La prima linea CLL: le conferme della terapia a progressione

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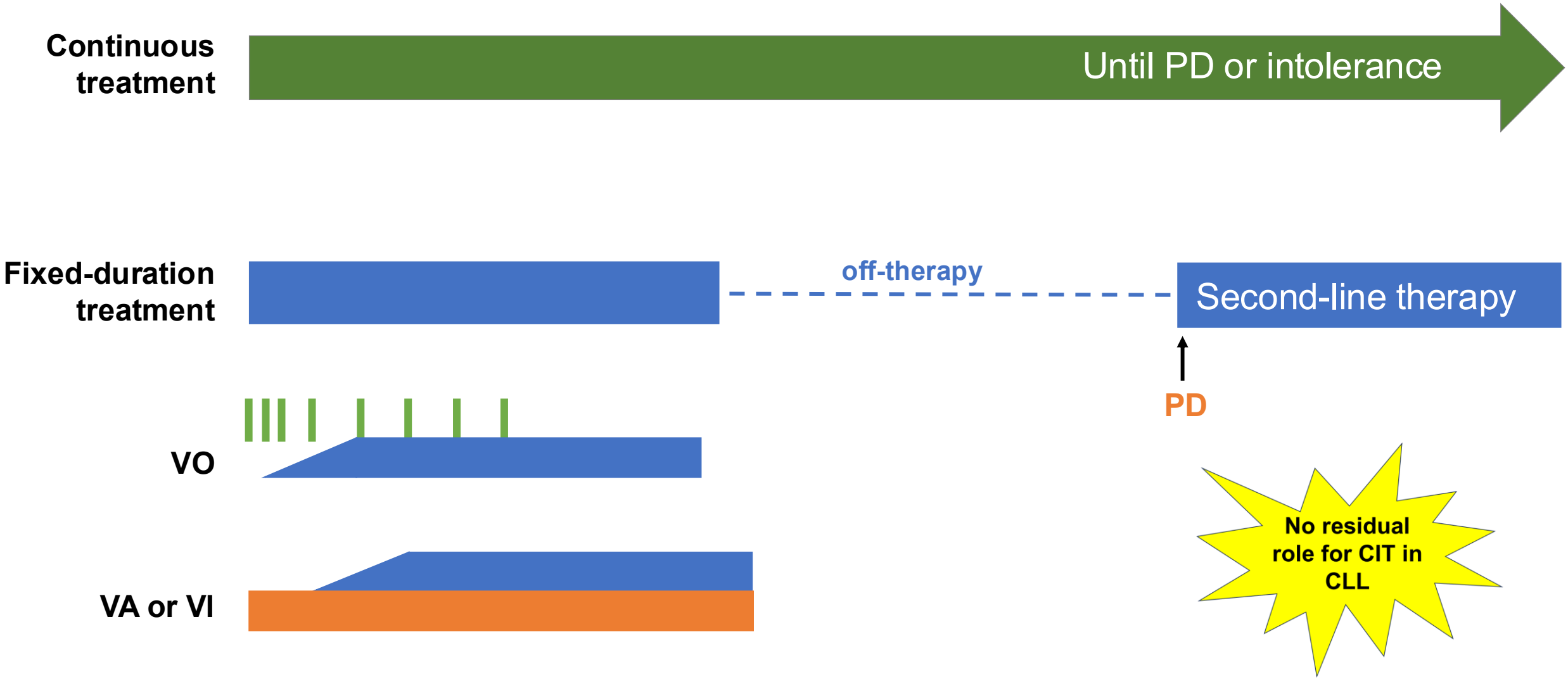
Beigene					X	X	
GSK	X		X			X	
Johnson&Jhonson	X				X	X	

TREATMENT STRATEGIES CURRENTLY AVAILABLE IN TN CLL



Factors driving frontline treatment choice in CLL

Disease characteristics

- *Del17p*
- *TP53* gene mutations
- IGHV mutational status (mIGHV vs umIGHV)

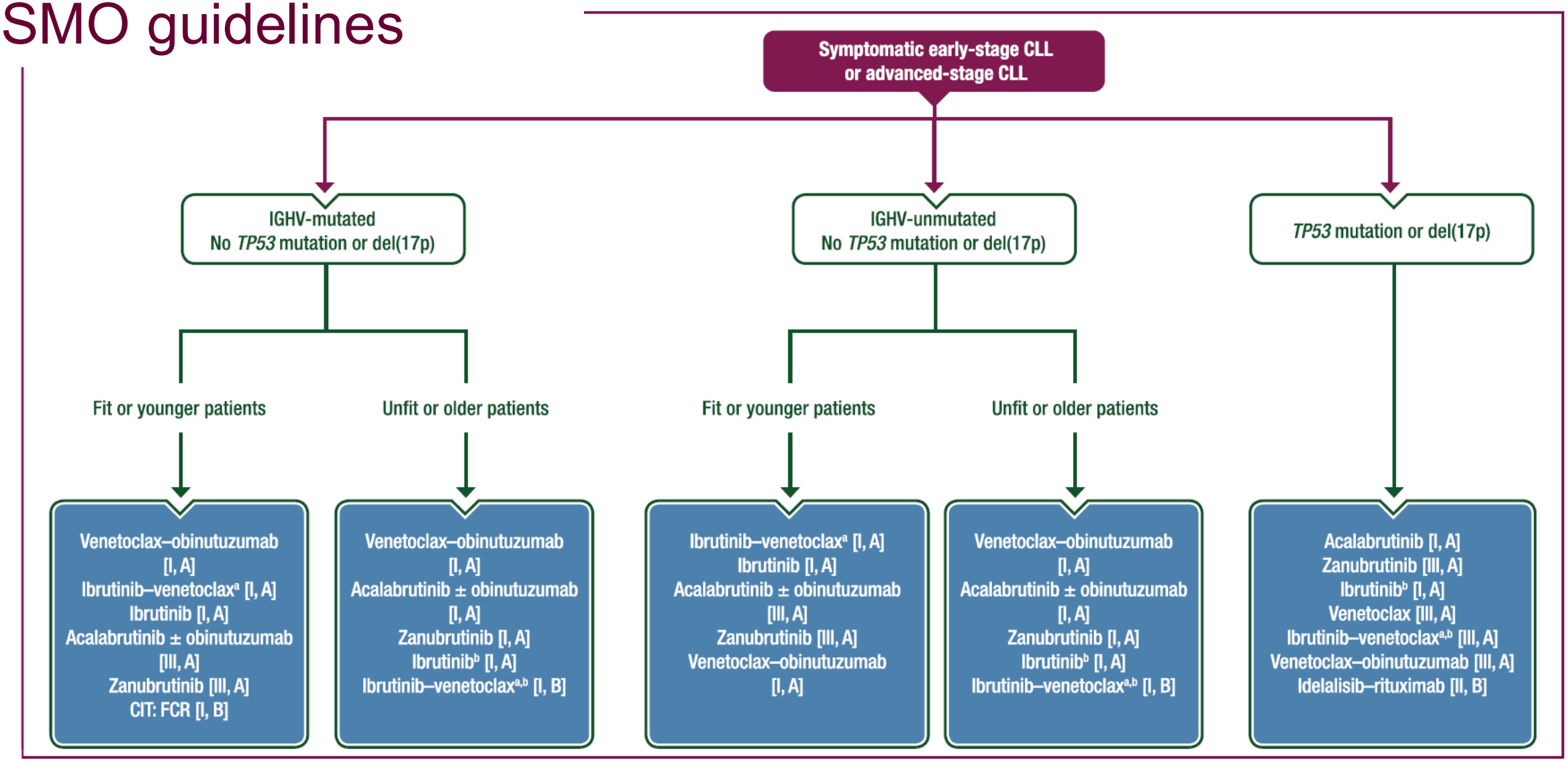
impact on efficacy

Patients characteristics

- Age (old-old patients)
- Comorbidity burden
  - ✓ Cardiovascular comorbidity, hypertension, bleeding risk, cefalea
  - ✓ renal impairment
  - ✓ risk of infections
- Concomitant medications and drug-drug interactions
- Social and familiar status

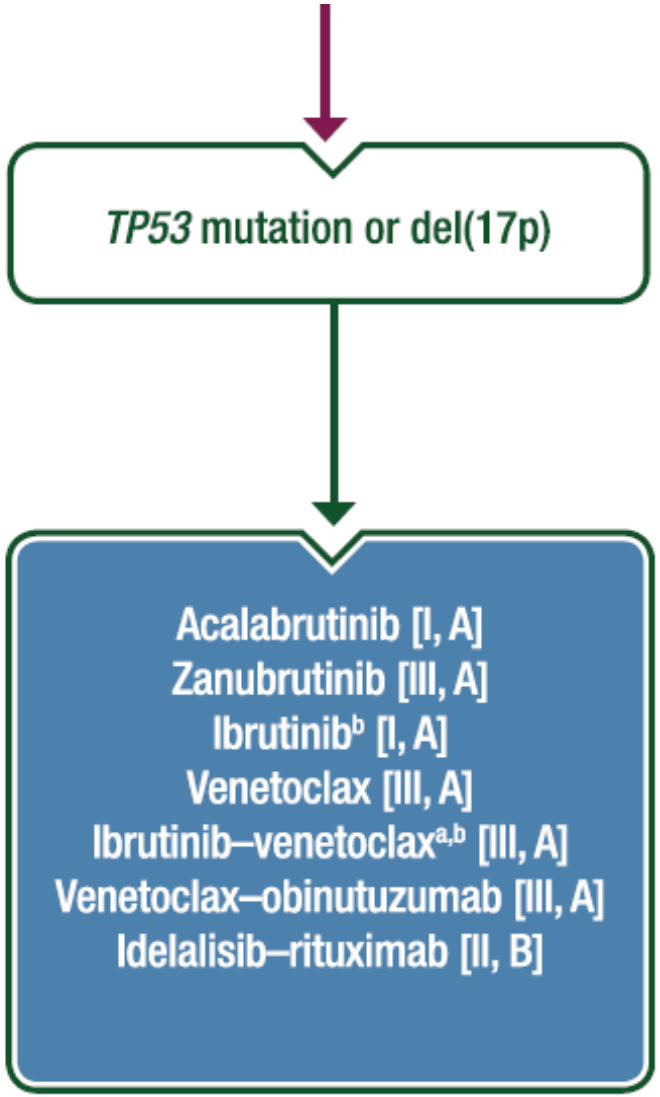
Risk of adverse events and treatment discontinuations

ESMO guidelines



Eichhorst B et al. Ann Oncol 2024

ESMO guidelines

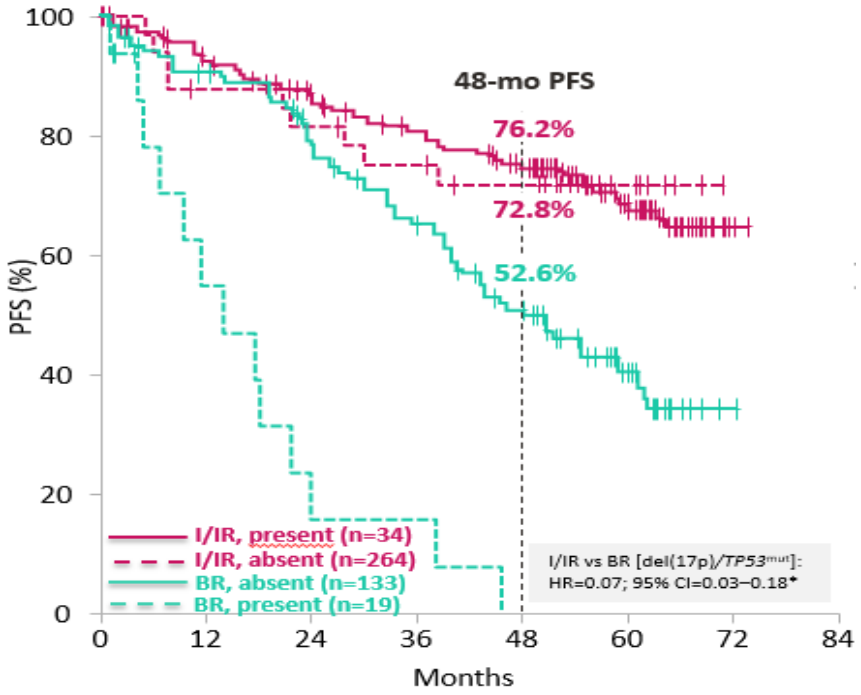


Continuous treatment

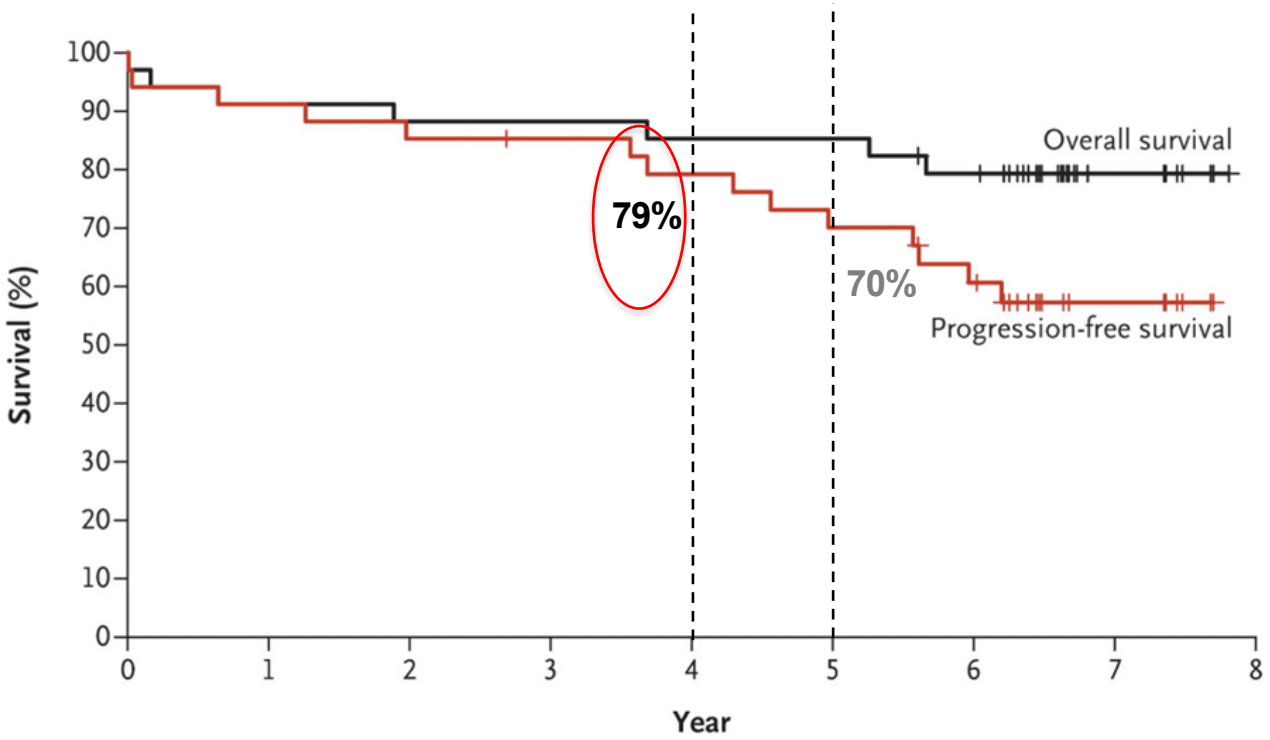
Eichhorst B et al. Ann Oncol 2024

Continuous BTKi in *TP53*dis patients - Ibrutinib

ALLIANCE
I ± R vs BR



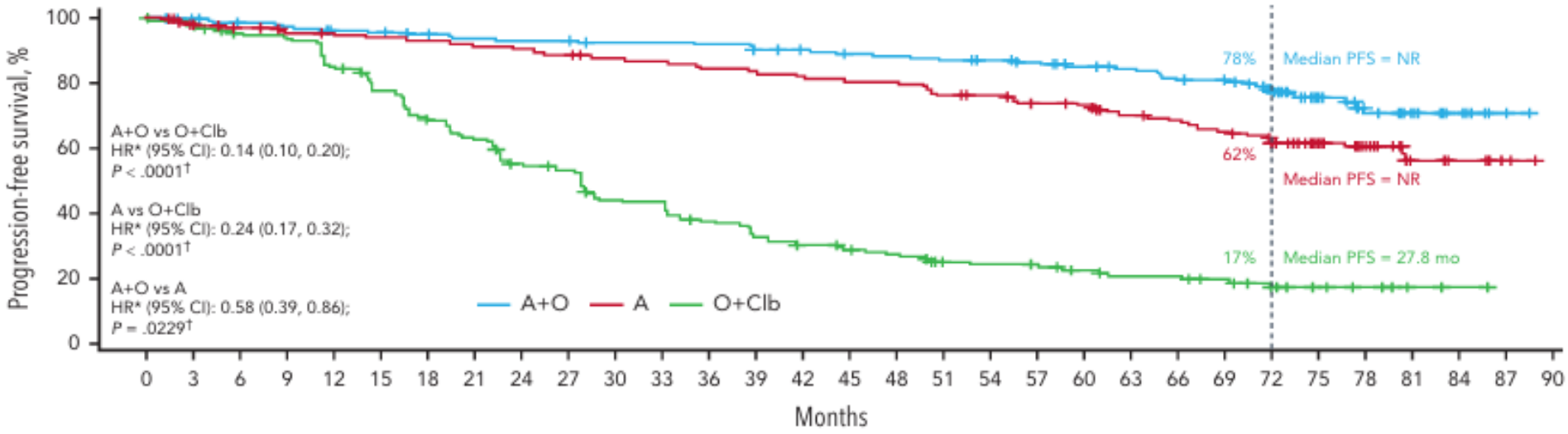
Phase II study



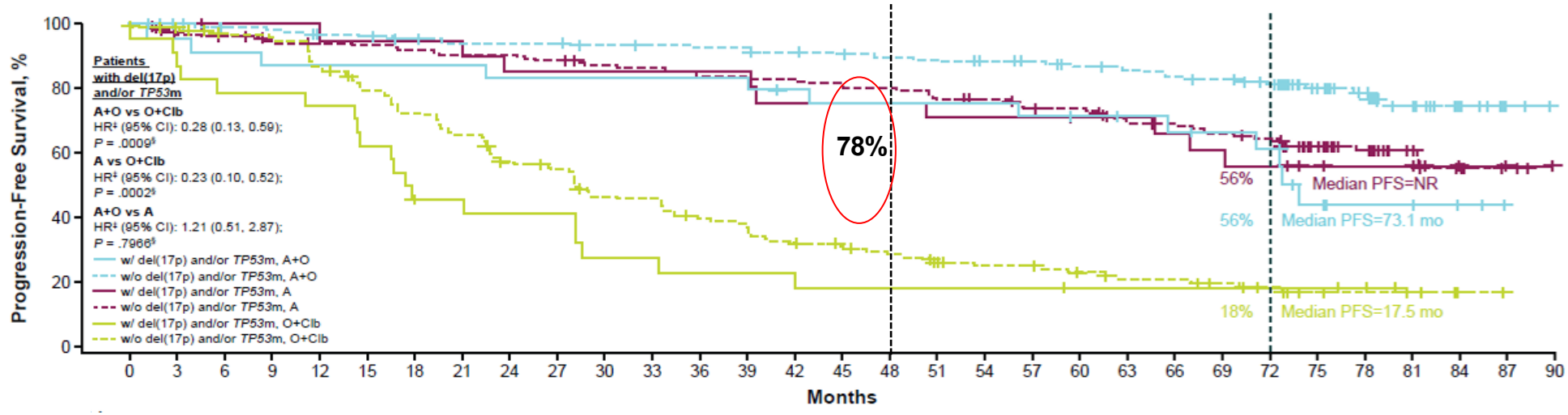
Woyach J, et al. ASH 2021. Abstract 639; Ahn IE et al. N Engl J Med 2020

Continuous BTKi in *TP53*dis patients - Acalabrutinib

Acalabrutinib ELEVATE-TN

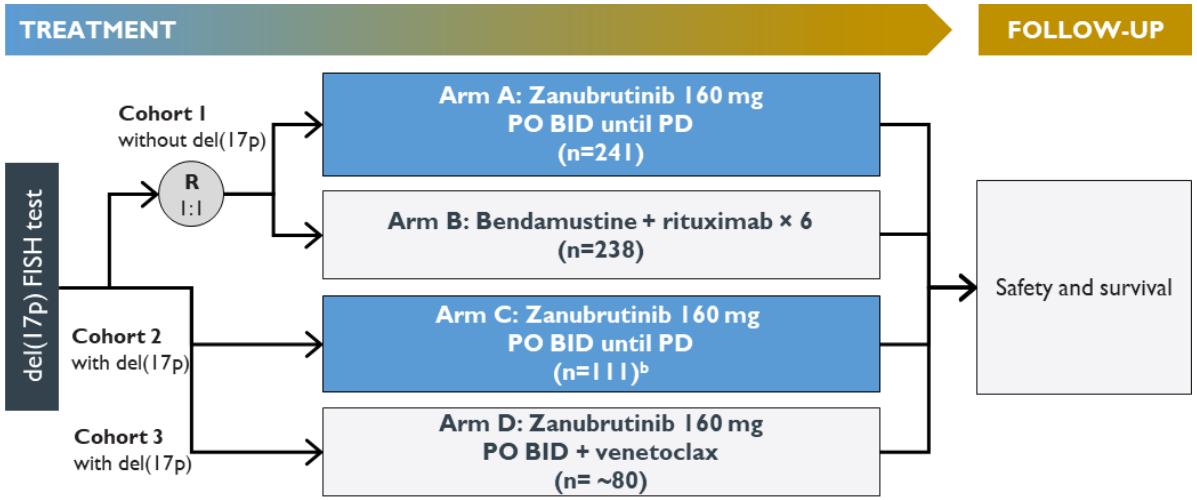


Acalabrutinib TP53 del/mut ELEVATE-TN



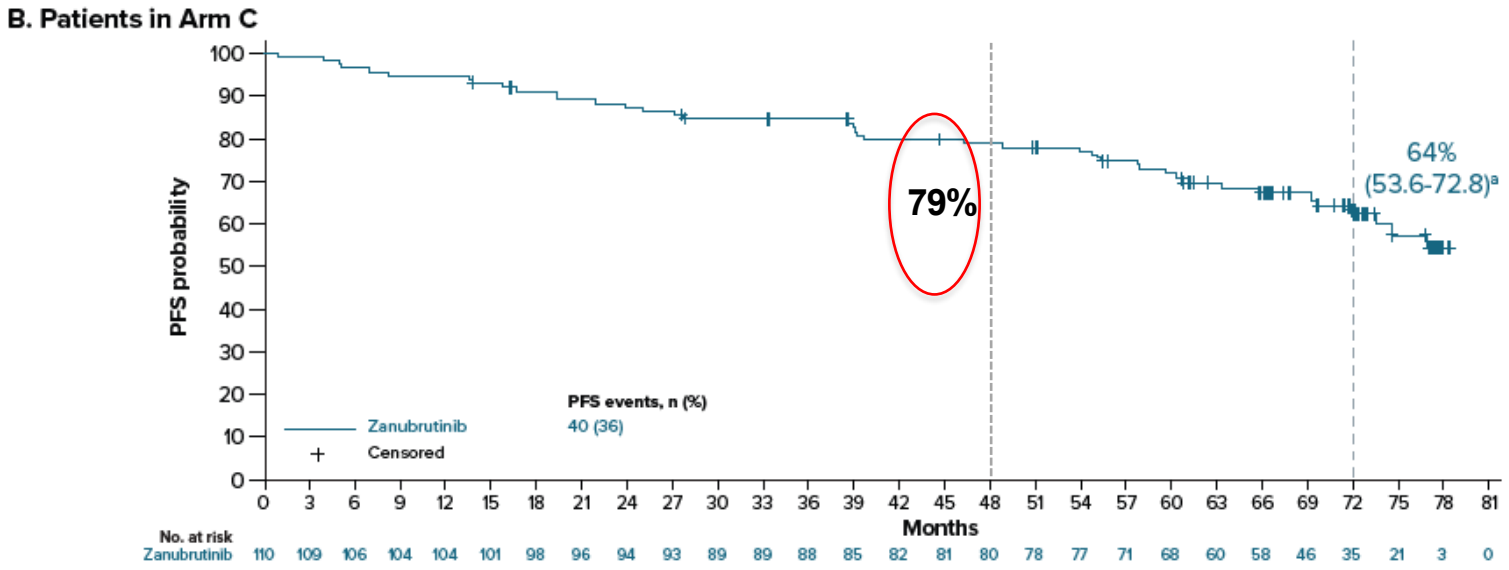
Sharman JP et al. Blood 2025

Continuous BTKi in *TP53*dis patients - Zanubrutinib



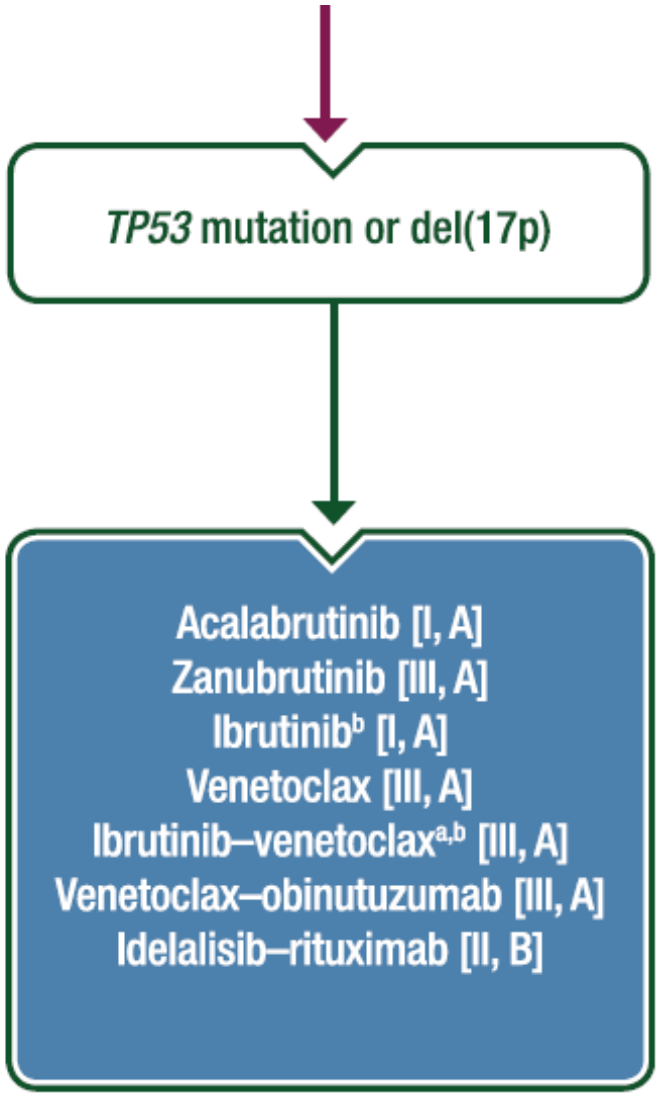
SEQUOIA TRIAL – Cohort 2

Estimated 60-month
PFS rate was 72%



Tam CS, et al. Poster Presentation at ASH 2025

ESMO guidelines

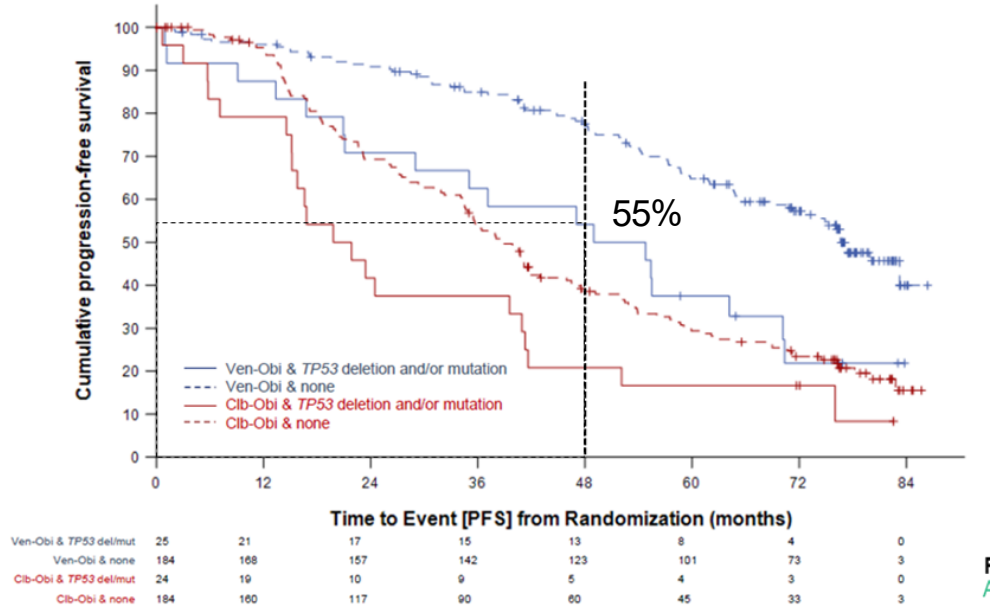


Time-limited treatment

Eichhorst B et al. Ann Oncol 2024

Fixed duration Ven-based therapy in TP53dis patients

CLL14
VenO vs Chl-O



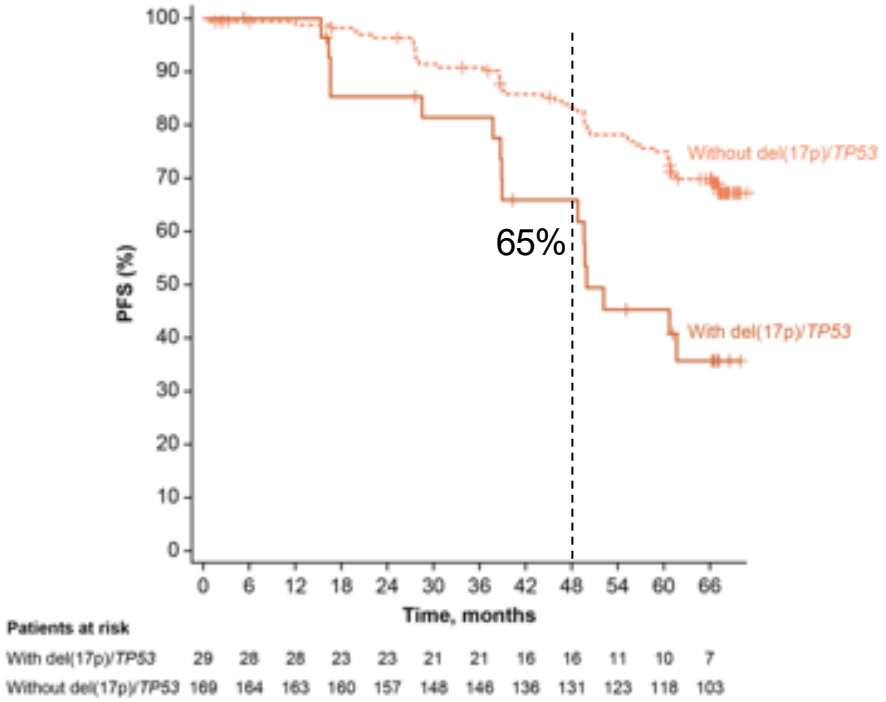
Median PFS

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

CAPTIVATE
Phase 2 – I + V



FD Cohort[a]	5.5-Year PFS Rate, % (95% CI)
With del(17p)/*TP53* (n=27; FD cohort only)	30 (12–49)
Without del(17p)/*TP53* (n=129; FD cohort only)	66 (57–74)

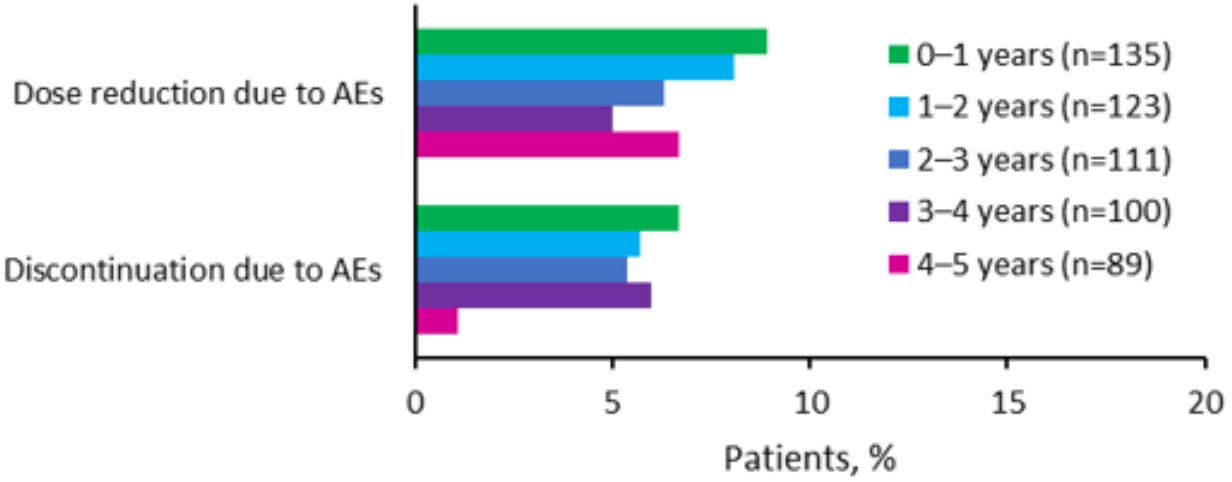
Wierda WG et al. ASCO 2024

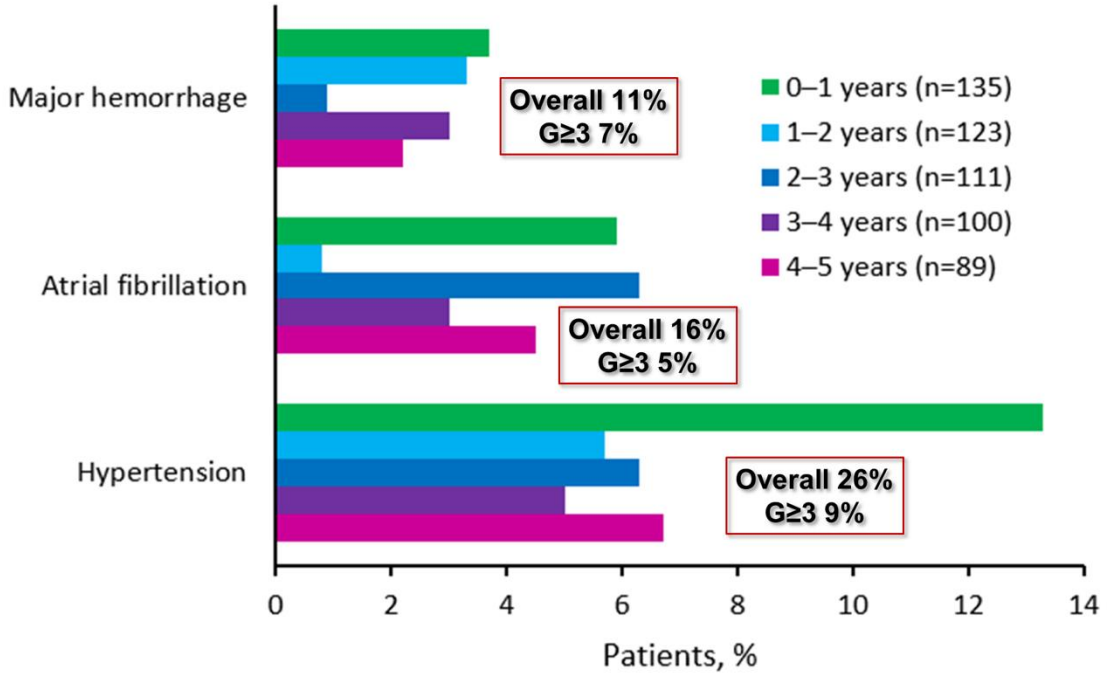
Main concerns of continuous treatments:

Safety profile of ibrutinib - RESONATE-2

Discontinued ibrutinib, *n* (%)	56 (41)
Adverse event	29 (21)
Progressive disease	8 (6)
Death	8 (6)
Withdrawal by patient	7 (5)
Investigator decision	4 (3)

5-year follow up





Burger JA et al. Leukemia 2020

Main concerns of continuous treatments:

Second generation BTKi have shown better tolerability compared to ibrutinib in head-to-head trials coducted in the R/R setting (ELEVATE RR and ALPINE)

- Acalabrutinib → Lower discontinuation rate + lower rates of AF and hypertension
- Zanubrutinib → Lower discontinuation rate + lower rates of AF

BTKi phase III trials in TN patients: Events of Clinical Interest @5-year Follow Up

	IBRUTINIB RESONATE-2[1]		ACALABRUTINIB ELEVATE-TN[2]		ZANUBRUTINIB SEQUOIA[3]	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Atrial fibrillation	**16%**	5%	**7.3%**	**1.1%**	**7.1%**	**1.4%**
Bleeding	NA	**11%**	43.6%	**3.4%**	52.1%	**7.5%**
Hypertension	**26%**	9%	**8.9%**	**3.9%**	**22.9%**	12.1%

1.Burger JA et al. Leukemia, 2020; 2. Sharman JP et al. Poster Presented at: ASCO 2022.; 3. Shadman M et al. Journal of Clinical Oncology, 2024

Impact of treatment tolerability - Ibrutinib in old-old patients

IBRUTINIB IN PATIENTS ≥ 80 YEARS OLD: A MULTICENTER ITALIAN COHORT

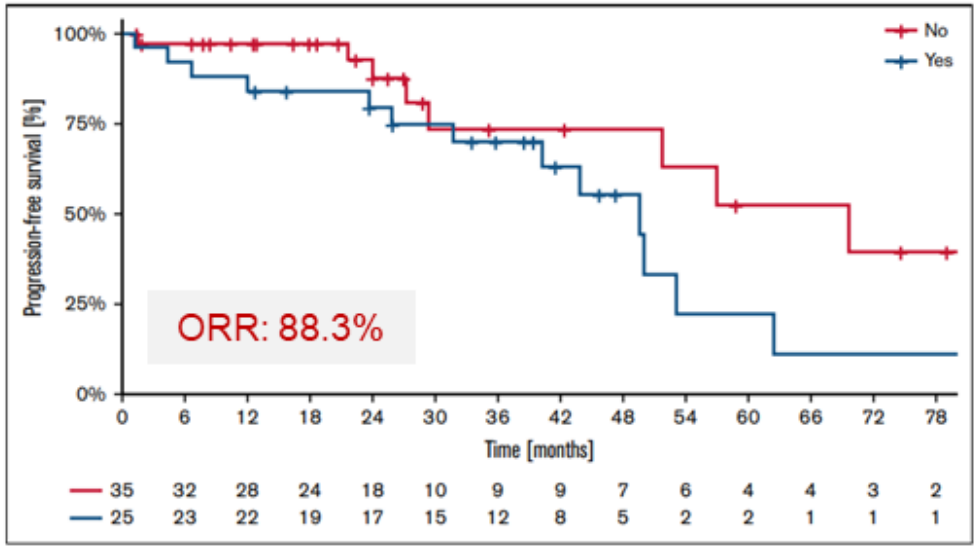
Multicenter, retrospective study.

60 consecutive patients with TN or R/R CLL, ≥80 years old

Median observation: 27 months

Concomitant cardioactive therapies, n (%)	
At least 1 cardioactive drug	44 (73.3)
>2 cardioactive drugs	18 (10.8)
Antihypertensive drugs	38 (63.3)
Anticoagulants	3 (5)
Lipid-lowering drugs	10 (16.7)
Antiplatelets drugs	21 (35)

PFS by treatment withholding



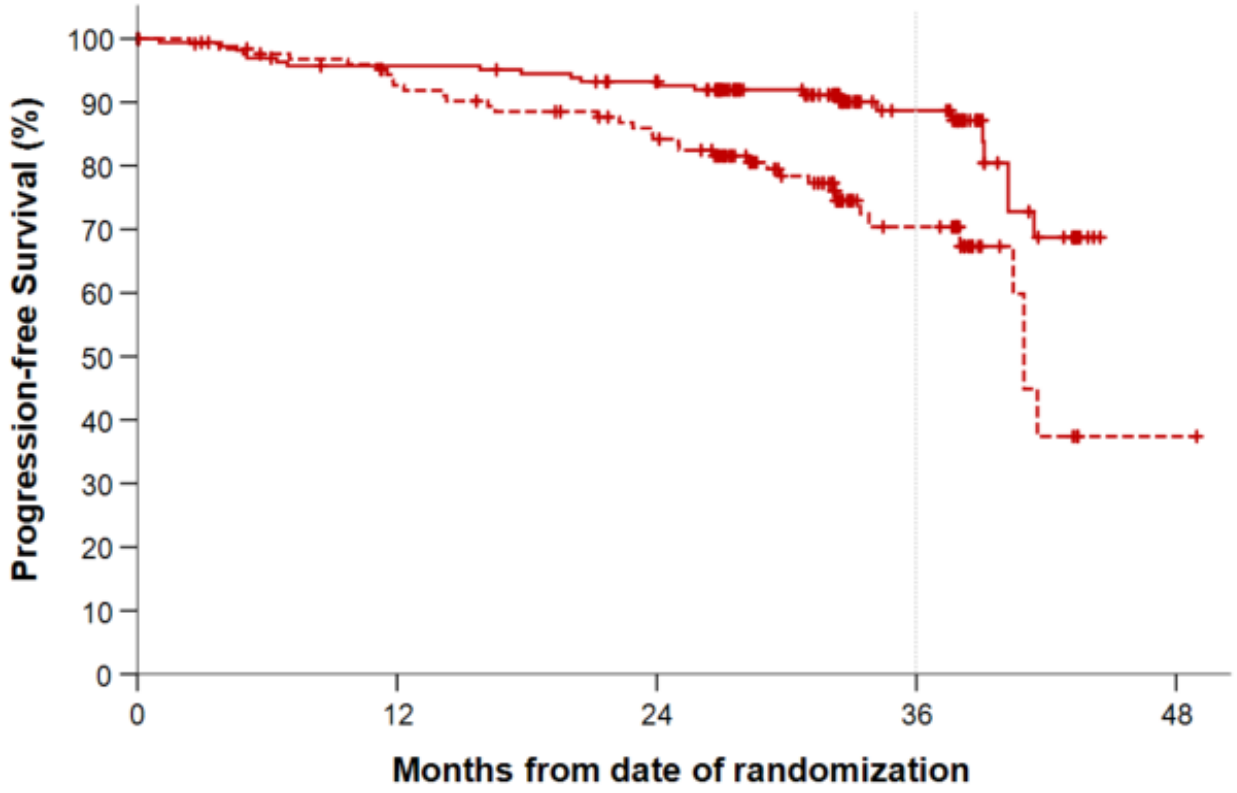
Median PFS 69.7 months in patients not experiencing temporary drug withholding (7-30 days) vs 49.7 months in patients who had drug interruptions (P = .079).

Handling AEs to keep patients on treatment is of crucial importance as therapy interruptions could negatively impact on PFS

Reda et al. Blood Adv. 2023

PROGRESSION-FREE SURVIVAL – CLL17 IBRUTINIB ARM

According to fitness (cumulative illness rating scale >6 and/or GFR <70 ml/min)



Patients at risk

I, unfit	130	112	97	33	1
I, fit	171	155	146	61	0

3-year-PFS

----	I, unfit	70.4%
——	I, fit	88.7%

[Higher discontinuation rate in the unfit patients group]

Al-Sawaf O et al. oral presentation, ASH 2025

Real-world safety and effectiveness of zanubrutinib vs ibrutinib in CLL (CLL-ZANU2024 study)

ZANU COHORT (N=393)

- ELDERLY: median age 76 years
- CV COMORBIDITY RATE: hypertension 39.4% ; AF 13%;
- HIGH RISK GENOMIC FEATURES:
  - 18.3% del(17p) and/or mut TP53;
  - 61.6% unmut IGHV

IBR COHORT (N=541)

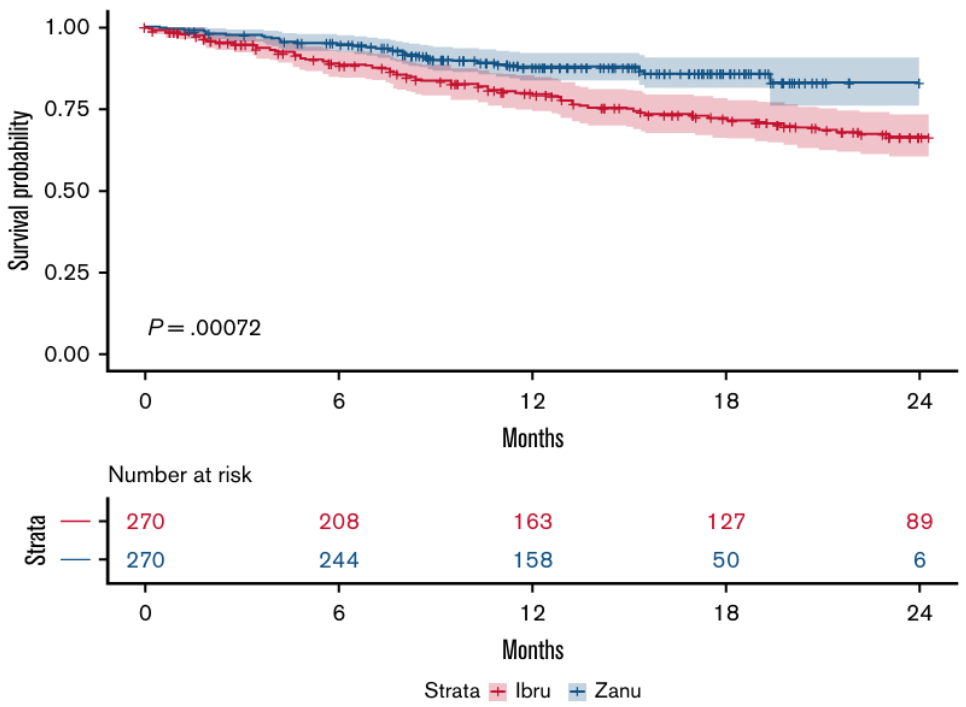
- ELDERLY: median age 70 years
- CV COMORBIDITY RATE: hypertension 39% ; AF 13%;
- HIGH RISK GENOMIC FEATURES:
  - 38.1% del(17p) and/or mut TP53;
  - 67% unmut IGHV

Time to treatment discontinuation (TTD) and time to next treatment or death (TTNTD) were evaluated in both the overall cohort and a propensity score–matched population (N=270).

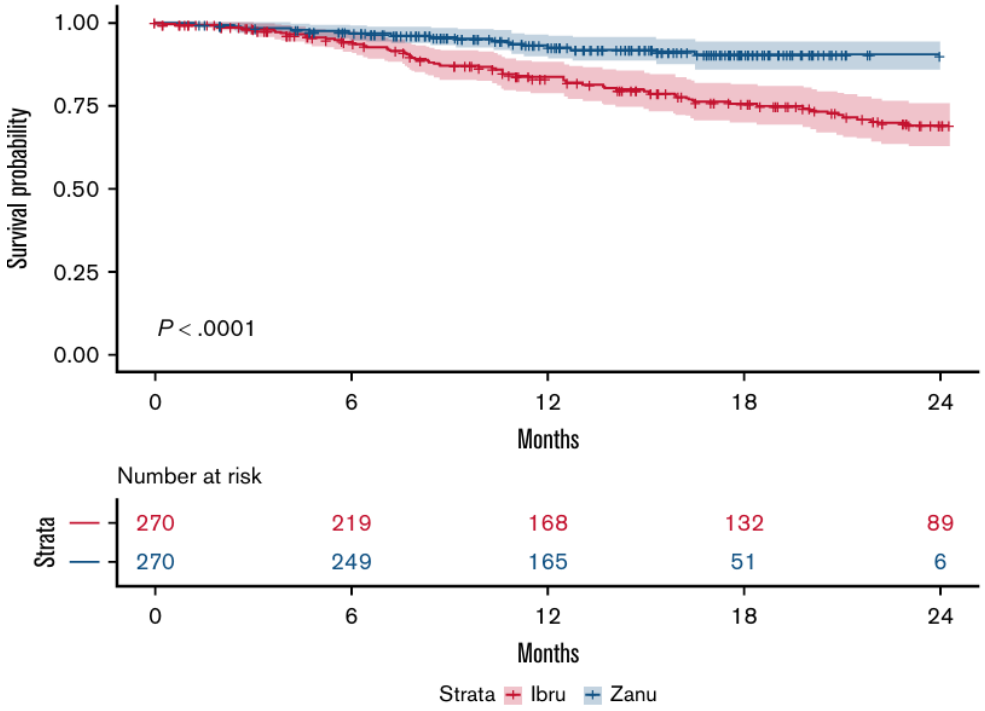
Martino EA et al. Blood Advances 2026

Real-world safety and effectiveness of zanubrutinib vs ibrutinib in CLL (CLL-ZANU2024 study)

Time to treatment discontinuation (TTD)



Time to next treatment or death (TTNTD)



Patients who were treated with zanubrutinib experienced lower 12-month discontinuation rates (overall: 12.5% vs 28.6%) and higher 12month TTNTD rates (matched: 93.2% vs 83.4%).

Martino EA et al. Blood Advances 2026

Efficacy and safety outcome of acalabrutinib in CLL (NAOS RW study)

- Adult patients (≥18 yeas) diagnosed with CLL who started acalabrutinib, with or without obinutuzumab, both as first line (L1, n=285) and for relapsed/refractory disease (L2+, n=200), according to national access criteria

L1 COHORT

- ELDERLY: median age 73 years; 45.6% ≥75 years
- HIGH CV COMORBIDITY RATE: 54% ≥1 CV comorbidity; 43.5% hypertension; 9.4% arrhythmias (AF 6.3%)
- HIGH RISK GENOMIC FEATURES:
  - 19.8% del(17p) and/or mut TP53;
  - 65.2% unmut IGHV

Quinquenel et al. Annals of hematology 2025

Time to discontinuation: TTD

The **discontinuation rate at M12 was 22.7%** and was not statistically associated to line of treatment

1L and 2L+ 12-month discontinuation rate
For any grade AEs: 12.8%
For G3-4 AEs: **5.9%**

1L and 2L+ → rate of discontinuation* was NOT associated to baseline CV comorbidities:

- no CV comorbidity: 17.5%, (95% CI, 10.3–26.3)
- CV comorbidity: 27.4%, (95% CI, 18.8–36.7)

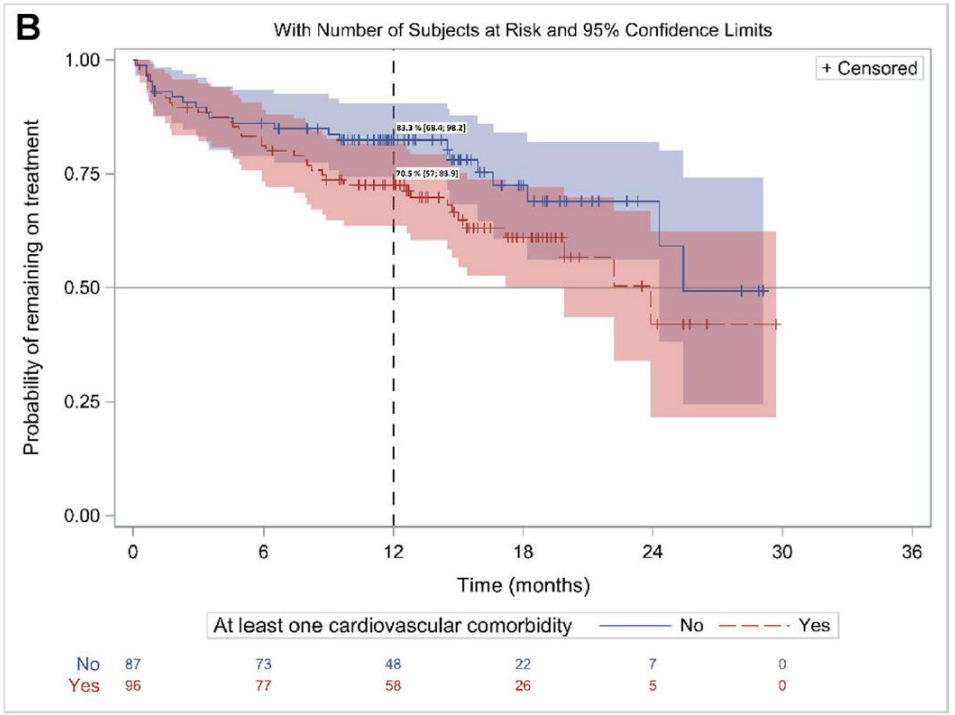
→ *p = 0.11*

1L and 2L+ → rate of discontinuation* was NOT associated to age:

- < 75 years: 17.8%, (95% CI, 10.7–26.4)
- ≥ 75 years: 27.3%, (95% CI, 18.7–36.5)

→ *p = 0.11*

***discontinuation for any reason (including progression)**



Quinquenel et al. Annals of hematology 2025

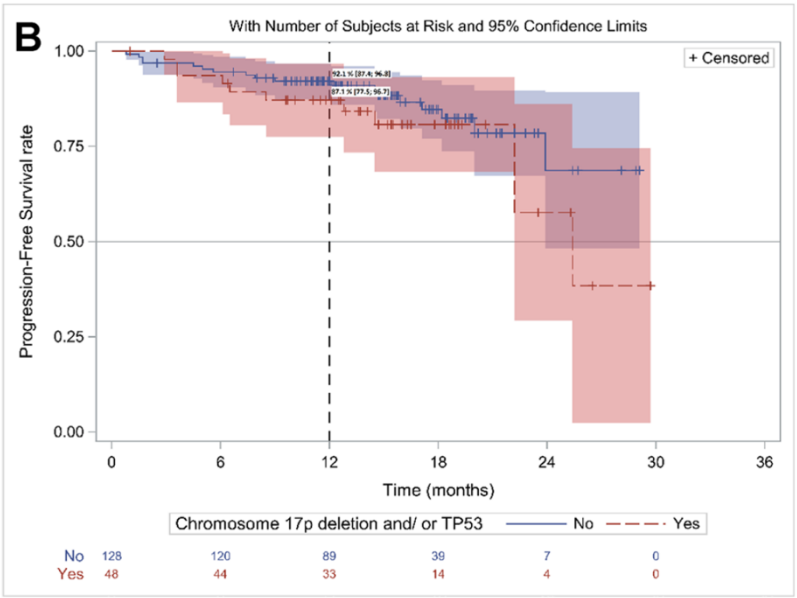
NO statistically significant difference in terms of rwPFS for patients with **del(17p)/TP53m** when compared to w/o del(17)/TP53m (92.1% vs 87.1; p = 0.21)

1L 12-month rwPFS

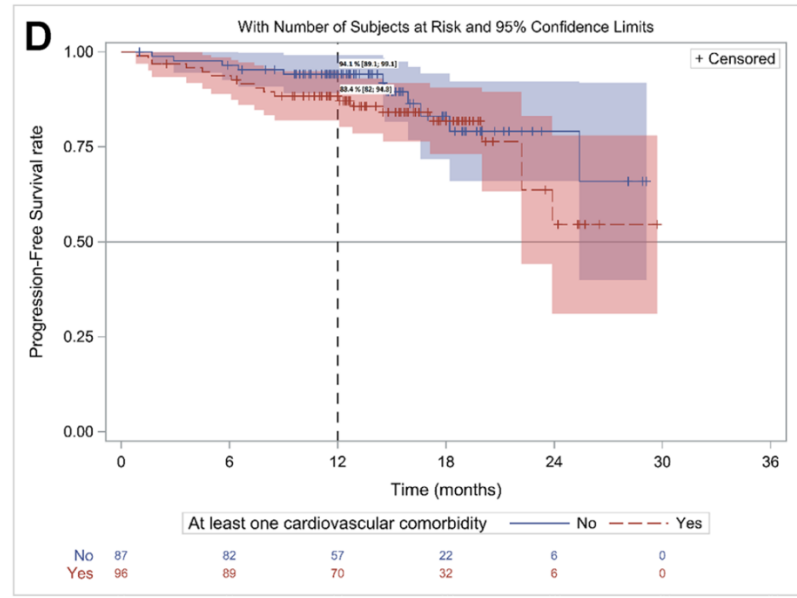
93.1% (95% CI: 88.5–97.7)

1L median rwPFS

NR



No statistically significant difference in terms of rwPFS for patients with **baseline CV comorbidities** when compared to patients with no CV comorbidities (88.4% vs 94.1%; p = 0.26)



Quinquenel et al. Annals of hematology 2025

ARISE: an Italian multicenter, retrospective, real-life observational study of acalabrutinib TTP

- ARISE (NCT06205498) is an **Italian, observational, multicenter, real-world** study based on a **retrospective** cohort of adult CLL patients who initiated acalabrutinib monotherapy between May 1 2021 and April 30 2022 under Italian legislation.

- The **primary objective** was to describe **time to treatment discontinuation (TTD)**

151 eligible pts 78.8% (n=**119**) treated in **first line**.

Demographics and biology (on 127 evaluable):

- Mean age = **69 years** (SD 10.28);
- **del(17p) and or *TP53* mutated = 8.7%** (n=11)

Cardiovascular comorbidities included

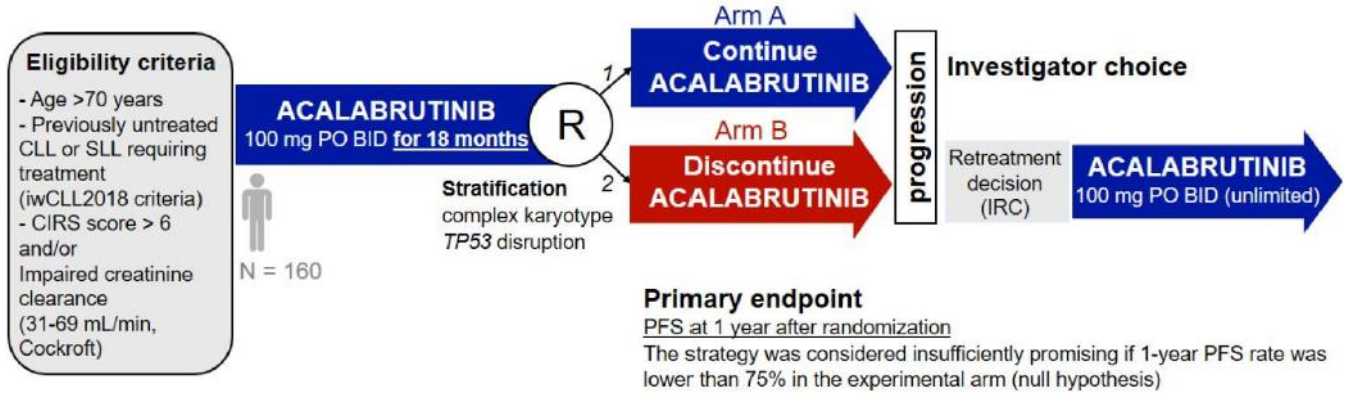
- **hypertension 52.8%** (n=67)
- cardiac rhythm disorders 11% (n=14)
- **atrial fibrillation 6.3%** (n=8)
- atrial flutter 0.8% (n=1)
- congestive heart failure 2.4% (n=3).

DISCONTINUATIONS AND TTD

- Median follow-up: **27 months**.
- **Permanent discontinuations**: 10/150 patients (**6.7%**) overall; in 1L, 8/119 (6.7%).
- Mostly due to **adverse events**
- No discontinuations due to disease progression, compliance issues, or death.

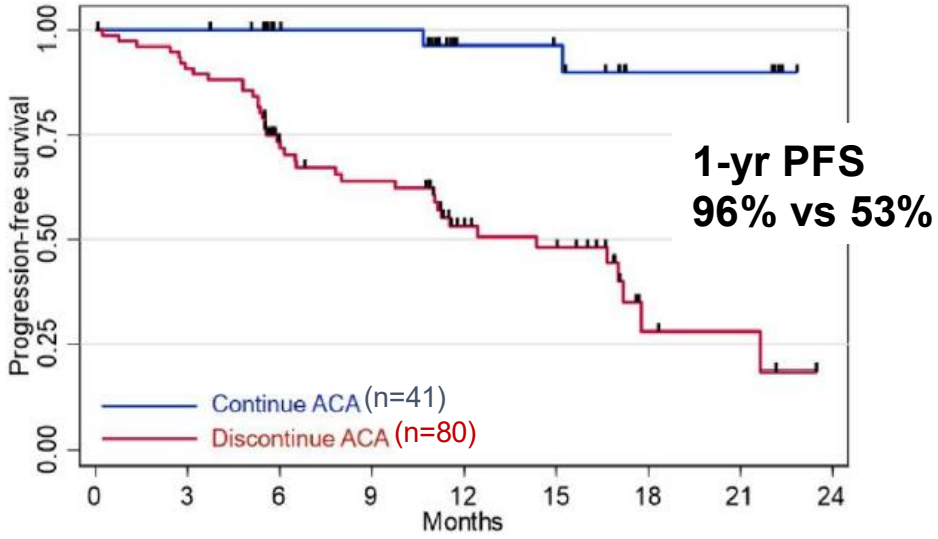
Gentile et al. Poster presented at SIE 2025

Time-Limited Acalabrutinib Monotherapy in Frail Patients with TN CLL: STAIR trial



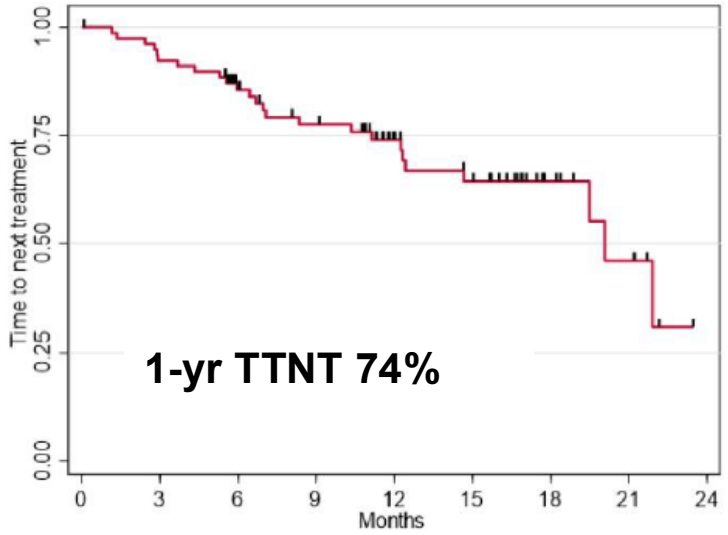
Median age 77 yrs
CIRS score >6 in ≈60% of pts
CrCl <70 in 78% of pts

PFS



1-yr PFS 96% vs 53%

TTNT



1-yr TTNT 74%

Among pts who discontinued Acala → 1-year PFS 90% in IGHV-M and 34% in IGHV-UM

Response to retreatment (n=25)

→ 24 restarted Acala per protocol, ORR 87.5% (21/24)

AEs (in the whole cohort)

AF 6.9%, Hypertension 2.5%, Bleeding 1.9%

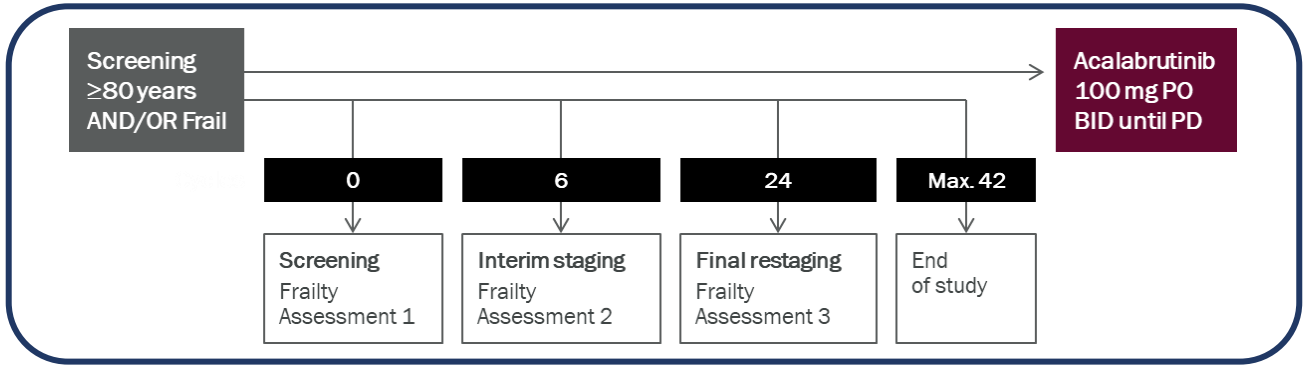
Lower burden of AEs in the group who discontinued Acala

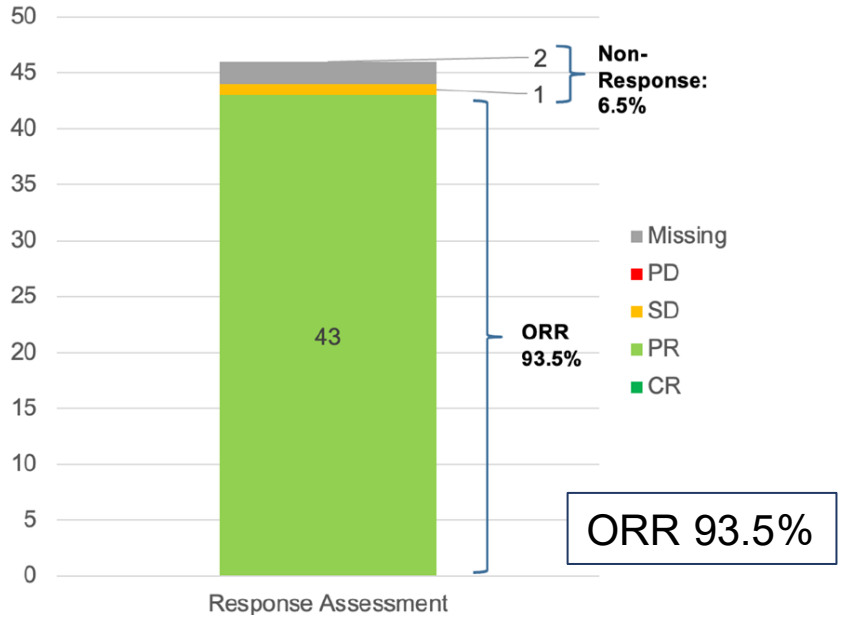
Guièze R et al., Abstract N. 684, oral presentation, ASH 2025

CLL-FRAIL – acalabrutinib on old-old patients

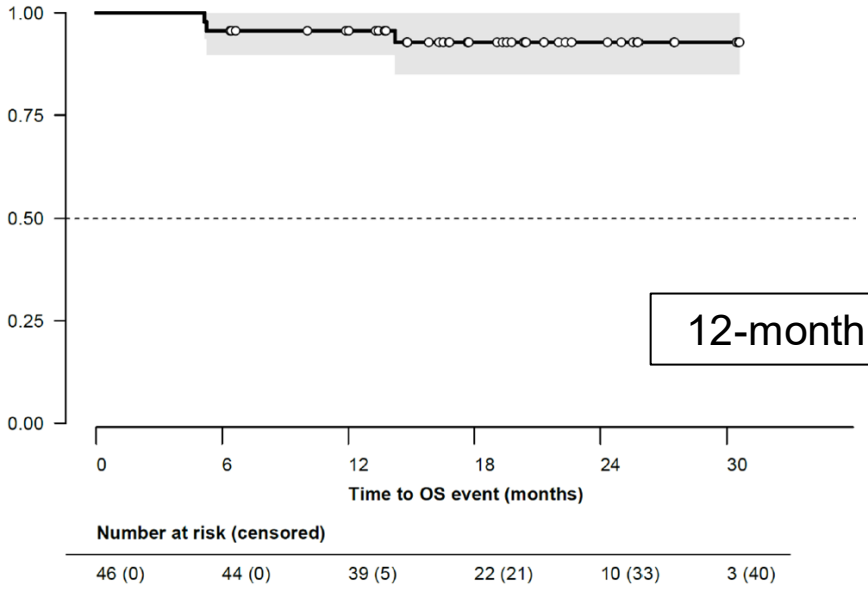
Key Eligibility[1,2]

- Age ≥80 years and/or FRAIL scale score of ≥3
- Maximum of 1 previous treatment for CLL





ORR 93.5%



Median age 81
Ongoing treatment 65%

12-month estimated OS was 95.7%

Simon F. et al. Poster presentation, ASH Annual Meeting, 2024

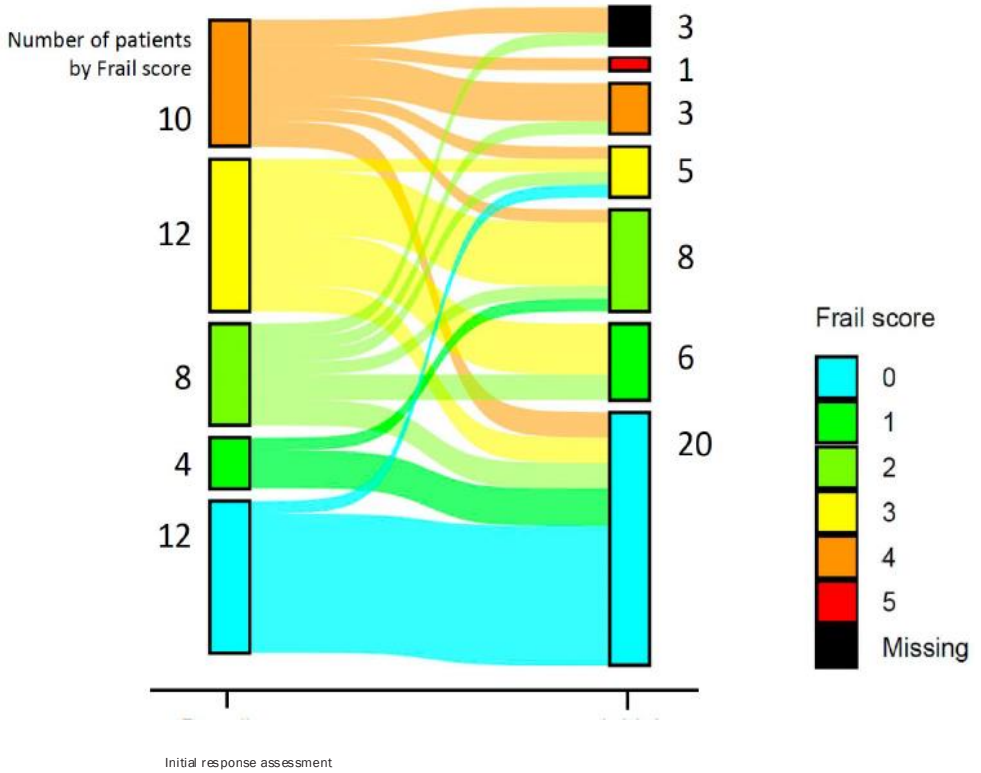
CLL-FRAIL – acalabrutinib on old-old patients

Adverse Events Summary (n=52) (median observation time 17.7 months)

Adverse Event, n (%)	All Grades	Grade ≥3
Any AE	**52 (100)**	**33 (63.5)**
COVID-19	19 (36.5)	3 (5.8)
Hematoma	19 (36.5)	0
Diarrhea	12 (23.1)	1 (1.9)
Anemia	9 (17.3)	6 (11.5)
Constipation	9 (17.3)	0
Headache	9 (17.3)	0
Fatigue	8 (15.4)	0
Edema	8 (15.4)	--
Contusion	7 (13.5)	0
Thrombocytopenia	6 (11.5)	1 (1.9)
Vertigo	6 (11.5)	0
Dehydration	6 (11.5)	1 (1.9)
Rash	6 (11.5)	2 (3.8)
Cardiac failure	**4 (7.7)**	**3 (5.8)**
Palpitations	4 (7.7)	0

Only frequent adverse events (≥10% of patients) and cardiac events are depicted

- Atrial fibrillation:
  - 2 cases
  - 4% all grades
- 5 patients (9%) died
  - There was one deadly SAE termed suspicion of cardiac event, in a case of a 85-year old patient with sudden death at home and known cardiac comorbidities.



53% of pts had an **improvement in their FRAIL scale scores**

Simon F. et al. Poster presentation, ASH Annual Meeting, 2024

Take home messages

- **Continuous BTKi therapy is highly effective in high-risk CLL** with TP53 aberrations
- TP53 aberrations remain prognostic even with fixed-duration combination therapies
- **Treatment discontinuation due to AEs negatively impacts efficacy**
- Second-generation BTKi show **good tolerability** with **low rates of clinically relevant AEs**
- Real-world data confirm **low discontinuation rates for 2nd generation BTKi**
- STAIR trial: **time-limited acalabrutinib → shorter PFS**, especially in IGHV unmutated patients
- FLAIR trial: **continuous acalabrutinib → high response rates and improved frailty** in old-old/frail patients

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Varese

Grazie per la vostra attenzione!