GIORNATE EMATOLOGICHE VICENTINE

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Terapia a termine vs terapia continuativa nella CLL: quali pazienti?

Jacopo Olivieri
Clinica di Ematologia, ASUFC, Udine

Disclosures of Jacopo Olivieri

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie						x	
BMS						x	
Kite						x	

Outline

- Fixed Duration Therapy (FDT) e Continuous Duration Therapy (CDT) in Italia
- Update con LT-FUP di studi registrativi 1st line e R-R
- Confronto efficacia e fattori prognostici
- Confronto tossicità…
- …beyond maximum grade
- Quali pazienti per CDT o FDT?

Frontline treatment algorithm in CLL

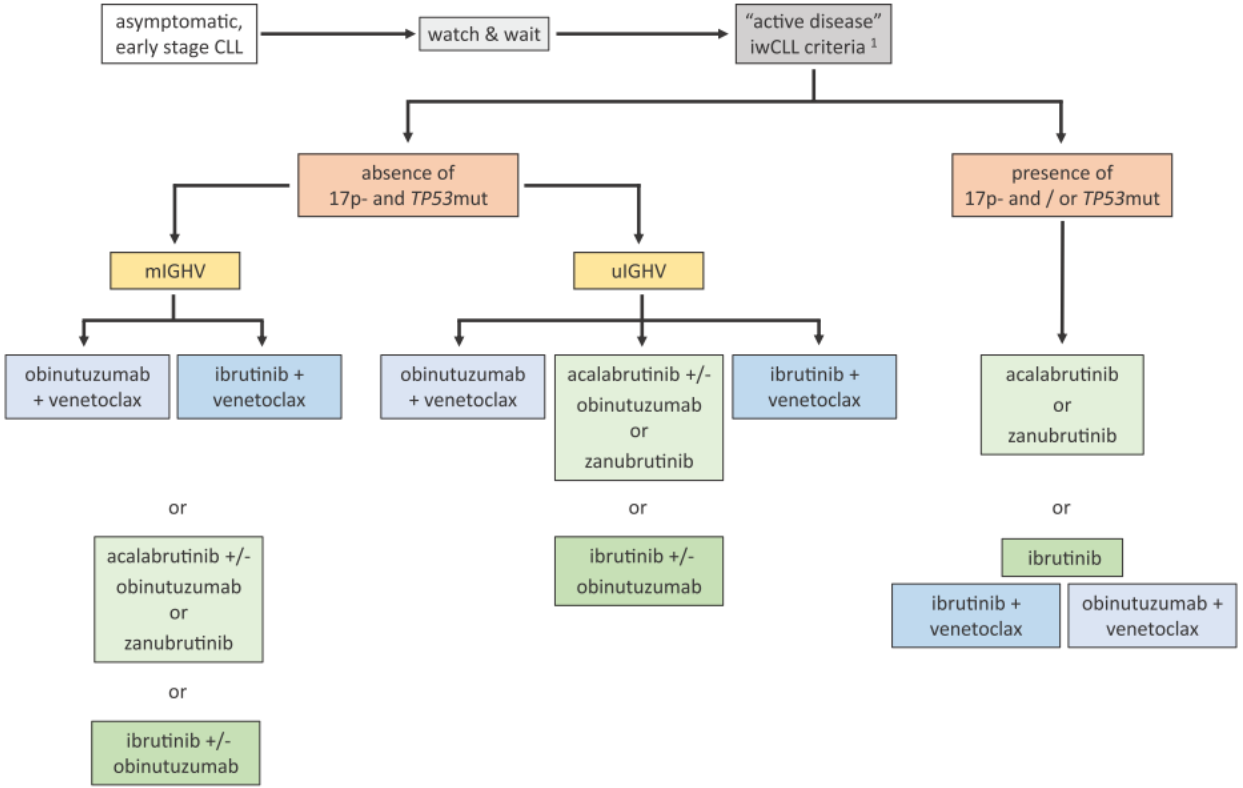
Disponibili in Italia

CDT

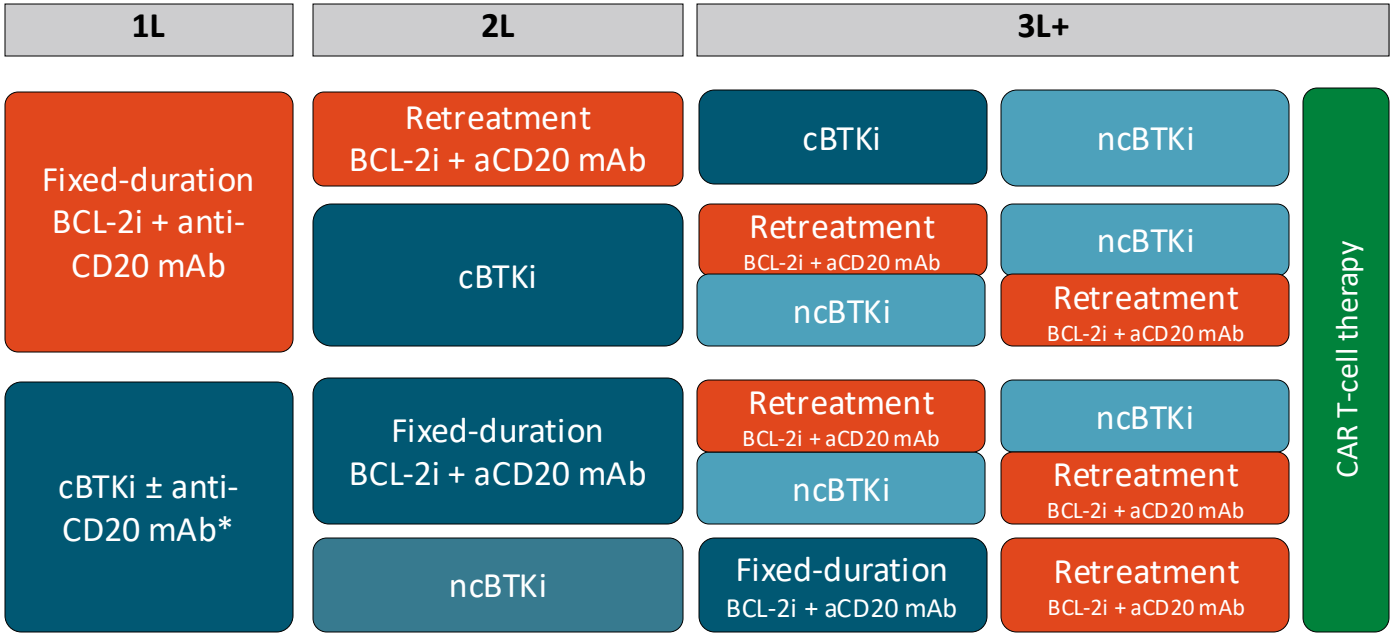
- Ibrutinib
- Acalabrutinib
- Zanubrutinib
- (Venetoclax)

FDT

- I + V
- G-Ven
- (A + V)



Sequencing algorithm for RR-CLL



*Dose reduction, alternate cBTKi for intolerance.

Un precedente trattamento con CIT viene gestito come nell'algoritmo di 1° linea (in assenza delle opzioni I+V e con sostituzione di G-Ven con R-Ven)

In Italia

CDT

- Ibrutinib
- Acalabrutinib
- Zanubrutinib
- Venetoclax
- (Pirtobrutinib)

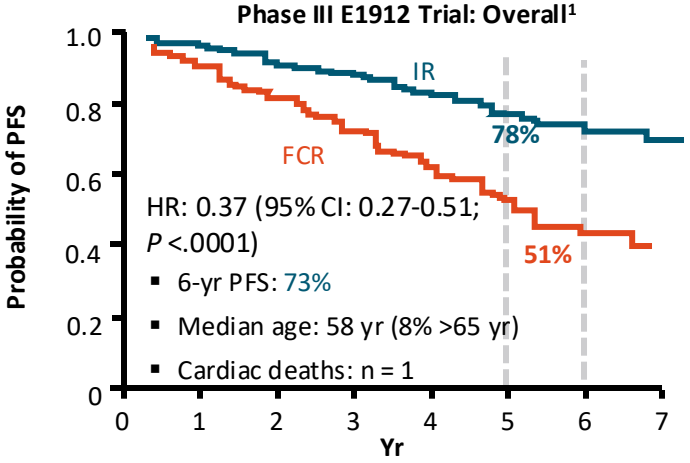
FDT

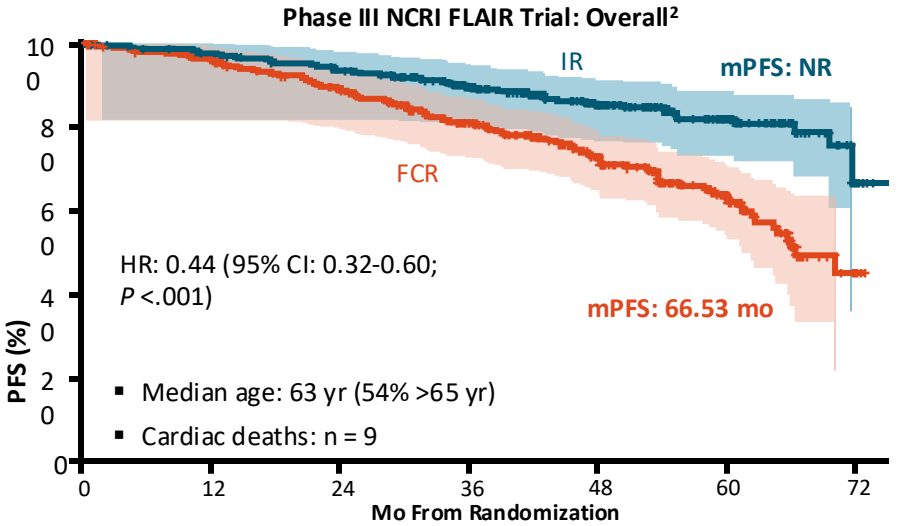
- R-Ven

Continuous Duration Therapy
1st line

First-Generation Covalent BTK Inhibitor (cBTKi) Ibrutinib: Superiority to CIT in young fit patients

- Outcomes with ibrutinib in combination with rituximab in CLL
  - Superior to CIT in younger and older patients
  - Superior to FCR in patients ≤65 yr in PFS

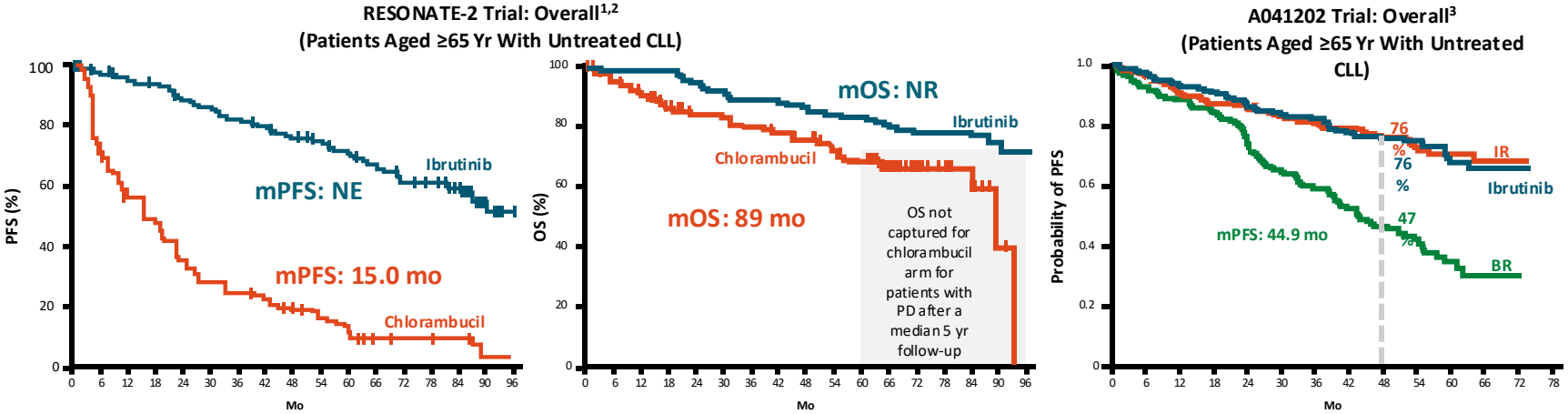




1. Shanafelt. Blood. 2022;140:112. 2. Hillmen. Blood. 2021;138:642.

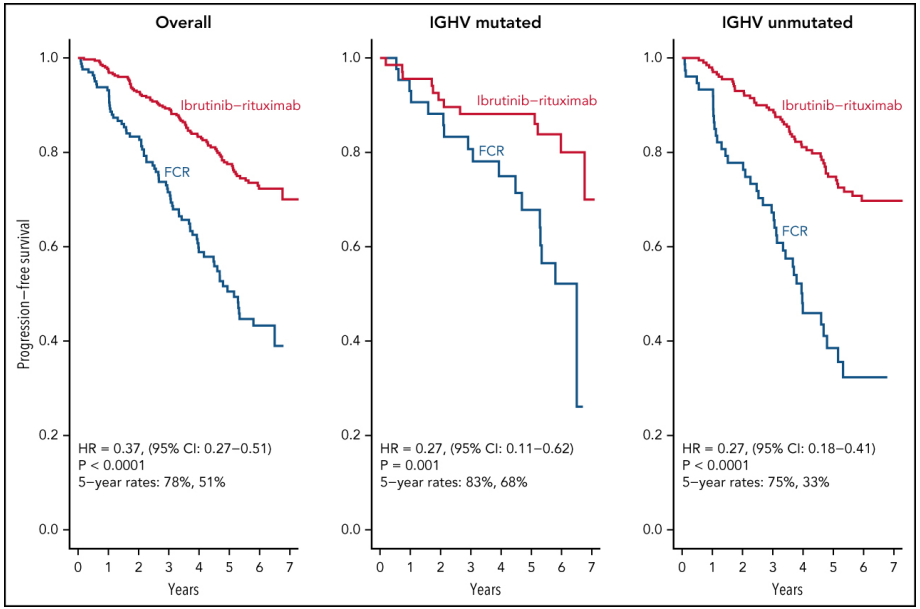
First-Generation Covalent BTK Inhibitor (cBTKi) Ibrutinib: Superior to Chl / BR in elderly unfit pts

- Outcomes with ibrutinib alone or in combination with rituximab in CLL
  - Superior to chlorambucil in patients ≥65 yr in PFS and OS (RESONATE-2)
  - Superior to BR in patients ≥65 yr in PFS
  - Associated with atrial fibrillation, bleeding, bruising, hypertension, myalgias, arthralgias, and diarrhea
    - Treatment was discontinued in 41% of patients in the RESONATE-2 trial, mostly due to AEs



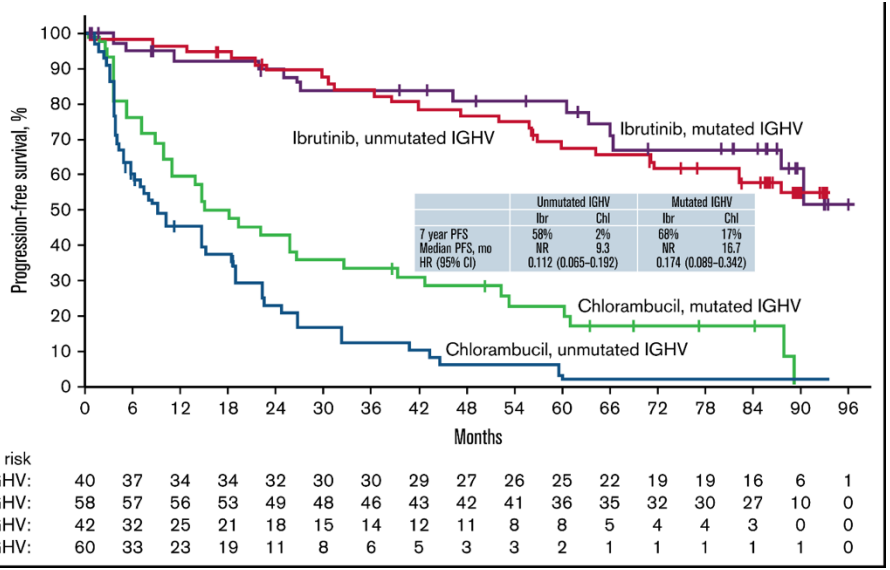
1. Barr. Blood Adv. 2022;6:3440. 2. Burger. Leukemia. 2020;34:787. 3. Woyach. Blood. 2024;143:1616.

ECOG 1912 (IR vs FCR): PFS by IGHV status

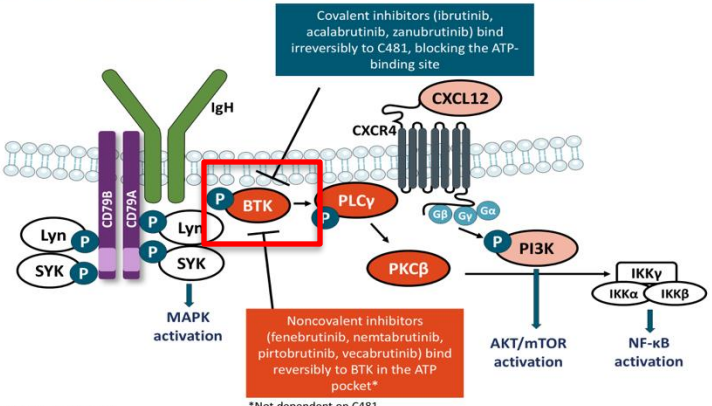


Role of IgHV status

8-year update of RESONATE-2: PFS by IgHV status



MOA of Covalent vs Noncovalent BTK Inhibitors



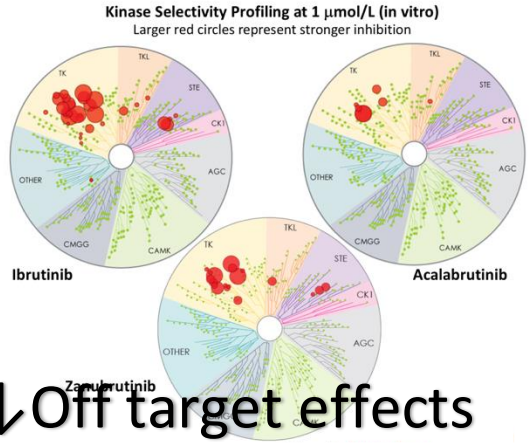
*Not dependent on C481.

Adapted from Lewis. J Pers Med. 2021;11:764.

Kinase Selectivity of Irreversible Covalent BTK Inhibitors

IC_{50}/EC_{50} (nM)

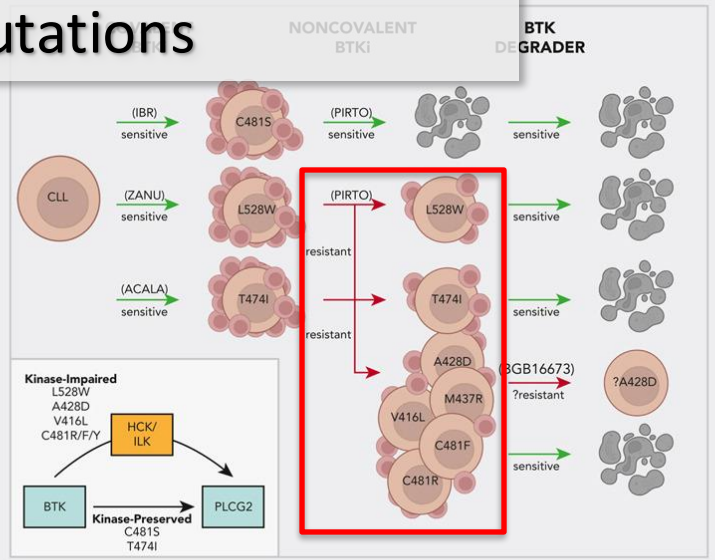
Kinase	Ibrutinib	Acalabrutinib	Zanubrutinib
BTK	1.5	5.1	0.5
TEC	10	126	44
ITK	4.9	>1000	50
BMX	0.8	46	1.4
EGFR	5.3	>1000	21
ERBB4	3.4	16	6.9
JAK3	32	>1000	1377
BLK	0.1	>1000	2.5



Kaptein. ASH 2018. Abstr 1871.

2nd gen BTKi: ↓Off target effects

Non-covalent BTKi: ↓resistance on some mutations

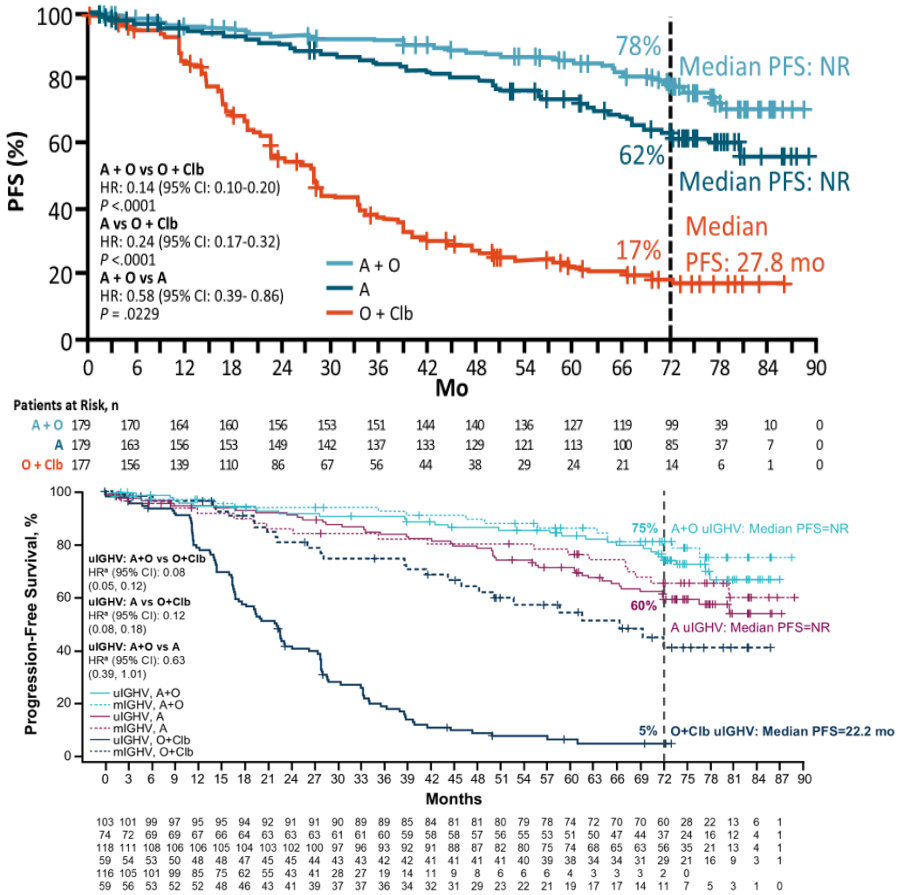


Conclusions: **Unlike the case of ibrutinib, where *BTK* C481S represents the majority of resistant mutations, treatment with second-generation and noncovalent BTKi is associated with newly described resistant *BTK* mutations both at the C481 site and at other sites. These mutations have clinical significance as they may confer resistance to multiple agents.**

*Tam et al. DOI: 10.1182/**blood**.2024026672*

blood Visual Abstract

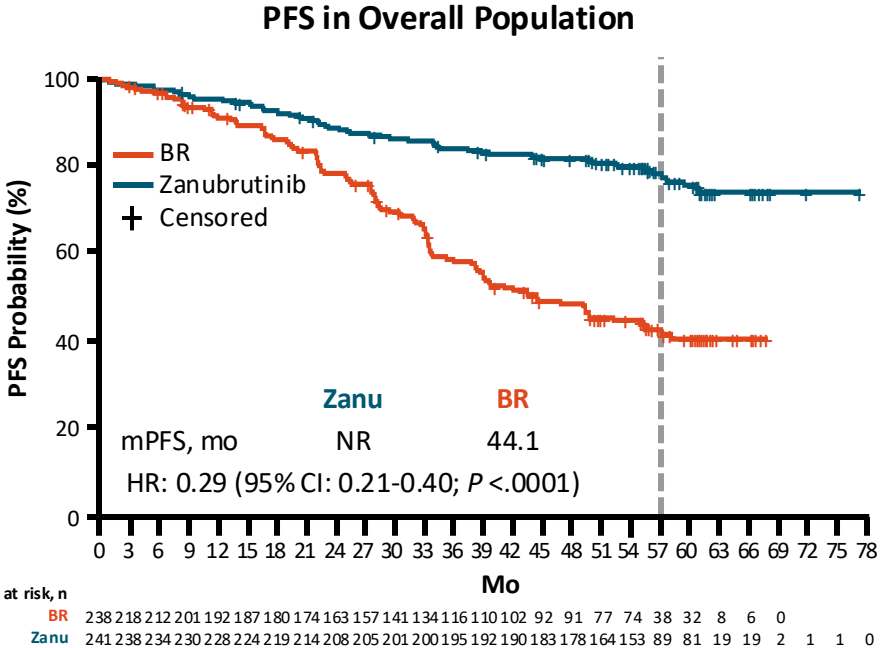
Acalabrutinib (ELEVATE-TN): PFS With 6-Yr Follow-up

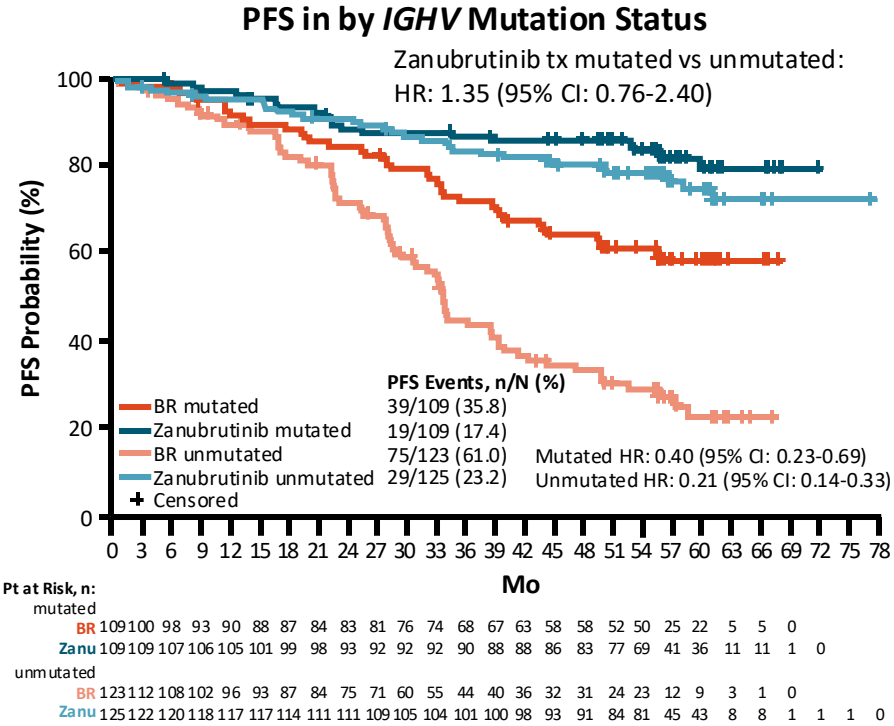


- After median follow-up of 74.5 mo, median PFS was significantly longer in A-containing arms compared with O + Clb
- In A-treated patients uIGHV slightly lower than mIGHV
- Addition of anti-CD20 to 2nd generation cBTKi seems to improve PFS, particularly if uIGHV

Sharman. ASH 2023. Abstr 636. Sharman. Blood. 2025;[Epub].

SEQUOIA 5 Yr Follow Up: Zanubrutinib vs BR



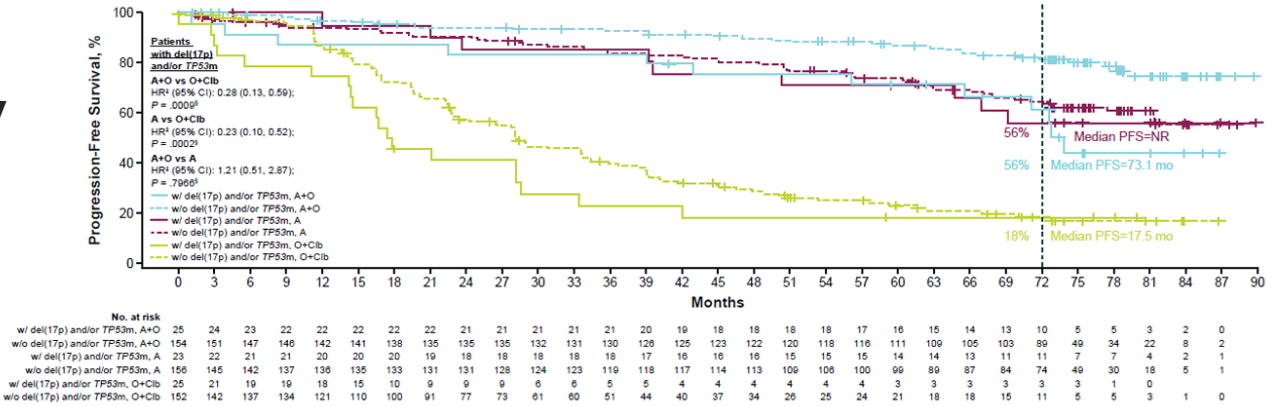


- IGHV status is almost neutralized with Zanu
- However, uIGHV status is slightly inferior to mIGHV

Shadman. JCO. 2024;43:780.

Acalabrutinib (ELEVATE-TN): PFS With 6-Yr Follow-up by TP53 mut

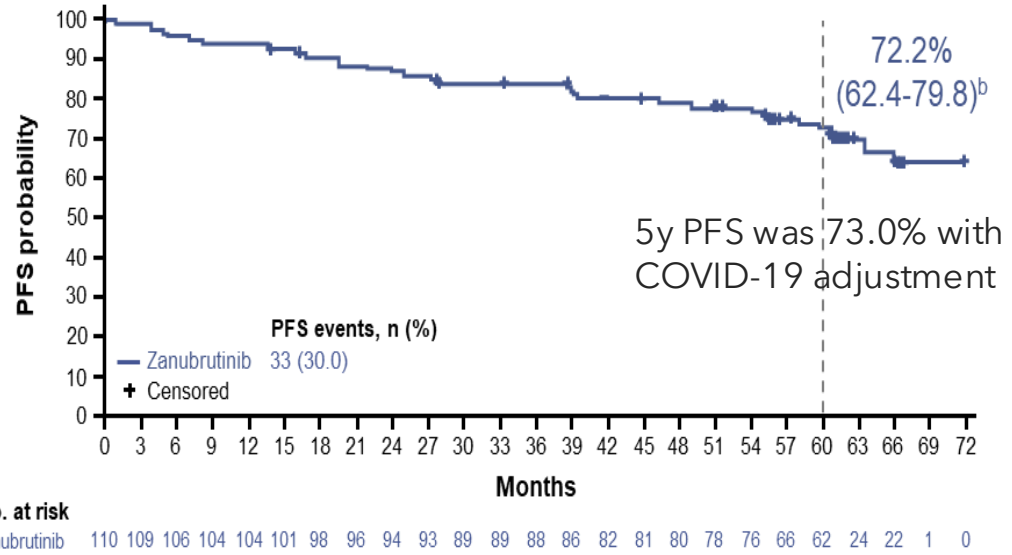
- In A monotherapy arm, PFS with or without TP53 mutation was superimposable
- Anti-CD20 may add some efficacy to TP53wt



Sharman. ASH 2023. Abstr 636. Sharman. Blood. 2025;[Epub].

Zanubrutinib: SEQUOIA Arm C (del17p): 5-year follow-up for Progression-free Survival[a]

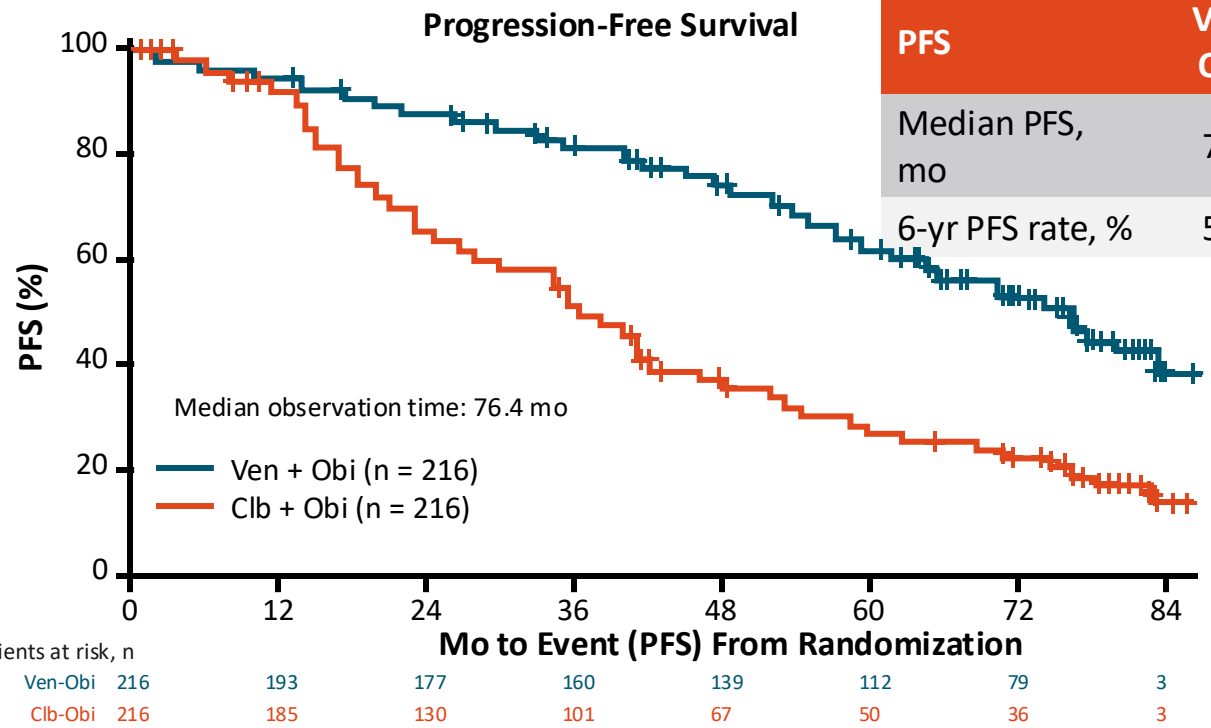
- Median PFS was not reached with zanubrutinib



Data cutoff: April 30, 2024.
[a]Data are presented in patients with del(17p), confirmed by central laboratory (N=110). [b]95% CI values.
CI=confidence interval, PFS=progression-free survival.
Tam CS, et al. Oral Presentation at ASCO 2025; abstract 7011.

Fixed Duration Therapy
1st line

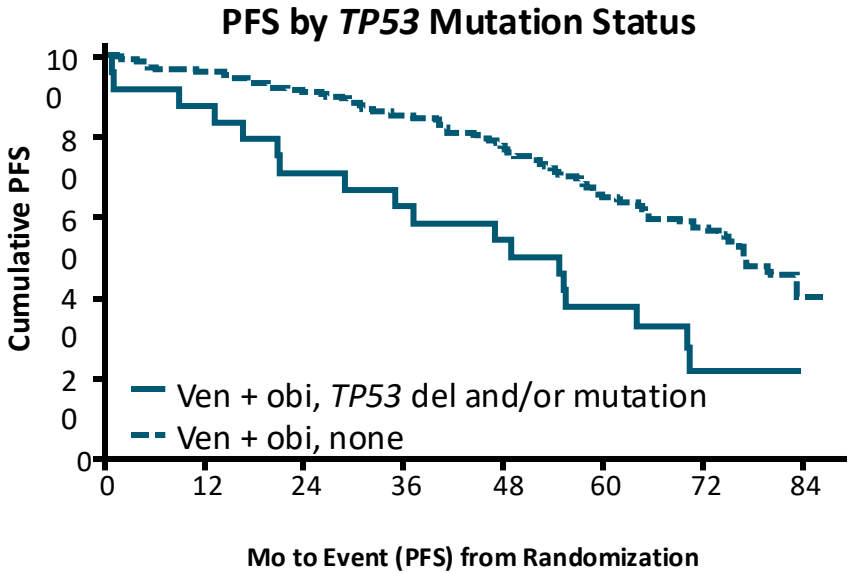
CLL-14 6-Yr Follow-up: PFS With Ven + Obi vs Clb + Obi (Time Limited)



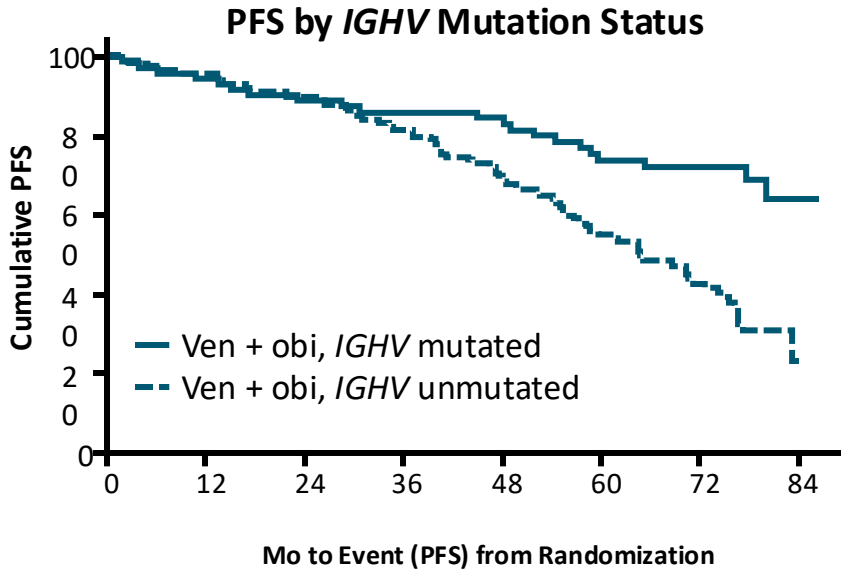
PFS	Ven + Obin	Clb + Obin	HR (95% CI)	*P* Value
Median PFS, mo	76.2	36.4	0.40 (0.31-0.52)	<.0001
6-yr PFS rate, %	53.1	21.7		

Al-Sawaf. Blood. 2024;144:1924.

CLL14: PFS by *TP53* and *IGHV* Mutation Status



PFS by *TP53* Status	*TP53* Del and/or Mut (n = 25)	No *TP53* Del and/or Mut (n = 184)
Ven/Obi: mPFS, mo	51.9	76.6

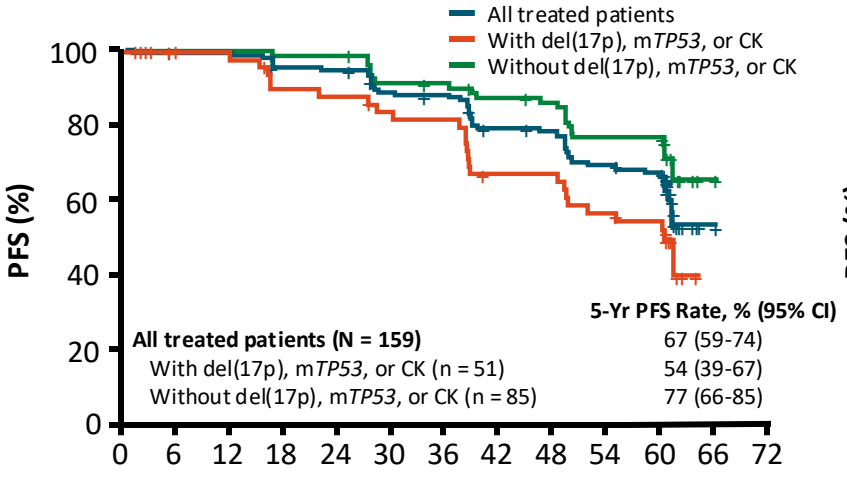


PFS by *IGHV* Status	*IGHV* Mutated (n = 68)	*IGHV* Unmutated (n = 110)
Ven/Obi: mPFS, mo	NR	64.8

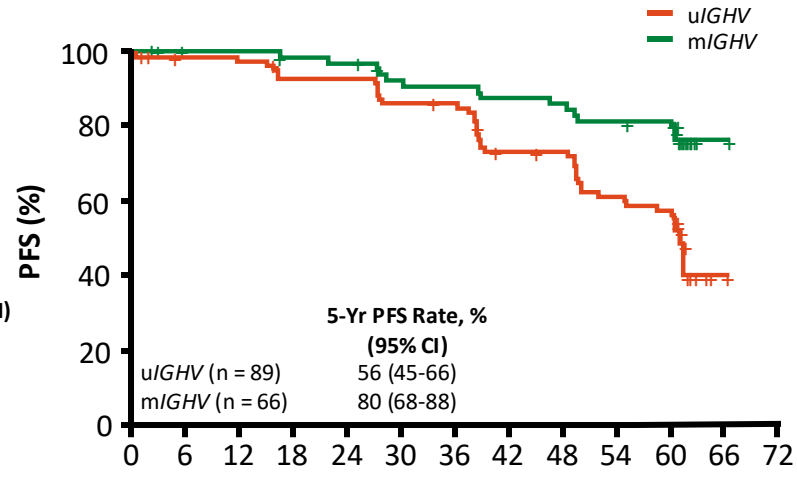
Al-Sawaf. Blood. 2024;144:1924.

CAPTIVATE: 5.5-Yr Follow-up Analysis From FD Cohort of First-line Ibrutinib Plus Venetoclax for CLL/SLL

- Multicenter, 2-cohort phase II trial. FD cohort: Fixed duration ibrutinib + venetoclax in 1st-line setting for CLL/SLL (N = 159)



Patients at Risk, n													
All treated patients	159	153	152	144	143	132	130	115	113	100	96	3	0
With del(17p), m*TP53*, or CK	51	50	50	44	43	40	39	31	31	26	24	0	
Without del(17p), m*TP53*, or CK	85	81	81	79	79	72	71	65	65	58	58	1	0



Patients at Risk, n													
u*IGHV*	8	8	8	7	7	7	7	5	5	4	4	1	0
m*IGHV*	9	5	5	9	9	3	2	9	8	8	5	1	0
	6	6	6	6	6	5	5	5	5	4	4		
	6	4	3	1	0	5	4	2	1	8	7		

Wierda. JCO. 2024;42:7009. Wierda. JCO. 2022;40:7519.

U-CLL and M-CLL: no difference in resistance mutations at relapse after I+V

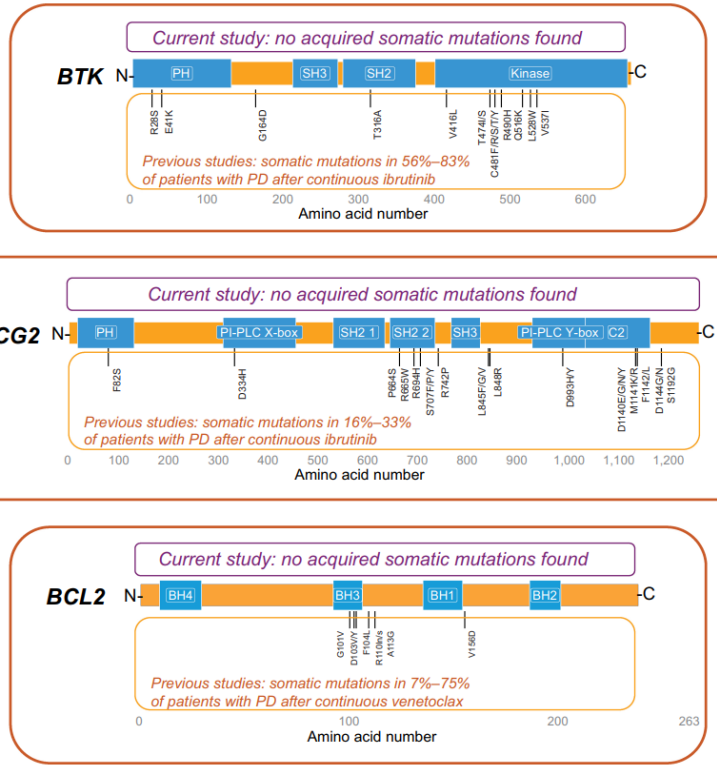
Patients evaluated (N=25 out of 29 with PD) from CAPTIVATE trial

Analysis of cytogenetic and mutational risk features **at baseline did not identify any risk feature or mutated gene as predictive of PD** after completion of fixed-duration ibrutinib plus venetoclax.

A greater total number of baseline genomic risk features was associated with PD development

No previously reported resistance-associated mutations in BTK, PLCG2, or BCL2 were identified in the 25 evaluable patients with PD after first-line, fixed-duration ibrutinib plus venetoclax.

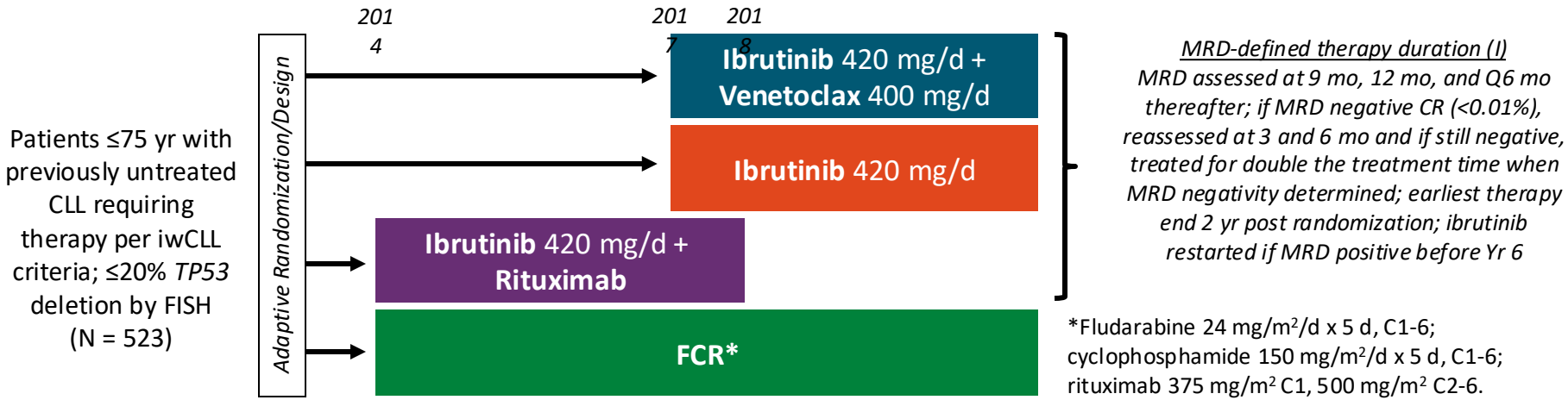
TP53 variant allele frequencies did not change from baseline to relapse in 8 of 9 patients with TP53 mutations and the TP53 variant clone at baseline was lost at PD in one patient, **suggesting that aggressive disease characteristics did not increase with fixed duration treatment.**



Jain, 2024

FLAIR: FCR vs Ibrutinib vs Ibrutinib + Venetoclax vs Ibrutinib + Rituximab in Previously Untreated CLL

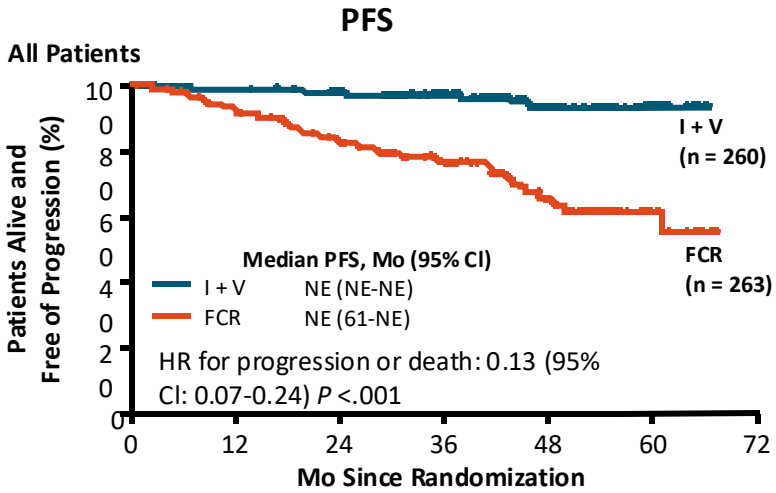
- Multicenter, randomized, open-label, parallel-group, adaptive-design phase III trial

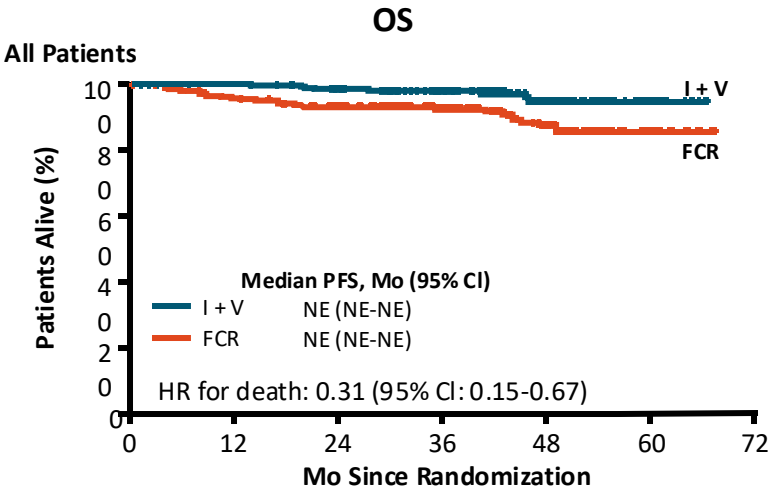


- **Coprimary endpoints (current analysis)**: PFS (I + V vs FCR), MRD (I + V vs I); **Key secondary endpoints (current analysis):** PFS (I + V vs I, I vs FCR), OS, uMRD, response per iwCLL criteria, safety, HRQoL, cost

Munir. NEJM. 2024;390:326. Hillmen. EHA 2022. Abstr S145.

FLAIR: PFS and OS With Ibrutinib + Venetoclax vs FCR



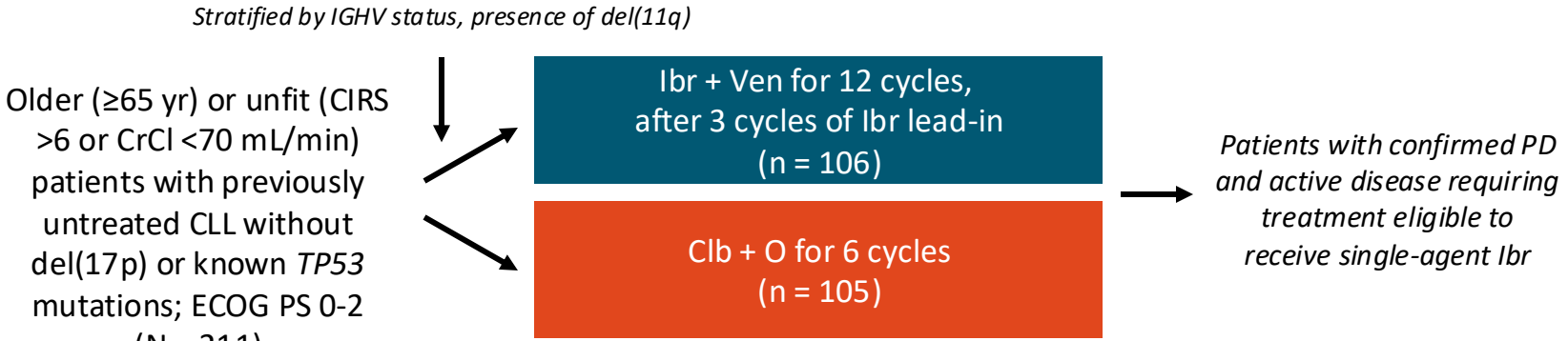


- At 3 yr, 58.0% of patients in the ibrutinib + venetoclax group had stopped therapy due to undetectable MRD
- After 5 yr of ibrutinib + venetoclax, 65.9% of patients had undetectable MRD in the bone marrow and 92.7% had undetectable MRD in the peripheral blood

Munir. NEJM. 2024;390:326.

GLOW: Ibrutinib + Venetoclax vs Chlorambucil + Obinutuzumab in Previously Untreated CLL

- Randomized phase III trial



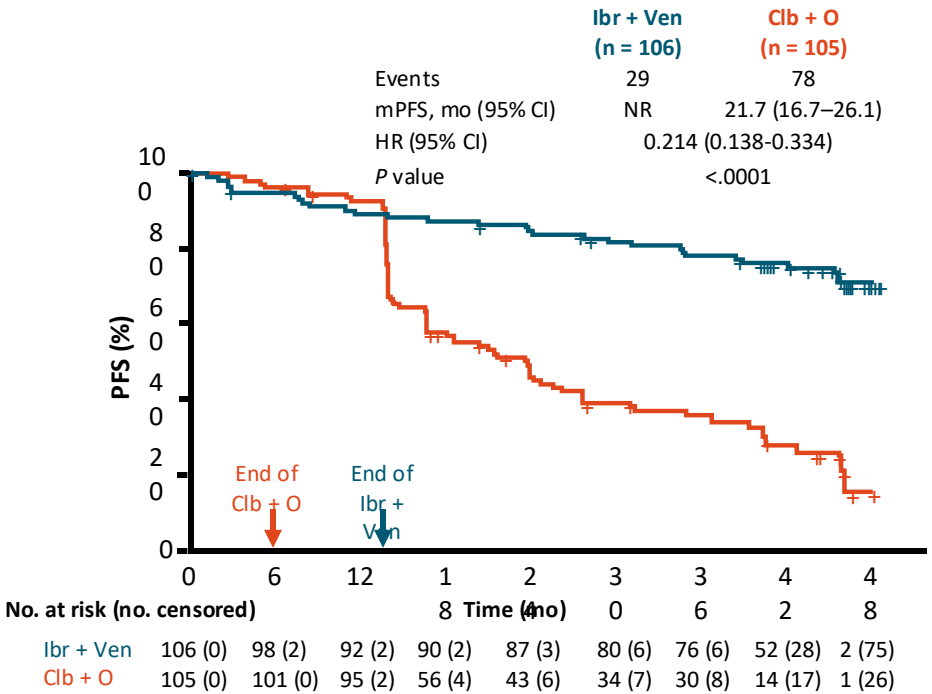
Dosing: Ibr 420 mg QD; Ven 20-400 mg QD ramp-up over 5 wk beginning at cycle 4; Clb 0.5 mg/kg on Days 1, 15; O 1000 mg on Days 1-2, 8, 15 of cycle 1, Day 1 of cycles 2-6.

- **Primary endpoint:** PFS by IRC
- **Secondary endpoints:** MRD, CRR, ORR, OS, DOR, time-to-next treatment, time to worsening, safety

Niemann. Lancet Oncol. 2023;24:1423. Munir. ASH 2021. Abstr 70.

GLOW: 4-Yr Follow-up PFS

Median follow-up: 46 mo



Characteristic, n (%)	Ibr + Ven	
	mIGHV (n = 35)	uIGHV (n = 57)
Events	3	23
mPFS, mo (95% CI)	90.0 (72.0-96.7)	69.8 (57.2-79.4)
HR (95% CI)	3.775 (1.133-12.576)	
P value	.031	

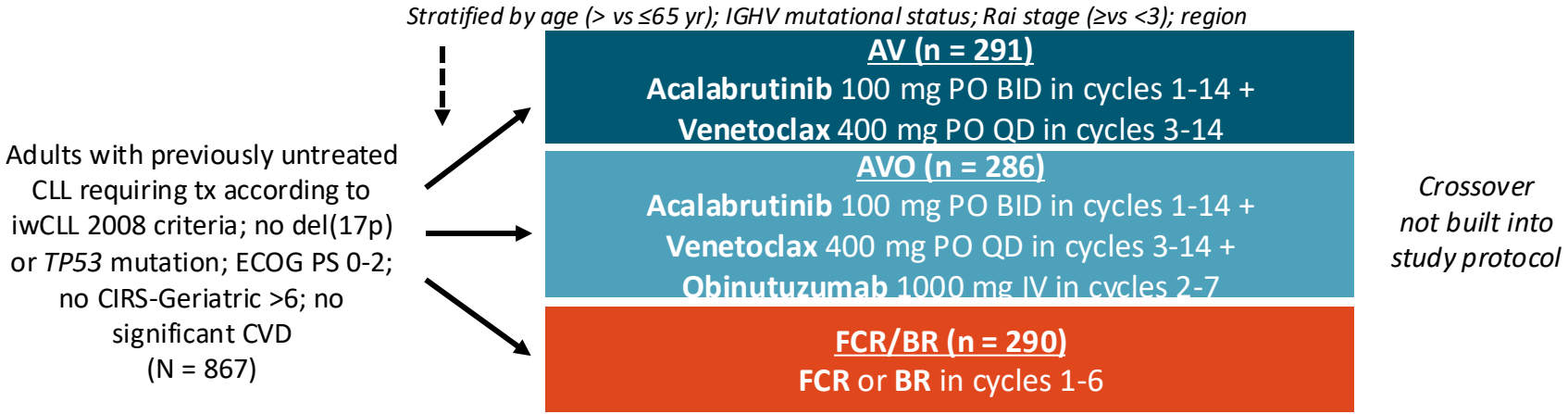
Characteristic, n (%)	Clb + O	
	mIGHV (n = 32)	uIGHV (n = 67)
Events	21	47
mPFS, mo (95% CI)	43.1 (23.1-59.0)	15.0 (6.7-26.4)
HR (95% CI)	2.172 (1.289-3.660)	
P value	.0036	

- 5-yr follow-up mPFS for Ibr + Ven vs Clb + O: 67% vs 20%; HR: 0.256

Niemann. Lancet Oncol. 2023;24:1423. Munir. SOHO 2024. Abstr CLL-487.

AMPLIFY: Study Design

- Prespecified interim analysis of international, randomized, open-label phase III trial

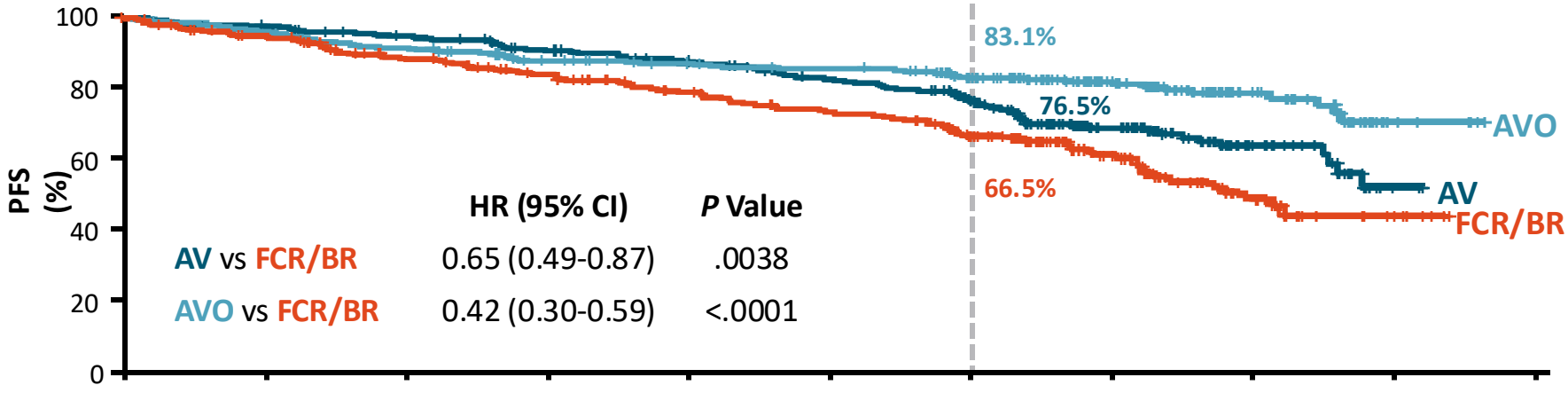


- **Primary endpoint**: PFS per IRC for AV vs FCR/BR
- **Secondary endpoints***: PFS per IRC for AVO vs FCR/BR; uMRD for AV vs FCR/BR; uMRD for AVO vs FCR/BR; OS for AV vs FCR/BR; OS for AVO vs FCR/BR

*Secondary endpoints tested in the order listed if primary endpoint is met.

Brown. ASH 2024. Abstr 1009. Brown. NEJM. 2025;392:748.

AMPLIFY: PFS per IRC



Patients at Risk, n

AV	291	282	289	251	237	219	177	102	35	3	0
AVO	288	272	258	237	225	219	191	118	51	7	0
FCR/BR	290	238	208	189	170	154	127	68	28	6	0

- Study met its primary endpoint, demonstrating significantly prolonged PFS per IRC for AV vs FCR/BR after a median follow-up of 48.0 mo

Brown. ASH 2024. Abstr 1009. Brown. NEJM. 2025;392:748.

AMPLIFY: PFS Subgroup Analyses

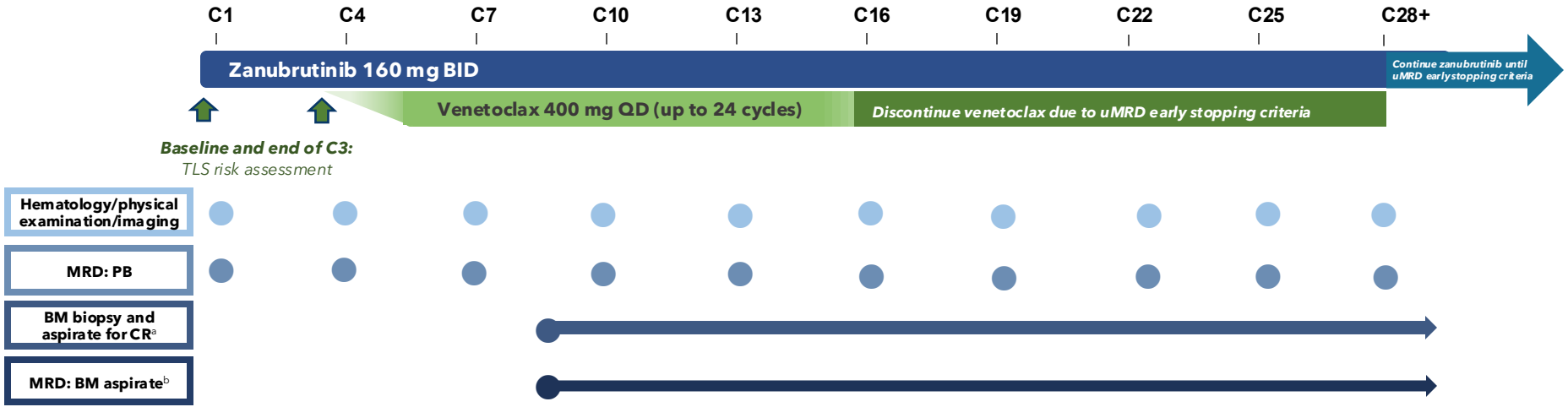
Median PFS by Subgroup	AV	AVO	FCR/BR
Unmutated *IGHV*	n = 167	n = 169	n = 172
▪ mPFS, mo	51.5	NR	43.3
▪ HR (95% CI) vs FCR/BR	HR: 0.69 (0.48-0.97)	HR: 0.35 (0.23-0.53)	–
Mutated *IGHV*	n = 124	n = 117	n = 118
▪ mPFS, mo	NR	NR	NR
▪ HR (95% CI) vs FCR/BR	0.67 (0.39-1.14)	0.58 (0.32-1.02)	–
uMRD* group at EOT	n = 100	n = 192	n = 132
▪ mPFS, mo	NR	NR	49.2
▪ HR (95% CI) vs FCR/BR	0.43 (0.24-0.76)	0.27 (0.16-.46)	–
MRD+* at EOT	n = 122	n = 10	n = 49
▪ mPFS, mo	NR	45.7	35.3
▪ HR (95% CI) vs FCR/BR	0.44 (0.28-0.71)	0.70 (0.21-1.78)	–

*uMRD defined as $<10^{-4}$ in PB per flow cytometry.

Brown. ASH 2024. Abstr 1009. Brown. NEJM. 2025;392:748.

Treatment and Assessment Schedule

SEQUOIA Arm D



uMRD-guided stopping criteria

All conditions must be met:

1. Response assessed as CR or CRi confirmed by a BM biopsy
2. uMRD $<1\times10^{-4}$ (uMRD4) achieved in 2 consecutive peripheral blood MRD tests conducted ≥12 weeks apart
3. uMRD4 achieved in 2 consecutive BM aspirate MRD tests conducted ≥12 weeks apart
4. Received
   - i) Minimum of 12 cycles of venetoclax (to stop venetoclax early)
   - ii) Minimum of 27 cycles of zanubrutinib (to stop zanubrutinib early)

[a]BM biopsy and aspirate are required to confirm a suspected CR/CRi (BM biopsy collection timepoint not defined per protocol), starting after cycle 9 and then annually if needed. [b]Patients with confirmed CR/CRi and 2 consecutive PB-uMRD results at least 12 weeks apart.

BID=twice daily, BM=bone marrow, C=cycle, CR=complete response, CRi=CR with incomplete bone marrow recovery, MRD=measurable residual disease, PB=peripheral blood, QD=once daily, TLS=tumor lysis syndrome, uMRD=undetectable measurable residual disease, uMRD4=undetectable measurable residual disease (<1 CLL cell in 10,000 leukocytes at 10-4 sensitivity by 8-color flow cytometry).

Shadman M, et al. Oral Presentation at ASCO 2025;abstract 7009.

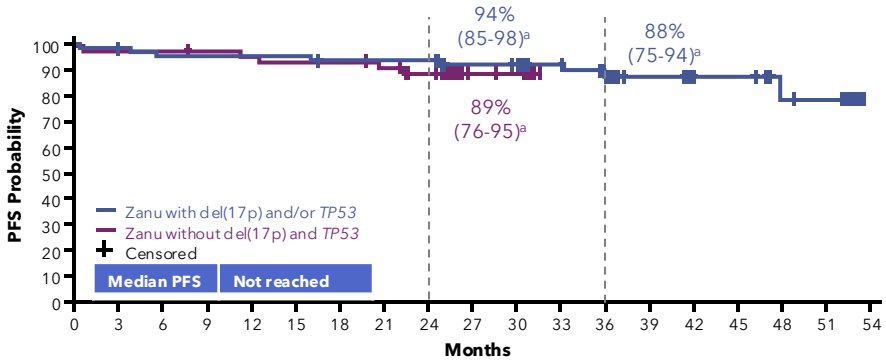
Progression-free Survival

SEQUOIA Arm D

- Similar PFS rates were achieved across subgroups

With and without del(17p) and/or *TP53* mutation

- Median study follow-up for patients with del(17p) and/or *TP53*mut was 38.7 mo (0.4-58.0) and 29.6 mo (0.6-31.9) for patients without del(17p) and *TP53*mut

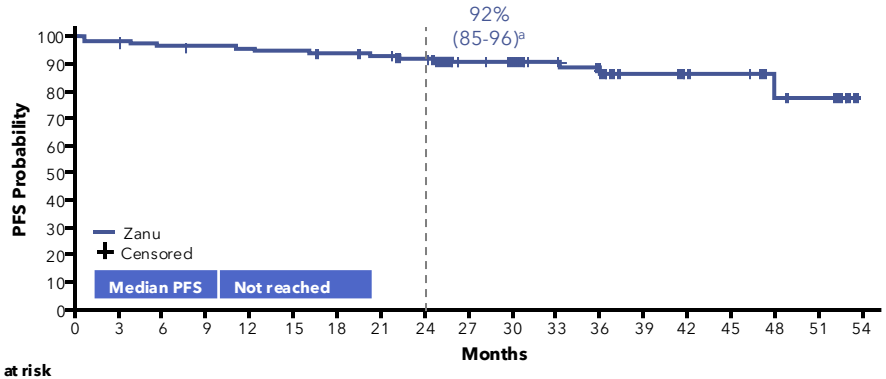


No. at risk

Zanu with del(17p)/*TP53*	66	65	62	62	62	62	60	60	60	55	54	45	35	23	17	16	9	8	0
Zanu w/o del(17p)/*TP53*	47	46	46	45	44	43	43	41	37	7	4	0							

All patients

- Median study follow-up for all patients was 31.2 mo (0.4-58.0)



No. at risk

Zanu	114	112	109	108	107	106	104	102	98	62	58	45	35	23	17	16	9	8	0

- Of the 11 patients who discontinued after meeting stringent uMRD-guided stopping criteria, only one patient with del(17p) has progressed

[a]95% CI values.
ITT=intention-to-treat, mut=mutation, PFS=progression-free survival, w/o=without.
Shadman M, et al. Oral Presentation at ASCO 2025;abstract 7009.

Comparison of PFS for 1° line options

Trial treatment no. of patients	Characteristics (median, if not indicated otherwise)	PFS at month	PFS rate (%)			
			All patients	uIGHV	mIGHV	17p−TP53m
RESONATE-2 Ibr (n = 136)	FU: 60; Age: 73; CIRS > 6: 31%; CrCl < 60 mL/min	48	74[a]	75[a]	80[a]	
iLLUMINATE Obi-Ibr (n = 113)	FU: 46; Age: 70; CIRS: 4; CrCl: 72	48	74	67	89	
ALLIANCE Ibr (n = 182)	FU: 55; Age: 71; CrCl: 69	48	76	73	84	73
ALLIANCE R-Ibr (n = 182)	FU: 55; Age: 71; CrCl: 67	48	76	66	78	80
ECOG 1912 R-Ibr (N = 354)	FU: 71; Age: 58; CrCl: 95	48	83	83	87	77[b]
FLAIR R-Ibr (n = 384)	FU: 53; Age: 63; CrCl: 79	48	86	88	92	67[b]
ELEVATE-TN Acala (n = 179)	FU: 75; Age: 70; CrCl: 75	48	78	77	81	76
ELEVATE-TN Obi-Acala (n = 179)	FU: 75; Age: 70; CrCl: 77	48	87	86	89	75
SEQUOIA Zanu (n = 241)	FU: 44; Age: 70	48	79	72	86	
CLL14 Obi-Ven (n = 216)	FU: 76; Age: 72; CIRS: 9; CrCl: 65.2	48	74	69	85	54
CLL13 Obi-Ven (n = 229)	FU: 51; Age: 62; CIRS: 2; CrCl: 86.3	48	82	74	92	n.a.
GLOW Ibr-Ven (n = 106)	FU: 57 ; Age: 71; CIRS: 9; CrCl: 66.5	48	70	63[a]	90[a]	
FLAIR Ibr-Ven (n = 260)	FU: 44; Age: 62; CrCl: 83	48	94			
CAPTIVATE FD Ibr-Ven (n = 159)	FU: 66; Age: 60	48	79	73	84	63
AMPLIFY A+V (n = 291)	FU: 48; Age: 61; CIRS: 2; CrCl: 13% <60 ml/min	36	77	69	86	n.a.
AMPLIFY A+V+O (n = 286)	FU: 48; Age: 60; CIRS: 3; CrCl: 14% <60 ml/min	36	83	83	84	n.a.
SEQUOIA Arm D Zanu + Son (n=114)	FU: 31; Age: 67	36	88			89 (2y)

48mo PFS in CDT

- 75-80% for cBTKi
- Not much different (5-10%) between m or uIGHV
- Superimposable to wt for 17p-/p53mut
- Maybe 5-10% higher with anti-CD20

48mo PFS in FDT

- 70-80% with doublets
- Drop of 15% in uIGHV: mIGHV perform equal or better than CDT
- Drop of 15-20% if 17p-/p53mut

After 1st line

Elevate-RR: Ibrutinib vs Acalabrutinib in Patients With High-Risk Relapsed/Refractory CLL

- Randomized, open-label, noninferiority phase III trial

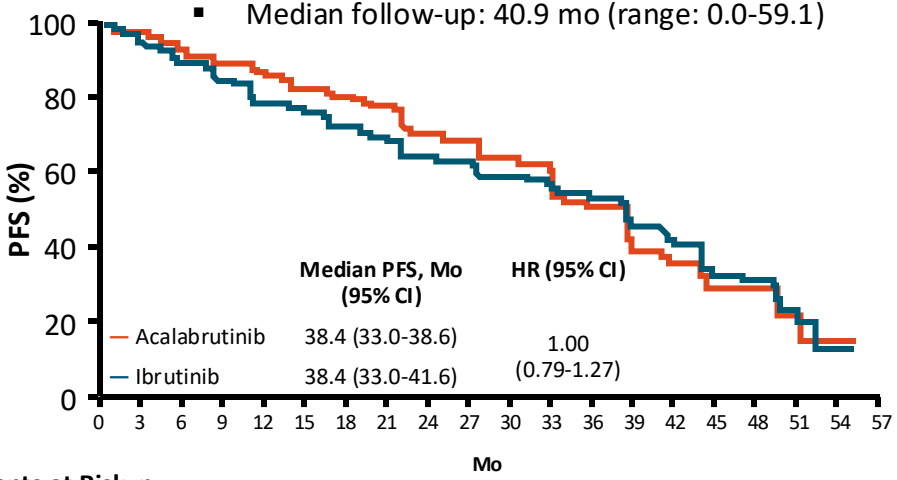
Patients with del(17p) or del(11q) CLL with active disease; ≥1 previous line of treatment; ECOG PS 0-2 (planned N = 533)

Ibrutinib
100 mg BID
(n = 268)

Acalabrutinib
420 mg QD
(n = 265)

- Primary endpoint: PFS

- Trial demonstrated noninferiority because upper bound of 2-sided 95% CI for HR <1.429
- Median follow-up: 40.9 mo (range: 0.0-59.1)

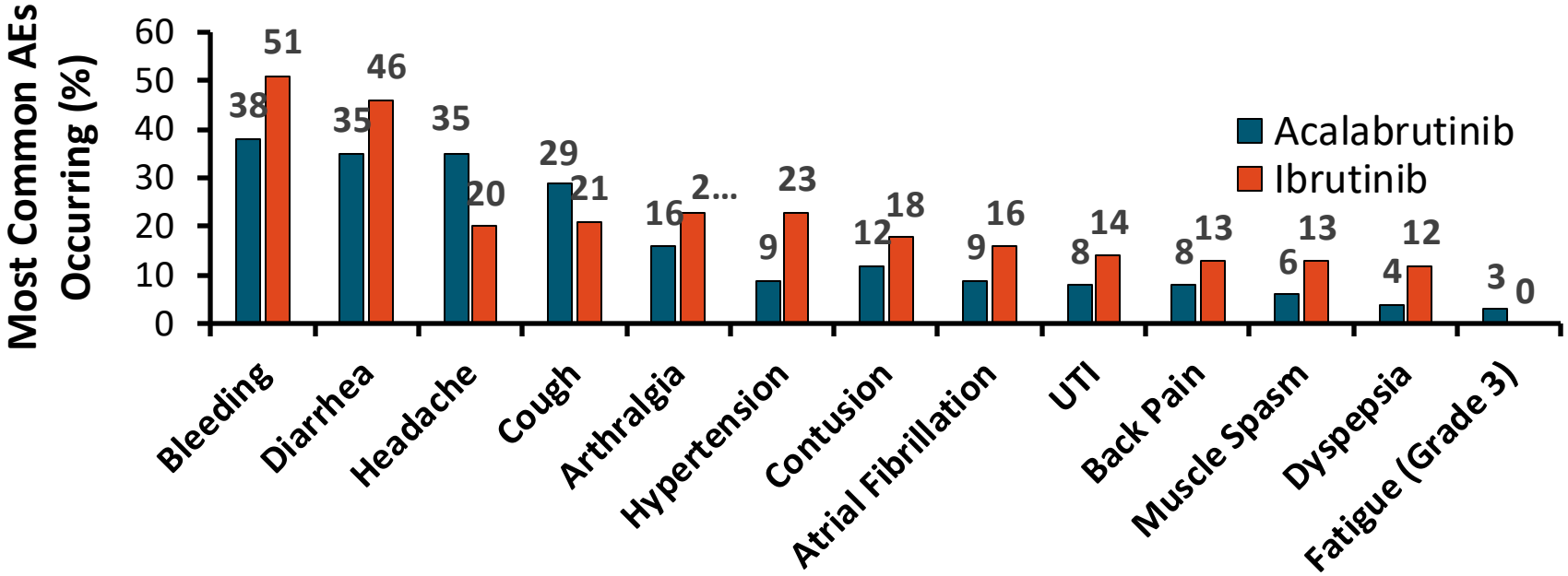


Patients at Risk, n

Acalabrutinib	268	250	235	227	219	207	200	193	173	163	148	110	84	59	31	21	13	3	1	0
Ibrutinib	265	240	221	205	186	178	168	160	148	142	130	108	81	66	41	26	15	8	2	0

Byrd. JCO. 2021;39:3441. NCT02477696.

ELEVATE-RR: Tolerability of Acalabrutinib vs Ibrutinib

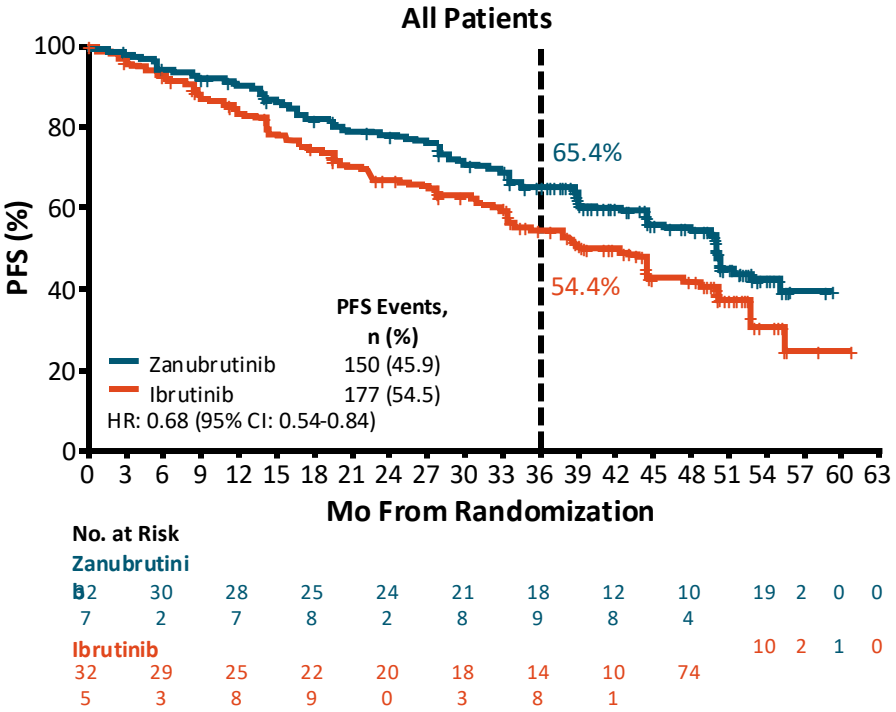


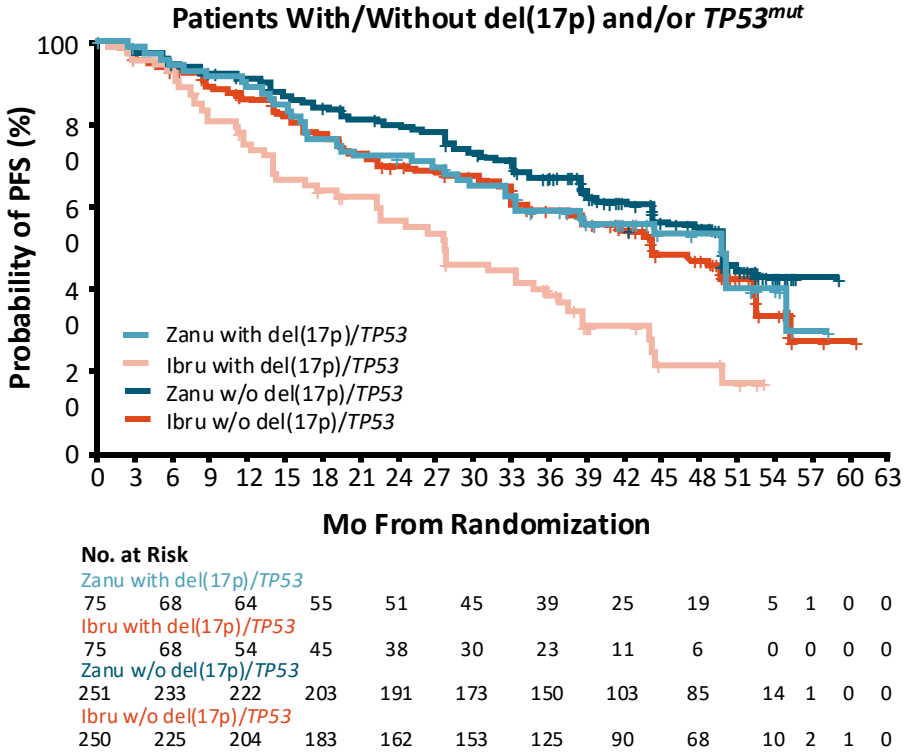
- Rates of major bleeding were similar among the groups (acalabrutinib 4.5% and ibrutinib 5.3%)
- **AE leading to treatment discontinuation: 14.7% (acalabrutinib) and 21.3% (ibrutinib)**

Byrd. J Clin Oncol. 2021;39:3441.

ALPINE: PFS at 42.5-Mo Follow-up and ORR

Brown. Blood. 2024. 144:2706.





- ORR: 85.6% (zanubrutinib) vs 75.4% (ibrutinib)
- **Zanubrutinib had lower discontinuation rates vs ibrutinib because of AEs (21.4% vs 28.3%)**

The dilemma of toxicity between FDT and CDT

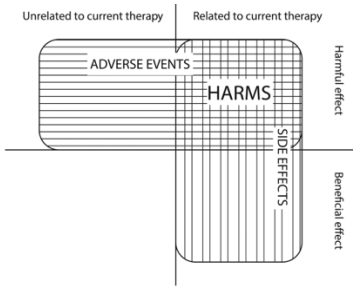
- Traditional AE reporting in hematology and oncology based on maximum grade of toxicity is now obsolete
  - Does not account for time profile of AE
  - Does not capture the impact of chronic, low grade toxicity on the ability to continue treatment
  - Does not incorporate PRO

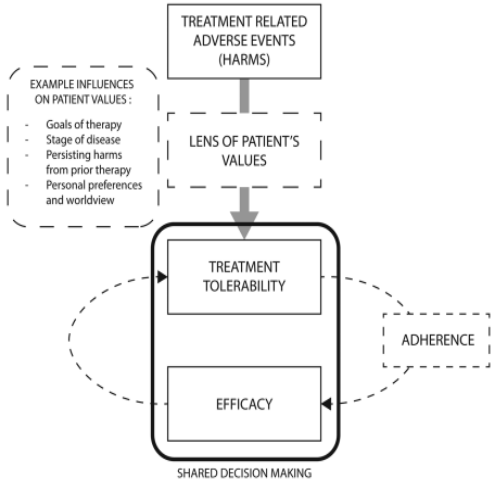
CDT efficacy hinges on treatment adherence

→ which is strongly associated with treatment tolerability

→ which depends on burden of harms

→ caused by treatment-related AE through the lens of patients' values





Preferenze dei pazienti

Patients' priorities in selecting chronic lymphocytic leukemia treatments

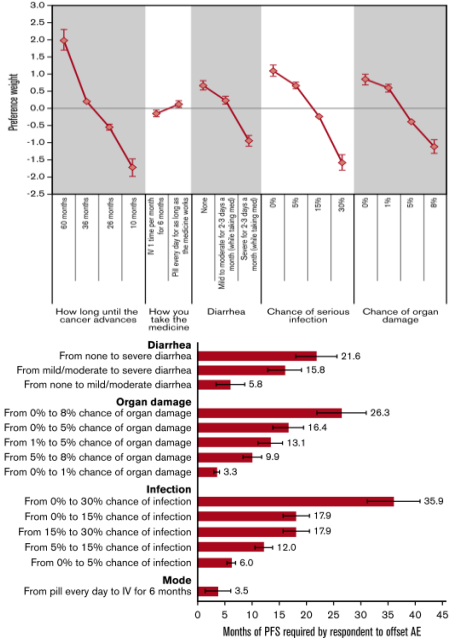
Carol Mansfield,[1] Anthony Masaquel,[2] Jessie Sutphin,[1] Elisa Weiss,[3] Meghan Gutierrez,[4] Jennifer Wilson,[3] Marco Boeri,[1] Jia Li,[2] and Carolina Reyes[2]

[1]RTI Health Solutions, Research Triangle Park, NC; [2]Genentech Inc., South San Francisco, CA; [3]The Leukemia & Lymphoma Society, Rye Brook, NY; and [4]Lymphoma Research Foundation, New York, NY

Survey su 384 pazienti con «discrete choice experiments»: 8 domande DCE
5 livelli di attributi:

- PFS (10, 26, 36, 60 mesi)
- Modo di somministrazione (EV 1-3 gg/mese x 6 mesi vs orale continuativo)
- Diarrea (nessuna / lieve-moderata per 2-3 gg/mese vs severa per 2-3 gg/mese)
- Probabilità di infezione severa (0 / 5% / 15% / 30%)
- Rischio di danno d'organo (TLS:: 0% / 1% / 5% / 8%)

Medication Feature	Medication A	Medication B
How long until the cancer advances	26 months (2 years and 2 months)	60 months (5 years)
How you take the medicine	IV 1 time per month **for 6 months**	Daily pill **for 60 months**
Diarrhea (2-3 days per month)	None	Mild to moderate **for 60 months** for 2-3 days per month
Chance of severe infection	15 out of 100 (15%) **for 6 months**	30 out of 100 (30%) **for 60 months**
Chance of organ damage	8 out of 100 (8%) **for 6 months**	None
Which medicine would you choose?	●	●



PFS è il criterio più importante

Gli eventi avversi sono molto rilevanti:

- Per bilanciare ↑ 30% del rischio di infezioni serve ↑ PFS di 36 mesi

Il modo di somministrazione è secondario a PFS ed eventi avversi

- Nello studio di Landfeldt (2016) era 3° su 6 (dopo OS ed eventi avversi)
- Dati confermati in un recente studio (Arlene, ASH 2023)

Mansfield, Blood Adv 2017

Table 2. Maximum Acceptable Risk of Treatment Side Effects in Exchange for Improvements in Chronic Lymphocytic Leukemia Treatment Characteristics

Attribute	From level	To level	MAR of tumor lysis syndrome	MAR of atrial fibrillation	MAR of fatigue
			Mean (95% CI)		
Duration of treatment	Until the cancer progresses (gets worse)	Fixed: 12 months	> 3.0	6.2 (4.2-8.1)	21.2 (12.3-30.2)
	Until the cancer progresses (gets worse)	Fixed: 6 months	> 3.0	7.4 (5.3-9.4)	26.2 (17.1-35.2)
	Fixed: 12 months	Fixed: 6 months	N/A[a]	N/A[a]	N/A[a]

CI = confidence interval; MAR = maximum acceptable risk; N/A = not applicable; TLS = tumor lysis syndrome.

Note: MAR estimates outside the range of levels included in the study are noted as greater than the largest difference in levels of risk of TLS, atrial fibrillation, and fatigue: 3%, 10%, and 35%, respectively. Confidence intervals are not reported for these estimates. It is possible to estimate a specific value for the MAR outside the range of levels included in the study only by making the strong assumption that the disutility of each unit increase in risk remains constant beyond the greatest level of risk.

[a] The difference between these levels was not statistically significant. Therefore, the MAR for this change cannot be calculated as the change from 1 level to the other does not have a statistically meaningful impact on the average respondent's preferences.

Arliene et al., Blood, 2023

Why traditional «maximum grade» reporting is inadequate in hematology

Shortcomings of traditional "maximum grade" reporting: chronic low grade AEs

Gastrointestinal disorders					
	Grade				
Adverse Event	1	2	3	4	5
Diarrhea	Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4 - 6 stools per day over baseline; moderate increase in ostomy output compared to baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by frequent and watery bowel movements.					

Table 4. Adverse Events Deemed Related to Panobinostat (≥ 10% any grade) As of June 11, 2010

	Any Grade		Grade 3 to 4	
Adverse Event	No.	%	No.	%
Thrombocytopenia	110	85	102	79
Diarrhea	85	66	4	3
Nausea	77	60	1	1
Anemia	49	38	27	21
Fatigue	49	38	12	9

Table 2. Adverse Events during Treatment.*

Event or Abnormality	Grade Any	Grade no. (%) ≥3
Diarrhea	54 (43)	16 (13)
Nausea	37 (30)	2 (2)
Fatigue	37 (30)	2 (2)
Cough	36 (29)	0

National Cancer Institute. CTCAE v.5.0. Bethesda, MD: US. Department of Health and Human Services; 2009
Younes et al. J Clin Oncol 2012;30:2197-203
Gopal et al. N Engl J Med 2014; 370;11:1008-18.

Shortcomings of traditional "maximum grade" reporting: lack of time profile of AEs

Two grade 3+ AEs with similar incidence (maximum grade reporting)

Grade 3 or higher	Carfilzomib + dex (n=463)	Bortezomib + dex (n=456)
Dyspnea	25 **(5%)**	10 (2%)
Peripheral neuropathy	6 (1%)	24 **(5%)**

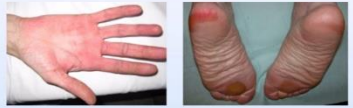
Conceptual patient AE experience: which is more burdensome?

Dimpoulous et al. Lancet Oncol 2016; 17:27-38
Grandin et al. J Cardiac Fail 2015;21:138-144
Siegel et al. Haematologica 2013; 98(11):1753-61

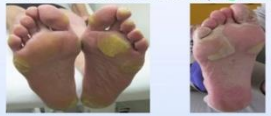
Shortcomings of traditional "maximum grade" reporting: lack of time profile of AEs

Two oral agents that produce a similar AE

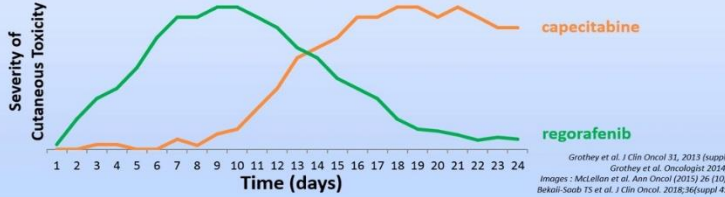
Hand-foot syndrome (capecitabine)



Hand-foot skin reaction (regorafenib)

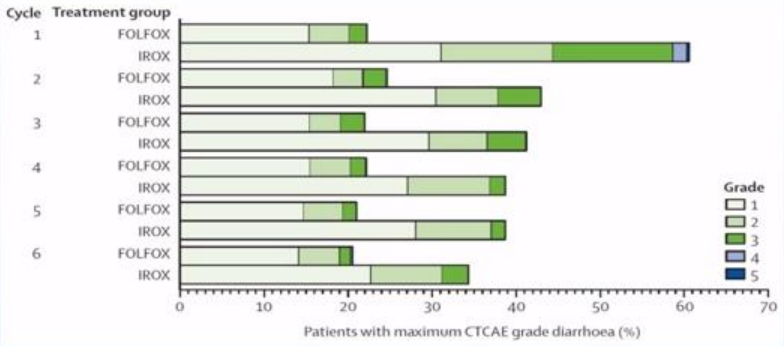


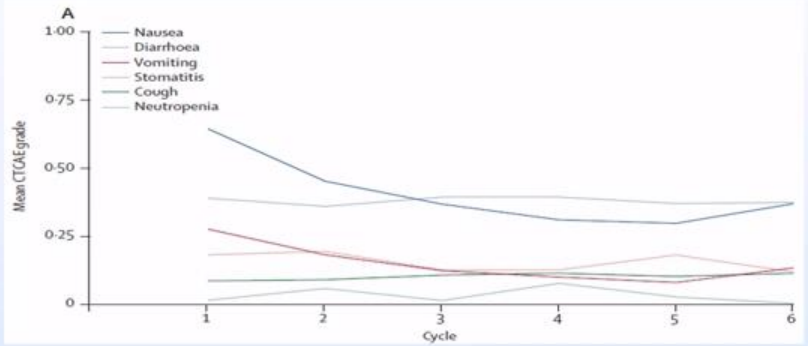
Clinical experience of time of AE occurrence: ramifications on AE intervention?

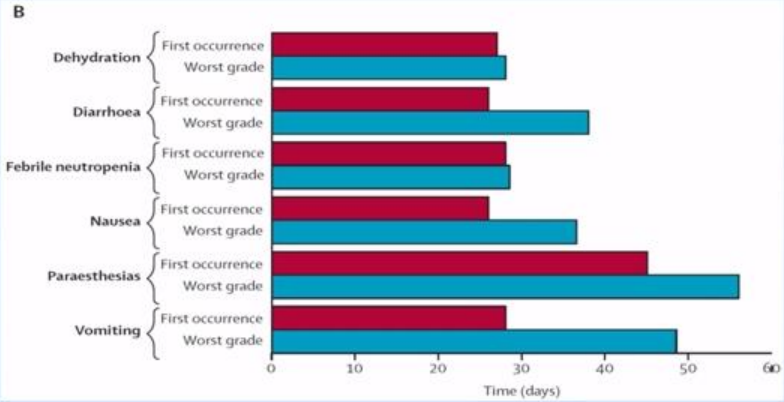


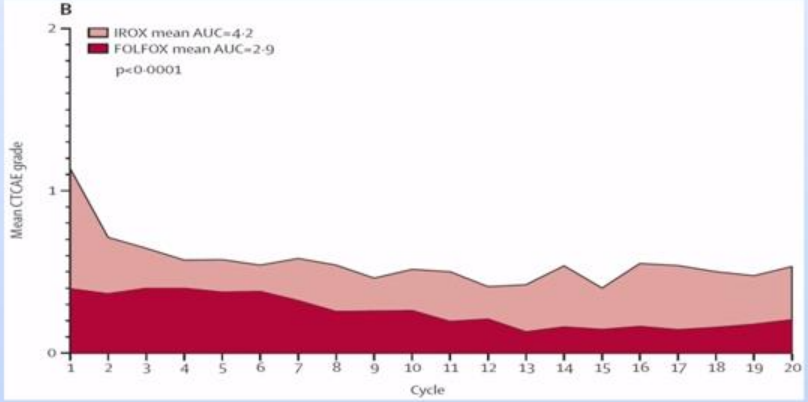
Grothey et al. J Clin Oncol 31, 2013 (suppl; abstr 3637)
Grothey et al. Oncologist 2014;19(6)669-80
Images : McLellan et al. Ann Oncol (2015) 26 (10): 2017-2026.
Bekaii-Saab TS et al. J Clin Oncol. 2018;36(suppl 4S; abstr 611).

Improving AE analysis: longitudinal analysis
Toxicity over Time (ToxT) approach





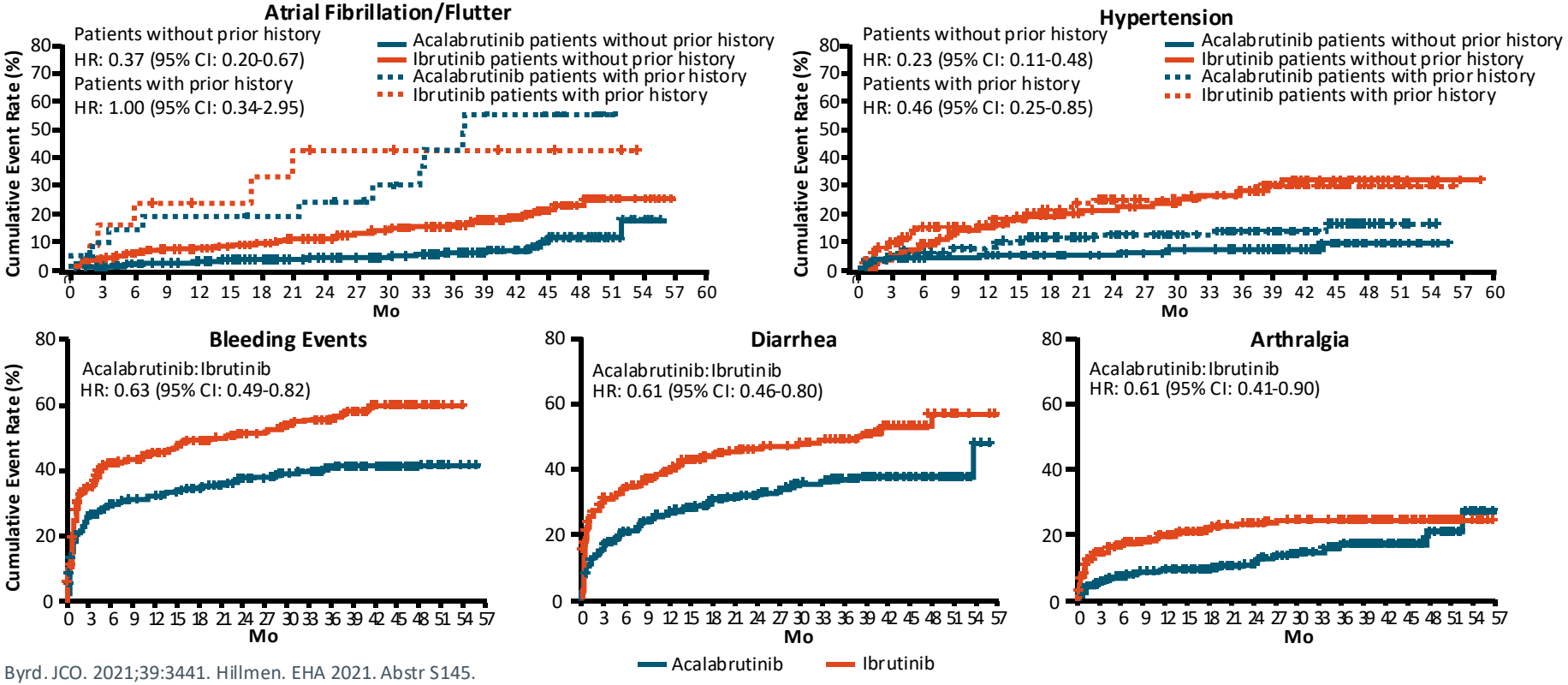




Thanarajasingam G. Lancet Oncol. 2016; 17:663-70

MAYO CLINIC

ELEVATE-RR: Cumulative Incidence of AESI



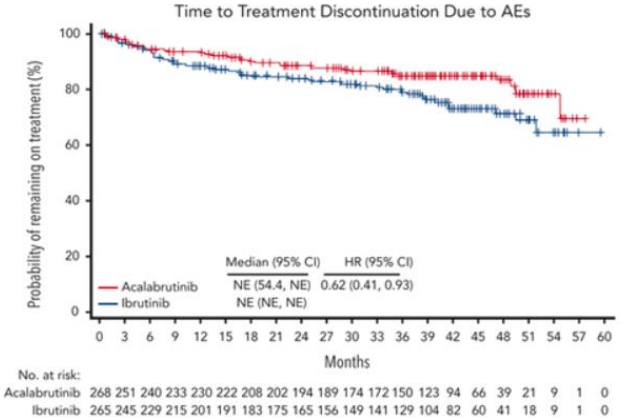
Byrd. JCO. 2021;39:3441. Hillmen. EHA 2021. Abstr S145.

ELEVATE-RR: details about toxicity

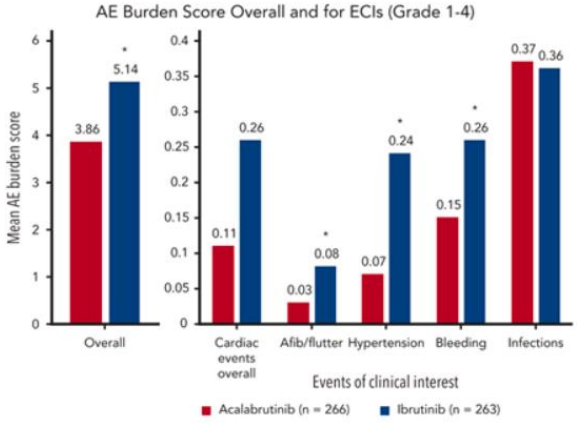
- Exposure-adjusted incidence rate was assessed for common BTK–associated AEs and for selected events of clinical interest (ECIs)→ AE burden score
- AE burden score was higher for ibrutinib vs acalabrutinib overall and for the ECIs AFib/flutter, hypertension, and bleeding; was higher for acalabrutinib only for headache

Exposure-adjusted Incidence

- Diarrhea, arthralgia, UTI, back pain, muscle spasms, and dyspepsia incidence rates were 1.5- to 4.1-fold higher with ibrutinib
- Headache and cough incidence rates were 1.6- and 1.2-fold higher, respectively, with acalabrutinib
- Afib/flutter, hypertension, and bleeding incidence rates were 1.6- to 2.8-fold higher with ibrutinib



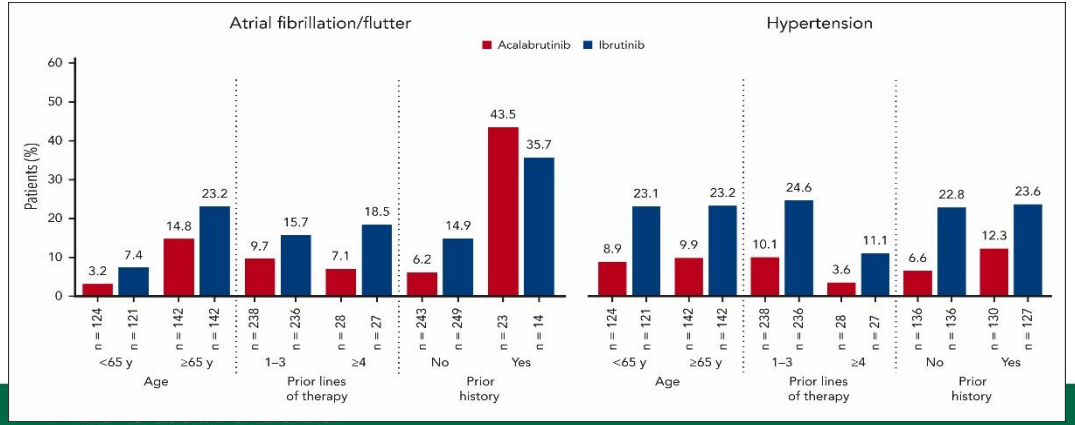
AE, adverse event; Afib/flutter, atrial fibrillation/atrial flutter; BID, twice daily; CI, confidence interval; CLL, chronic lymphocytic leukemia; ECI, event of clinical interest; HR, hazard ratio; NE, not estimable; PO, orally; QD, once daily; UTI, urinary tract infection.

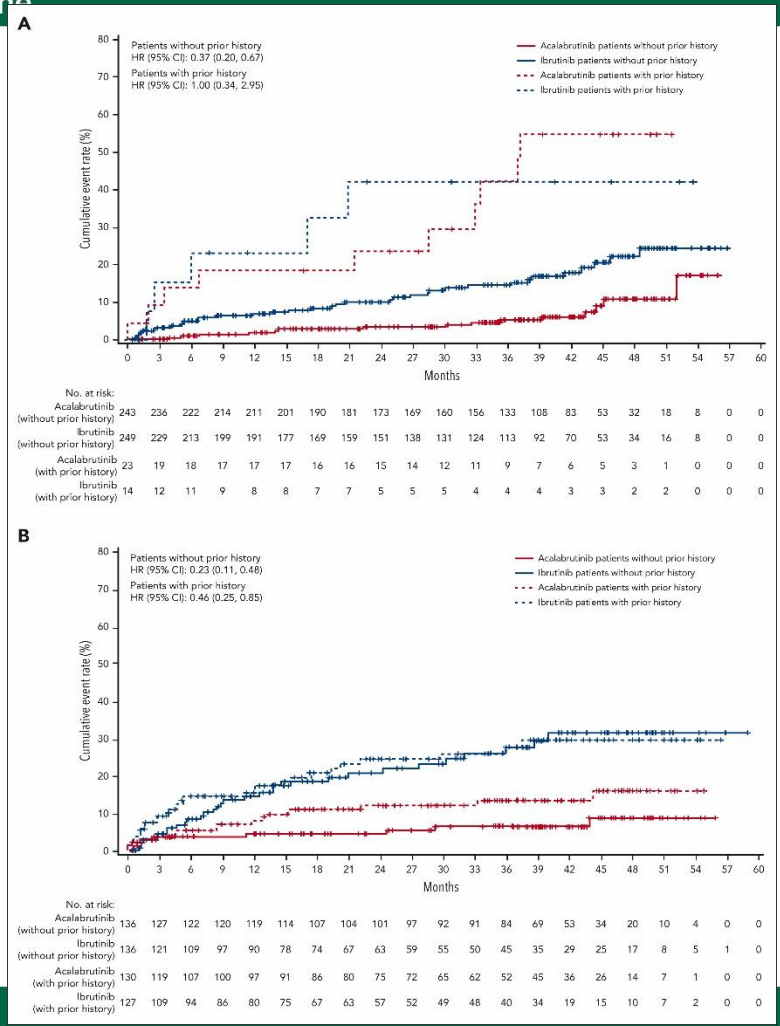


*Two-sided *P*-value < .05 without multiplicity adjustment based on Wilcoxon rank-sum test. *P*-value compares difference in overall distribution rather than mean score.

ELEVATE-RR: details on CV AE

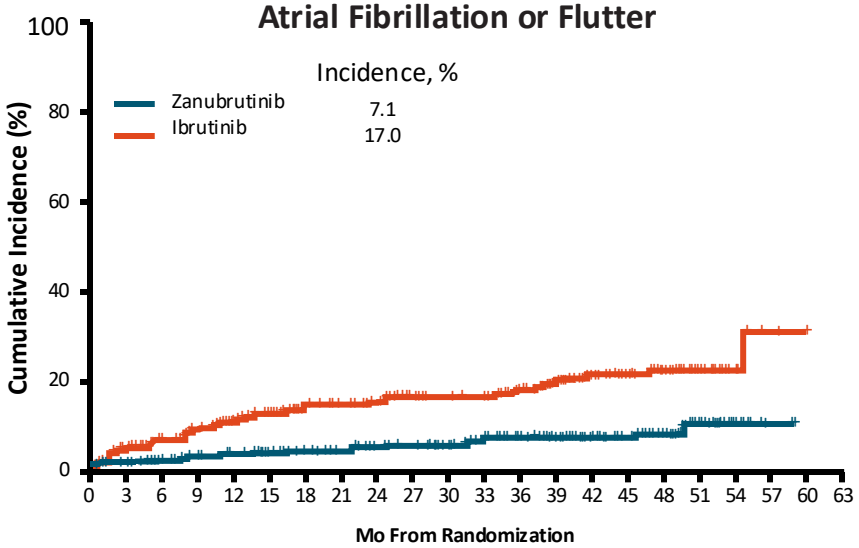
- Cox PH of new-onset AFib/flutter and new-onset HTN showed HR reductions of 63% and 77%, with acalabrutinib
- Among patients with histories of AFib/flutter or hypertension, there was no evidence of a difference in on-study AFib/flutter between treatment arms



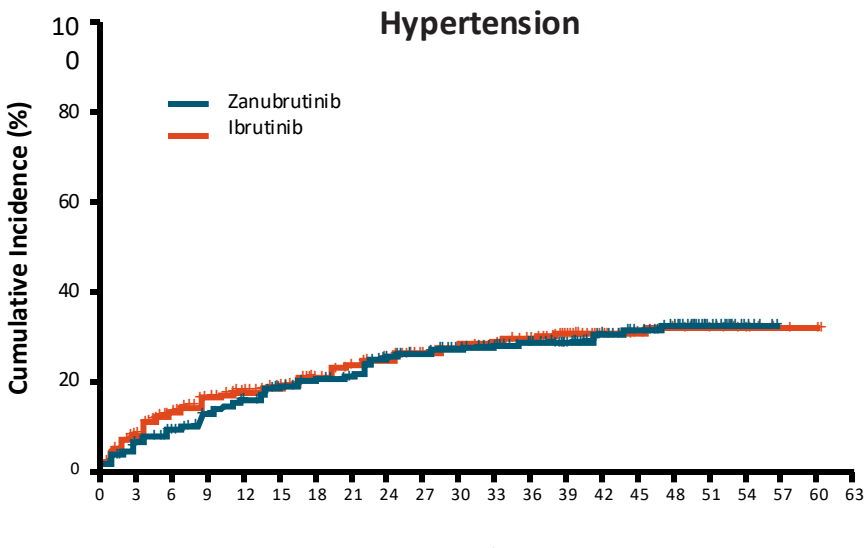


ALPINE: Cumulative Incidence of Any-Grade AFib/Flutter and Hypertension

After a median follow-up of 42.5 mo: none of the patients on the zanubrutinib arm died due to a cardiac disorder vs 6 deaths due to cardiac disorders with ibrutinib



Patients at Risk, n												
Zanubrutinib	324	302	288	268	250	231	204	145	114	17	0	0
Ibrutinib	324	278	247	210	190	167	153	100	76	13	1	0



Patients at Risk, n												
Zanubrutinib	324	279	247	219	194	173	149	102	78	10	0	0
Ibrutinib	324	253	221	185	164	139	124	77	57	9	2	0

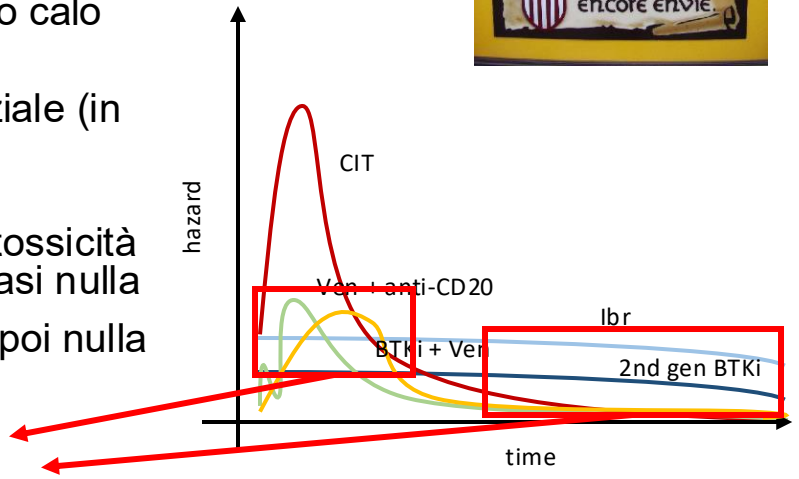
Brown. Blood. 2024. 144:2706.

Terapia a durata fissa vs indefinita

A parità di efficacia e tossicità, è sempre preferibile una terapia a durata fissa vs indefinita

Quali sono i pattern temporali di tossicità dei farmaci utilizzati per la LLC-B?

- CIT: alta tossicità ematologica e infettiva iniziale, drastico calo dopo 6 mesi, poi molto bassa
- BTK inhibitors: bassa tossicità infettiva, ematologica iniziale (in pz TN), persistente tossicità cardiovascolare (Ibrutinib > Acalabrutinib / Zanubrutinib)
- Venetoclax + anti-CD20: piccolo spike iniziale per TLS, tossicità prevalentemente ematologica per i primi 6 mesi, poi quasi nulla
- BTKi + Ven: tossicità limitata nell'anno di associazione, poi nulla



Quali sono le conseguenze per il trattamento dei pazienti?

- Tossicità a lungo termine maggiore con FDT: CDT sempre preferibile se non differenze sostanziali di efficacia
- Nel primo anno le doppiette hanno maggiore tossicità rispetto a BTKi di 2° generazione: per i pazienti unfit non in grado di tollerare questo surplus di tossicità, meglio CDT

Rare adverse events…

Cardiac deaths: Ibrutinib vs zanubrutinib

- The NNH with ibrutinib vs zanubrutinib in 2L+ CLL resulting in an incremental cardiac death was calculated for each time-on-treatment period using cardiac death data from the ALPINE study
- The modeling NNH analysis suggests that **over a 5-year period, 61 cardiac deaths may be avoidable if 2L+ patients were treated with zanubrutinib vs ibrutinib**

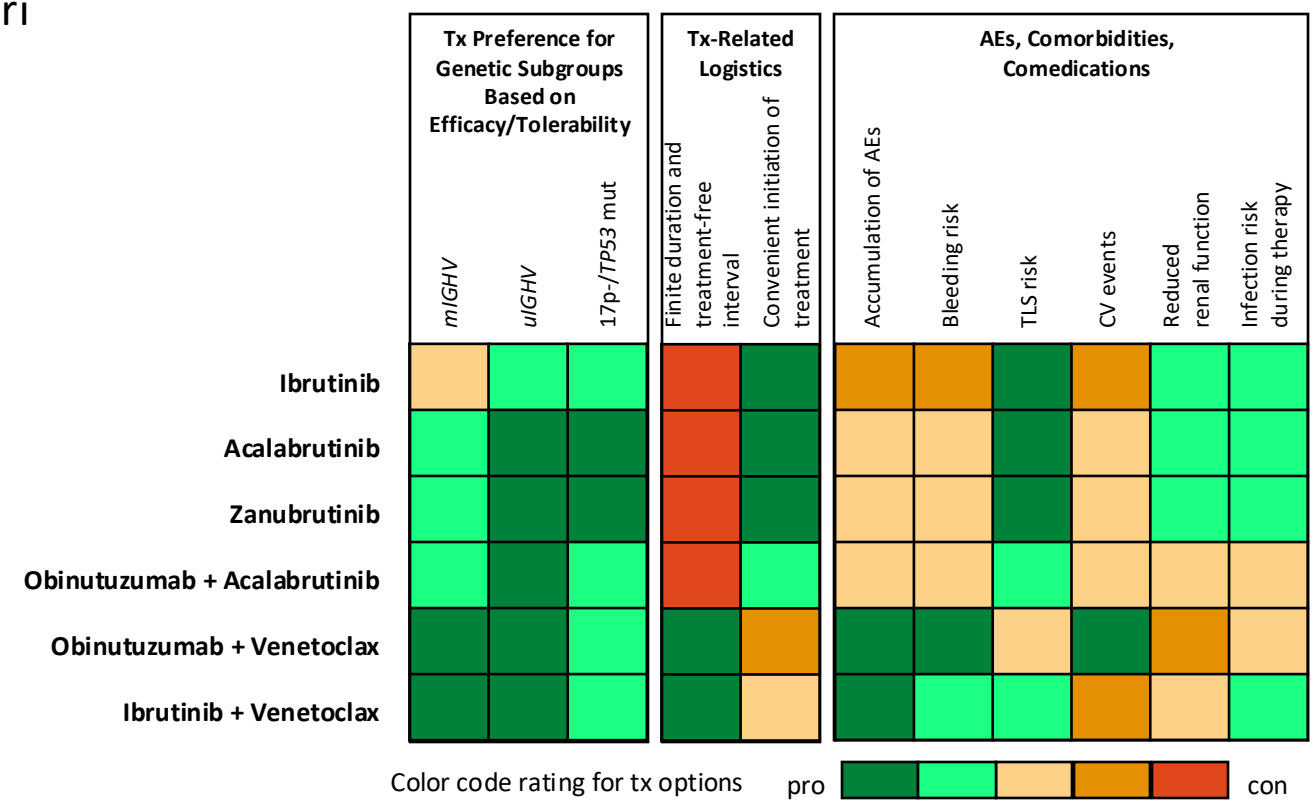
NNH Results of Ibrutinib vs Zanubrutinib in 2L+ CLL

		Time on Treatment (months)			
		0-12	>12-36	>36-60	>60
Ibrutinib cardiac death risk		0.926%	1.852%	1.852%	1.852%
Zanubrutinib cardiac death risk		0.000%	0.000%	0.000%	0.000%
NNH		**108**	**54**	**54**	**54**
Cardiac deaths avoided with zanubrutinib	Per treatment Period	19	26	15	1
	Total		61		

2L+=second-line or later, CLL=chronic lymphocytic leukemia, NNH=number needed to harm.
Munir T, et al. Poster Presentation at iwCLL 2025;Poster 1528.

Fattori da considerare per la scelta del trattamento

- Efficacia in base a fattori prognostici
- Sequencing
- Comorbidità
- Fitness
- Logistica
- Pattern di tossicità
- Valori dei pazienti
  - Via di somministrazione
  - Accessi in DH
  - Durata terapia
  - Impatto eventi avversi
- Sostenibilità…



Tausch. Hematology Am Soc Hematol Educ Program. 2024;2024:457.

FDT vs CDT: quali pazienti?

Fixed Duration Therapy

- Da considerare lo standard se fattibile (preferenze dei pazienti, sostenibilità)
- Da considerare un'opzione se:
  - Forti preferenze del paziente per FDT
  - Tossicità a lungo termine problematica
  - Profilo prognostico permissivo

Continuous Duration Therapy

- Quando FDT non è vantaggiosa…
  - Efficacia subottimale FDT (p53m/del17p)
  - Pazienti anziani/frail non in grado di tollerare l'aumentata tossicità iniziale di una terapia di combinazione
  - Logistica sfavorevole per accessi ripetuti in DH

Grazie per l’attenzione!