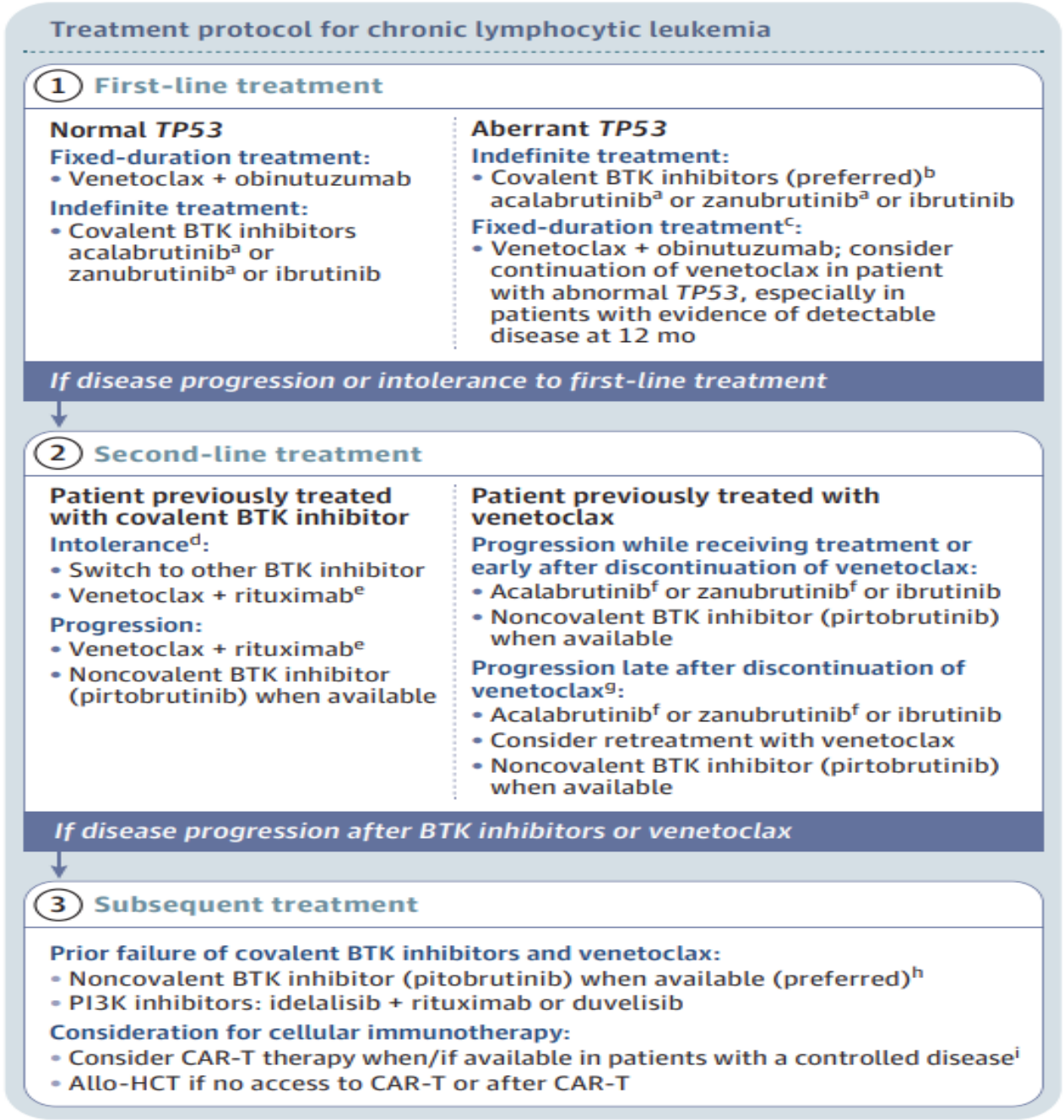
- Median follow up for efficacy (range) was 86.8 months (0.3–99.2) for VenR and 84.4 months (0.0−95.0) for BR
- No new safety signals were identified since the 5-year data cut,[1] with all patients outside of the AE reporting window§

Kater, 17-ICML,

Delay between MRD Conversion and Clinical Progression



Kater, 17-ICML,

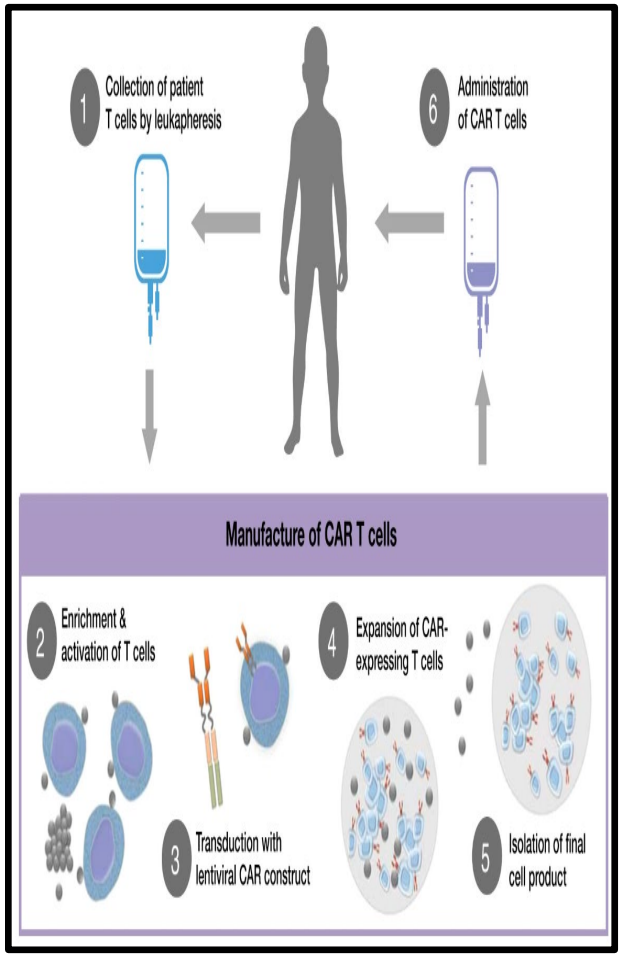


Shadman, JAMA,2023

Cellular therapies for CLL

CAR-T for CLL

- Investigational, not FDA approved
- Registration studies are currently ongoing
- Long-term remissions ~ 30-35%
- Best predictor od response: MRD neg after treatment
- Recommend before alloSCT, if available



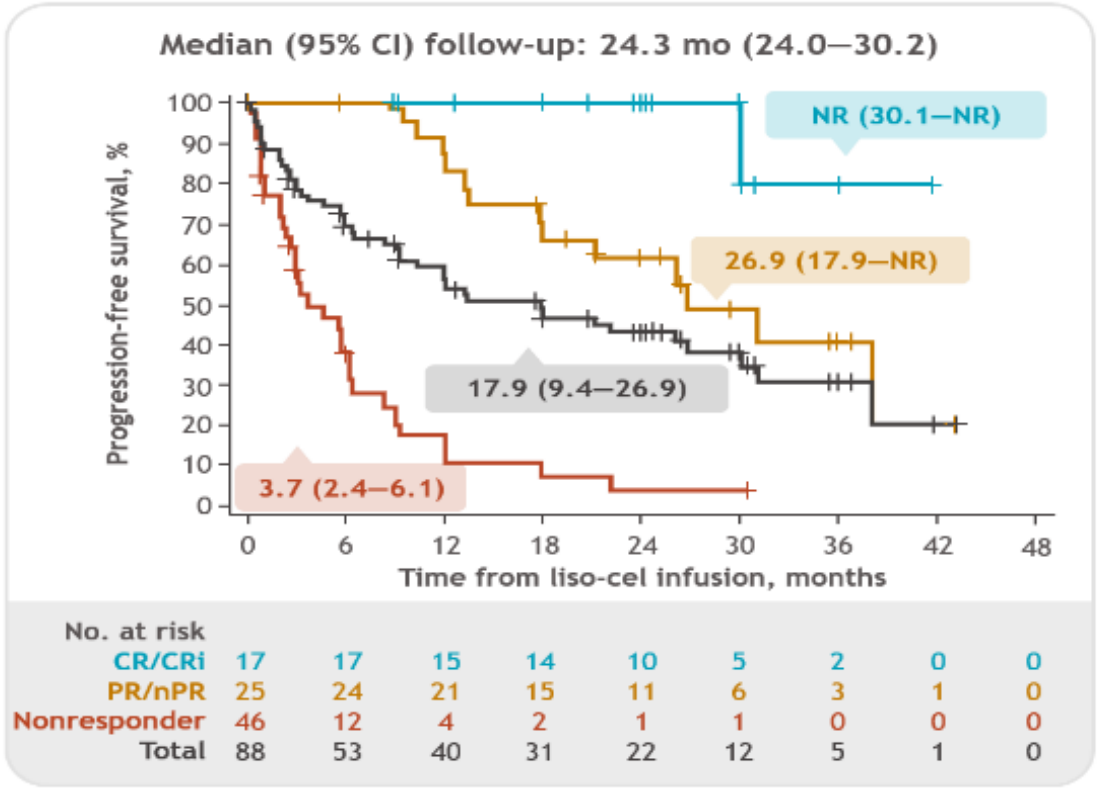
lisocabtagene maraleucel (liso-cel) for CLL

- CD19 directed CAR-T
- N=127
- High-risk features:
  - del17p (43%%), mutated TP53 (46%), complex karyotype (48%)
  - Ibrutinib refractory (88%), Venetoclax refractory (77%), double refractory (61%)
- Side effects
  - Grade 3-4 CRS: 9% , grade 3-4 neurotoxicity: 19%
- Responses:
  - **CR/Cri: 18%**
  - Undetectable MRD in blood (65%) and bone marrow (59%)
- Follow-up
  - Median follow-up 20.8 months
  - Median duration of response (not reached) – more than half of the responders have not relapsed

Siddiqi, Lancet, 2023

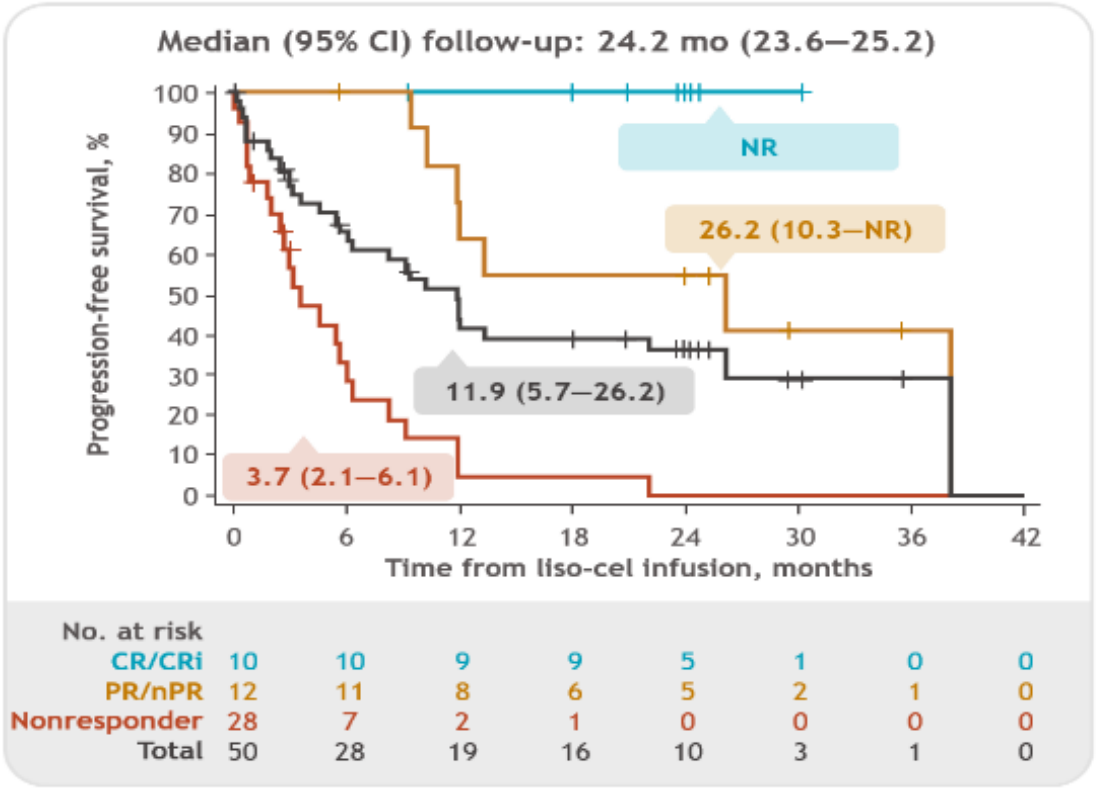
Lisocabtagene Maraleucel (liso-cel) for CLL

(A) Full study population at DL2 (n = 88)



No. at risk									
CR/CRi	17	17	15	14	10	5	2	0	0
PR/nPR	25	24	21	15	11	6	3	1	0
Nonresponder	46	12	4	2	1	1	0	0	0
Total	88	53	40	31	22	12	5	1	0

(B) PEAS (BTKi progression/venetoclax failure subset) at DL2 (n = 50)



No. at risk									
CR/CRi	10	10	9	9	5	1	0	0	
PR/nPR	12	11	8	6	5	2	1	0	
Nonresponder	28	7	2	1	0	0	0	0	
Total	50	28	19	16	10	3	1	0	

Data on KM curves are expressed as median (95% CI, if available).

Siddiqi T, et al. ASH 2023 [Presentation #330]

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Siddiqi T, et al. ASH 2023. Abstract 330.

Allogeneic SCT for High Risk CLL

- Reduced intensity/ Nonmyeloablative allogeneic transplant

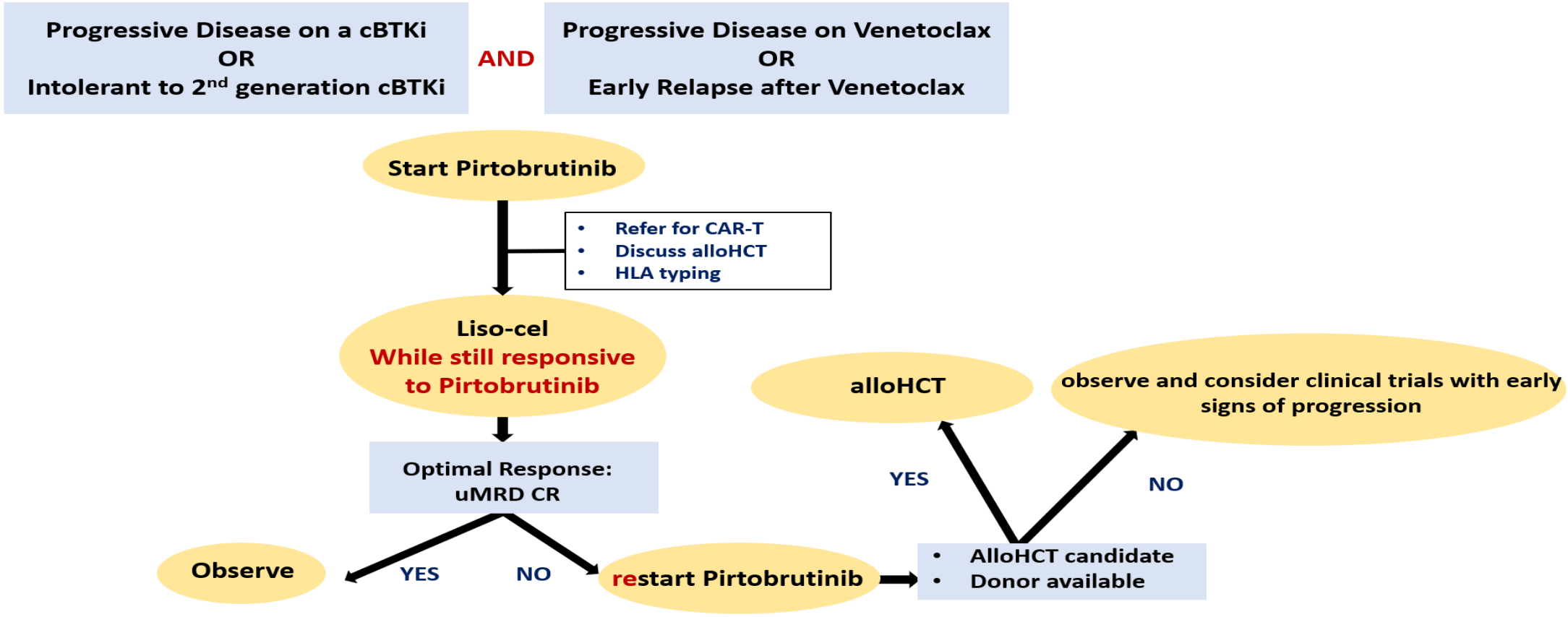
Author	Kim	Roeker	Paul	Shadman	Andersen
Year	**2020**	**2020**	**2020**	**2019**	**2019**
N	108	65	64	55	432
Conditioning	RIC	RIC	RIC (haplo)	NMA	RIC/NMA
Follow-up (yr)	3	2	4	3	5
OS	**69-87**	**81**	**52**	**54**	**46-52**
PFS	**58-72**	**63**	**37**	**45**	**38-43**
NRM	**7-17**	**13**	**24**	**38 (<12)***	**32-35**
aGVHD (3-4)	8-13	24	3	20	?
Extensive cGVHD	45-57	27	7	66	?

50
40
20-25

*** in pts without comorbidities**

Shadman, Hematol Oncol Clin N Am, 2021

Suggested Approach for Treating Patients with “Double Refractory” CLL



Summary facts:

1. Covalent BTKi (indefinite) and venetoclax + anti CD20 abs (fixed-duration) are the first 2 options and they are both reasonable to be used in first-line
2. Second generation cBTKis (zanubrutinib or acalabrutinib) are preferred over ibrutinib
3. Obinutuzumab is the preferred anti CD20 ab (vs. rituximab) in CLL
4. MRD is an important prognostic marker for time-limited therapies (chemo, Venetoclax, CAR-T). However, MRD-guided therapy is considered investigational at the current time. Studies are ongoing.
5. The field is moving toward combination therapy with Venetoclax as the backbone plus a BTKi with or without the CD20 antibodies.
6. Pirtobrutinib, liso-cel (CD19 CART) are options for patients with “double refractory” disease after covalent BTKi and BCL2 inhibitors
7. It is critical to have good disease control before CAR-T therapy. Refer for CAR-T when disease is stable on pirtobrutinib
8. Venetoclax + Ibrutinib is approved in Europe and Canada but not in the US.
9. Expected approvals: venetoclax+acalabrutinib
10. In the pipeline: BTK degraders, bispecific abs (CD20/CD30; CD20/CD8), Novel autologous and allogeneic immune effector cell therapy, new BCL2 inhibitors, etc.

CLL (Night before the test)

1. Flow cytometry is critical (and adequate) to make the diagnosis
2. Remember CLL immunophenotype (and differences with MCL and other lymphomas)
3. Review Indications for treatment. This hasn't change even with new agents.
4. Check FISH before each line of treatment (r/o del 17p/P53 mutation)
5. Frontline: Ven-O or BTKi (acalabrutinib or zanubrutinib)
6. Relapsed setting: Ven-O(or R) or BTKi (acalabrutinib or zanubrutinib), Pirtobrutinib. Liso-cel, idelalisib/duvelisib.
7. BTKi AEs (less with 2nd gen): initial lymphocytosis (is OK), bleeding, Afib, HTN, body pain.
8. Idelalisib/duvelisib: lymphocytosis (is OK), colitis, pneumonitis, hepatitis (more with idela), PJP, CMV – Don't use in frontline setting
9. Venetoclax: watch for TLS at the beginning. Ramp-up HAS to be done!
10. Liso-cel: CRS,ICANS, prolonged cytopenia, infection

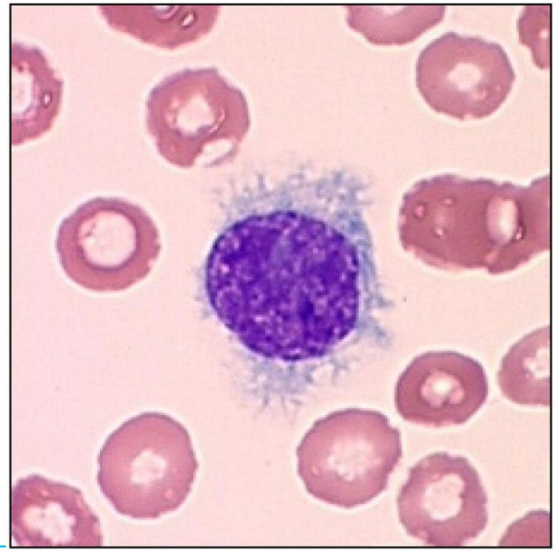
Hairy Cell Leukemia

Hairy Cell Leukemia

- Uncommon chronic B cell lymphoid neoplasm

- Small mature B cell lymphoid cells with abundant cytoplasm and "hairy" projections within the peripheral blood, bone marrow, and splenic red pulp

- Splenomegaly and cytopenias



Hairy cell Leukemia: (Diagnosis)

	CD11c	CD25	CD103	CD123	CD10	CD21	CD23	CD5	CD20	CD19	CD22	Annexin A1
HCL	+	+	+	+	-	-	-	-	+	+	+	+

BRAF V600E mutation is a disease-defining event

HCL variant:

CD25 (-) , CD123 (-), annexin A1 (-) and BRAF V600E (-)

Hairy cell Leukemia

- **Clinical presentation**
  - Splenomegaly
  - Cytopenias (infections, bleeding)
  - Constitutional symptoms

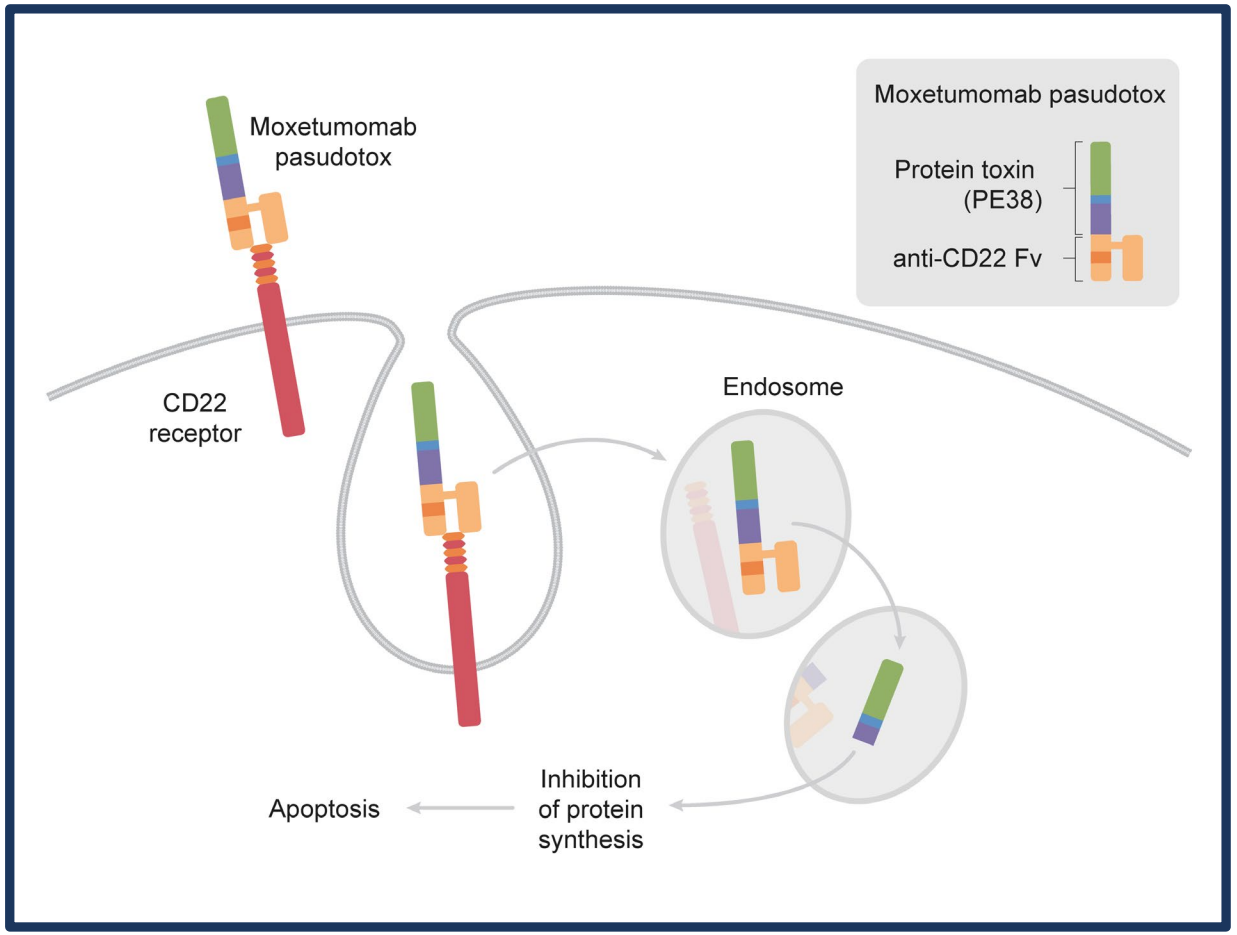
- **Treatment Indications:**
  - Systemic symptoms
  - Splenic discomfort
  - Recurrent infections
  - Cytopenias (Hb <11, ANC < 1000, bleeding due to plt <100,000)

Hairy Cell Leukemia: Treatment

- **First Line**
  - Purine analogs
    - **Cladrabine (2-CdA) + rituximab** – Up to 80% CR with a CR duration of 57 months (7 – 246) after a single cycle
    - **Pentostatin**
- **Refractory (failure in less than a year) or Relapsed disease**
  - purine analogs ± Rituximab
  - INF-alfa
  - rituximab
  - **BRAF targeting agents (Vemurafenib) ± rituximab**
  - **moxetumomab Pasudotox** (anti CD22 immunotoxin conjugate)

Moxetumomab Pasudotox for R/R HCL

- Anti CD22 immunotoxin conjugate
- IV ; D1,3,5 of 28D cycle (up to 6 cycles)
- At least 2 prior systemic therapies, including a purine analog
- **Efficacy:**
  - ORR: 75%
  - durable CR: 30%
  - MRD eradication 34% of all CRs
- **Unique side effects**
  1. Hemolytic-uremic syndrome
  2. Capillary leak syndrome
  - supportive care and discontinuation were effective
  - could occur at any cycle



Kreitman, Blood, 2018

Please Consider Clinical Trials!

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