

MEET THE **EXPERT** *in CLL*

MESTRE (VE), 19 OTTOBRE 2026

Aula Verde-Padiglione Giovanni Rama, Ospedale dell'Angelo



I vantaggi della terapia a durata fissa e la sostenibilità dei farmaci:
il punto di vista dell'ematologo e del farmacista

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Disclosures: Gianluca Gaidano

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie					√	√	
AstraZeneca			√		√	√	
BeOne						√	
Gilead	√						
Incyte					√	√	
Johnson & Johnson					√	√	
Oncopeptides						√	



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Considerations for treatment: Continuous vs FTD (1L and RR)

	Advantages	Disadvantages
Continuous	- Route of administration¹ - Efficacy (PFS1) sustained over long periods² - Minor effect of adverse prognostic factors on efficacy²⁻⁴ - Assurance of continuous therapy¹	- Cumulative toxicity² - CV side effects^{2,3,5} - Burden of therapy; lack of compliance^{2,6} - Cost^{1,2} - Potential for resistance⁷
FTD	- Patient preference¹ - Convenience and time off treatment¹ - Cost/anticipating expenses¹ - Reduced potential for resistance⁷	- Initial management (TLS monitoring, potential hospitalizations)^{2,3,8} - Patient's worry that CLL might worsen or spread during time off treatment¹



CLL, chronic lymphocytic leukemia; CV, cardiovascular; FTD, fixed treatment duration; PFS1, time from start of therapy to the occurrence of first relapse; TLS, tumor lysis syndrome.

1. Ravelo A, et al. ASH 2023. Abstract P3706 (Poster); 2. Seymour JF. *Blood Adv* 2022; **6**:1365–1370; 3. Brem EA & O'Brien S. *Blood Adv* 2022; **6**:1361–1364; 4. Barr PM, et al. *Blood Adv* 2022; **6**:3440–3450;

5. Bhat SA, et al. *Blood* 2022; **140**:2142–2214; 6. Alu A, et al. *J Hematol Oncol* 2022; **15**:138; 7. Al-Sawaf O & Davids MS. *Clin Cancer Res* 2024; **30**:471–473; 8. Coombs C, et al. Fixed-Duration vs Continuous Therapy–First-Line Choices in CLL. Onco Live 2025. Available at: <https://www.onclive.com/view/fixed-duration-vs-continuous-therapy-first-line-choices-in-cll> (accessed August 2025).



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Agenda

- **Safety**
- Resistance mutations
- Patient's preferences
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Heatmap of individual features to guide treatment decision



Finite duration,
treatment-free interval and
accumulation of AEs
not mentioned in the figure

CLL First-Line Integrated vision of individual features to guide treatment decision

	Biological Profile			Infection risk	Ease of treatment	Concomitant comorbidities & comedication		
	M-IGHV	UM-IGHV	TP53mut/del(17p)			Cardio-vascular Disease	Impaired Renal Function	Anticoagulation/bleeding risk
Venetoclax - Obinutuzumab	A	A	B	C	C	A	B ²	A
Venetoclax + Ibrutinib ¹	A	A	B	B	B	C	B ²	B ³
Venetoclax + Acalabrutinib	A	A	B	B	B	B	B ²	B ³
Venetoclax + Acalabrutinib + obinutuzumab	A	A	B	C	C	C	B ²	B ³
Acalabrutinib	B	A	A	A	A	B	A ²	B ³
Zanubrutinib	B	A	A	A	A	B	A ²	B ³
Ibrutinib	B	A	A	A	A	C	A ²	B ³

Assess specific interactions

A= Strongly recommended; **B**= Recommended; **C**= consider alternatives.

¹: This combination appears particularly effective in UM-IGHV when used within an MRD-guided strategy, but is not currently approved.

²: caution with CrCl < 50 mL/min for venetoclax and < 30 mL/min for BTKi. For venetoclax recommended TLS preventions should be followed in patients with CrCl 50 -79 mL/min.

³: contraindicated with anti-Vitamin K.

Figure adapted from Ref. 85.

Eichhorst, B et al. HemaSphere 2026; 10:e70403



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Treatment Choice: the value of Treatment Duration and Cumulative Tox

 **Finite duration, treatment-free interval and accumulation of AEs not mentioned in the figure**

Continuous
BTK inhibition

Fixed
Ven-Based

	treatment preference for genetic subgroups based on efficacy and tolerability			treatment-related logistics		adverse events, comorbidities and comedication					
	mIGHV	uIGHV	17p- / TP53 mut	finite duration and treatment-free interval	convenient initiation of therapy	accumulation of adverse events	bleeding risk	TLS risk	cardiovascular events	reduced renal function	infection risk during treatment
ibrutinib	yellow	green	green	red	green	orange	orange	green	orange	green	green
acalabrutinib	green	green	green	red	green	yellow	yellow	green	yellow	green	green
zanubrutinib	green	green	green	red	green	yellow	yellow	green	yellow	green	green
obinutuzumab + venetoclax	green	green	green	green	orange	green	green	yellow	green	orange	yellow
ibrutinib + venetoclax	green	green	green	green	yellow	green	green	green	orange	yellow	green

Color code rating for treatment options: pro      con

Tausch E et al., ASH Educational Program 2024; 2024, 457-466



AMPLIFY: Events of clinical interest

	AV (n=291)		AVO (n=284)		FCR/BR (n=259)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any ECI	222 (76.3)	136 (46.7)	242 (85.2)	188 (66.2)	185 (71.4)	141 (54.4)
Cardiac events	27 (9.3)	5 (1.7)	34 (12.0)	7 (2.5)	9 (3.5)	3 (1.2)
Atrial fibrillation	2 (0.7)	1 (0.3)	6 (2.1)	2 (0.7)	2 (0.8)	2 (0.8)
Ventricular tachyarrhythmias^a	2 (0.7)	0	3 (1.1)	0	0	0
Hypertension	12 (4.1)	8 (2.7)	11 (3.9)	6 (2.1)	7 (2.7)	2 (0.8)
Hemorrhage	94 (32.3)	3 (1.0)	86 (30.3)	6 (2.1)	11 (4.2)	1 (0.4)
Major hemorrhage	3 (1.0)	3 (1.0)	8 (2.8)	6 (2.1)	2 (0.8)	1 (0.4)
Neutropenia (any)^b	108 (37.1)	94 (32.3)	143 (50.4)	131 (46.1)	132 (51.0)	112 (43.2)
Infections (any)	148 (50.9)	36 (12.4)	153 (53.9)	67 (23.6)	82 (31.7)	26 (10.0)
Second primary malignancies	15 (5.2)	5 (1.7)	12 (4.2)	5 (1.8)	2 (0.8)	0
Excl. non-melanoma skin	8 (2.7)	5 (1.7)	7 (2.5)	4 (1.4)	1 (0.4)	0
Tumor lysis syndrome	1 (0.3)	1 (0.3)	1 (0.4)	1 (0.4)	8 (3.1)	8 (3.1)

Data are n (%). ECIs listed by category and sub-category.

^aVentricular tachyarrhythmias consisted of ventricular extrasystoles (n=1 in AV arm; n=2 in AVO arm) and ventricular tachycardia (n=1 each in AV and AVO arms).

^bIncludes neutropenia, neutrophil count decreased, and febrile neutropenia.

AEs with an onset date or that worsen on or after the date of first dose and up to and including 30 days following the date of last dose of treatment or up to the day prior to start of subsequent anti-CLL therapy, whichever comes first.

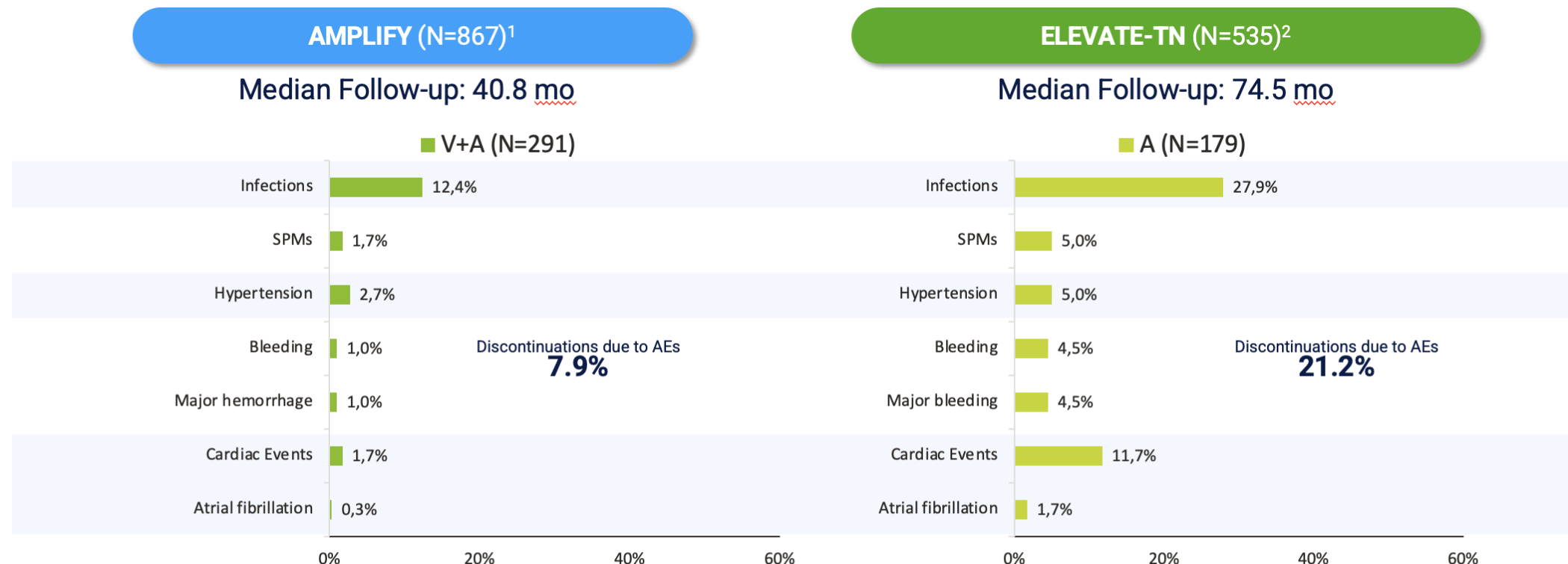
Brown JF et al, oral presentation ASH 2024; N Eng J Med 2025



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V+A vs A mono - Safety (Grade ≥ 3 TEAEs)



Venetoclax FTD reduces the accumulation of AE observed with treat-to-progression regimens,
and thus offers a favorable safety profile

1. Brown JR, et al. *N Engl J Med.* 2025;**392**(8):748-762. 2. Sharman JP, et al. ASH 2023. Abstract 636 (Oral).



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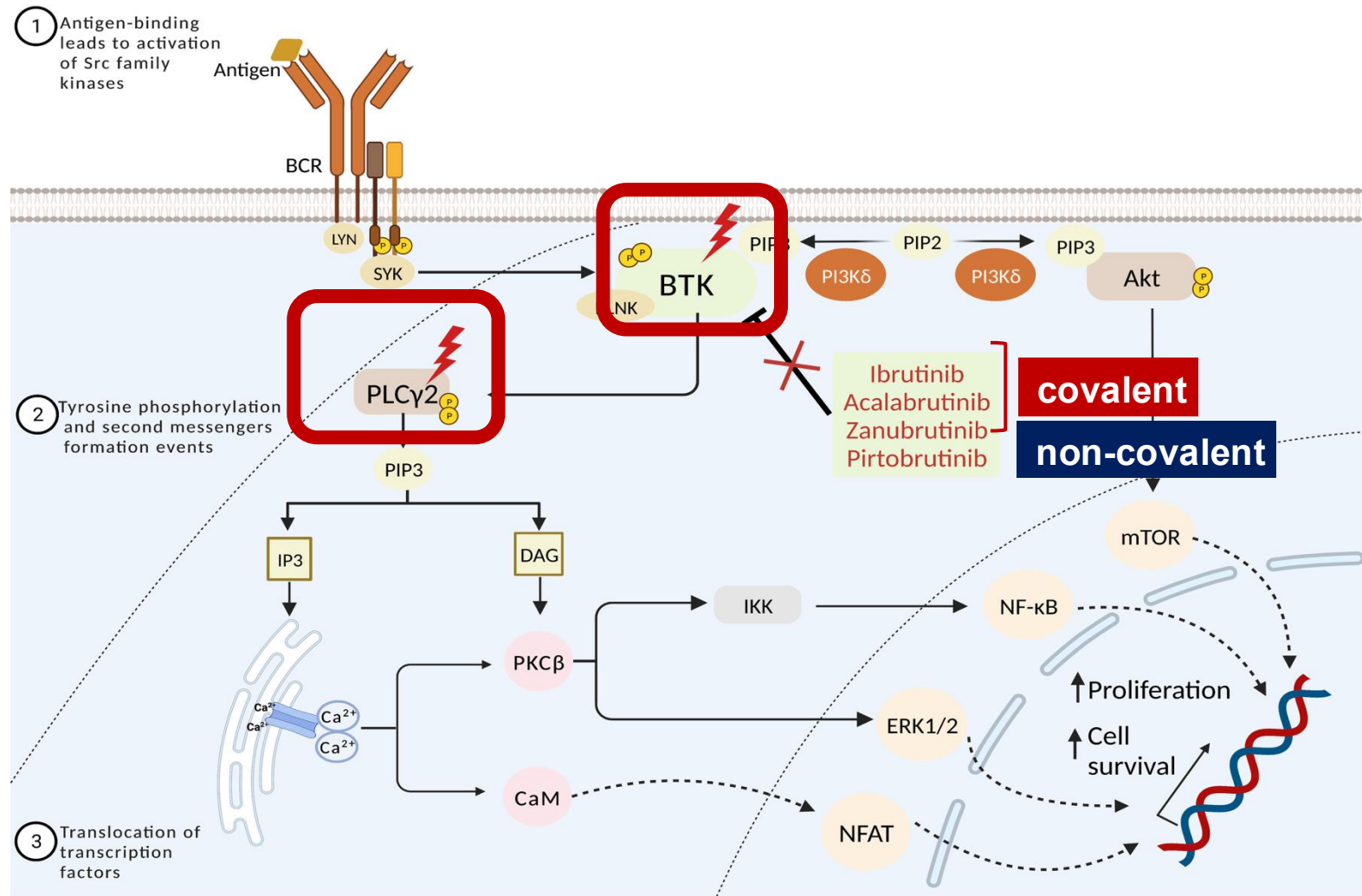
- Safety
- **Resistance mutations**
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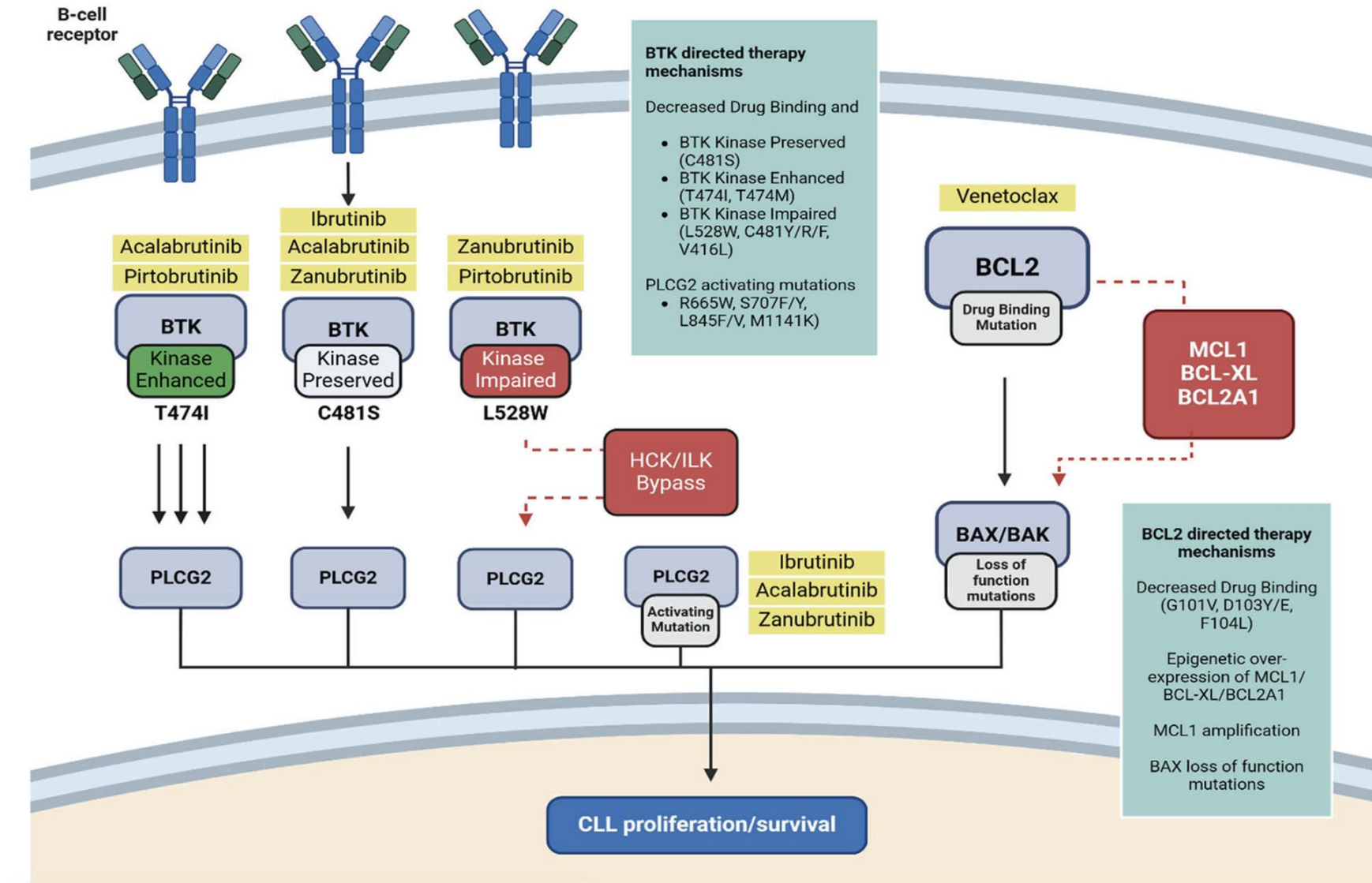
Resistance mutations after covalent BTKi



Akt, Ak strain transforming; BCR, B cell receptor; BLNK, B cell linker scaffold protein; BTK, Bruton tyrosine kinase; CaM, calmodulin; DAG, diacylglycerol; ERK1/2, extracellular signal-regulated kinases 1/2; IKK, I κB kinase complex; IP3, inositol 1,4,5-trisphosphate; mTOR, mammalian target of rapamycin; NFAT, nuclear factor of activated T cells; NF-κB, nuclear factor kappa B; PKCβ, protein kinase Cβ; *PLCG2* or *PLCγ2*, phospholipase C gamma 2; SYK, spleen tyrosine kinase.

Adapted from Maher N et al, *Int. J. Mol. Sci.* 2023;24(12):10374.

Resistance mutations after covalent BTKi



Mutations of resistance to BTKi

***BTK C481* mutations**

- preclude irreversible binding of covalent BTKi to BTK
- result in a greatly reduced drug potency

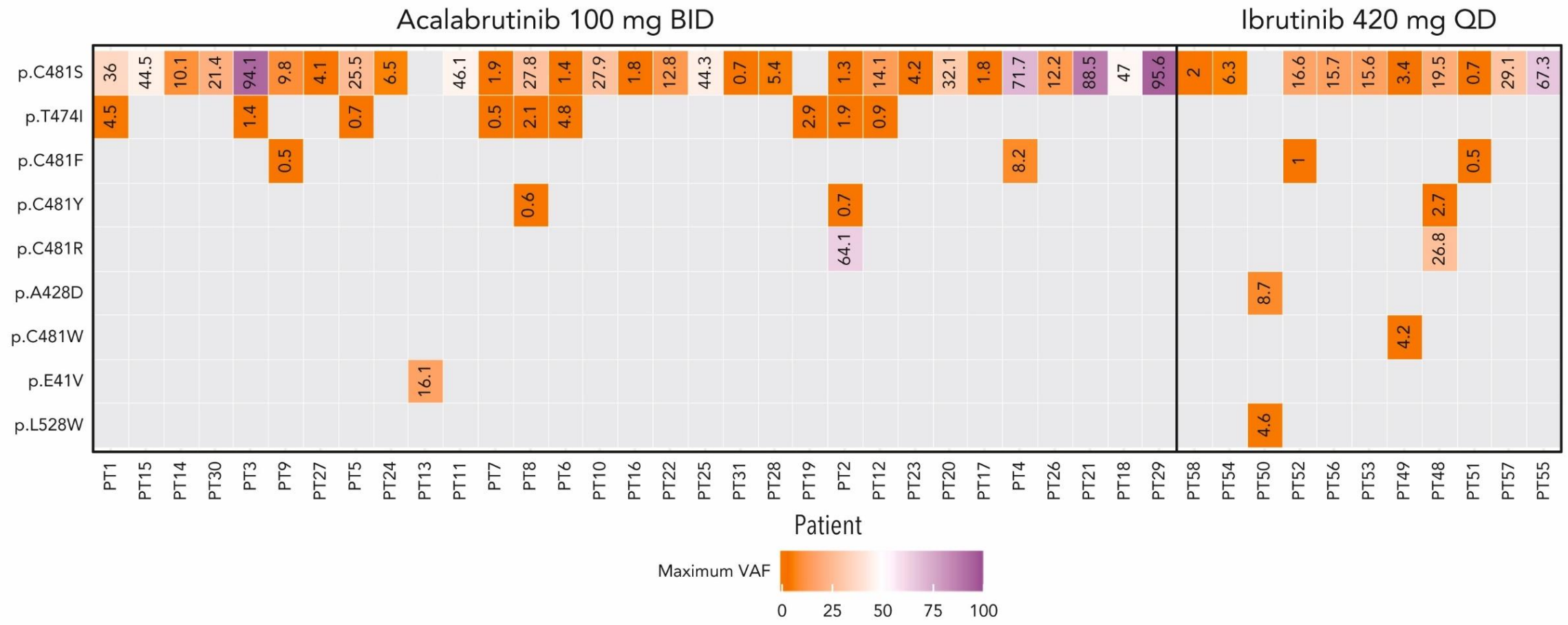
***BTK T474* gatekeeper**

- interfere with BTKi (both covalent and noncovalent) binding to BTK
- allow for normal B-cell signaling

***BTK L528W* kinase-dead**

- hinder BTK catalytic activity
- B-cell signaling is thought to continue via a BTK scaffolding

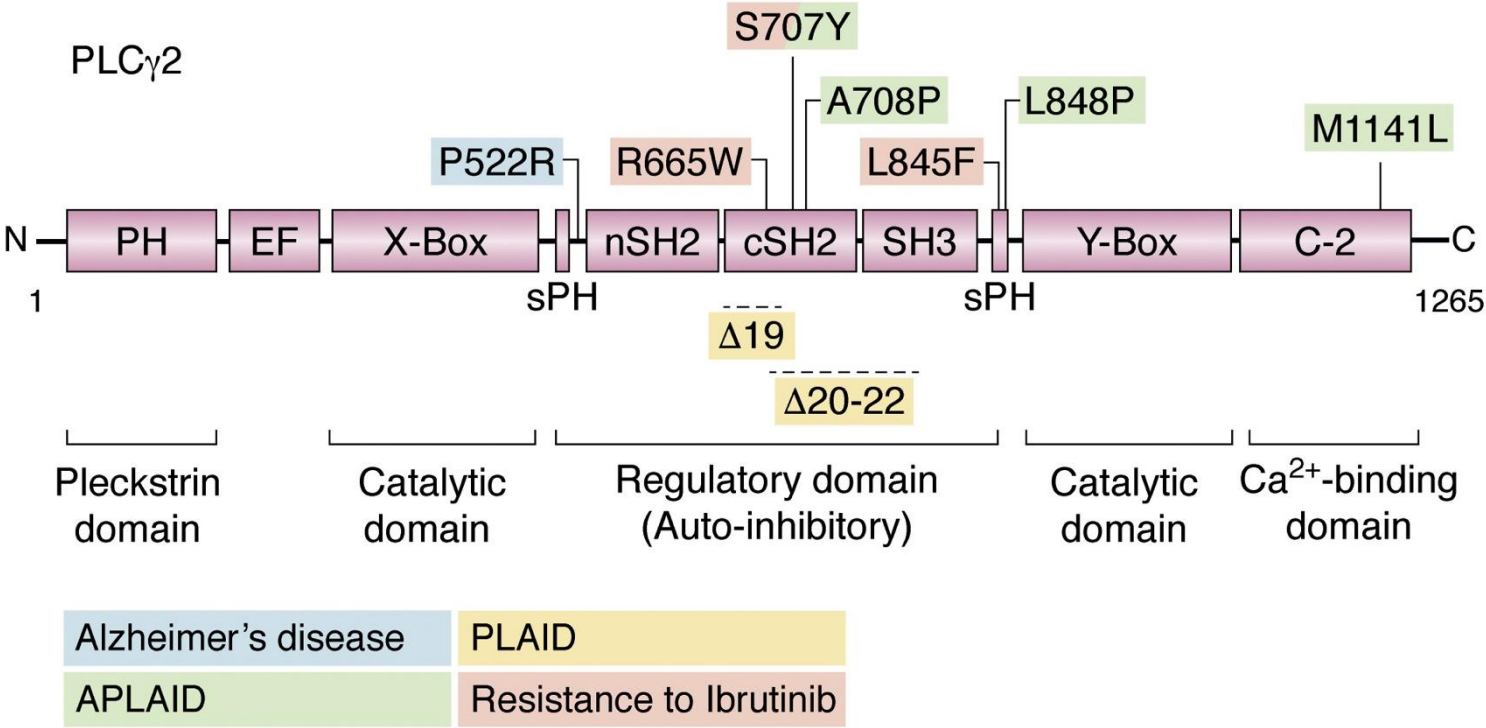
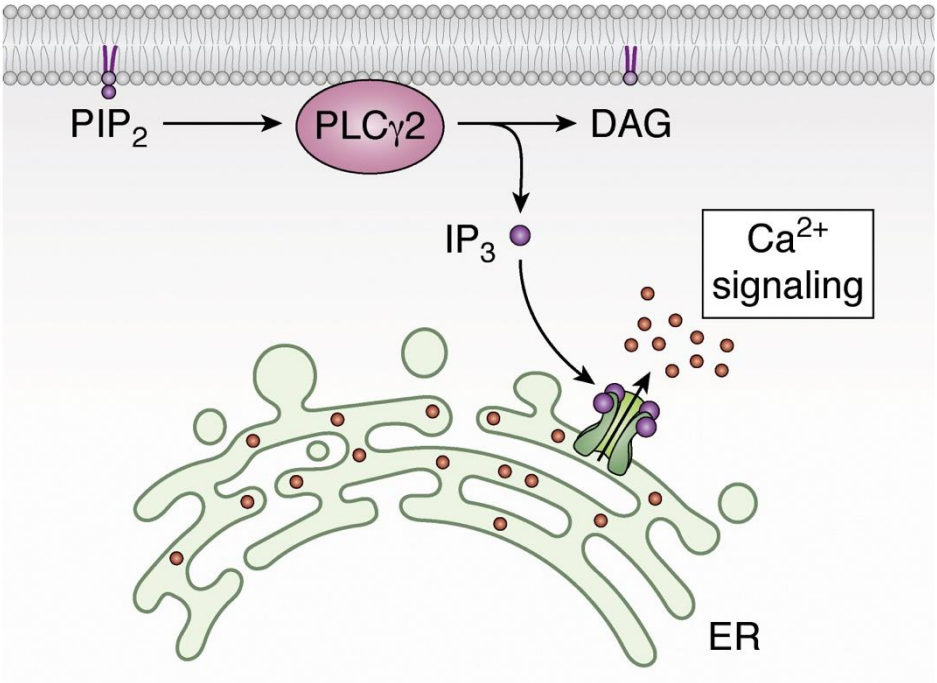
BTK mutations have low VAF in PB: implications for diagnostics



BTK mutations: binding affinity of BTKi

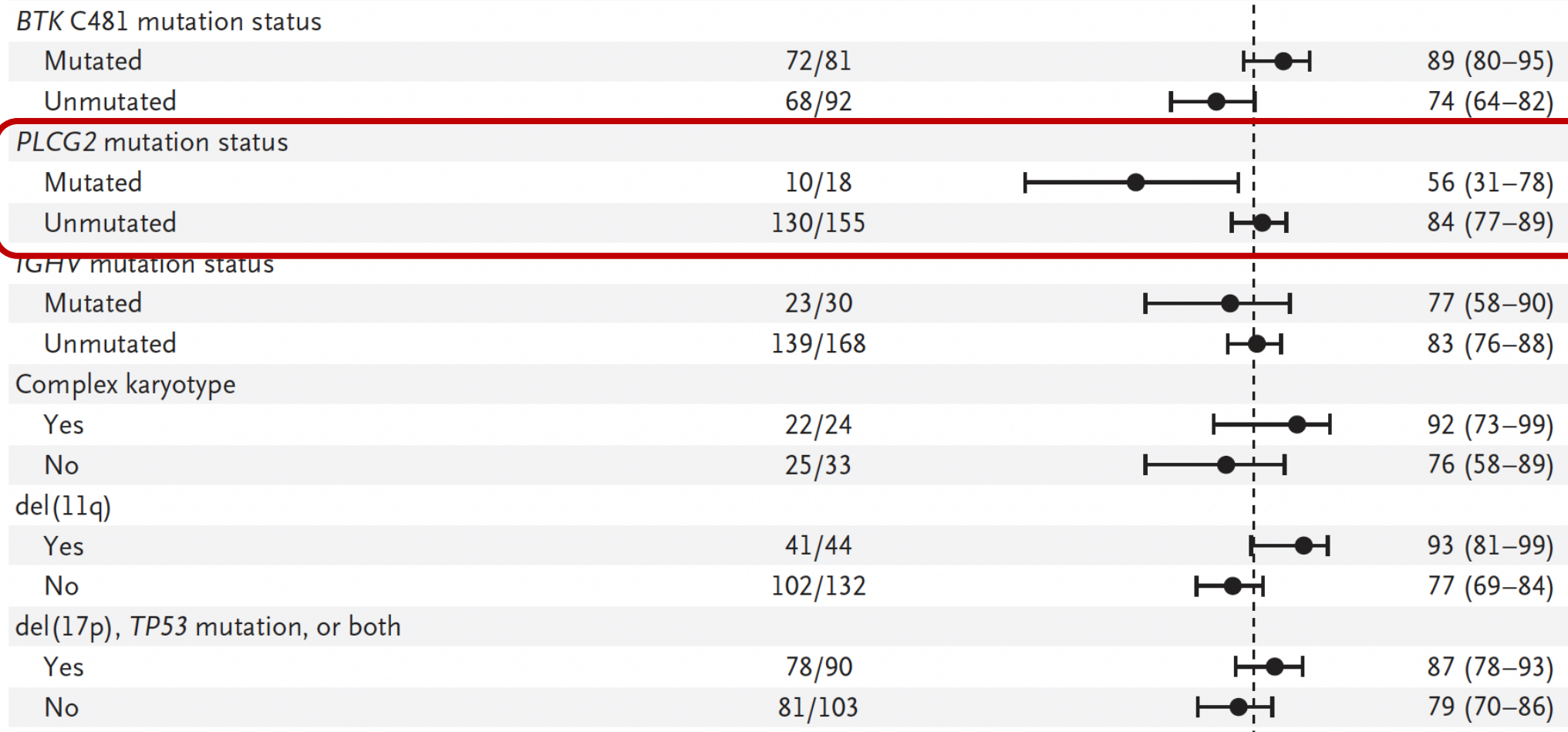
	Noncovalent				Covalent
	Pirtobrutinib	ARQ-531	Vecabrutinib	Fenebrutinib	Ibrutinib
Wild type	Normal	Normal	Normal	Normal	Normal
A428D	None	Decreased	None	None	None
M437R	Decreased	Normal	Decreased	Decreased	Normal
T474I	Decreased	Decreased	Decreased	Normal	Normal
L528W	None	None	Decreased	Normal	None
C481S	Normal	Normal	Normal	Normal	Decreased

PLCG2 mutations



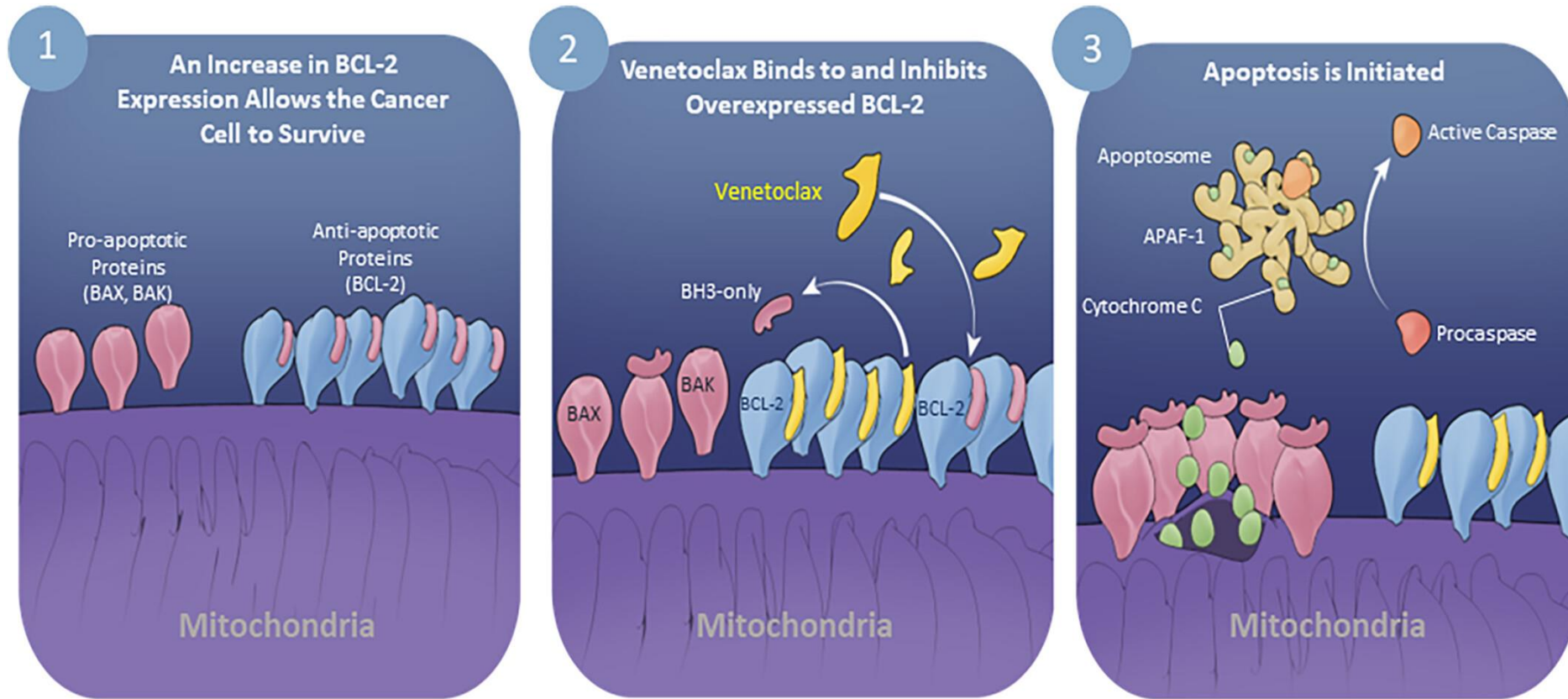
APLAID: PLCγ2-associated antibody deficiency and immune dysregulation with autoinflammation
LAID: PLCγ2-associated antibody deficiency and immune dysregulation

Response to the non-covalent BTK inhibitor Pirtobrutinib according to biomarkers in the Bruin phase 1-2 trial for CLL previously treated with covalent BTKi

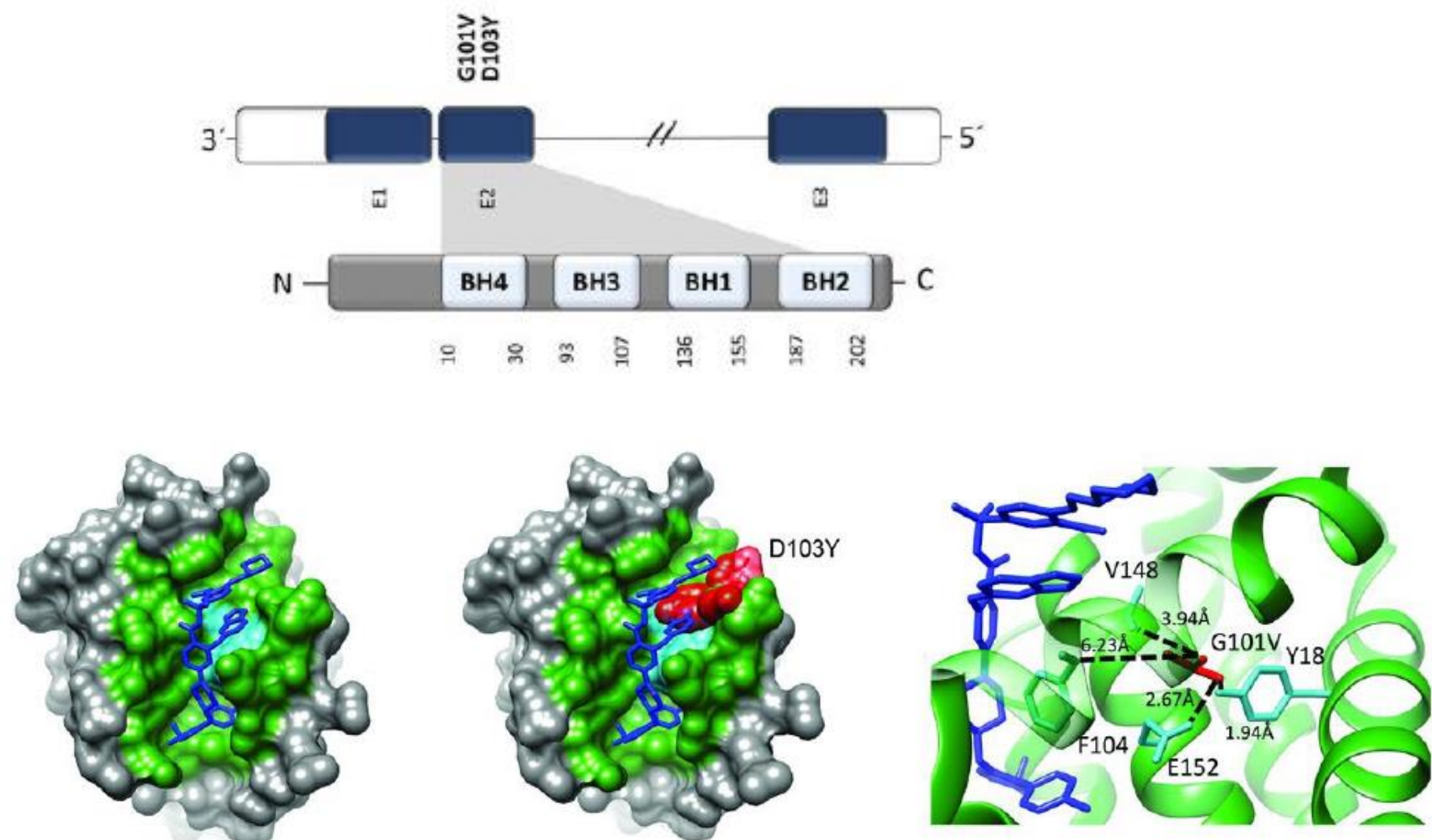


Response was 70-80% across clinical and molecular subgroups, with the **exception of patients expressing PLCG2 mutations**, for which additional data are needed

BCL2 and the apoptotic pathway



Mutations of resistance to BTKi

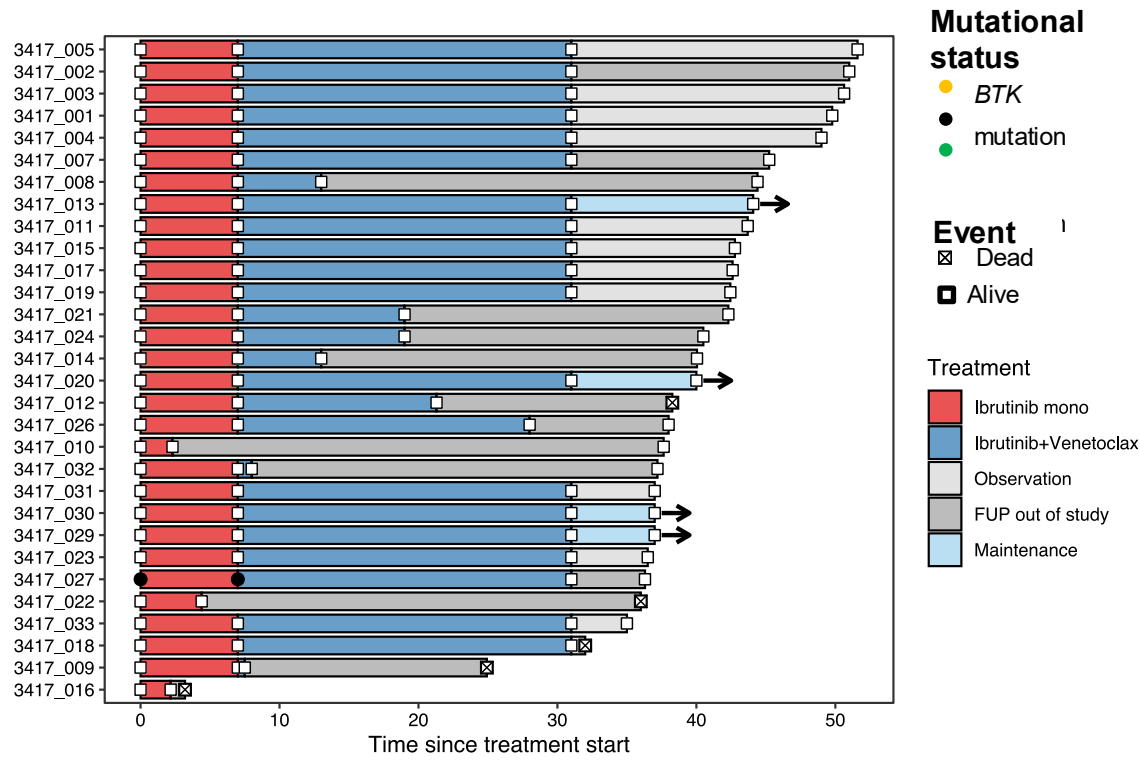


Incidence and risk factors

- 50-70% among patients who discontinue BTKi due to progression
- 50% among patients who discontinue venetoclax due to progression
- Risk factors
 - Continuous treatment
 - Relapsed disease
 - TP53 abnormalities

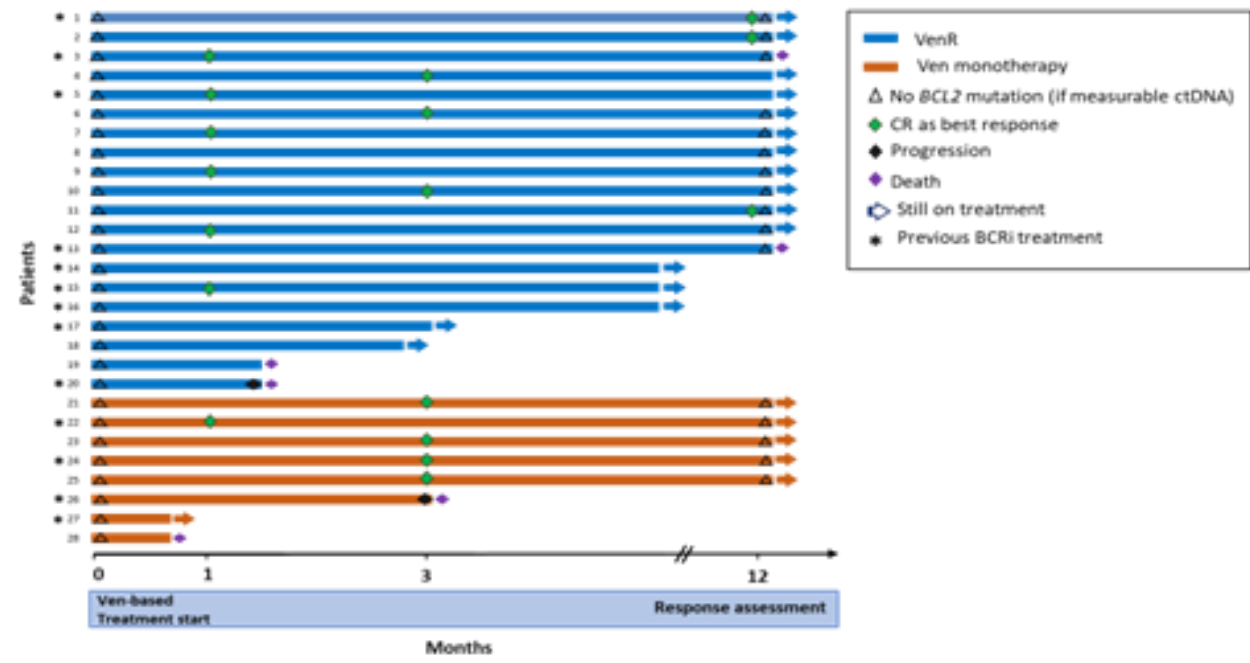
No mutations after time-limited venetoclax-based Tx

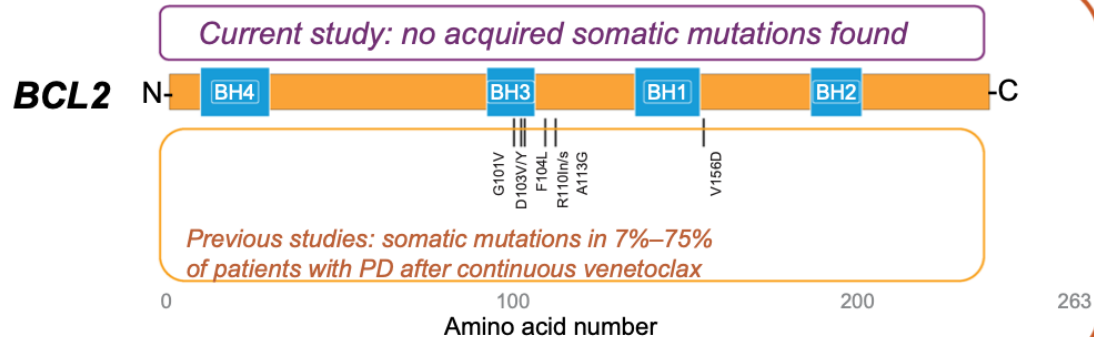
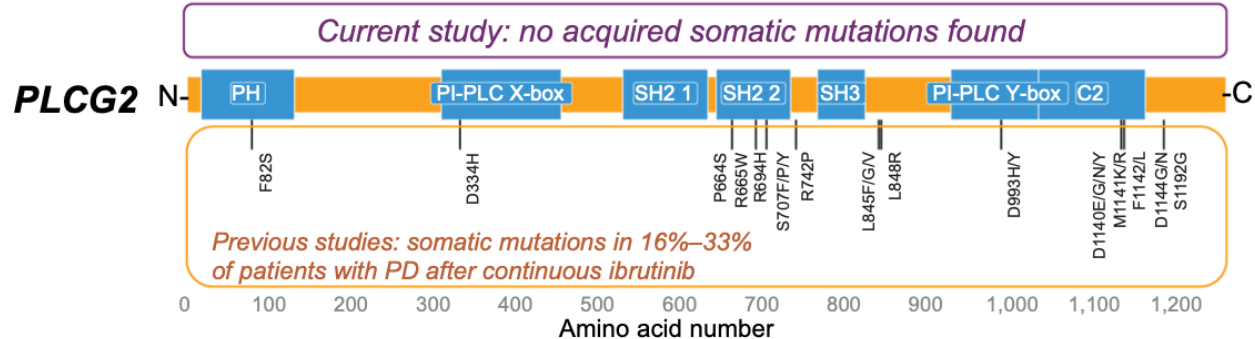
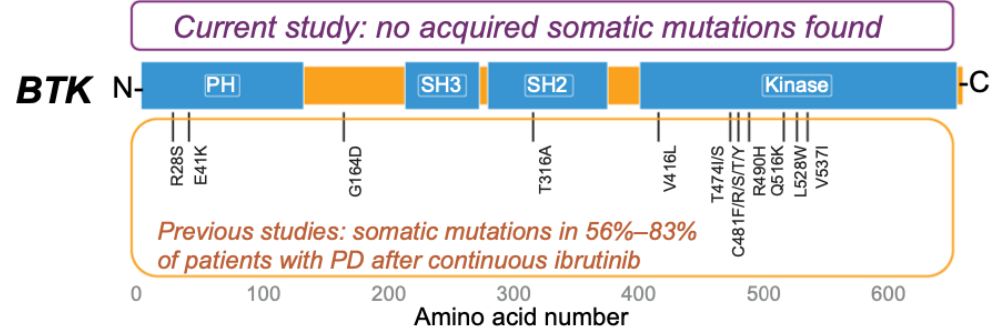
Venetoclax + Ibrutinib in R/R CLL (SAKK 34/17)



BCL2 mutation detected for patient SAKK-027:
BCL2:NM_000633:exon2:c.C67T:p.L23L, *BCL2*:NM_000633:c.-512T>A

Venetoclax +/- Rituximab in R/R CLL (VeRVe)





Fixed-duration combination treatment with ibrutinib plus venetoclax:

- may mitigate the development of resistance mechanisms associated with continuous single-agent targeted therapies
- may allow for effective retreatment with ibrutinib or ibrutinib plus venetoclax, thereby extending clinical benefit with these agents

Agenda

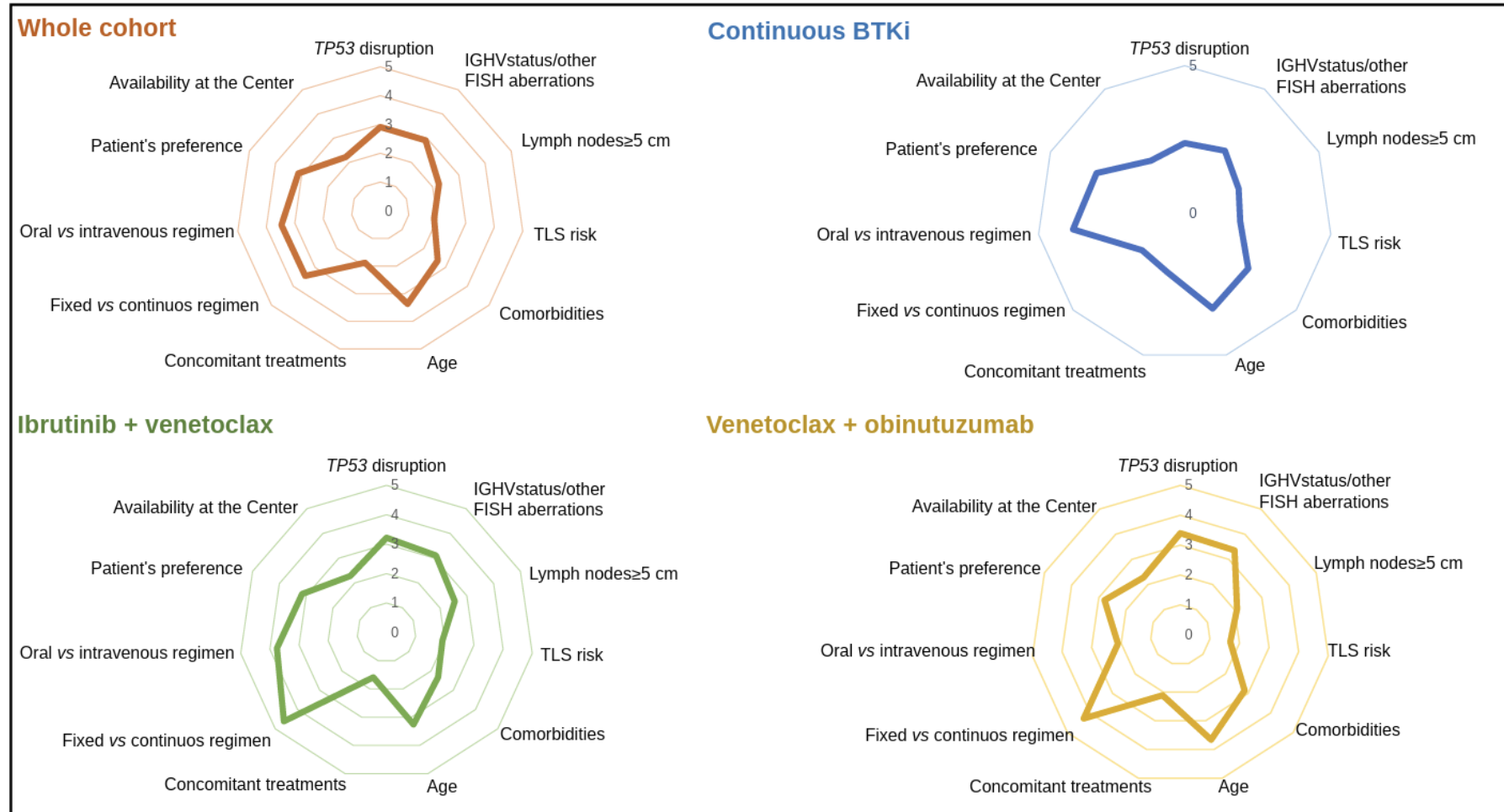
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FIRST-CLL study: Impact of different parameters on choice of 1L treatment



Perutelli et al. Hematol Oncol 2026



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Regimi Ven-based a durata fissa vs. regimi in monoterapia a durata cronica e continuativa

1L – regimi a durata fissa Ven-based

Anno 1	Anno 2	Anno 3
		
		
		
		

venetoclax + obinutuzumab (V+O) o ibrutinib (V+I) sono gli unici a offrire rispettivamente 12 e 15 cicli di 28 giorni di trattamento per pazienti naïve alla terapia

R/R – regimi a durata fissa Ven-based

Anno 1	Anno 2	Anno 3
		
		
		
	 	 

venetoclax + rituximab (V+R) rappresenta l'unica opzione a durata fissa (24 mesi) per pazienti con LLC recidivata/refrattaria



1L e R/R – regimi in monoterapia con ibrutinib, acalabrutinib, zanubrutinib a durata cronica e continuativa

Anno 1	Anno 2	Anno 3
		
		
		
	 	  

Ibrutinib, acalabrutinib e zanubrutinib in monoterapia hanno una durata di trattamento cronica e continuativa fino a progressione della malattia