Il suono DELL' INNOVAZIONE
now live
Milano, Milan Hilton Hotel
4-5 maggio 2026

Il ruolo dei BTKi covalenti nella seconda linea

Dott.ssa Marzia Varettoni
S.C. Ematologia 1
Fondazione IRCCS Policlinico San Matteo, Pavia

Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Speaker honoraria
AbbVie						x	x
AstraZeneca						x	x
Beone	x		x			x	x
J&J						x	x
Lilly					x	x	x

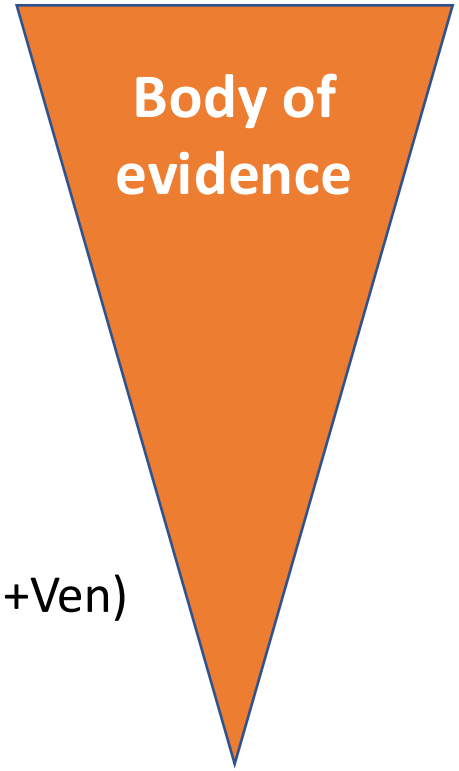
Background

The therapeutic landscape of CLL has undergone a profound shift over the past decade, with targeted agents largely replacing chemoimmunotherapy (CIT) both frontline and in the relapsed/refractory setting

PAST Patients mostly relapsed after chemo-immunotherapy

PRESENT Patients mostly relapse after cBTK inhibitors

FUTURE Patients will relapse also after fixed-duration therapies (Obi+Ven or cBTKi+Ven)



Which are the drivers of choice among second-line options?

Drivers of treatment choice at first relapse/progression

Patients' characteristics

age/fitness
comorbidities/concomitant therapies

Disease characteristics

bulky disease
biological characteristics (IGHV, TP53)

Drivers of treatment choice at first relapse/progression

Previous therapy

type of therapy
reason for discontinuation
duration of response after FD therapy

Patients' characteristics

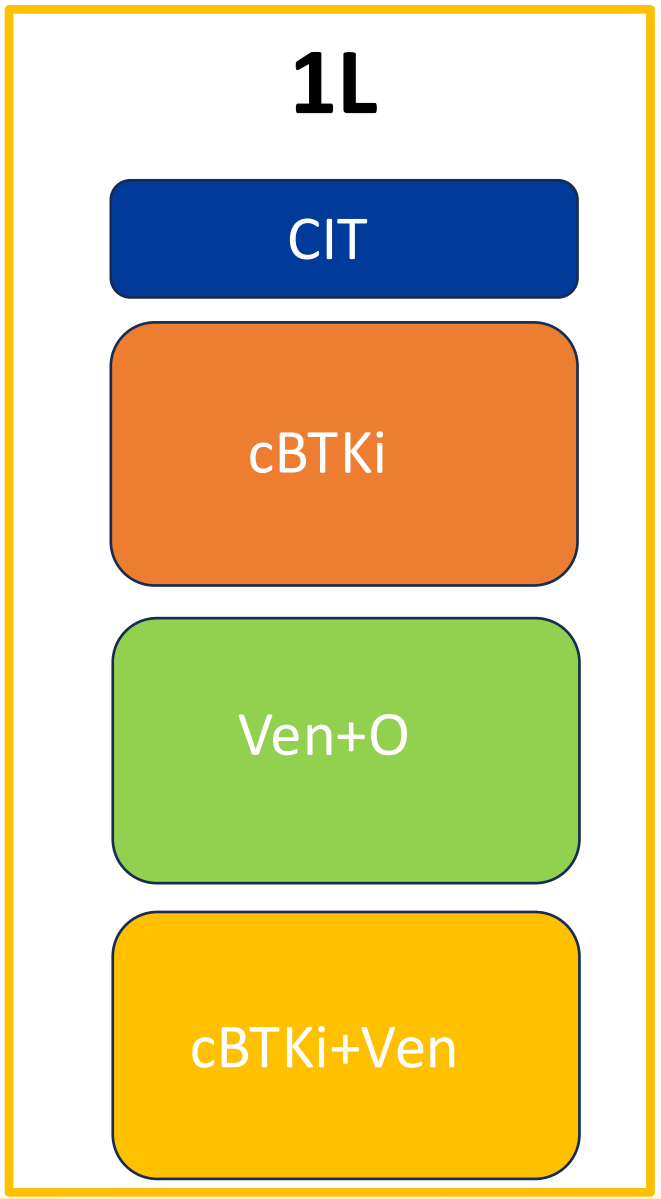
age/fitness
comorbidities/concomitant therapies

Disease characteristics

bulky disease
biological characteristics (IGHV, TP53)

Second-line treatment options available based on frontline therapy

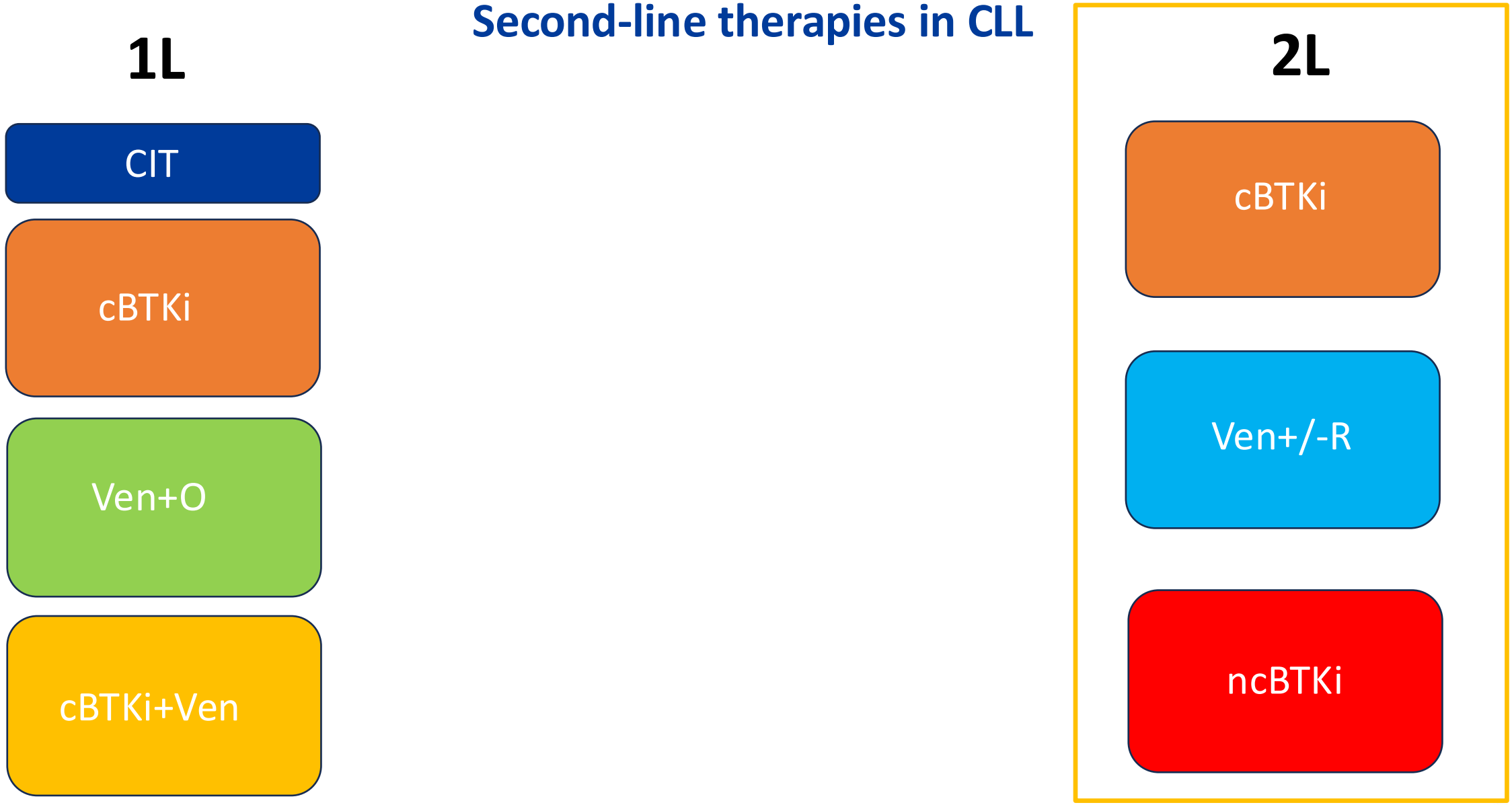
Second-line therapies in CLL



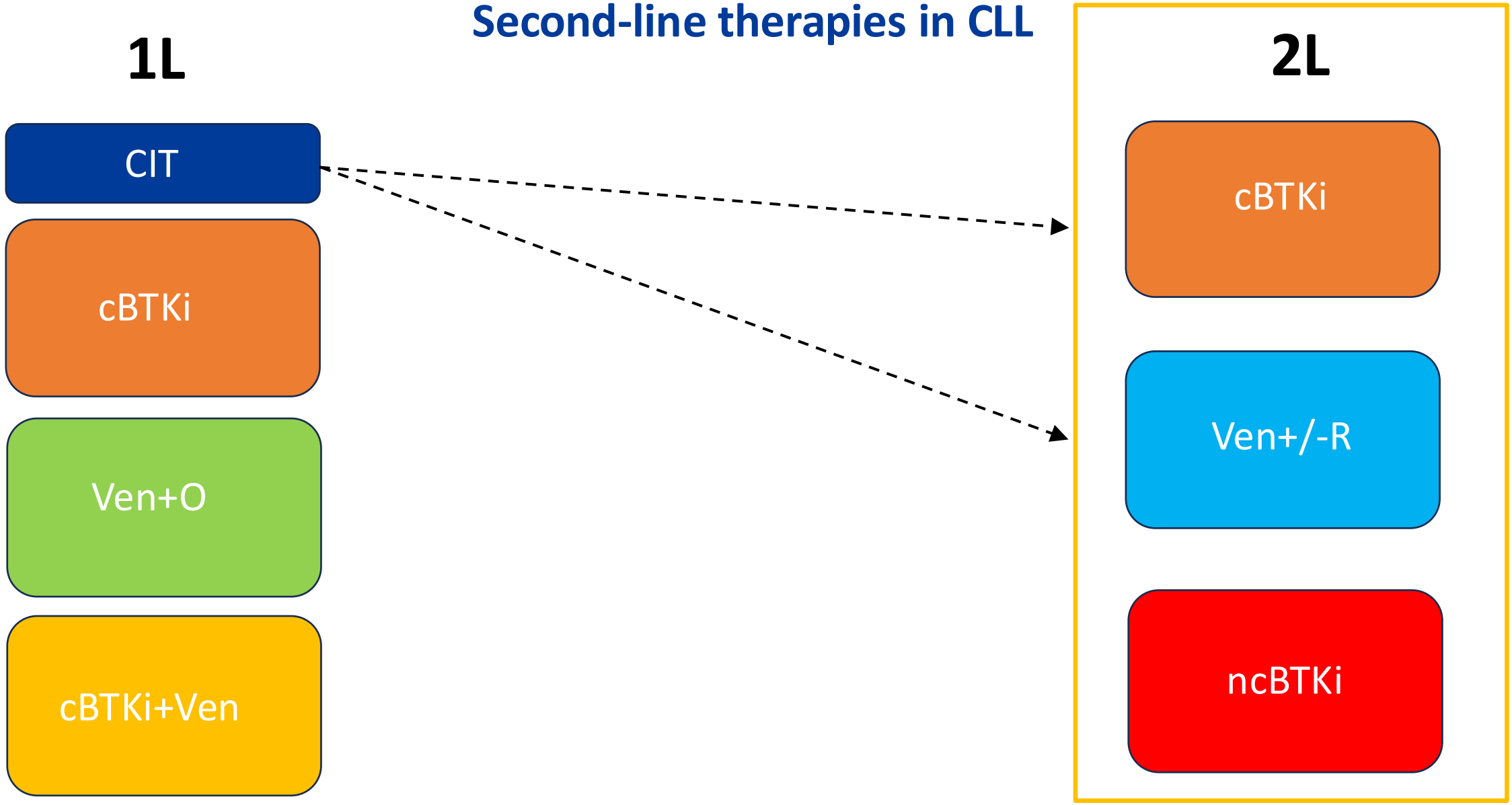
2L

- cBTKi
- Ven+/-R
- ncBTKi

Second-line therapies in CLL

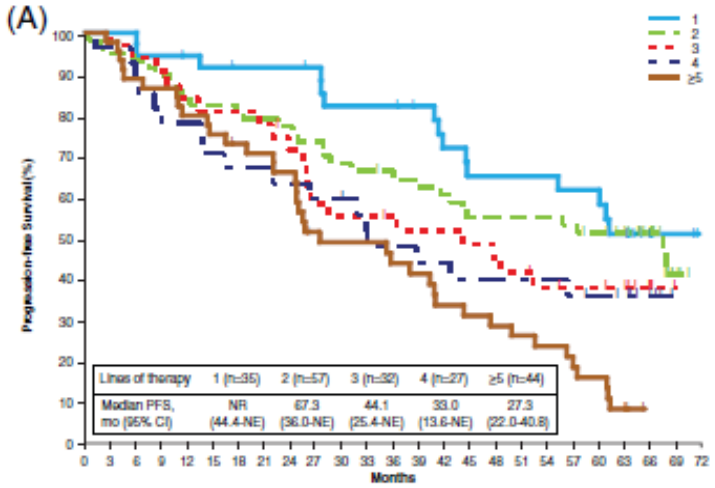


Second-line therapies in CLL



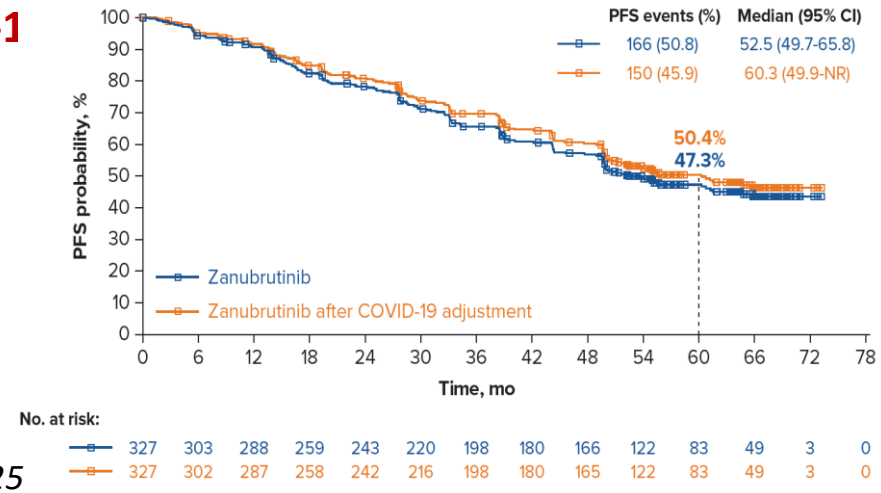
Efficacy of cBTKi in patients with CLL relapsing after CIT

RESONATE (ibrutinib vs ofatumumab)
– n=391
– heavily pretreated population
– median n. of prior therapies 3 (1-12)
– uIGHV 73%, TP53 mut 51%, 17p del 32%
– Median follow-up 65.3 months



Median PFS with ibrutinib 2° line: not reached

ALPINE (zanubrutinib vs ibrutinib): LTE-1
– n= 176
– earlier relapse setting
– median 1 prior line (1-6)
– ~23% with TP53 disruption
– Median follow-up: 63.4 months



Median PFS with zanubrutinib 52.5 months

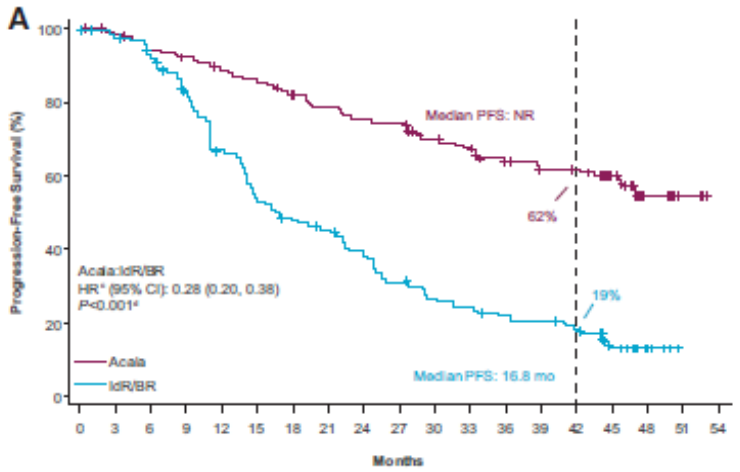
All pivotal cBTKi trials enrolled patients mainly relapsing after CIT, with minimal/no exposure to prior targeted agents

Byrd J. et al, Blood 2019; Tam C. et al, poster ASH2025

Efficacy of cBTKi in patients with CLL relapsing after CIT

ASCEND (acalabrutinib vs investigator's choice)

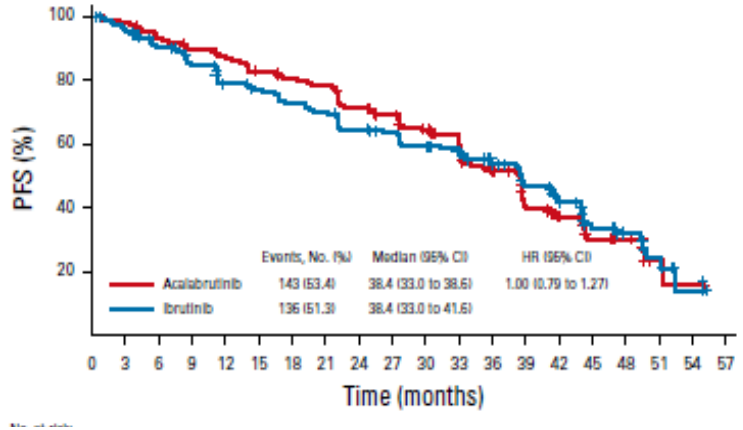
– Median 2 prior lines
– Majority previously exposed to CIT
– Comparator are Idela-R or or CIT
– Del 17p and/or TP53 mutations: 28%
– Median follow-up 46.5 months



Median PFS: not reached

ELEVATE-RR (acalabrutinib vs ibrutinib)

– High-risk population (del17p/del11q)
– Median 2 prior lines
– Del 17p: 13.8%
– No prior BTKi or venetoclax allowed
– Median follow-up 40.9 months



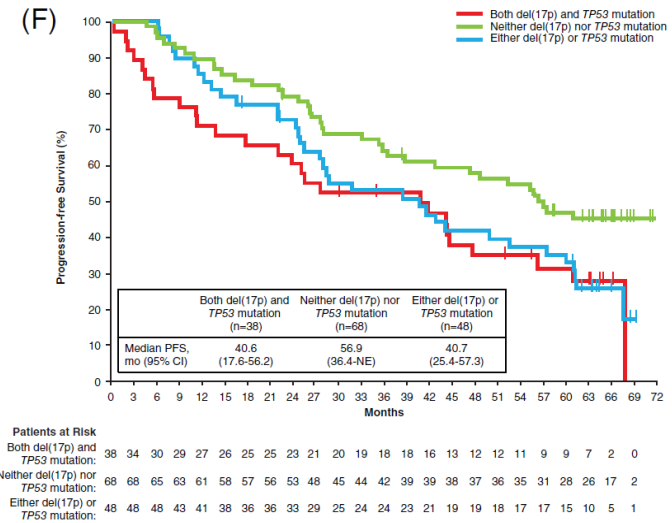
Median PFS: 38.4 months

All pivotal cBTKi trials enrolled patients mainly relapsing after CIT, with minimal/no exposure to prior targeted agents

Ghia P et al., JCO 2020; Byrd JC et al., JCO 2021

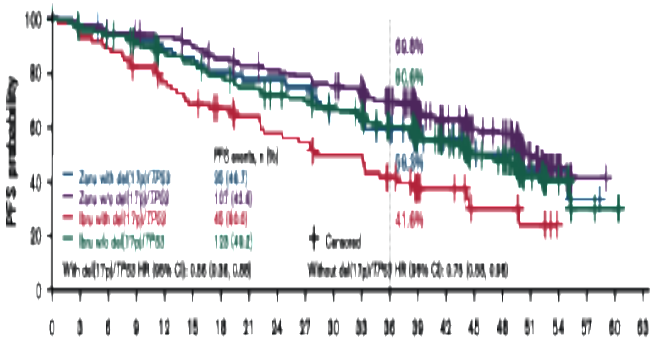
Efficacy of cBTKi in high-risk CLL patients relapsing after CIT

RESONATE

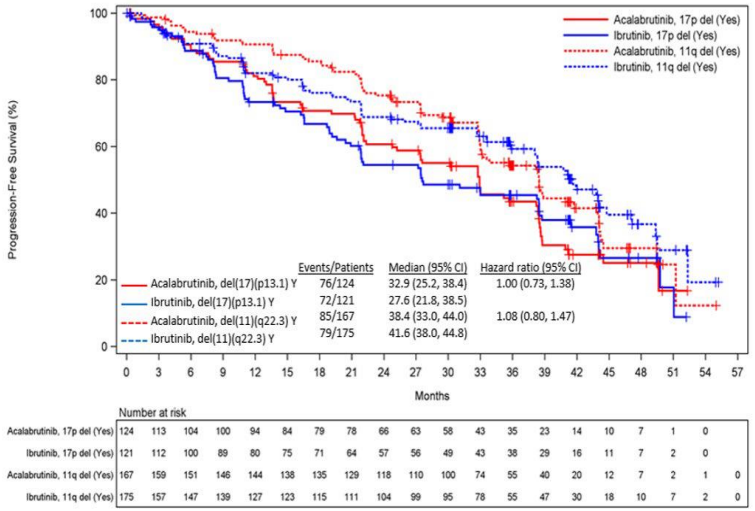


ALPINE

Zanu in pts with del 17p/TP53 mut: Median PFS 50.2 months
Ibrutinib in pts with del 17p/TP53: Median PFS 28 months



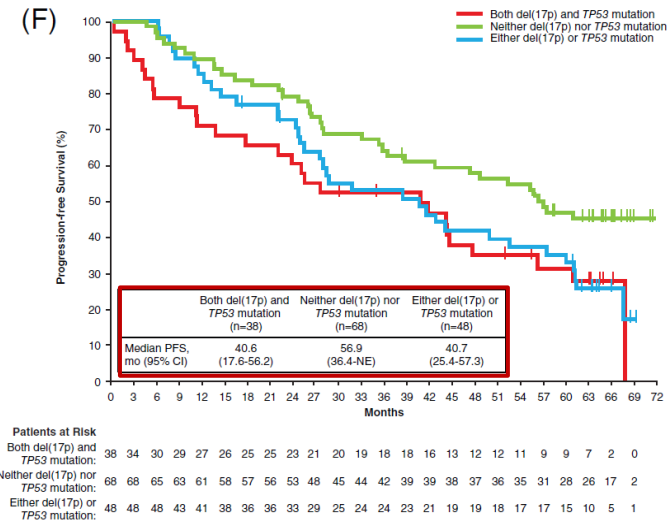
ELEVATE-RR



Munir T. et al, Am J Hematol 2019; Byrd J. et al, Blood 2019; Brown J. et al, Blood 2024

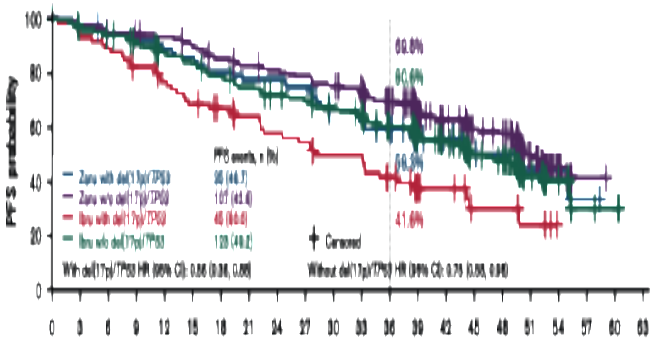
Efficacy of cBTKi in high-risk CLL patients relapsing after CIT

RESONATE

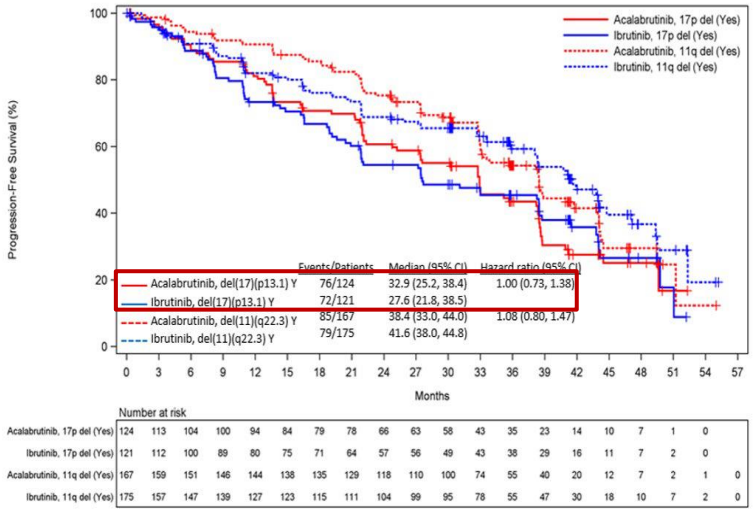


ALPINE

Zanu in pts with del 17p/TP53 mut: Median PFS 50.2 months
Ibrutinib in pts with del 17p/TP53: Median PFS 28 months



ELEVATE-RR



In head-to-head studies, second-generation BTKi showed a better safety profile as compared with ibrutinib

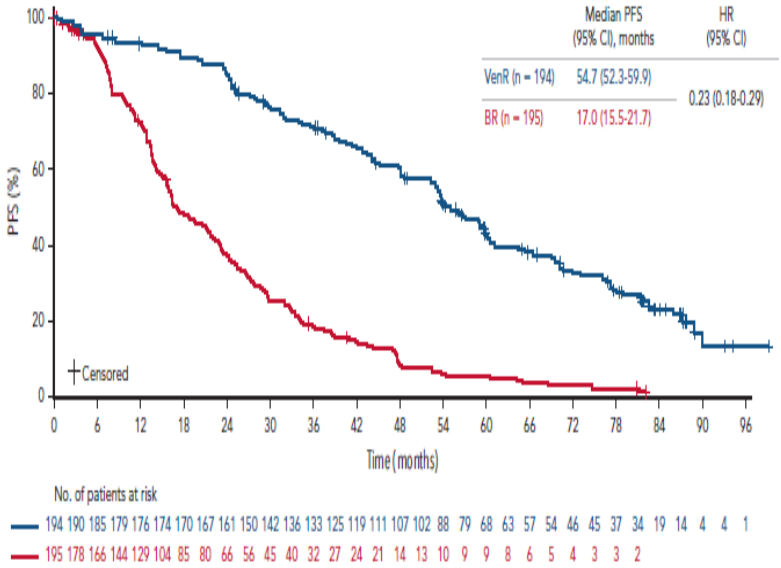
Munir T. et al, Am J Hematol 2019; Byrd J. et al, Blood 2019; Brown J. et al, Blood 2024

Second-line therapy with bcl2 inhibitors after CIT: MURANO study

Pts' characteristics

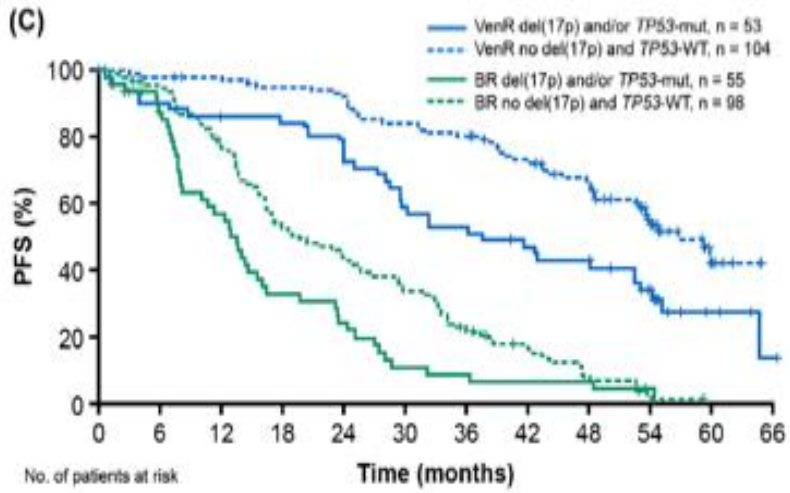
	Main study (N = 389)	
	VenR (n = 194)	BR (n = 195)
Mean age (SD), y	63.9 (10.5)	64.4 (9.6)
Sex, n (%)		
Male	136 (70.1)	151 (77.4)
Female	58 (29.9)	44 (22.6)
No. of prior cancer therapies, n (%)		
1	111 (57.2)	117 (60.0)
2	58 (29.9)	43 (22.1)
≥3	25 (12.9)	35 (17.9)
del(17p) and/or *TP53* mutation, n (%)		
Yes	72 (37.1)	75 (38.5)
No	106 (54.6)	95 (48.7)
Unknown	16 (8.2)	25 (12.8)
del(17p), n (%)		
Yes	46 (23.7)	46 (23.6)
No	127 (65.5)	123 (63.1)
Unknown	21 (10.8)	26 (13.3)
***TP53* mutation, n (%)**		
Yes	48 (24.7)	51 (26.2)
No	144 (74.2)	132 (67.7)
Unknown	2 (1.0)	12 (6.2)
IGHV, n (%)		
Mutated	53 (29.4)	51 (28.3)
Unmutated	123 (68.3)	123 (68.3)
Unknown	4 (2.2)	6 (3.3)
GC, n (%)		
0-2	106 (54.4)	114 (58.5)
3-4	34 (17.4)	29 (14.9)
≥5	14 (7.2)	17 (8.7)
Unknown	40 (20.5)	35 (17.9)

Median PFS 54.7 months with Ven+R



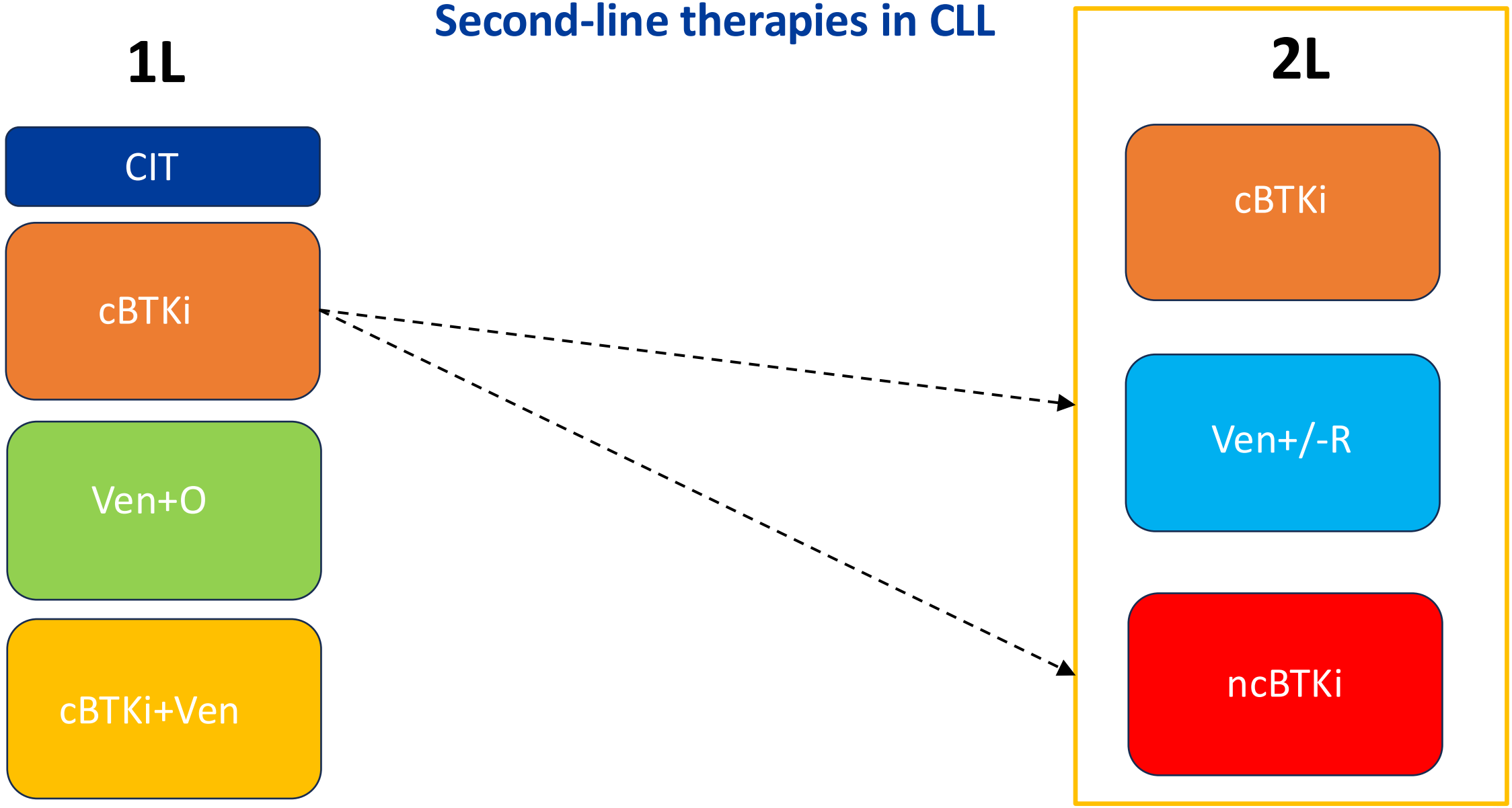
Impact of TP53 disruption on PFS

Median PFS 37.4 months in pts with TP53 abn treated with Ven+R (n=53)



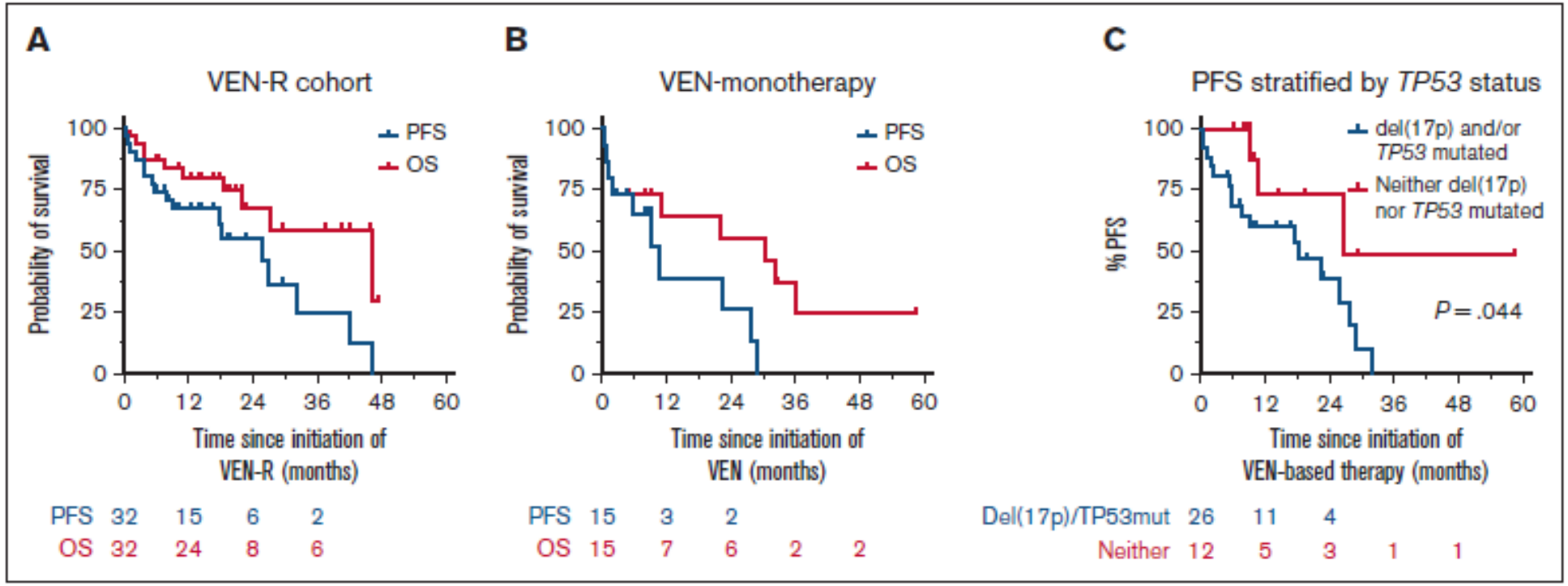
Seymour J et al. Blood 2022; Kater AP et al. Blood 2025

Second-line therapies in CLL



Venetoclax+/- Rituximab after cBTKi

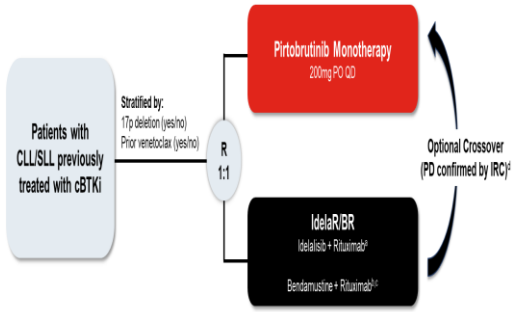
n=47 patients



Ven-R is active in patients with BTKi-exposed CLL, but durable treatment-free remissions are uncommon

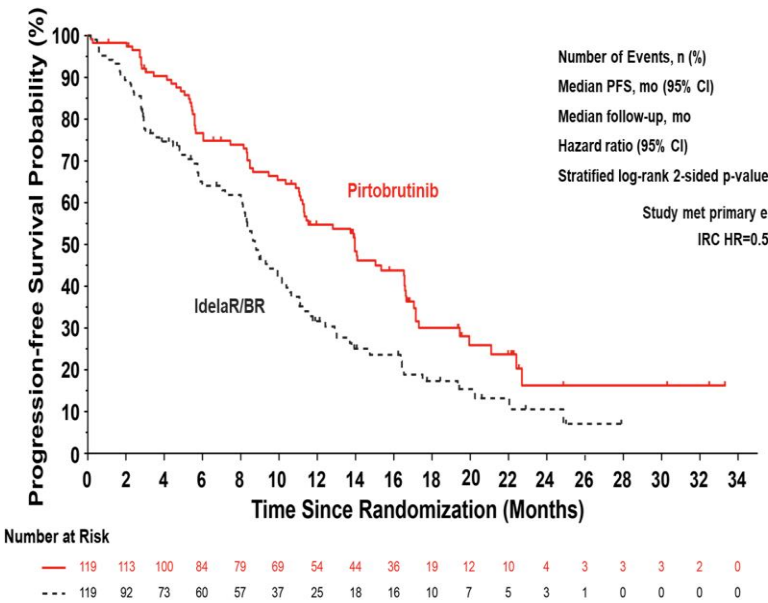
Lew et al, Blood Adv 2024

Non-covalent BTKi Pirtobrutinib after cBTKi: BRUIN 321 study



Characteristics	Pirtobrutinib n=119
Median lines of prior systemic therapy, n (range)	3 (1-13)
Prior therapy, n (%)	
cBTKi	119 (100)
Ibrutinib	100 (84)
Acalabrutinib	17 (14)
Zanubrutinib	10 (8)
Other[c]	5 (4)
>1 Prior cBTKi	17 (14)
BCL2 inhibitor[d]	60 (50)
Chemotherapy	81 (68)
Anti-CD20 Antibody	86 (72)
PI3K inhibitor	11 (9)
Immunomodulator	2 (2)
Autologous Stem Cell Transplant	1 (1)
Allogeneic Stem Cell Transplant	2 (2)
Reason for any prior cBTKi discontinuation[e], n (%)	
Disease progression	85 (71)
Toxicity	20 (17)
Other	14 (12)

PFS in the overall study population



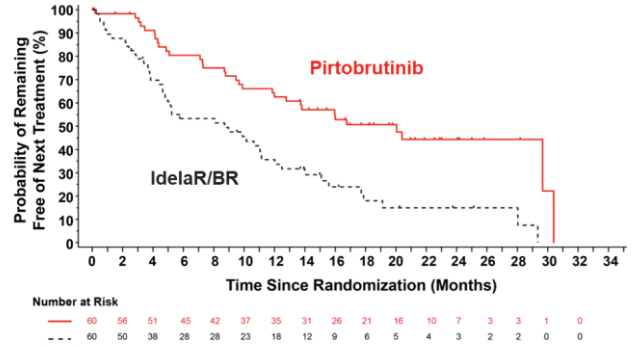
	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	**0.54 (0.39-0.75)**	
Stratified log-rank 2-sided p-value	0.0002*	

Study met primary endpoint at earlier data cut (Aug 2023)
IRC HR=0.58 (95% CI 0.38-0.89); p=0.01

Pirtobrutinib reduced risk of progression or death by 46% according to IRC assessment

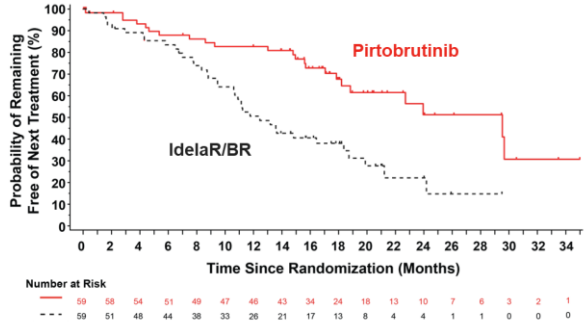
Sharman J. Et al, JCO 2025

TTNT - Venetoclax exposed



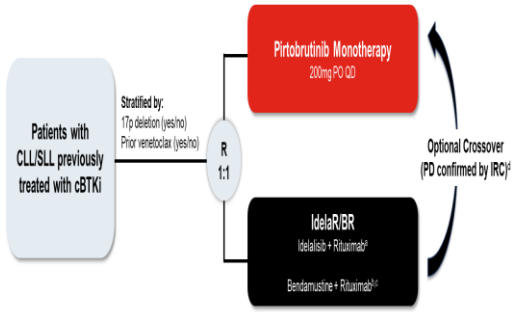
	Pirtobrutinib n=60	IdelaR/BR n=60
Median TTNT, mo (95% CI)	**20.0**	**8.7**
Hazard ratio (95% CI)	**0.37 (0.23-0.60)**	
Stratified log-rank 2-sided p-value	<0.0001*	

TTNT - Venetoclax naïve



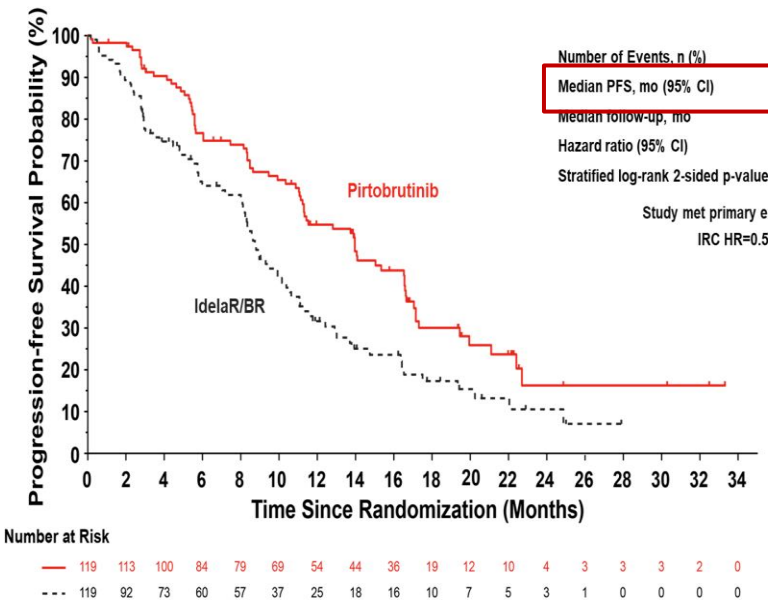
	Pirtobrutinib n=59	IdelaR/BR n=59
Median TTNT, mo (95% CI)	**29.5**	**12.5**
Hazard ratio (95% CI)	**0.36 (0.21-0.61)**	
Stratified log-rank 2-sided p-value	0.0001*	

Non-covalent BTKi Pirtobrutinib after cBTKi: BRUIN 321 study



Characteristics	Pirtobrutinib n=119
Median lines of prior systemic therapy, n (range)	3 (1-13)
Prior therapy, n (%)	
cBTKi	119 (100)
Ibrutinib	100 (84)
Acalabrutinib	17 (14)
Zanubrutinib	10 (8)
Other[c]	5 (4)
>1 Prior cBTKi	17 (14)
BCL2 inhibitor[d]	60 (50)
Chemotherapy	81 (68)
Anti-CD20 Antibody	86 (72)
PI3K inhibitor	11 (9)
Immunomodulator	2 (2)
Autologous Stem Cell Transplant	1 (1)
Allogeneic Stem Cell Transplant	2 (2)
Reason for any prior cBTKi discontinuation[e], n (%)	
Disease progression	85 (71)
Toxicity	20 (17)
Other	14 (12)

PFS in the overall study population



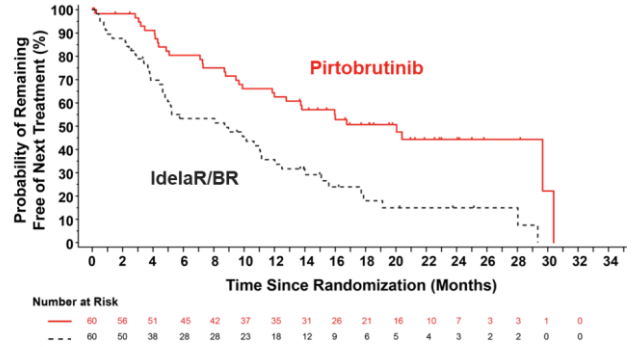
	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	74 (62)	79 (66)
Median PFS, mo (95% CI)	**14.0** (11.2-16.6)	**8.7** (8.1-10.4)
Median follow-up, mo	19.4	17.7
Hazard ratio (95% CI)	**0.54 (0.39-0.75)**	
Stratified log-rank 2-sided p-value	0.0002*	

Study met primary endpoint at earlier data cut (Aug 2023)
IRC HR=0.58 (95% CI 0.38-0.89); p=0.01

Pirtobrutinib reduced risk of progression or death by 46% according to IRC assessment

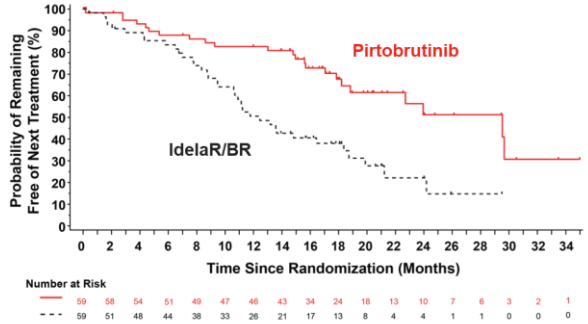
Sharman J. Et al, JCO 2025

TTNT - Venetoclax exposed



	Pirtobrutinib n=60	IdelaR/BR n=60
Median TTNT, mo (95% CI)	**20.0**	8.7
Hazard ratio (95% CI)	**0.37 (0.23-0.60)**	
Stratified log-rank 2-sided p-value	<0.0001*	

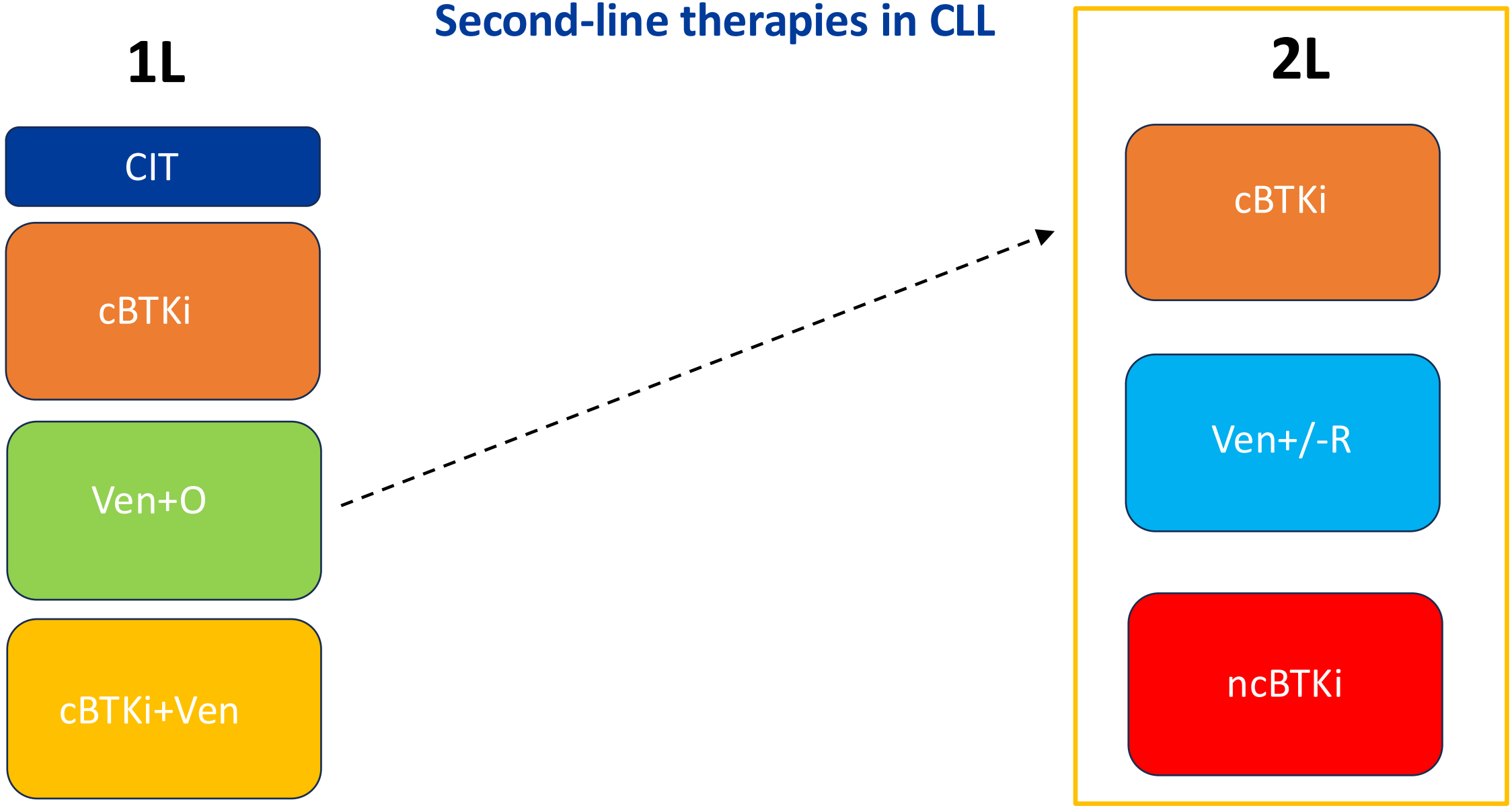
TTNT - Venetoclax naïve



	Pirtobrutinib n=59	IdelaR/BR n=59
Median TTNT, mo (95% CI)	**29.5**	12.5
Hazard ratio (95% CI)	**0.36 (0.21-0.61)**	
Stratified log-rank 2-sided p-value	0.0001*	

Patients relapsing after fixed duration therapies

Second-line therapies in CLL



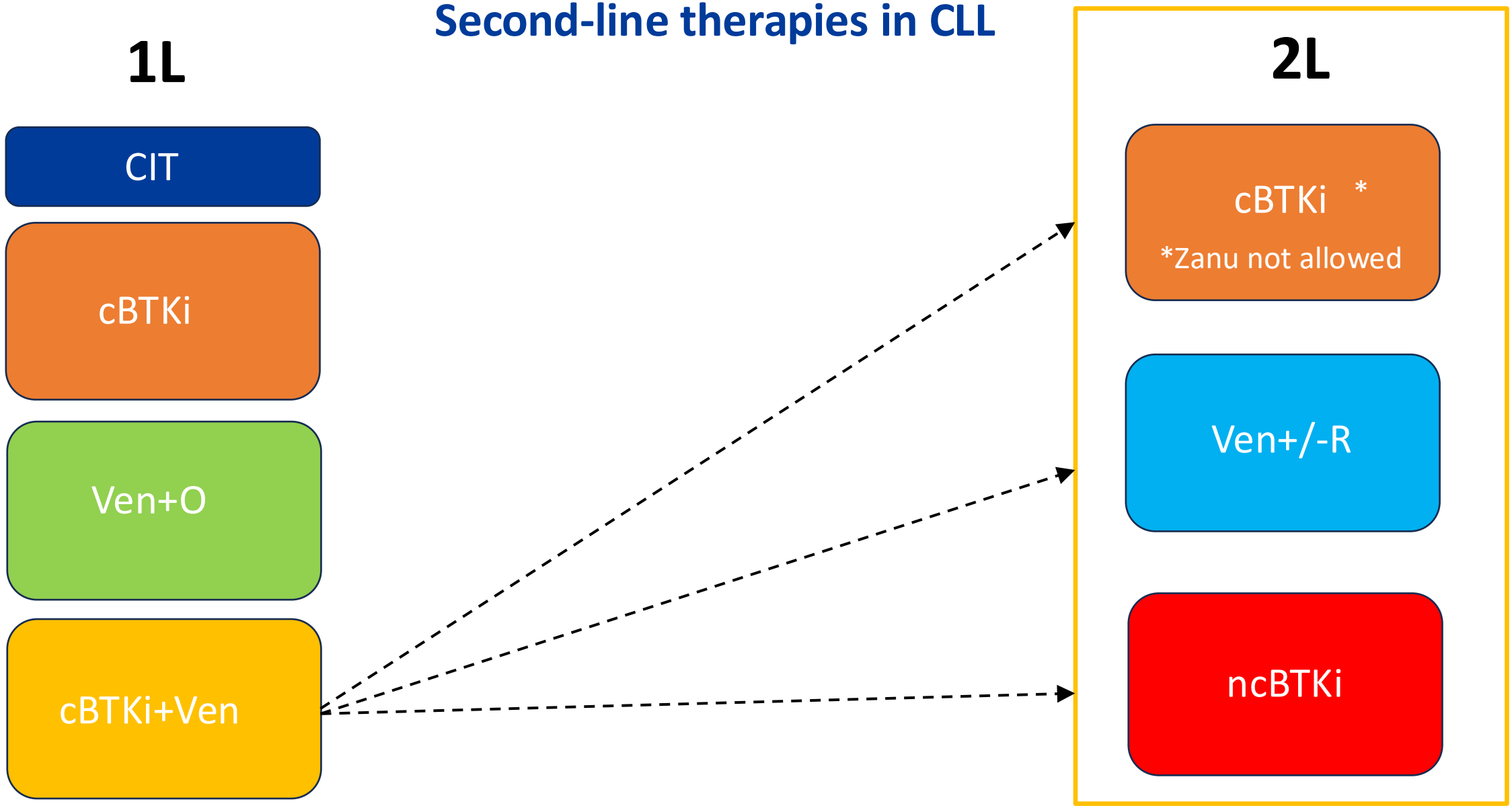
Patients relapsing after fixed-duration Ven+Obinotuzumab

- No prior exposure to BTK inhibition
- No selection of BTK resistance mutations (e.g. C481)

Full sensitivity to covalent BTK inhibitors expected

cBTKi represent a rational and effective standard of care after VenO relapse in BTKi-naïve patients

Second-line therapies in CLL

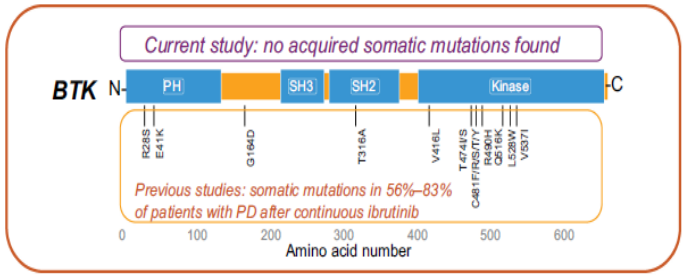


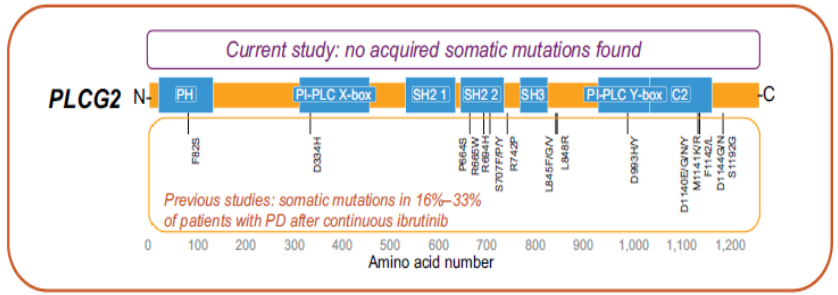
Patients relapsing after fixed-duration BTKi+BCL2-i

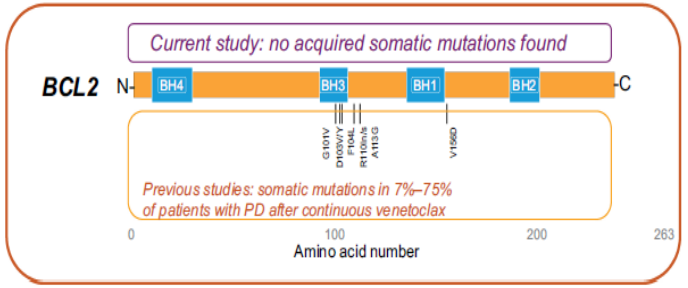
- Prior exposure to BTK inhibition
- Patients relapse after a treatment-free interval
- BTK exposed ≠ BTK refractory
- Lower selective pressure of FD therapy vs continuous BTKi

- ✓ Expected sensitivity to cBTKi, retreatment rationale
- ✓ Time matters: how should be DoR to consider retreatment with BTKi?
  AIFA PD >6 months from EoT/CAPTIVATE PD ≥24 months from EoT
- ✓ Retreatment with I+V not allowed
  The only data available on retreatment are with Ibrutinib
  No data on retreatment with Venetoclax

No BTK, Bcl-2 or PLCG2 mutations found in CLL relapsing after I+V

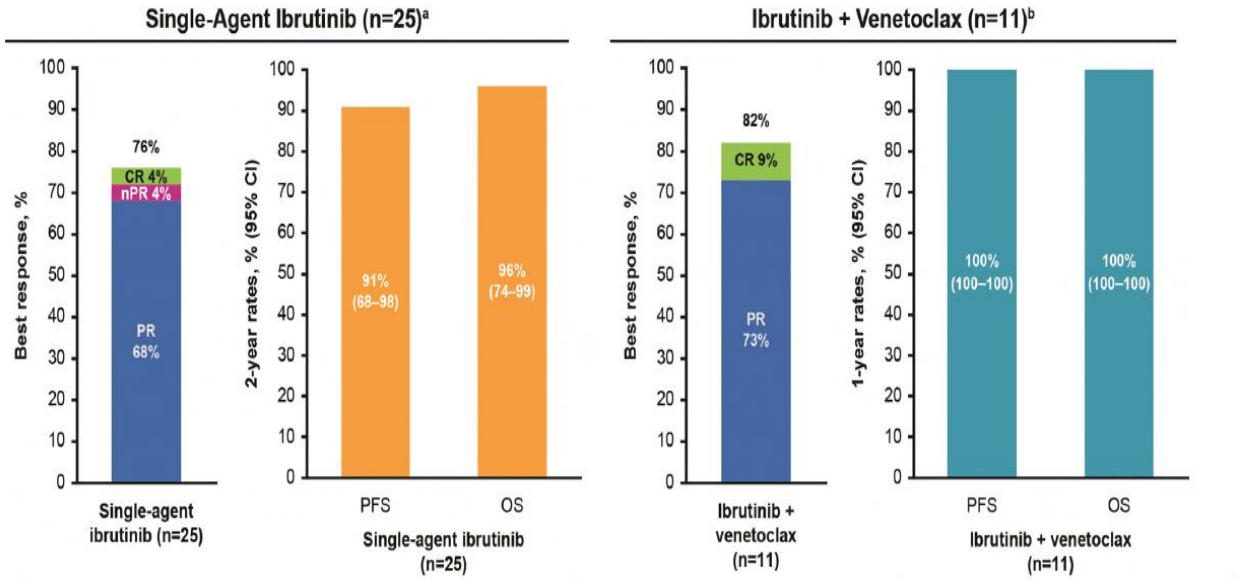






Ibrutinib-Based Retreatment after I+V in the CAPTIVATE study: efficacy and safety

- ✓ Patients relapsing or progressing at least 24 months after completion of I+V could be retreated with FD I+V or with single agent Ibrutinib until progression
- ✓ In total, **36 patients** (who met iwCLL criteria for treatment) initiated retreatment with either single-agent ibrutinib (n=**25**) or FD ibrutinib + venetoclax (n=**11**)
- ✓ No new safety signals were observed during retreatment, relative to the safety profile of 1L treatment with single agent ibrutinib or FD ibrutinib + venetoclax

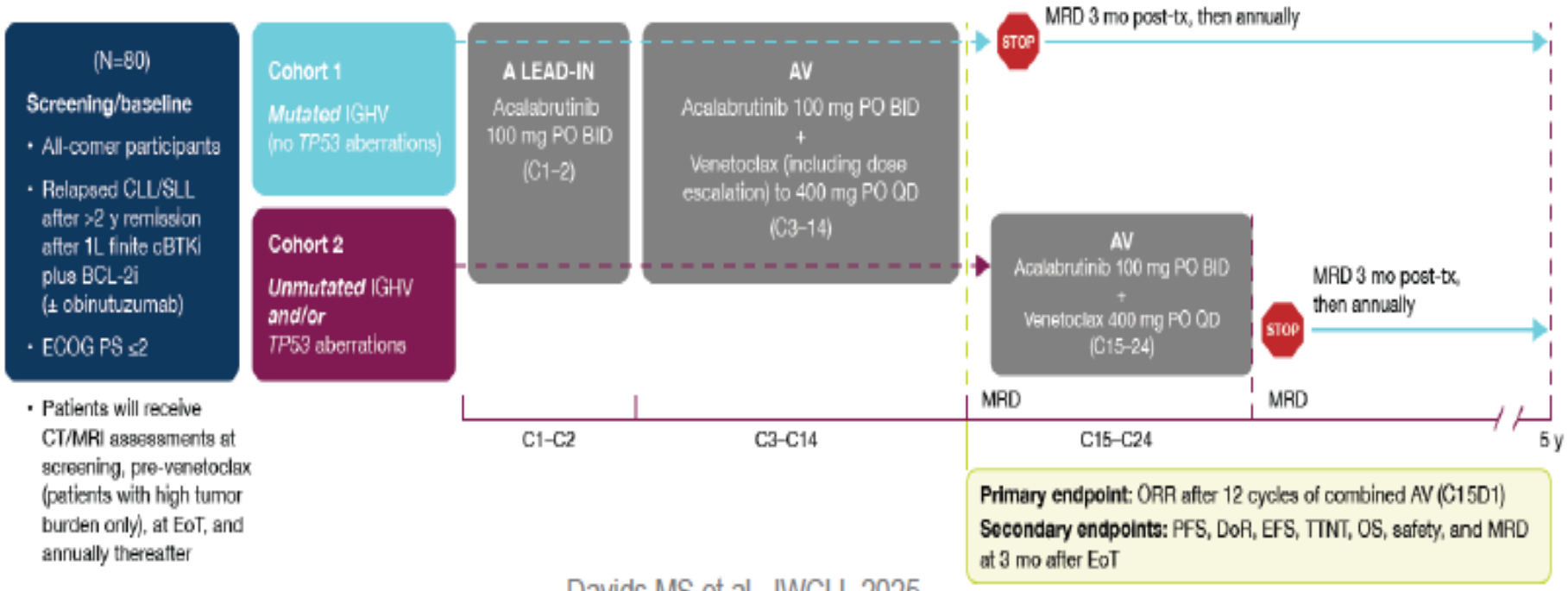


	Single-agent ibrutinib	FD ibrutinib + venetoclax
Median duration of follow-up, months (range)	28.4 (3.7–59.1)	15.2 (7.4–29.3)
Median duration of retreatment, months (range)	27.0 (1.1–59.1)	13.8 (6.7–18.3)

Wierda, poster presentation @ASCO 2025, Ghia, oral presentation @EHA 2025

MAVRiC (Mutation-Guided Finite-Duration AV for Relapse in CLL/SLL; NCT07024706)

Phase 2, Open-Label, Multicenter, Single-Arm, Global Study Assessing the Efficacy and Safety of IGHV- and *TP53*-Mutation Risk-Guided, Finite-Duration AV-Based Combination Therapy After Prior Finite-Duration cBTKi Plus BCL-2i Treatment



Davids MS et al., IWCLL 2025

Davids MS et al., IWCLL 2025

The role of cBTKi as 2L treatment in the current landscape: take-home messages

- ✓ Evidence on second line therapy with covalent BTKi is largely derived from studies conducted in patients relapsing after chemo-immunotherapy, and applicability to patients relapsing after targeted therapies is unknown

The role of cBTKi as 2L treatment in the current landscape: take-home messages

- ✓ Evidence on second line therapy with covalent BTKi is largely derived from studies conducted in patients relapsing after chemo-immunotherapy, and applicability to patients relapsing after targeted therapies is unknown
- ✓ Single-agent covalent BTKi until progression represent a valuable option as second-line treatment with prolonged disease control also in high-risk patients and a favorable safety profile (2^{nd} generation >1^{st} generation)

The role of cBTKi as 2L treatment in the current landscape: take-home messages

- ✓ Evidence on second line therapy with covalent BTKi is largely derived from studies conducted in patients relapsing after chemo-immunotherapy, and applicability to patients relapsing after targeted therapies is unknown
- ✓ Single-agent covalent BTKi until progression represent a valuable option as second-line treatment with prolonged disease control also in high-risk patients and a favorable safety profile (2^{nd} generation >1^{st} generation)
- ✓ Acalabrutinib may soon become the only second-generation BTK inhibitor that may be used in patients relapsing after any frontline therapy, i.e. CIT, V+O, I+V and A+V


Il suono
DELL' INNOVAZIONE
now live
Milano, Milan Hilton Hotel
4-5 maggio 2026

grazie