



Convegno Regionale

**SIE**

LE NUOVE FRONTIERE NELLA  
TERAPIA DEL LINFOMA:  
INNOVAZIONE E FUTURO

**30 Marzo 2026**

*Napoli, Centro Congressi Federico II*

DELEGAZIONE CAMPANIA

## **Farmacocinetica e farmacodinamica dei BTKi**

Giorgio Minotti

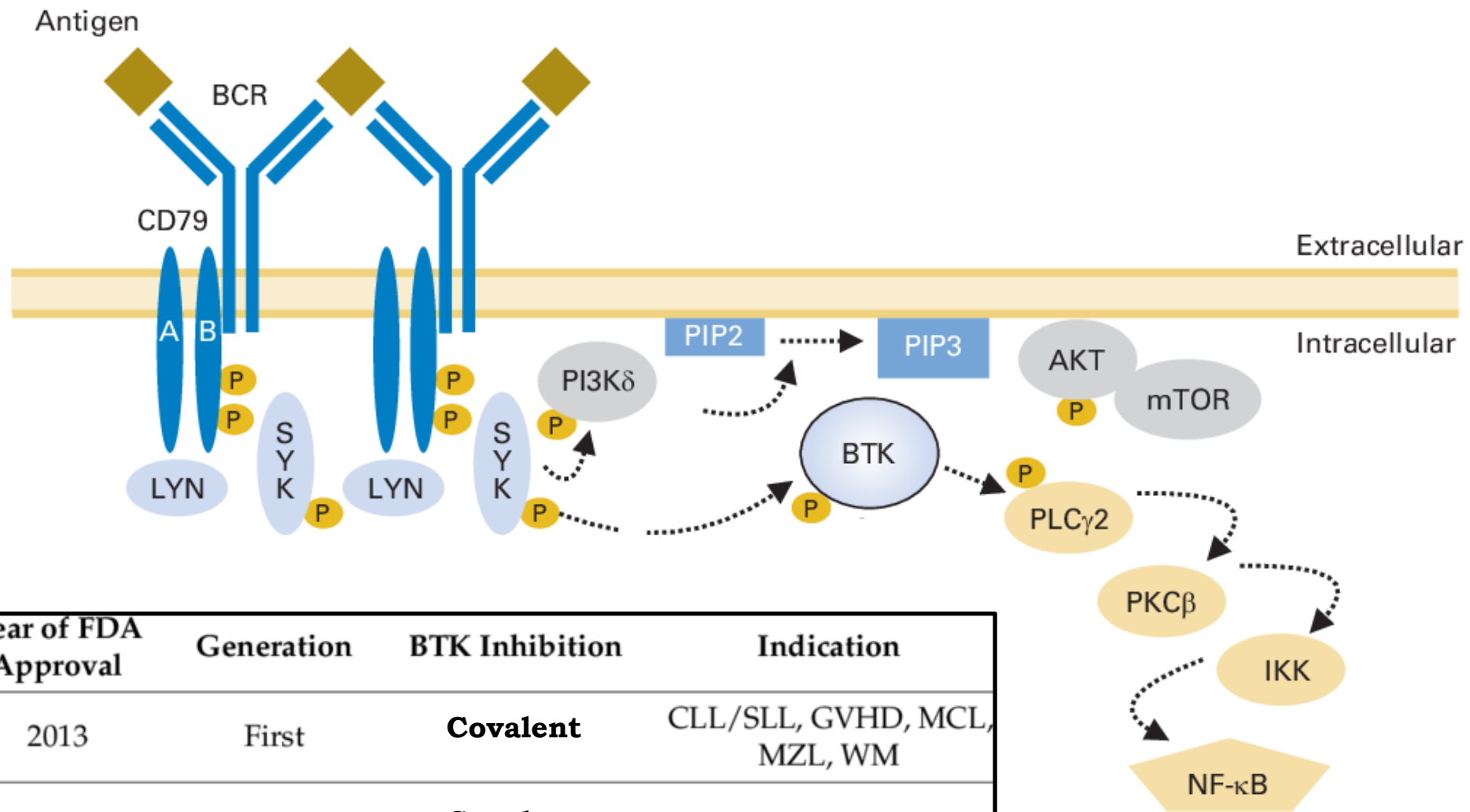
Università e Fondazione Policlinico Universitario

Campus Bio-Medico

Roma

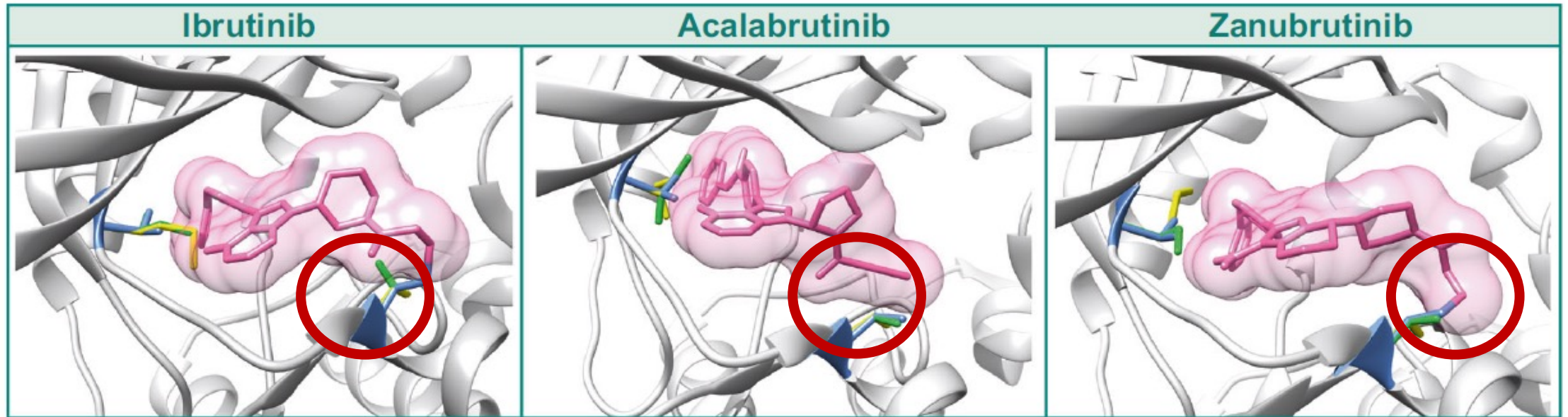
# My COIs

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen			X		X	X	
Incyte	X		X			X	
BeONE			X		X		
Servier			X				
Daiichi-Sankyo					X		
Eli Lilly					X		
Abbvie					X		



BTK Inhibitor	Year of FDA Approval	Generation	BTK Inhibition	Indication
Ibrutinib (Imbruvica)	2013	First	<b>Covalent</b>	CLL/SLL, GVHD, MCL, MZL, WM
Acalabrutinib (Calquence)	2017	Second	<b>Covalent</b>	CLL/SLL, MCL
Zanubrutinib (Brukinsa)	2019	Second	<b>Covalent</b>	CLL/SLL, MCL, MZL, WM
Pirtobrutinib (Jaypirca)	2023	Third	<b>Noncovalent</b>	CLL/SLL, MCL

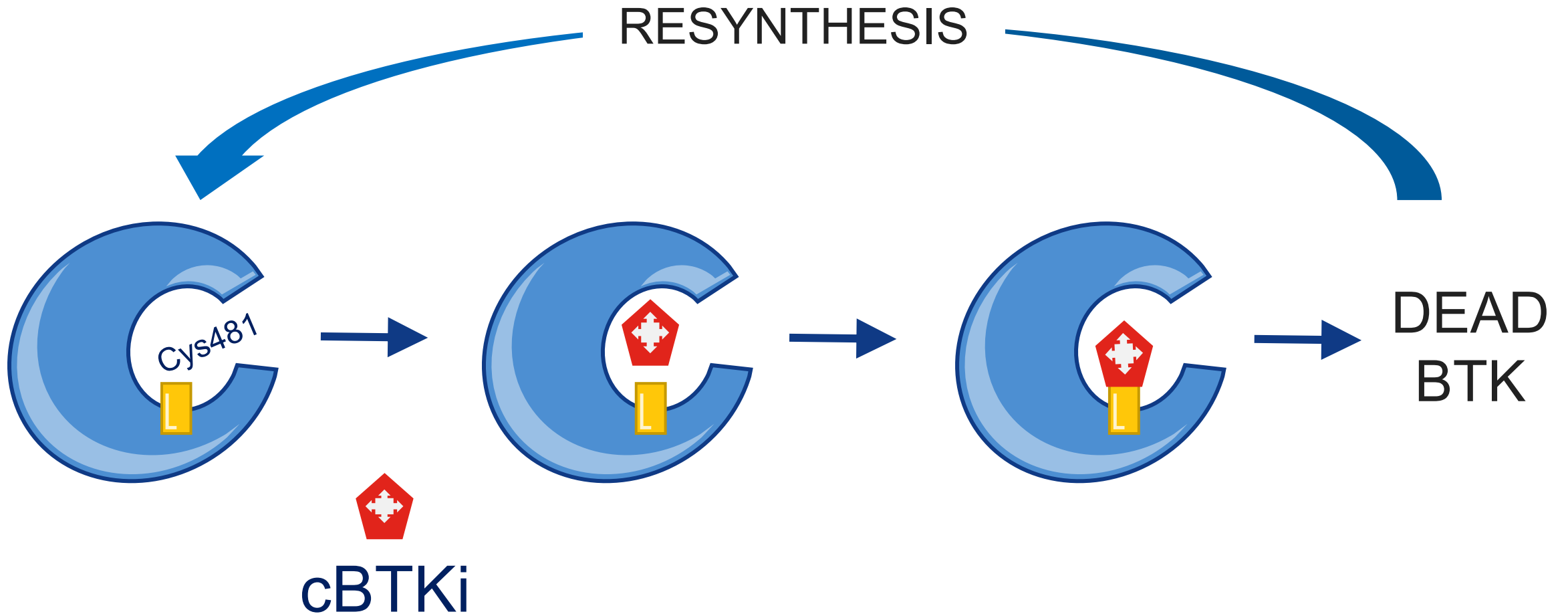
# Covalent BTKi bind to Cys 481 in the kinase domain of BTK



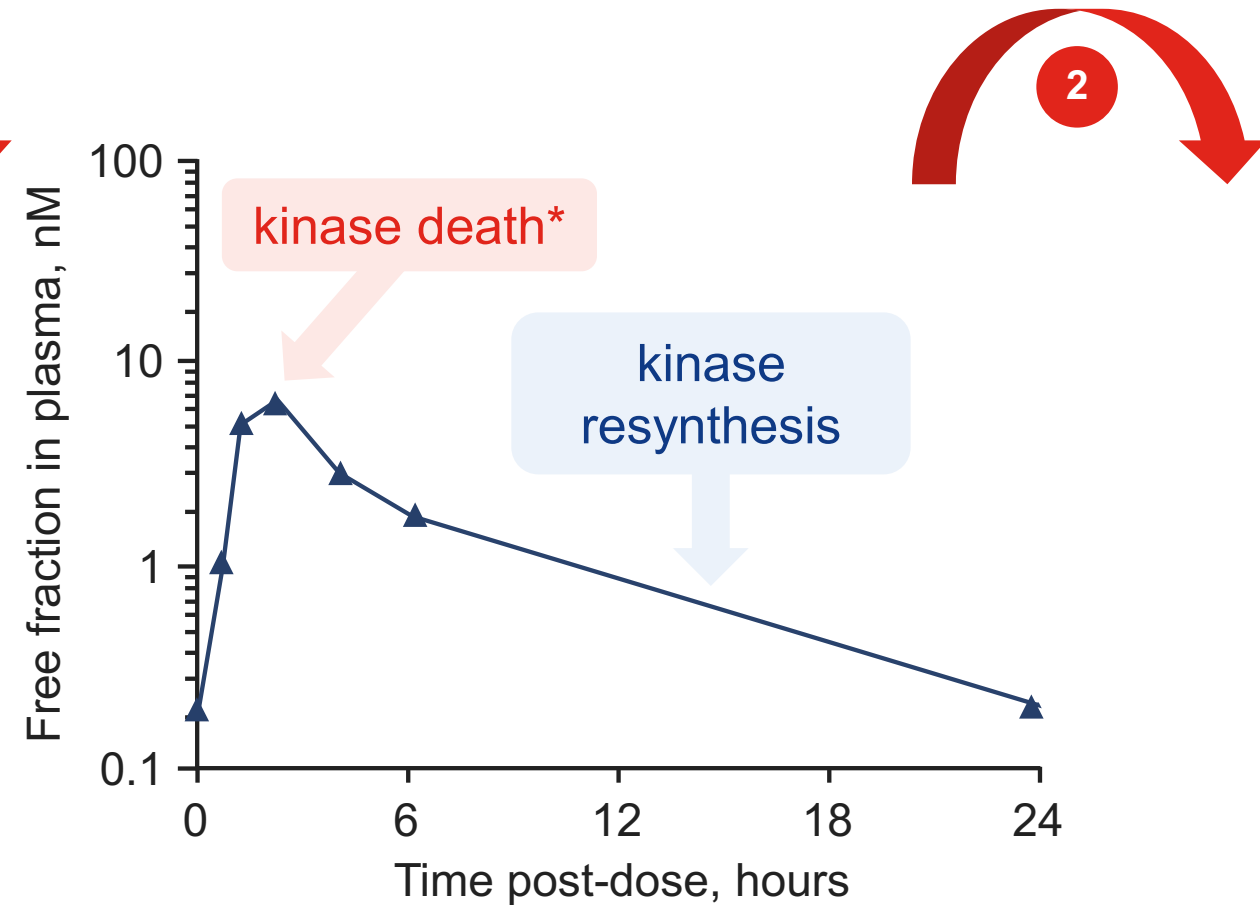
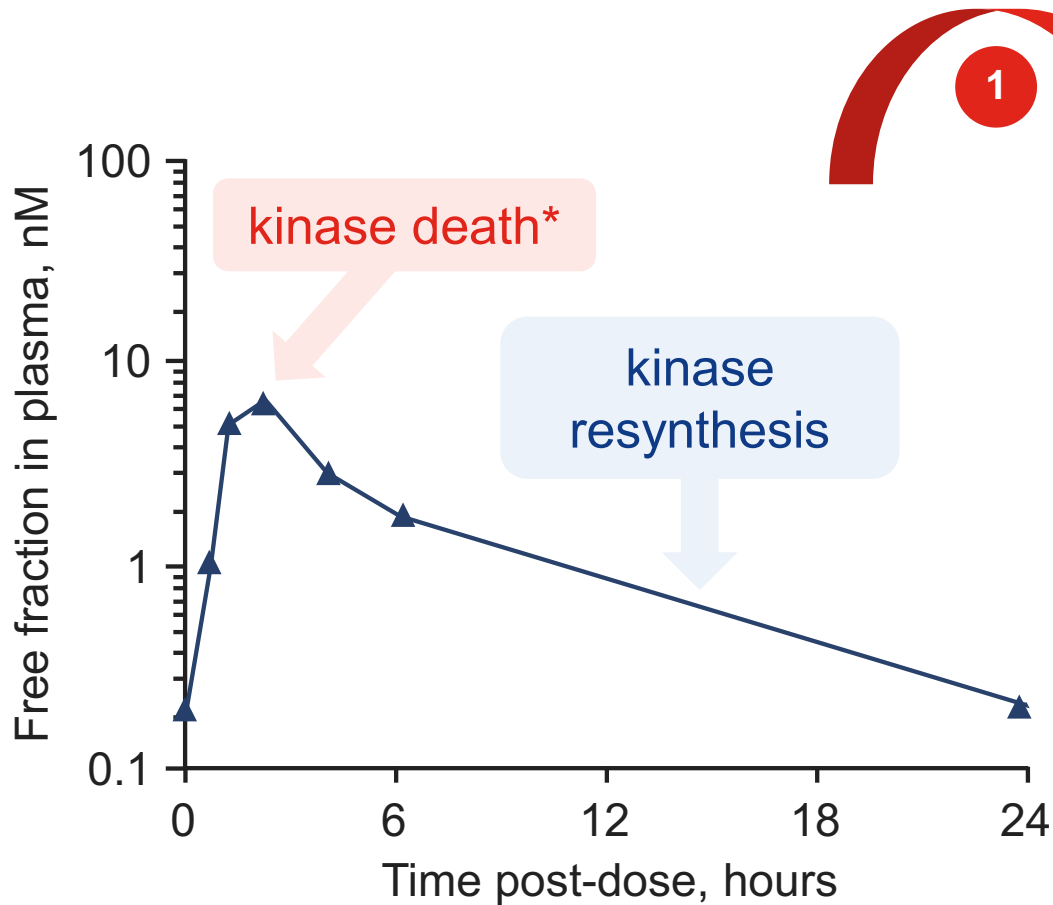
Leukemia (2021) 35:1317–1329

<https://doi.org/10.1038/s41375-021-01123-6>

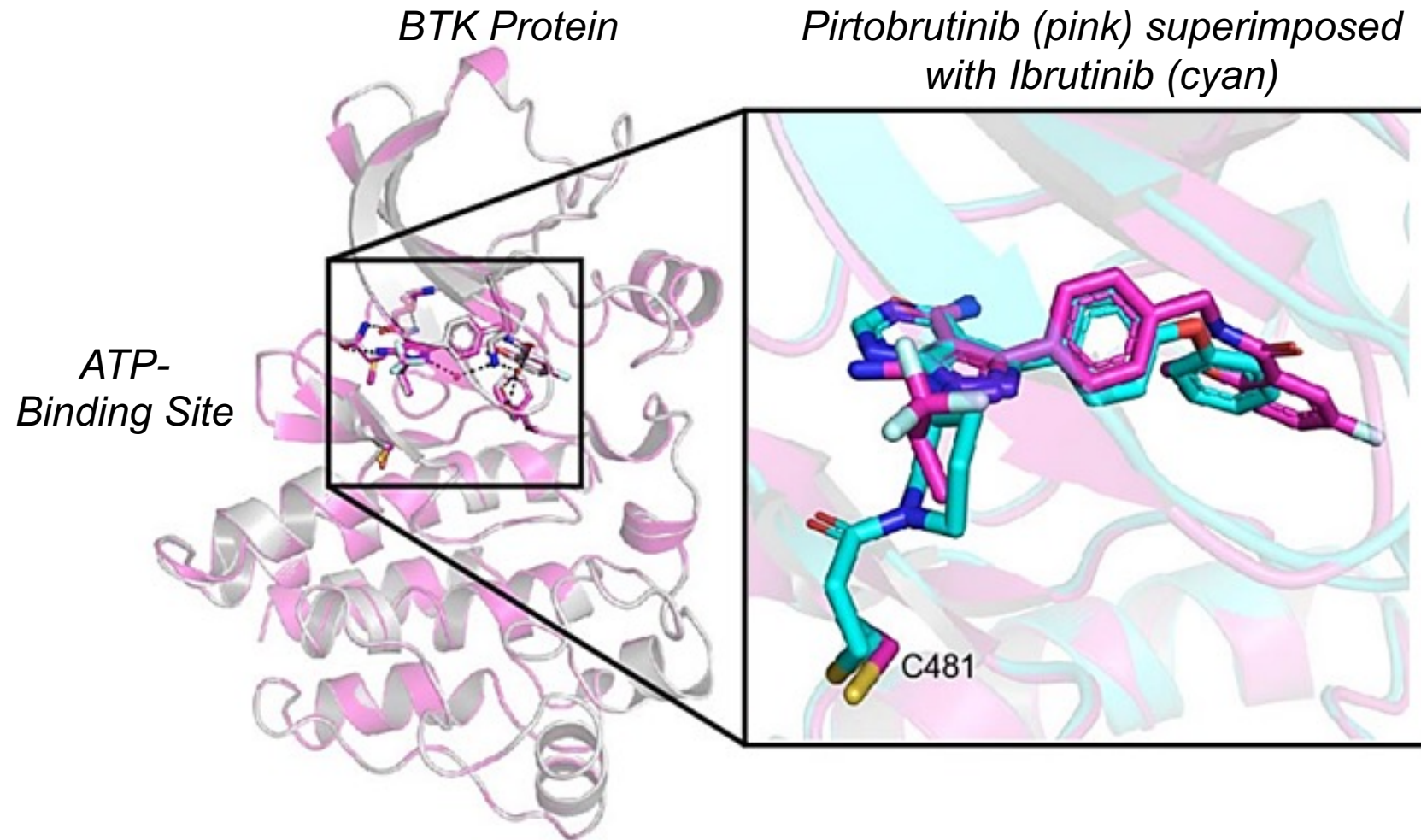
# Irreversible inhibition of BTK is counteracted by enzyme resynthesis



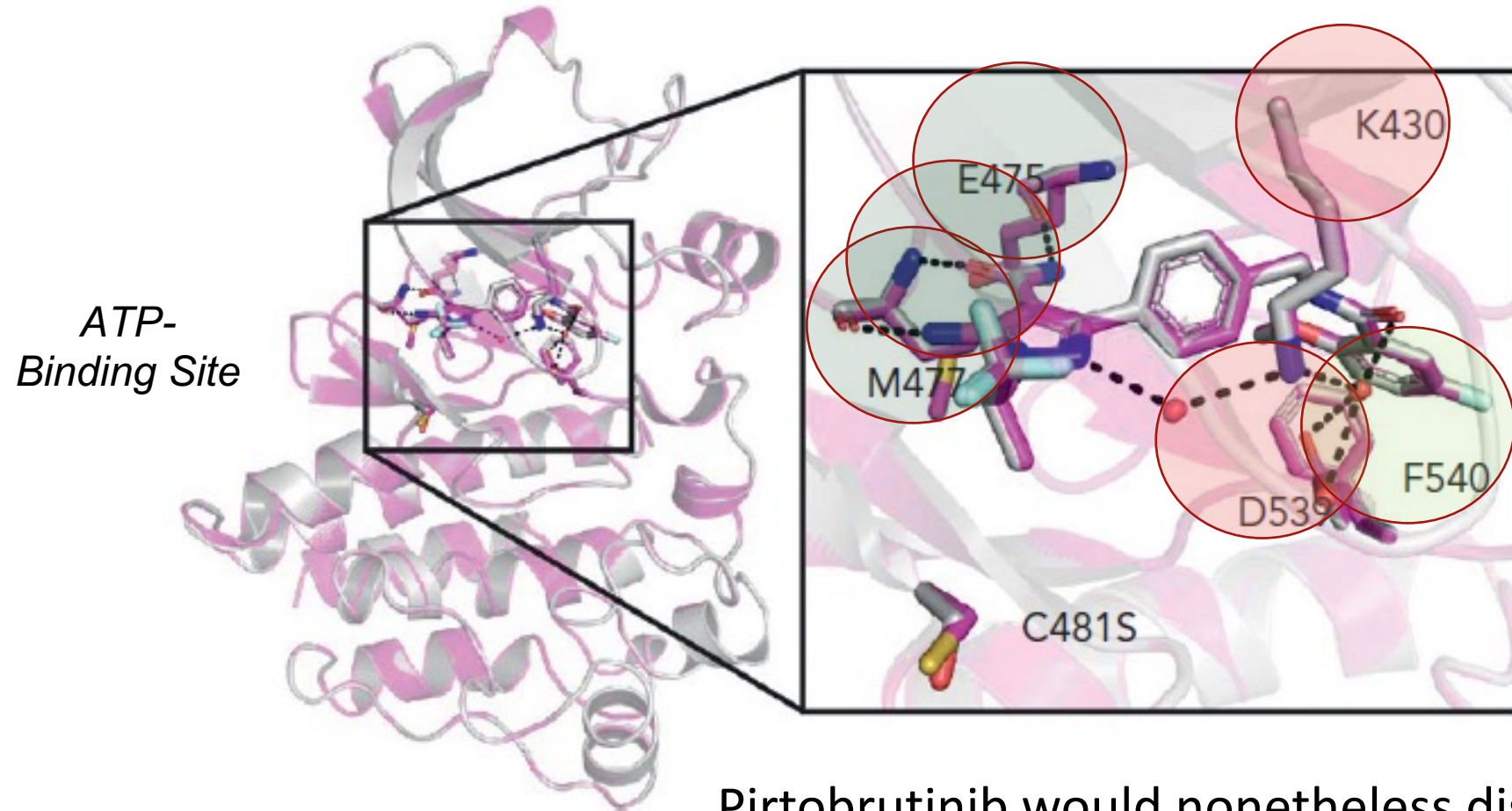
# cBTKI show PK parameters that facilitate resynthesis



# Pirtobrutinib does not bind to Cys481

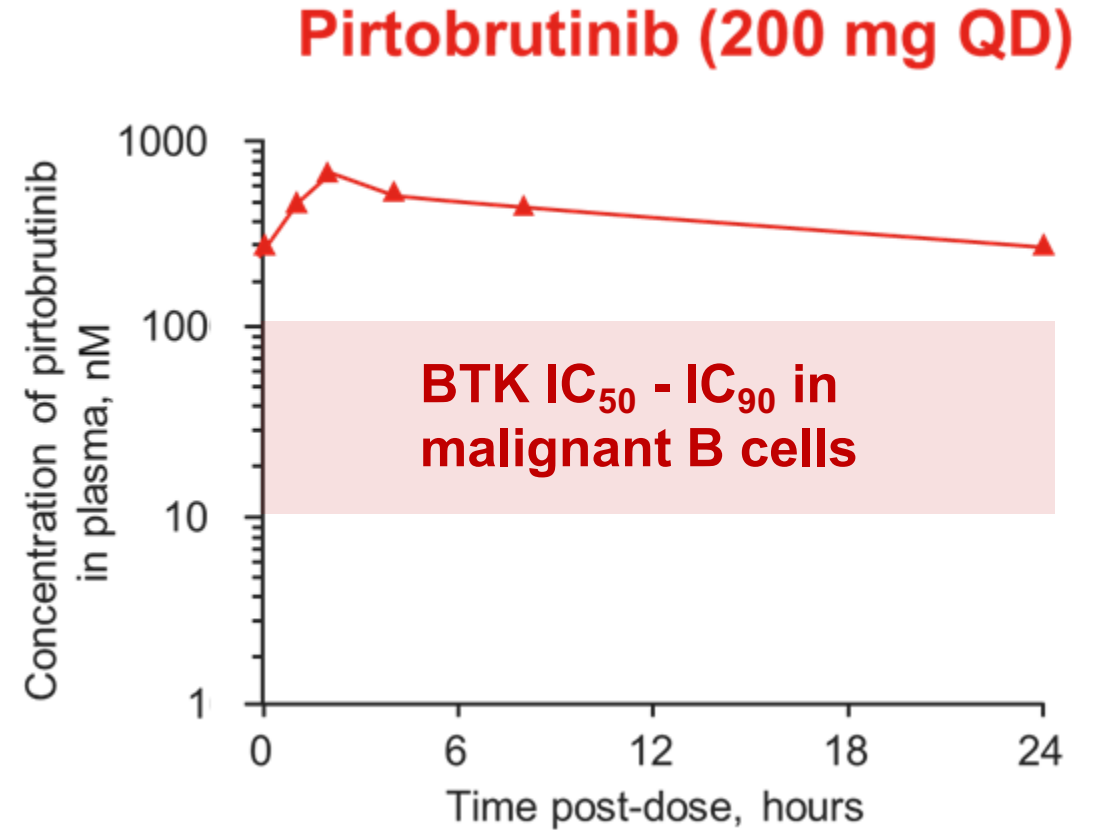
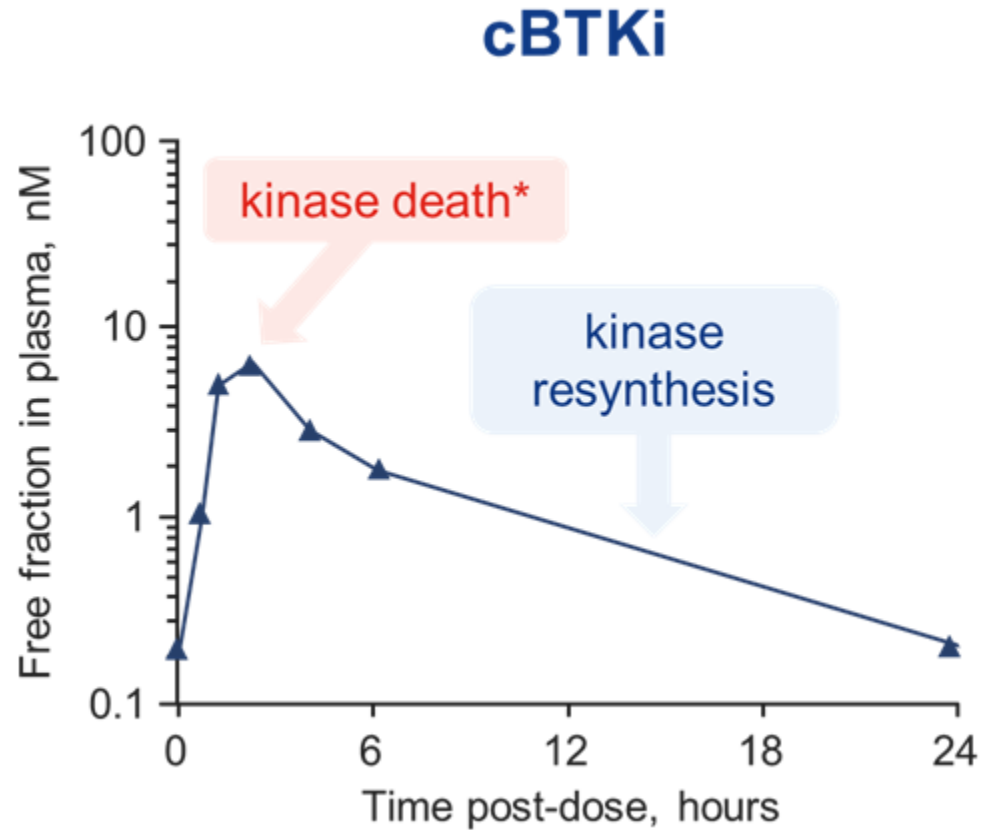


# But engages with BTK through several noncovalent bonds

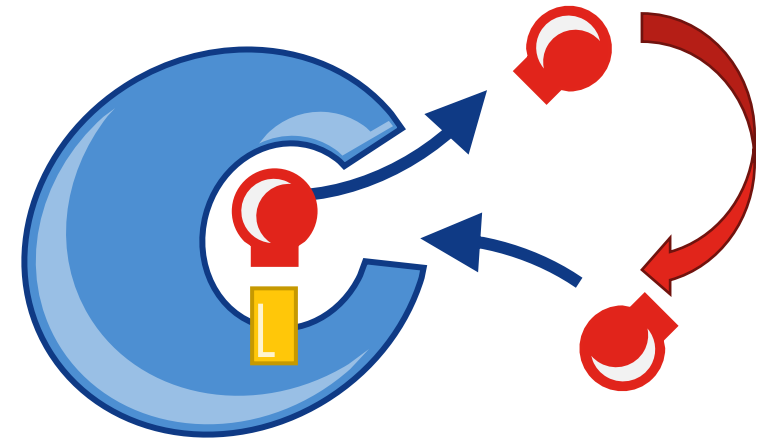


Pirtobrutinib would nonetheless dissociate from BTK with a half life of 2.4 h

# PK of pirtobrutinib vs cBTKi



# Neither reversible nor irreversible but tonic



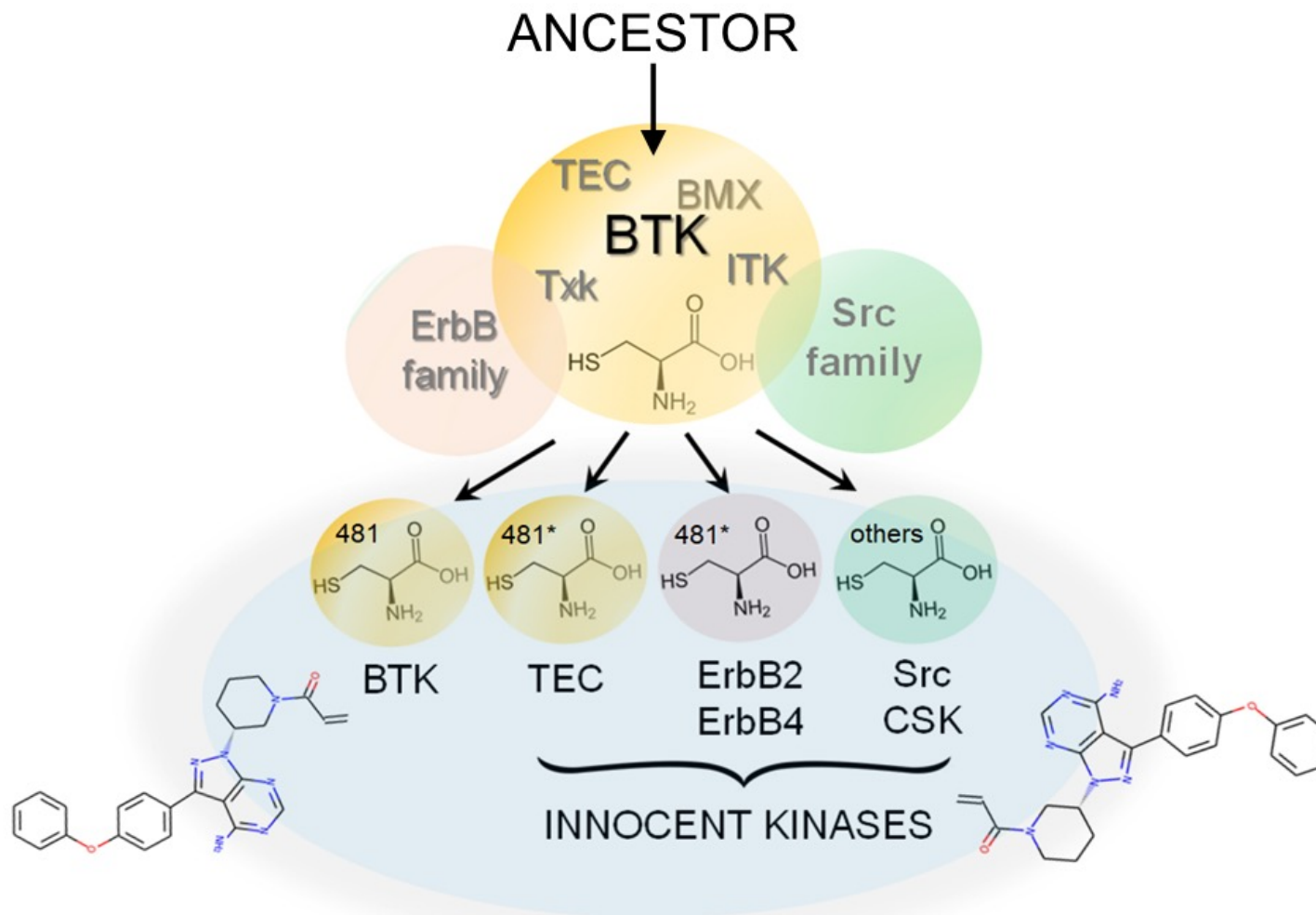
3

# **Phylogeny of Tec Family Kinases: Identification of a Premetazoan Origin of Btk, Bmx, Itk, Tec, Txk, and the Btk Regulator SH3BP5**

*Advances in Genetics, Vol. 64*

Copyright 2008, Elsevier Inc. All rights reserved.

# 1. Ancestry disseminates druggable cysteines



# Class effects of BTKi

---



**ATRIAL  
FIBRILLATION**



**BLEEDING**



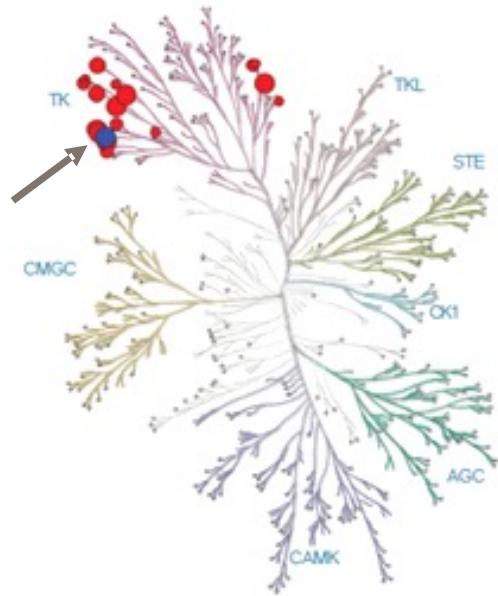
**HYPERTENSION**



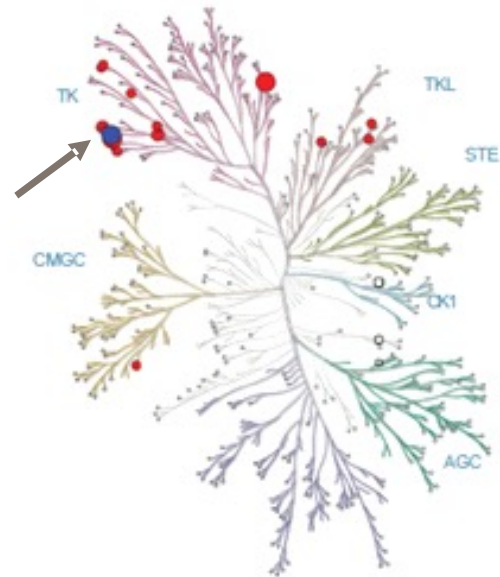
**HEART  
FAILURE**



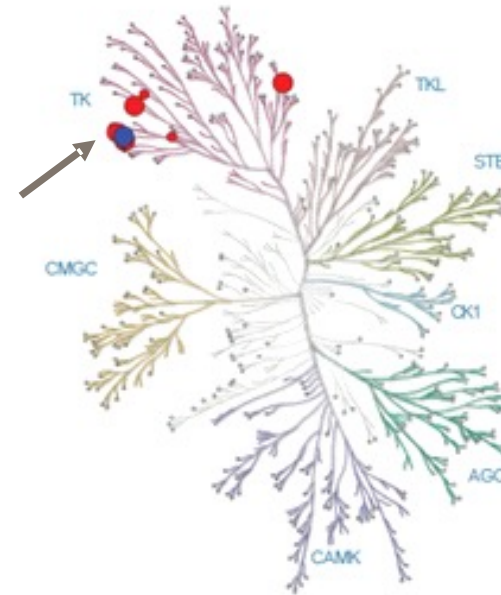
## Ibrutinib



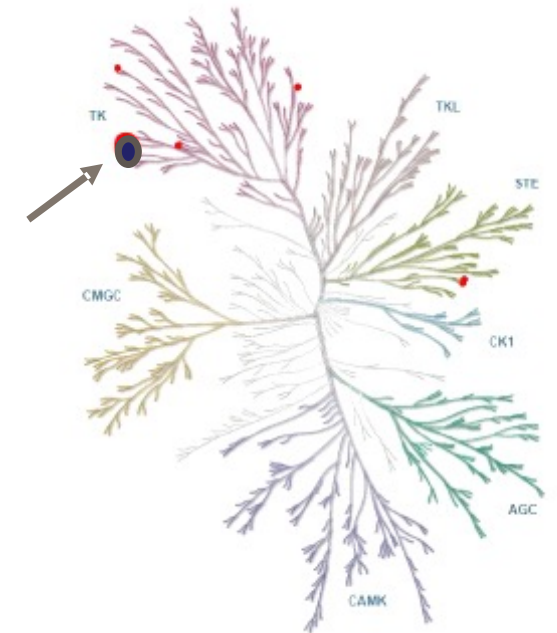
## Acalabrutinib



## Zanubrutinib



## Pirtobrutinib<sup>3</sup>



- BTK
- Innocent kinases

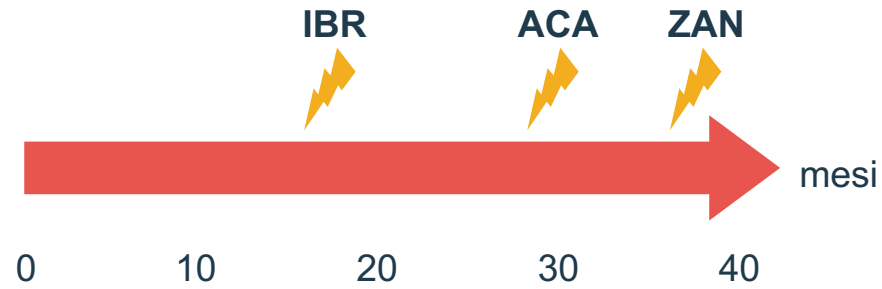
(c)BTKi, (covalent) Bruton's tyrosine kinase inhibitor.

1. Minotti G, et al. Br J Pharmacol. 2025;182(7):1446-1451. 2. Shadman M, et al. ASH 2024. Abstract 4632 (Poster). 3. Bernstein JA, et al. J Allergy Clin Immunol. 2024;153(5):1229-1240.

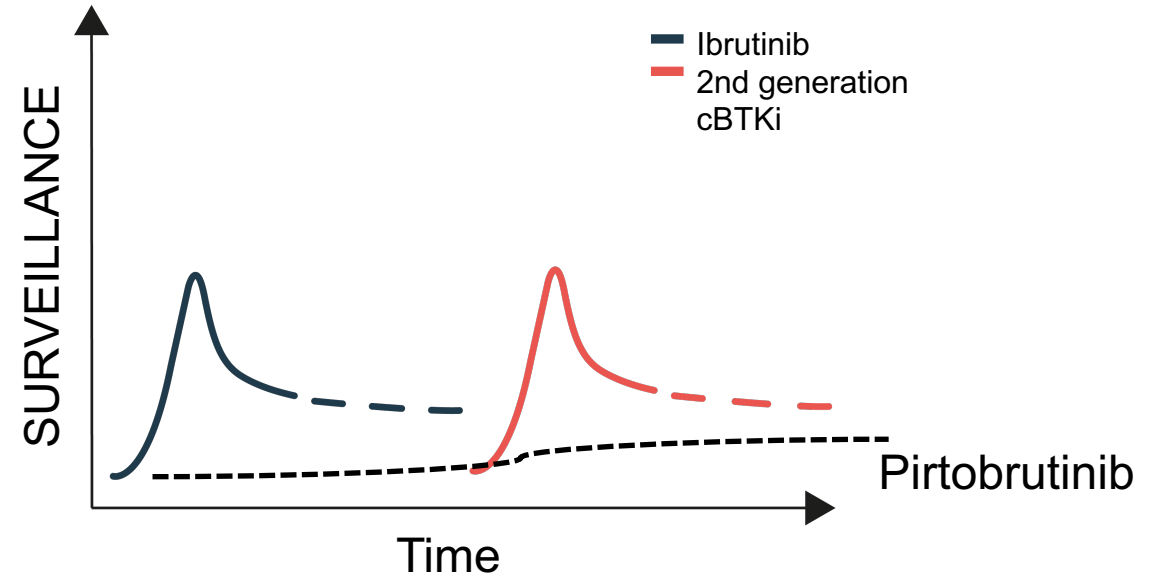
TO THE EDITOR:

Cardiovascular toxicity of Bruton tyrosine kinase inhibitors: forget about selectivity but watch the clock

Giorgio Minotti

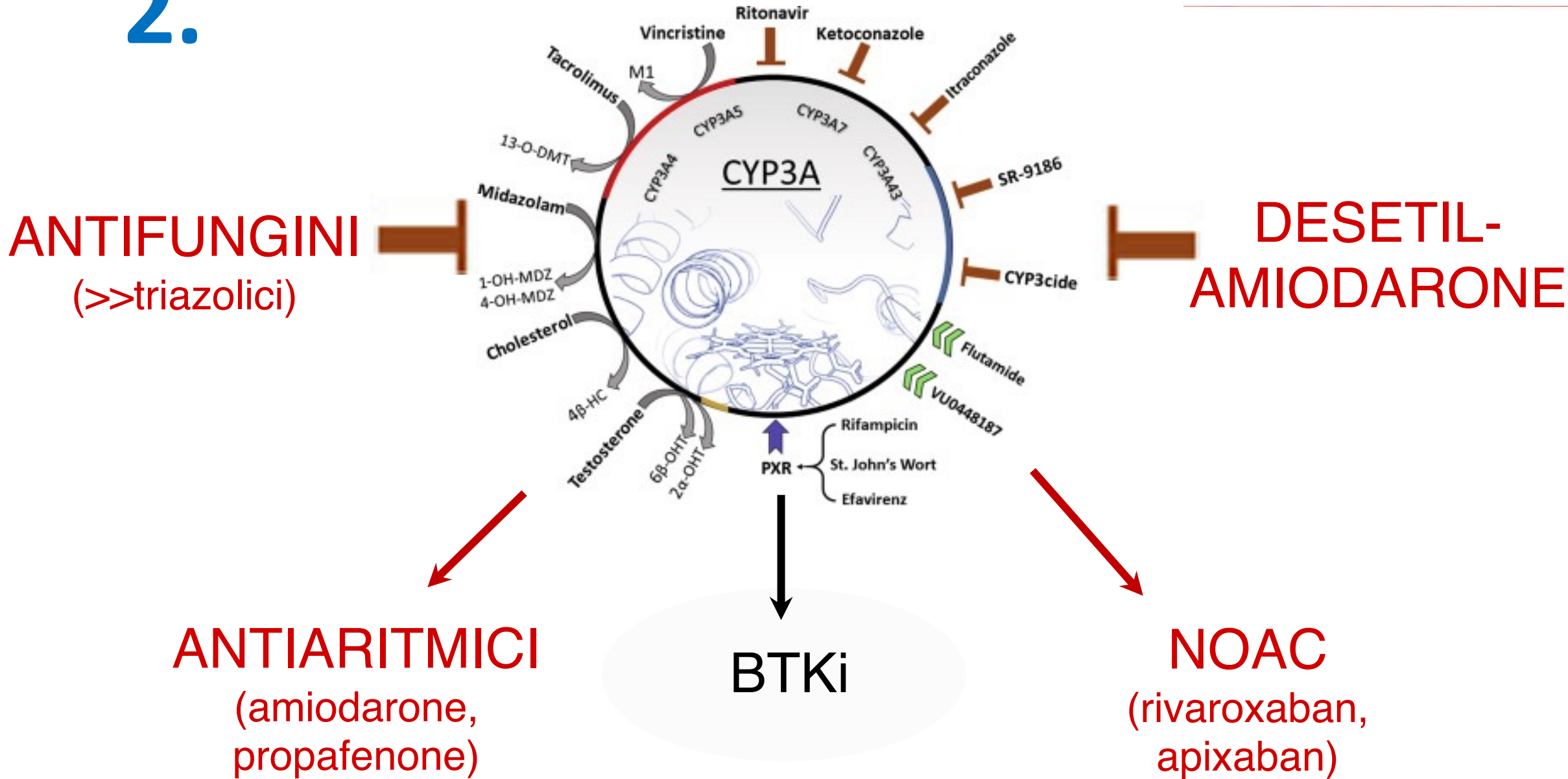


Longer time to AFIB with 2nd generation cBTKi



Time-tailored surveillance in patients treated with different cBTKi

# 2.



**ANTIFUNGINI**  
(>>triazolici)

**DESETIL-AMIODARONE**

**ANTIARITMICI**  
(amiodarone, propafenone)

**NOAC**  
(rivaroxaban, apixaban)

**BTKi**

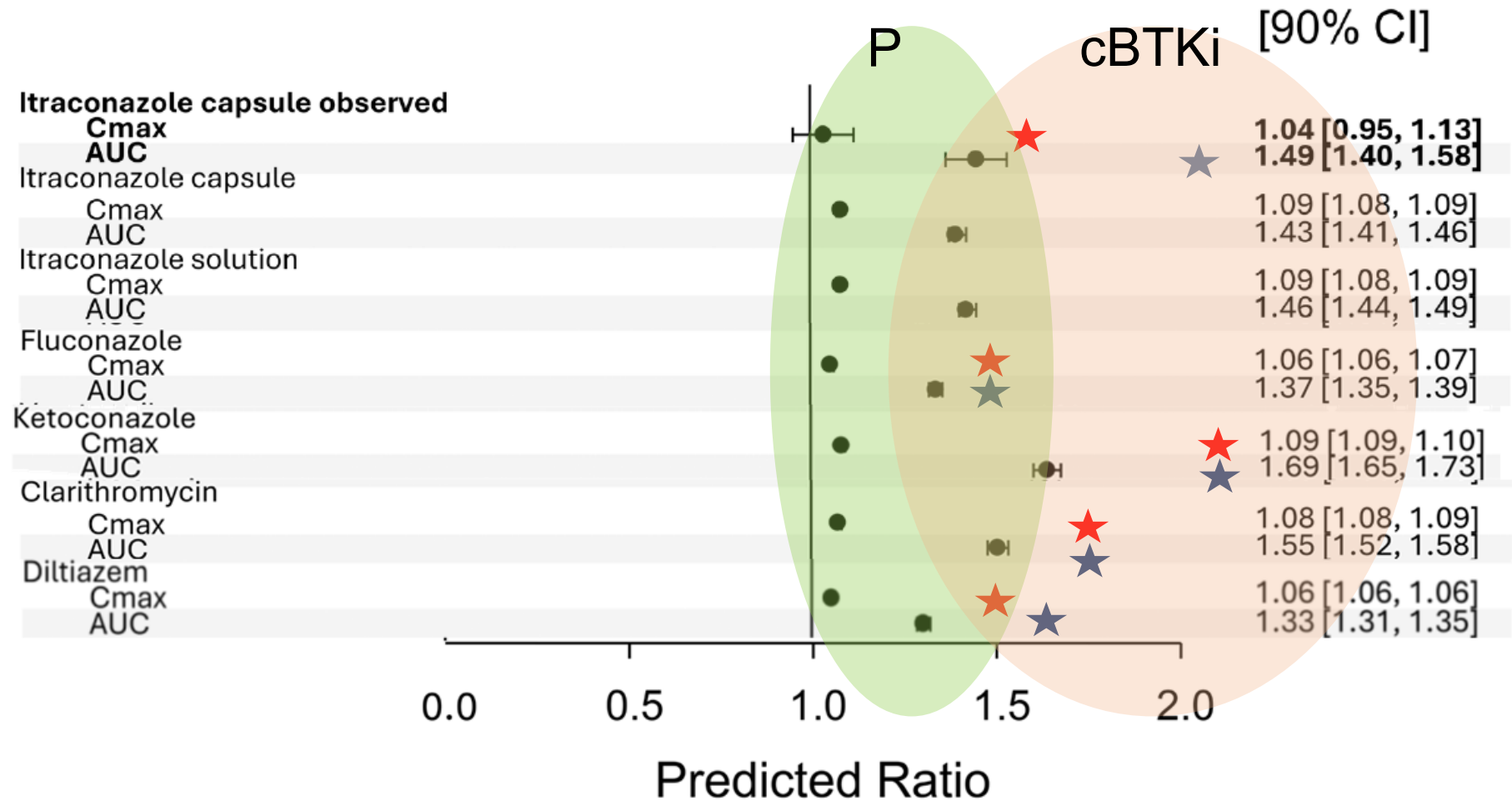


---

<b>Co-administered CYP3A Inhibitor</b>	<b>Increase in <math>C_{max}</math></b>	
		<i>Observed</i>
Itraconazole (200 mg once daily)	157%	
		<i>Predicted</i>
Clarithromycin (250 mg twice daily)	175%	
Diltiazem (60 mg three times daily)	151%	

# CYP3A perpetrators

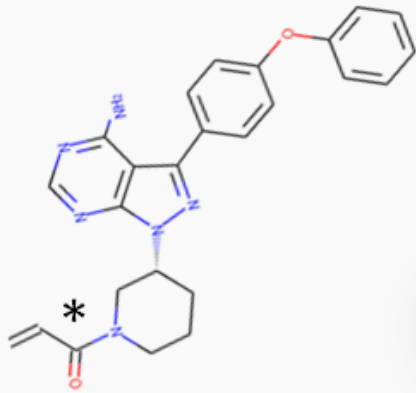
Geometric mean



## 3.

1<sup>st</sup> GENERATION cBTKi

ibrutinib

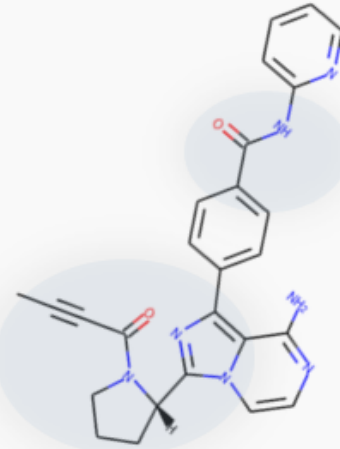


MOA

C481S

2<sup>nd</sup> GENERATION cBTKi

acalabrutinib



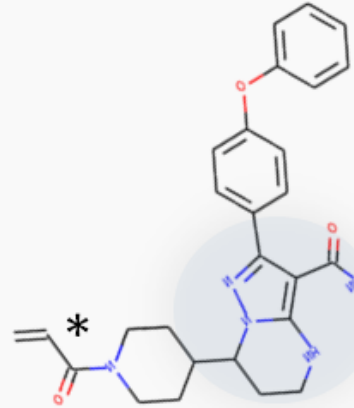
MOA AND PHYLOGENY

C481S

T474I (gatekeeper)

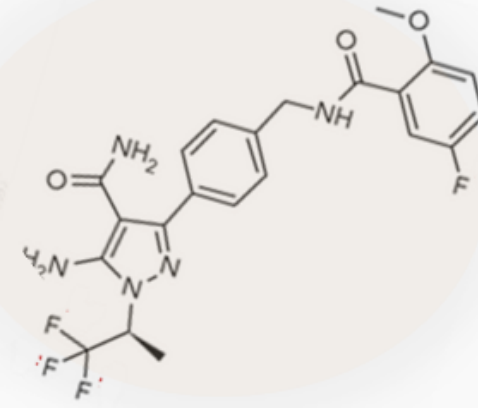
L528W (pseudokinase)

zanubrutinib



NON-COVALENT BTKi

pirtobrutinib



END STAGE PHYLOGENY

L528W and other  
pseudokinases  
(V416L, A428D, M437R)

continuous  
**BTKi**

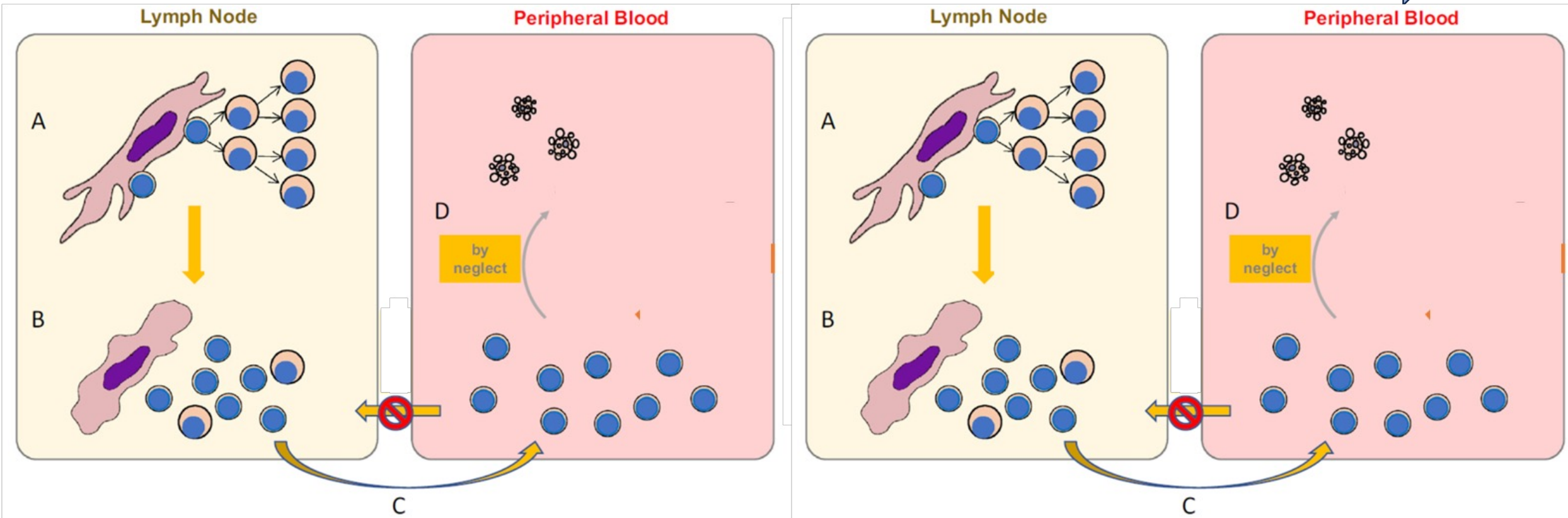
fixed-duration  
**BCL2i+BTKi**

TREATMENT PARADIGMS

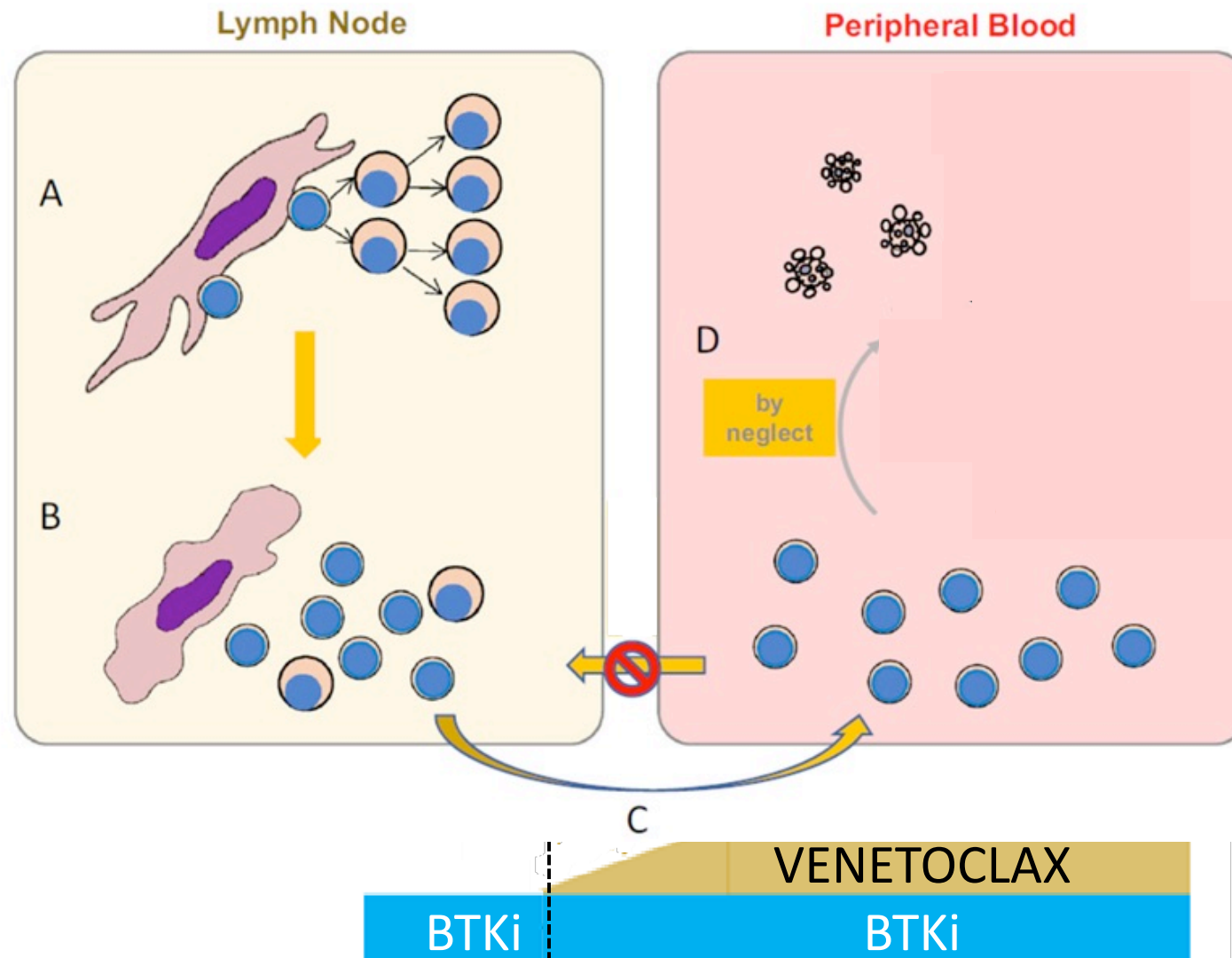


The diagram consists of two light blue rectangular panels. The left panel contains a dark blue circle with the text 'continuous BTKi'. The right panel contains a light blue circle with the text 'fixed-duration BCL2i+BTKi'. A large, light gray arrow points from the right panel to the left panel, with the text 'TREATMENT PARADIGMS' centered on it. On the left end of this arrow, there are four smaller, overlapping light gray arrows pointing to the left, indicating a trend or evolution.

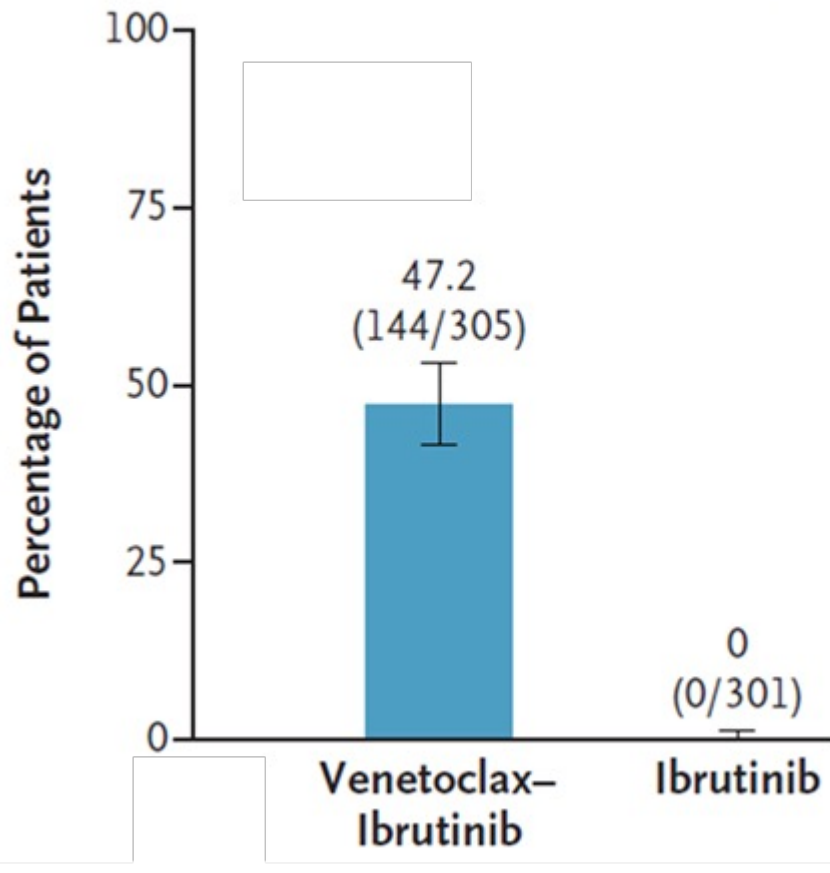
# CONTINUOUS



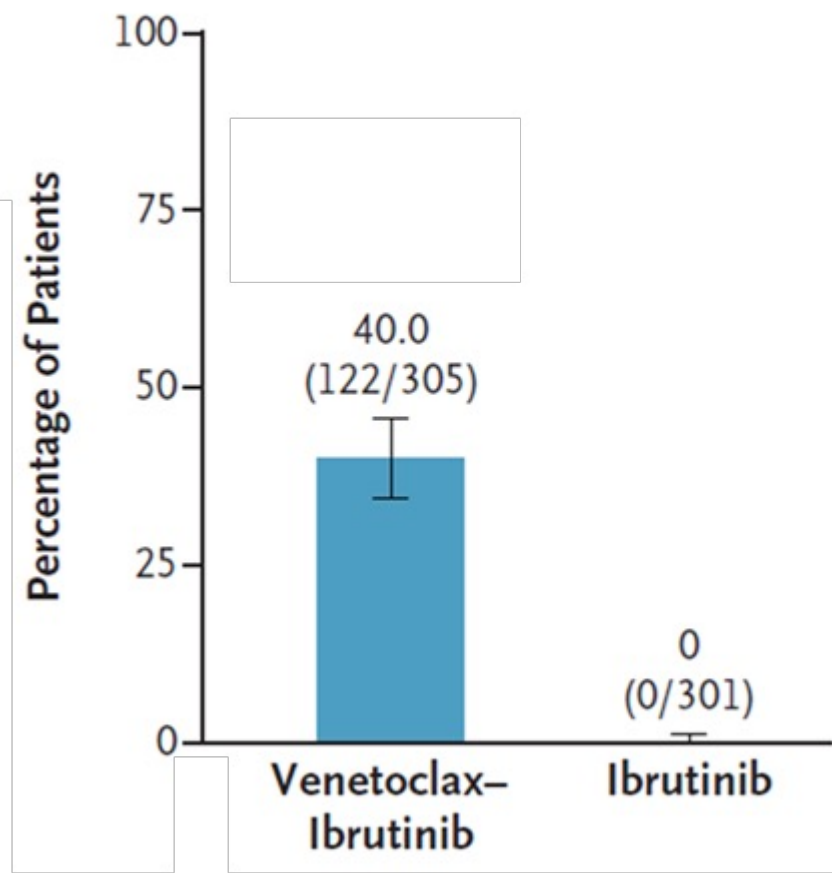
# FIXED DURATION



**A Undetectable MRD in Peripheral Blood**

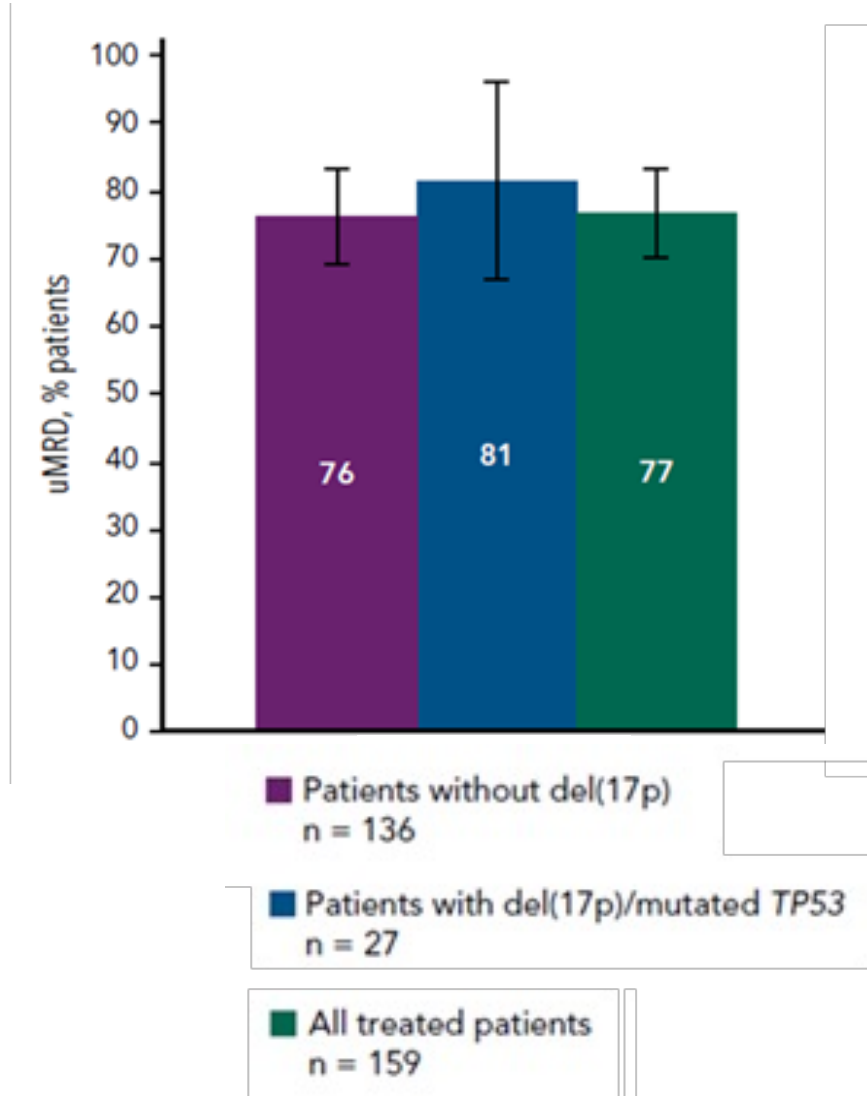


**B Undetectable MRD in Bone Marrow**

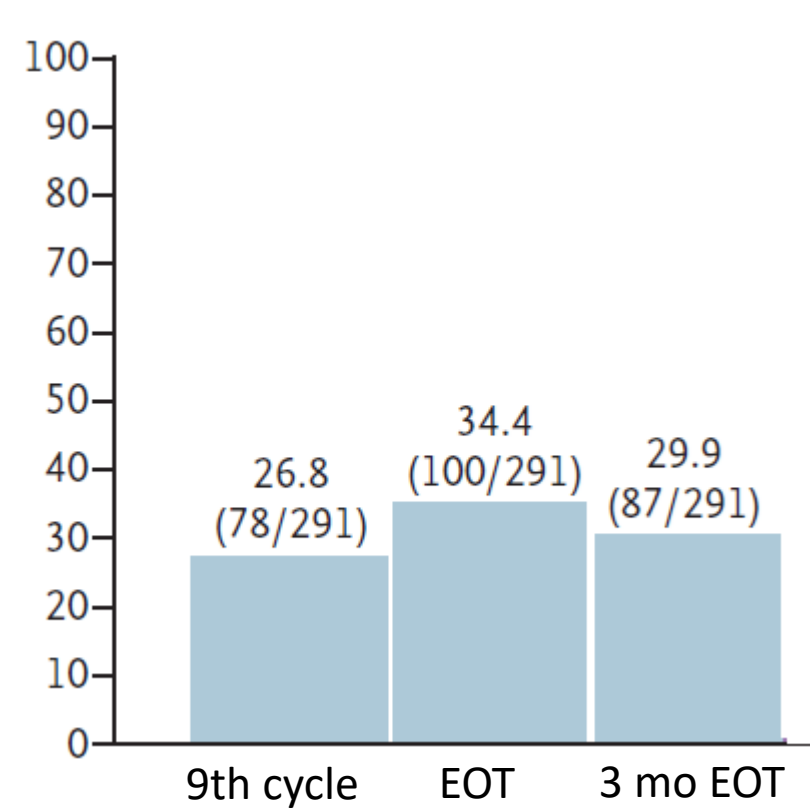


**Would all cBTKi prove equally effective?**

## CAPTIVATE (I+ V)




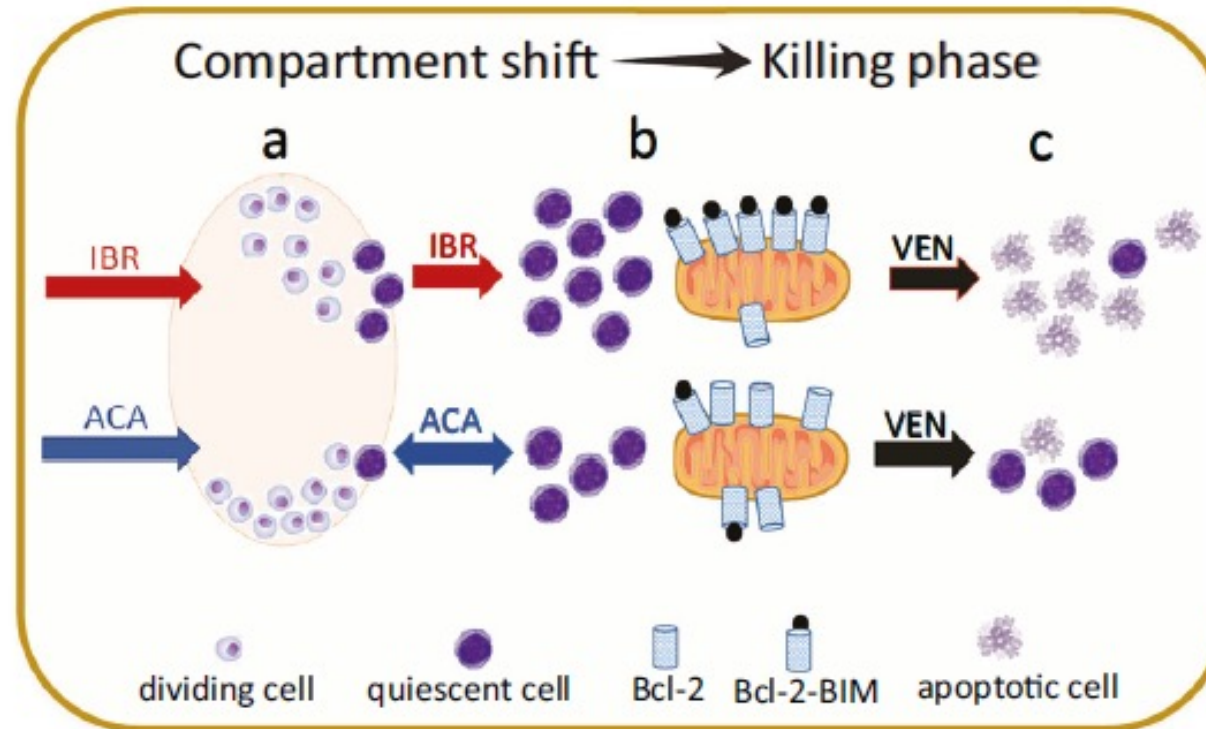
## AMPLIFY (A+ V)



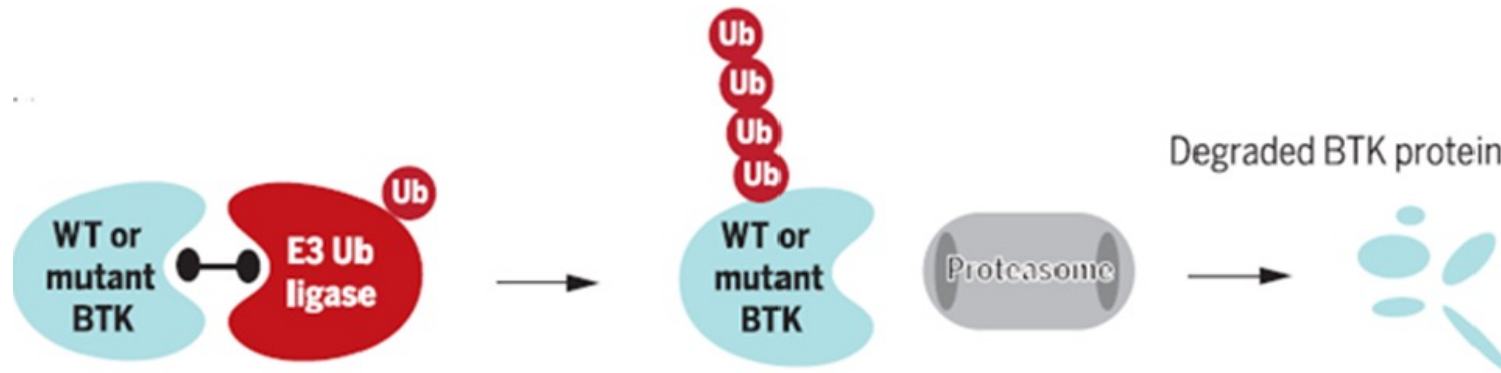
**PERSPECTIVE**

# Fixed-duration therapy of chronic lymphocytic leukemia with venetoclax and Bruton tyrosine kinase inhibitors: an insight into differences between ibrutinib and acalabrutinib

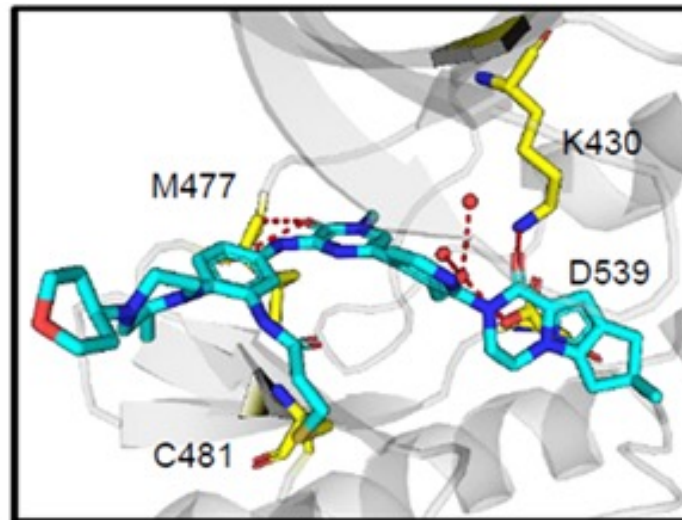
Alessandra Tedeschi<sup>1</sup>, Anna Maria Frustaci<sup>1</sup>, Pierantonio Menna <sup>2</sup> and Giorgio Minotti <sup>3</sup>✉



# DEGRADERS



# DUAL MODE BTKi



# SOME CONCLUSIONS

Pharmacokinetics and pharmacodynamics are intimately intertwined

Exposure-efficacy relationships build on PK governing target engagement, and hence PD

Phylogeny dictates off target effects, and hence toxicity

Continuous vs fixed duration

Future drugs

