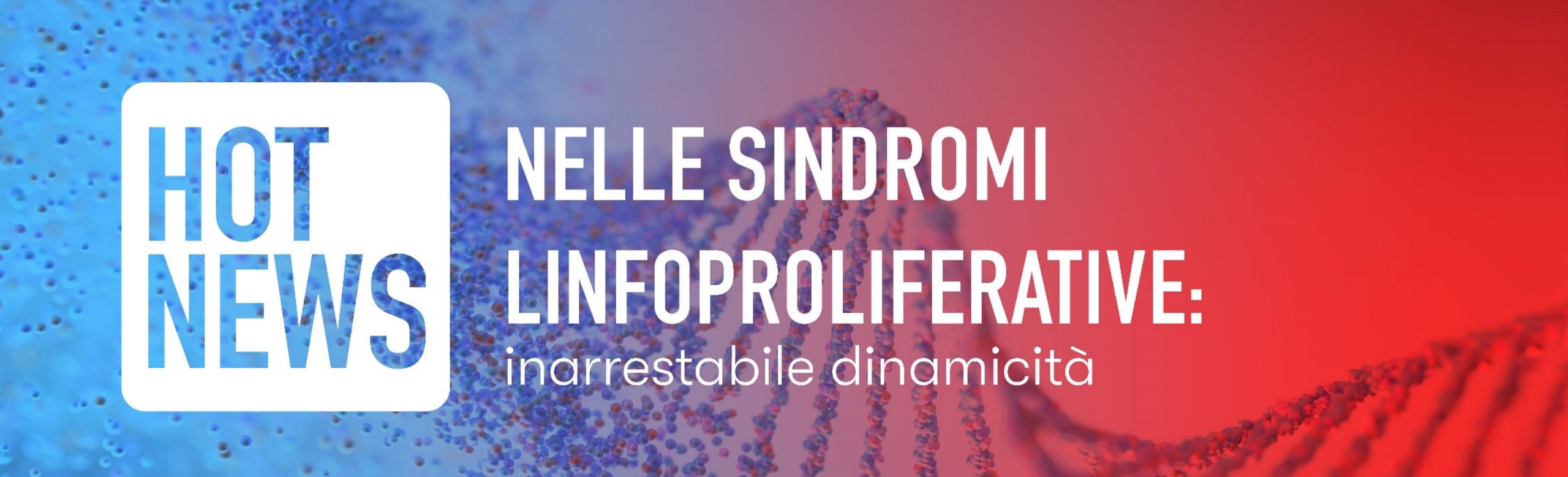




**HOT
NEWS**

NELLE SINDROMI LINFOPROLIFERATIVE: inarrestabile dinamicità

**La tossicità cardiologica dei BTKi e l'impatto sull'aspetto della gestione terapeutica:
il punto di vista del farmacologo clinico**

Giorgio Minotti

Università e Fondazione Policlinico Campus Bio-Medico di Roma

PALERMO

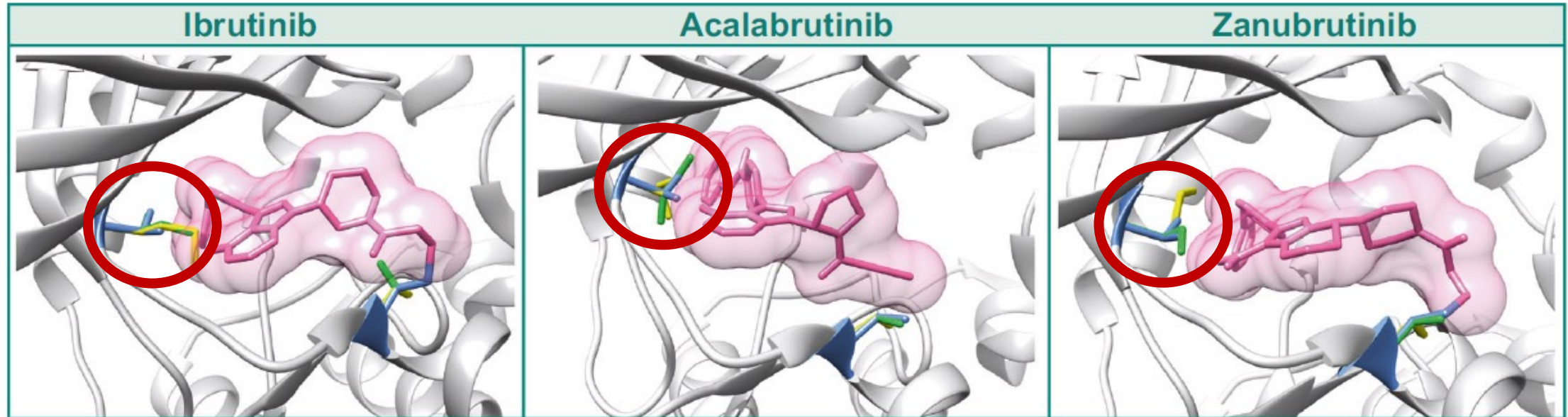
2 Settembre 2024

Hotel NH Palermo

DISCLOSURES

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen					X	X	
Incyte	X		X			X	
BeiGene			X		X		
Servier			X			X	
Astellas							
Eli Lilly					x		

They all bind to Cys 481 in the kinase domain of BTK



Leukemia (2021) 35:1317–1329

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

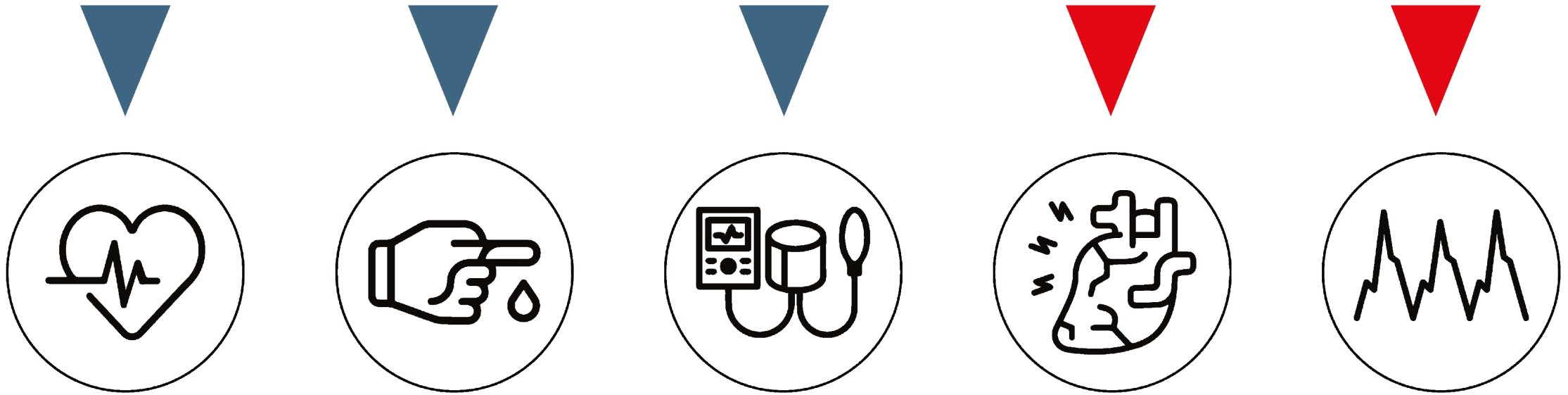
Phylogeny of Tec Family Kinases: Identification of a Premetazoan Origin of Btk, Bmx, Itk, Tec, Txk, and the Btk Regulator SH3BP5

Advances in Genetics, Vol. 64

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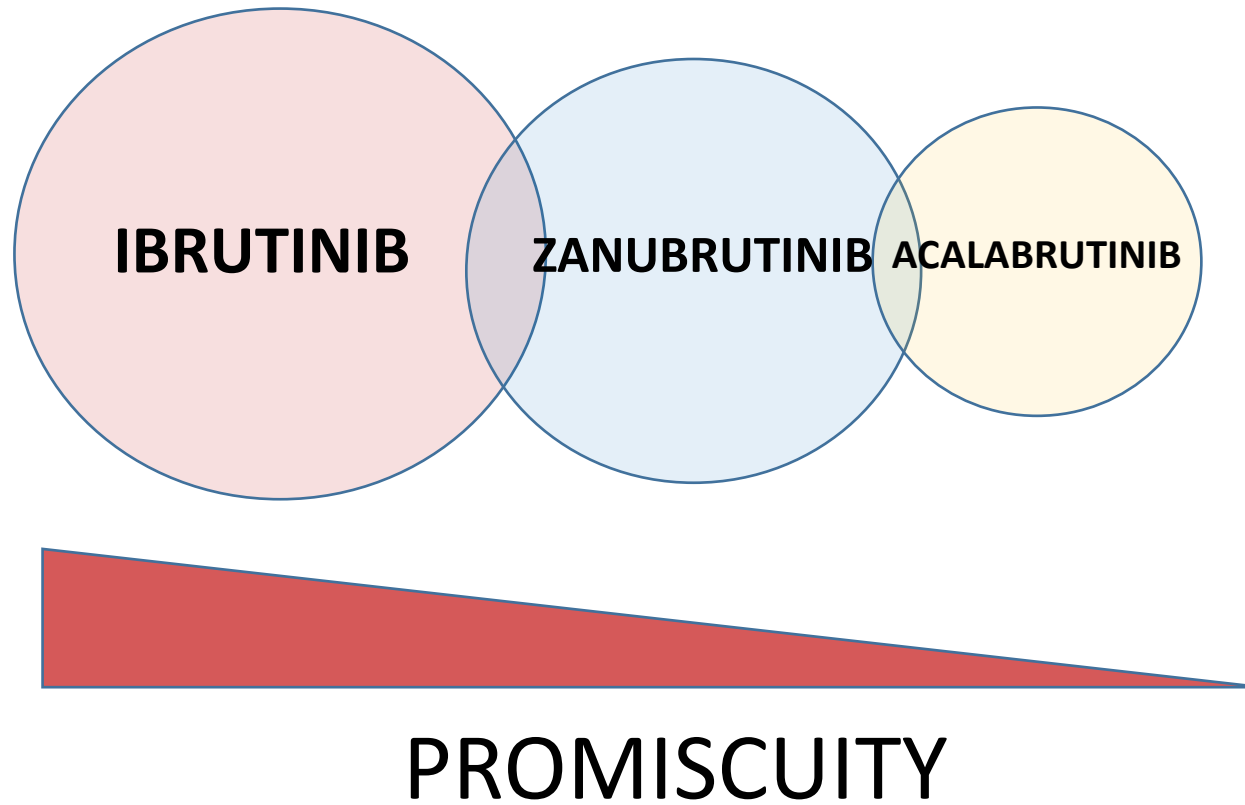
- BTK highly homologous to many other kinases (including members of TEC and Src super families)
- Cys481 in 9 other kinases (including HER2/HER4)
- Druggable cysteines in >200 other kinases

CV EFFECTS ASSOCIATED WITH COVALENT BTKi

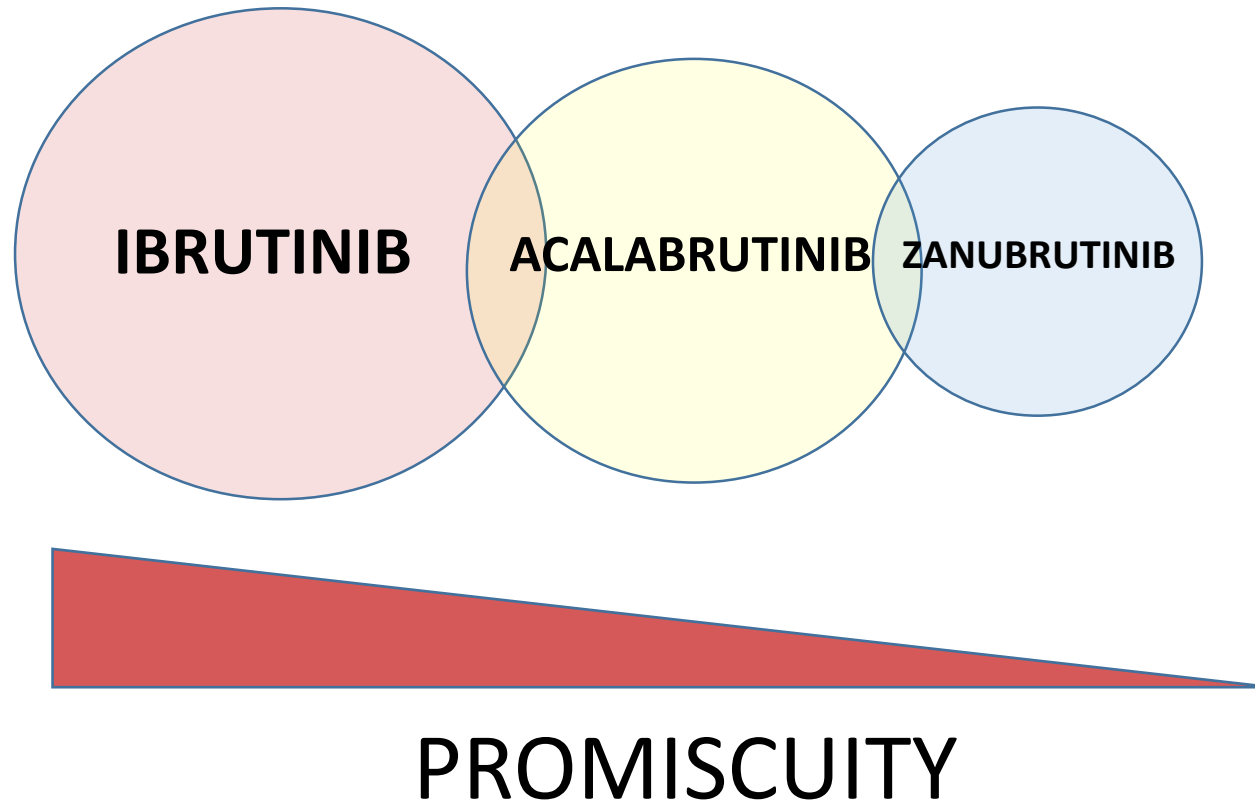


Likely *off target* effects, certainly *class effects*

WHO DOES MORE?



WHO DOES MORE?



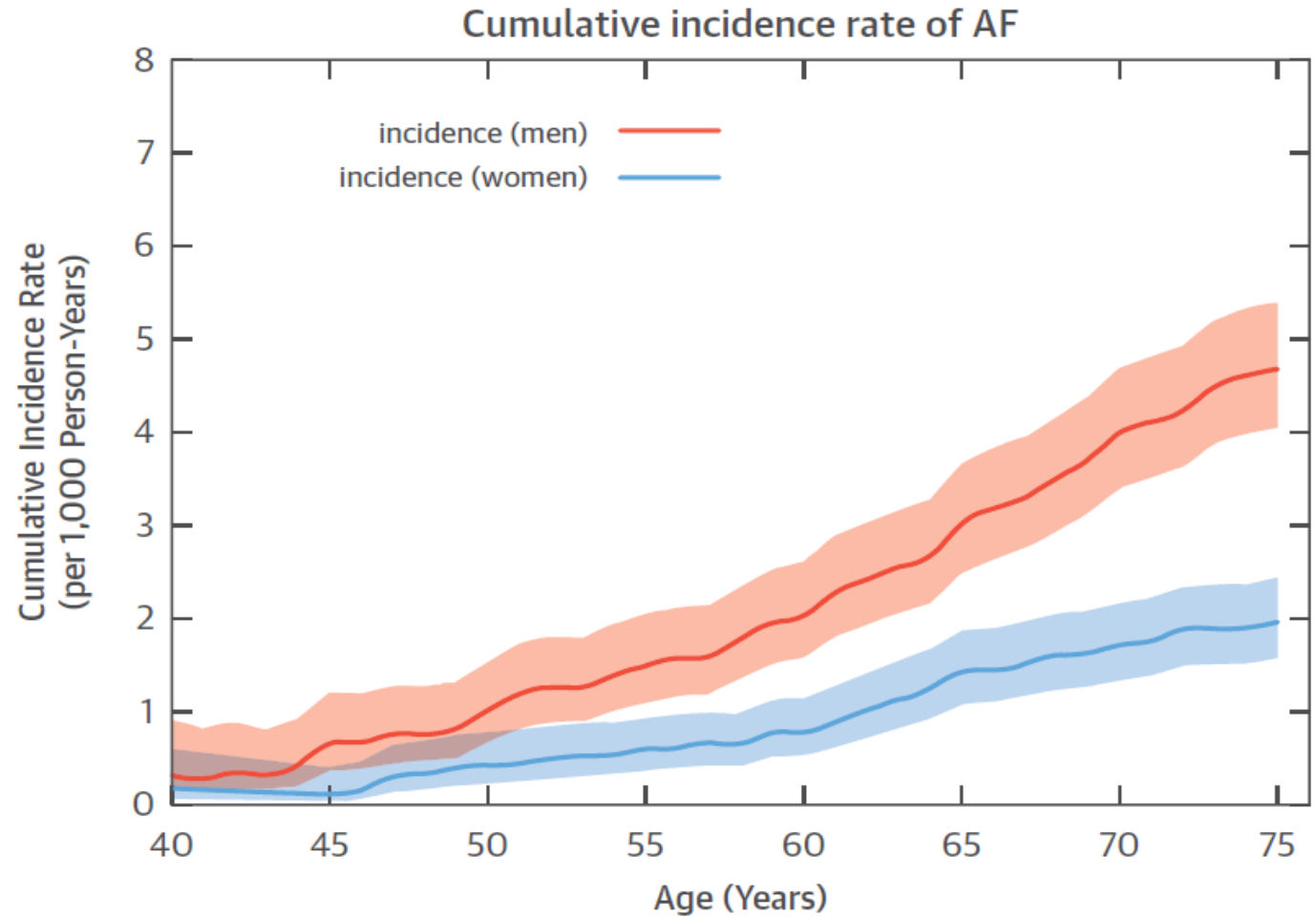
UNSETTLED TECHNICAL PROBLEMS

- Shadman M et al. Lancet Haematol, 2022
- Podoll et al. J Pharmacol Exp Ther, 2023
- Minotti, Blood Adv, 2024

THE PATIENT

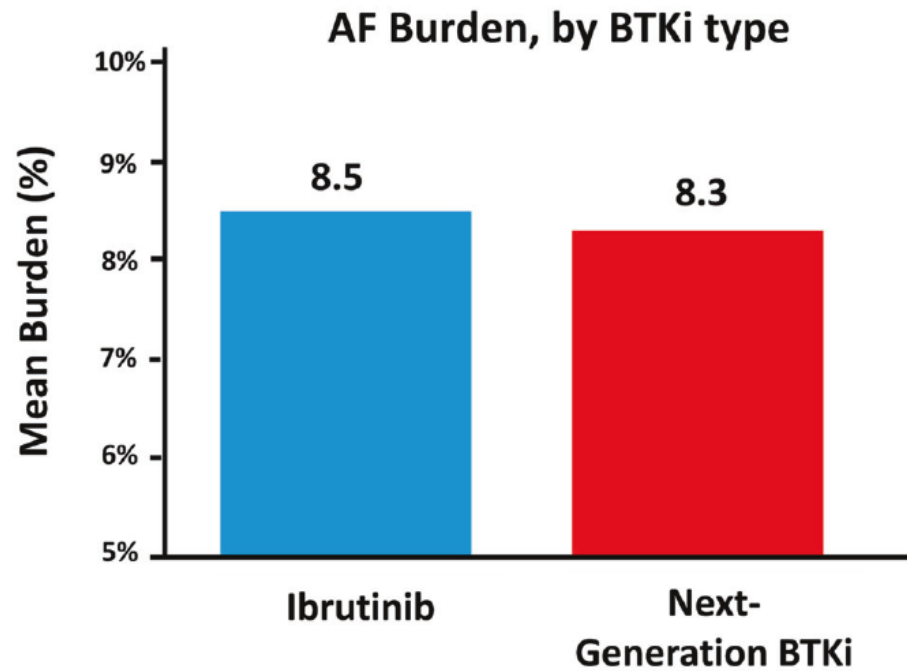


Age, pre-existing or
expected CV
morbidity

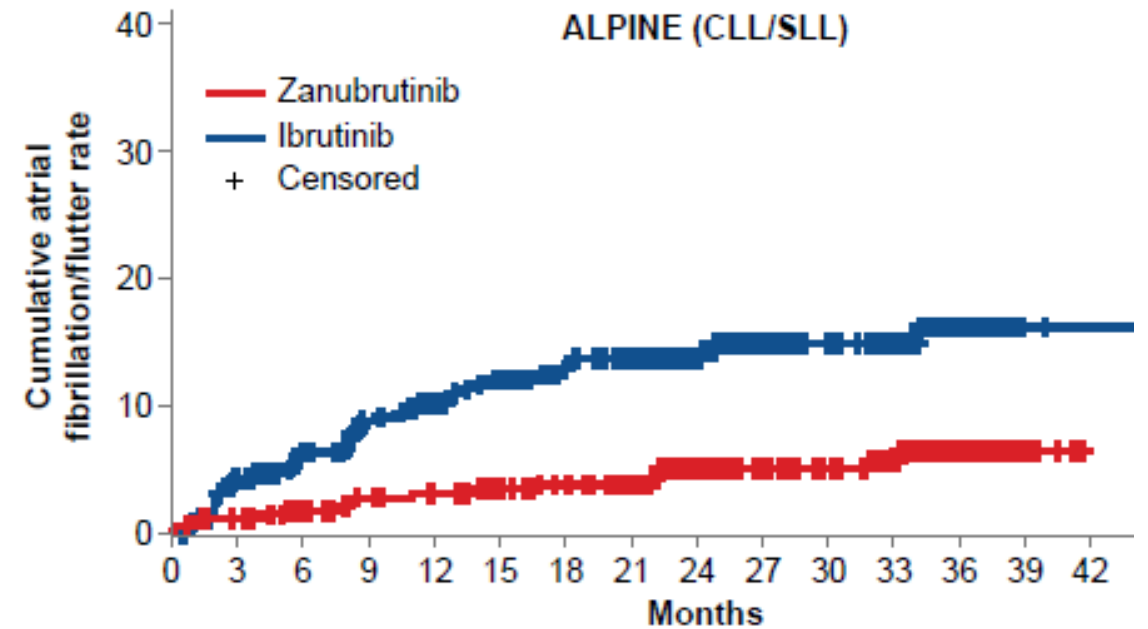


J Am Coll Cardiol; 66:1000-1007, 2015

CULPRITS OF CONFUSION

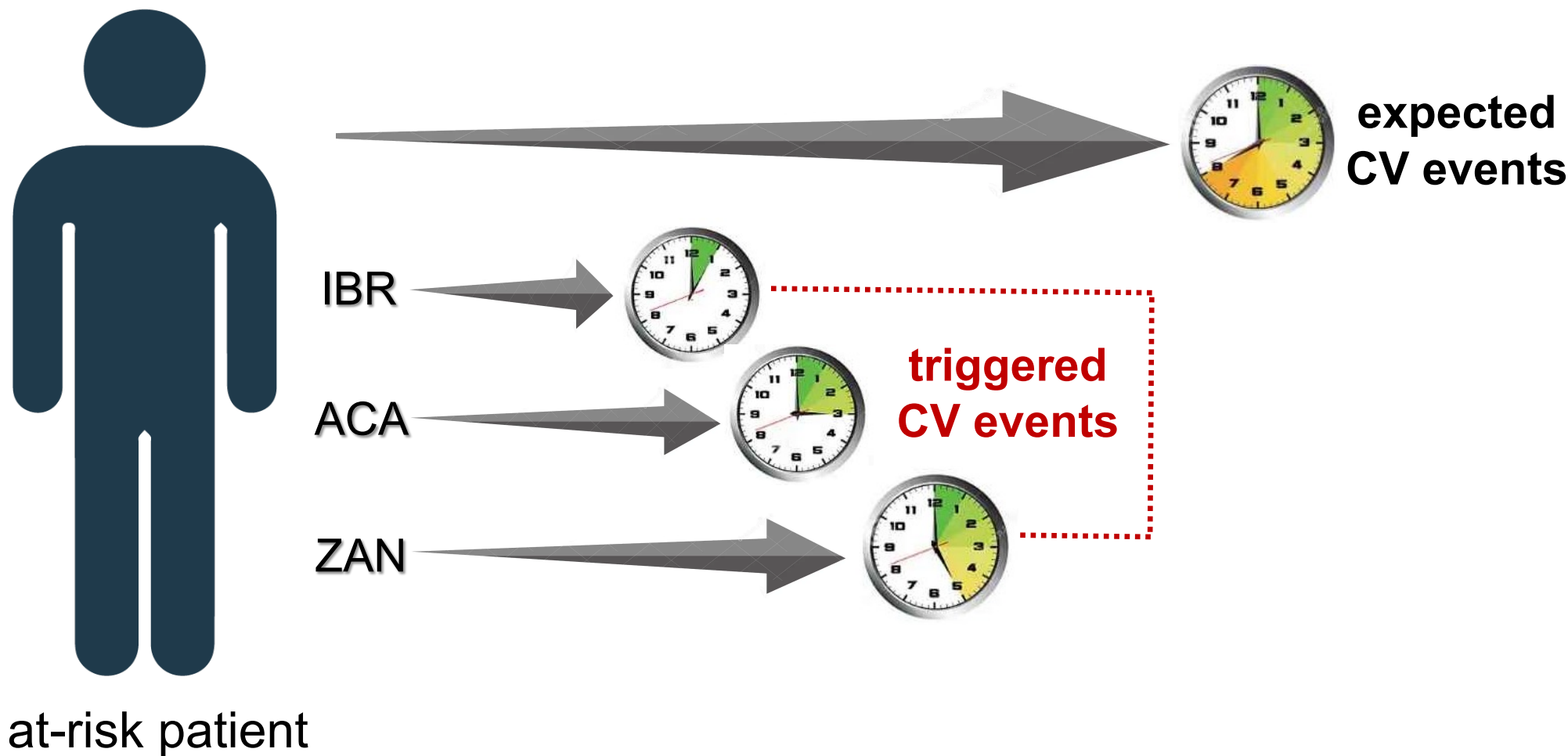


Leukemia; <https://doi.org/10.1038/s41375-024-02334-3>

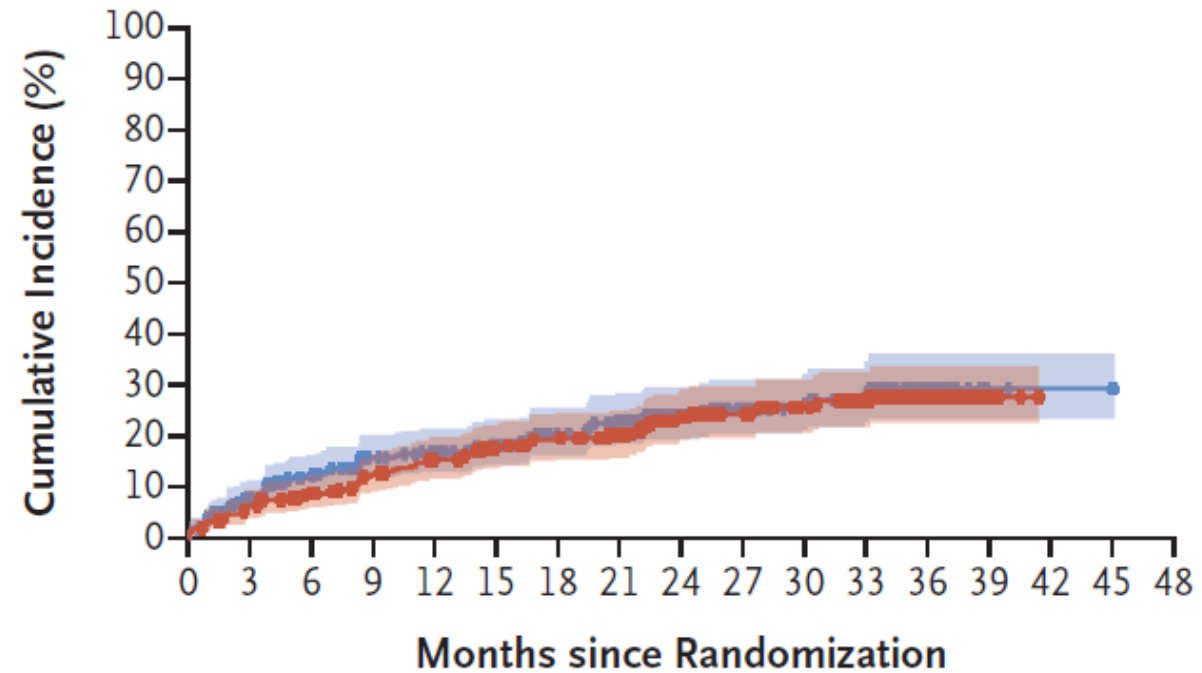


Blood Adv; <https://doi:10.1182/bloodadvances.2023011641>

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



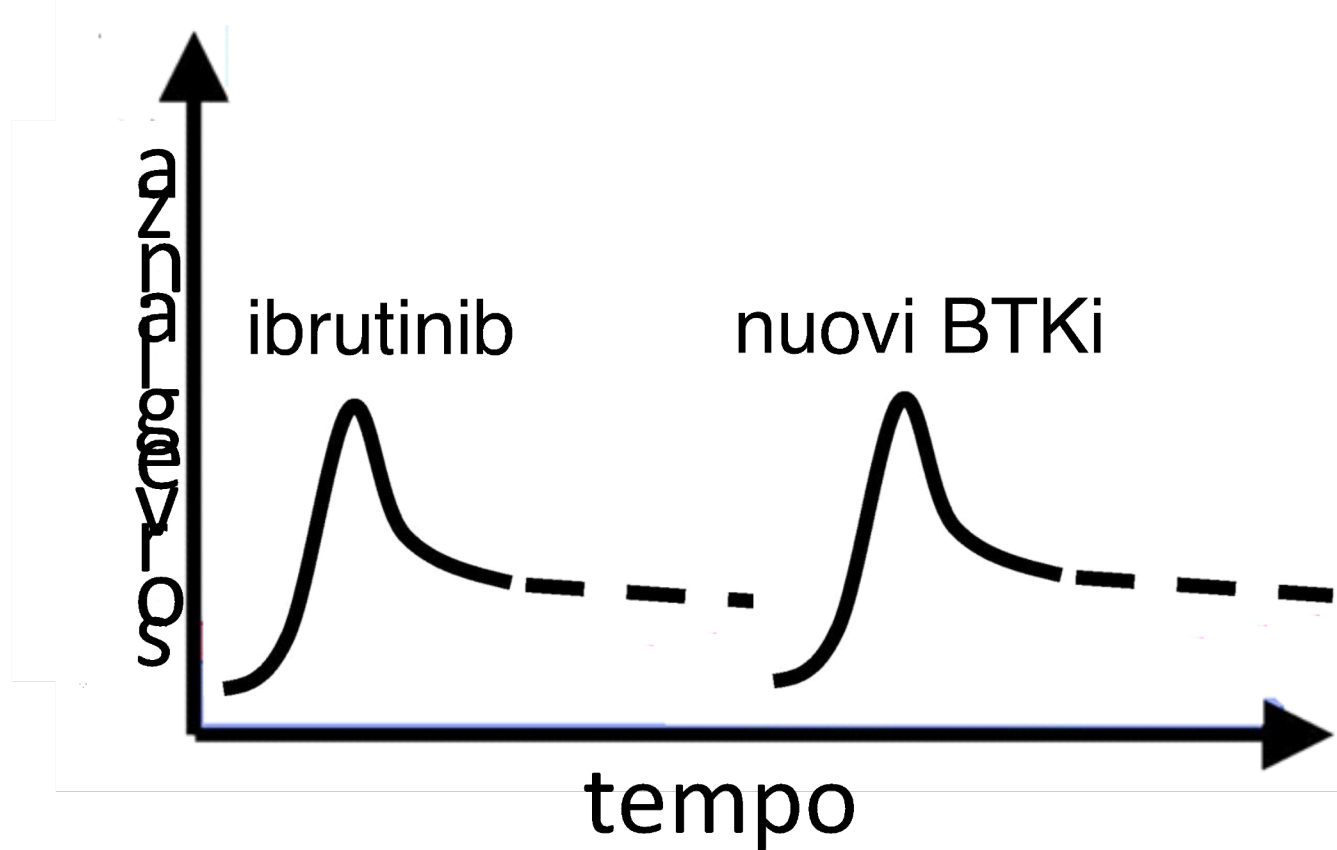
THE ALPINE CASE



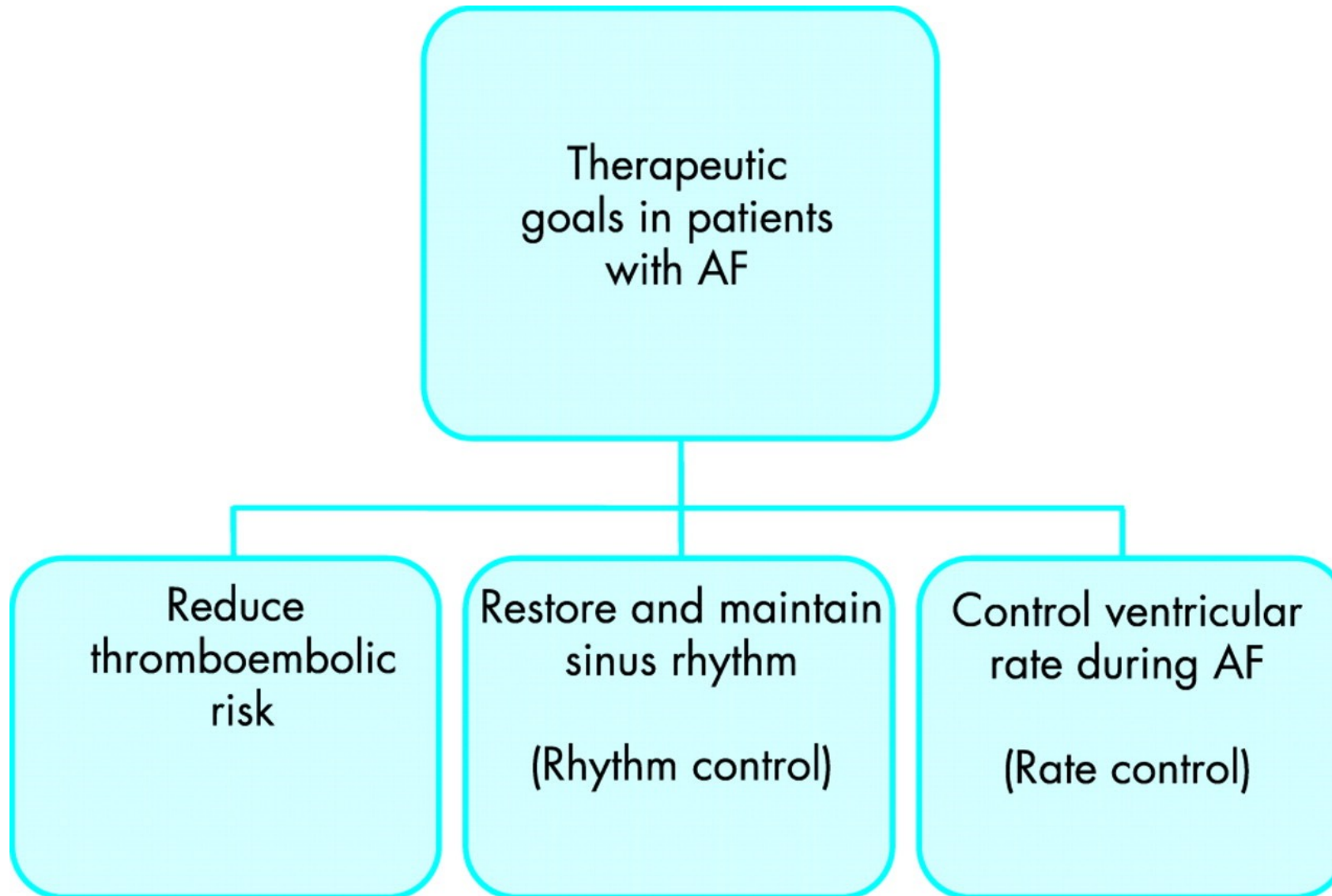
N ENGL J MED 388;4 NEJM.ORG JANUARY 26, 2023

HOW TO MANAGE *CLASS EFFECTS* OF BTKi

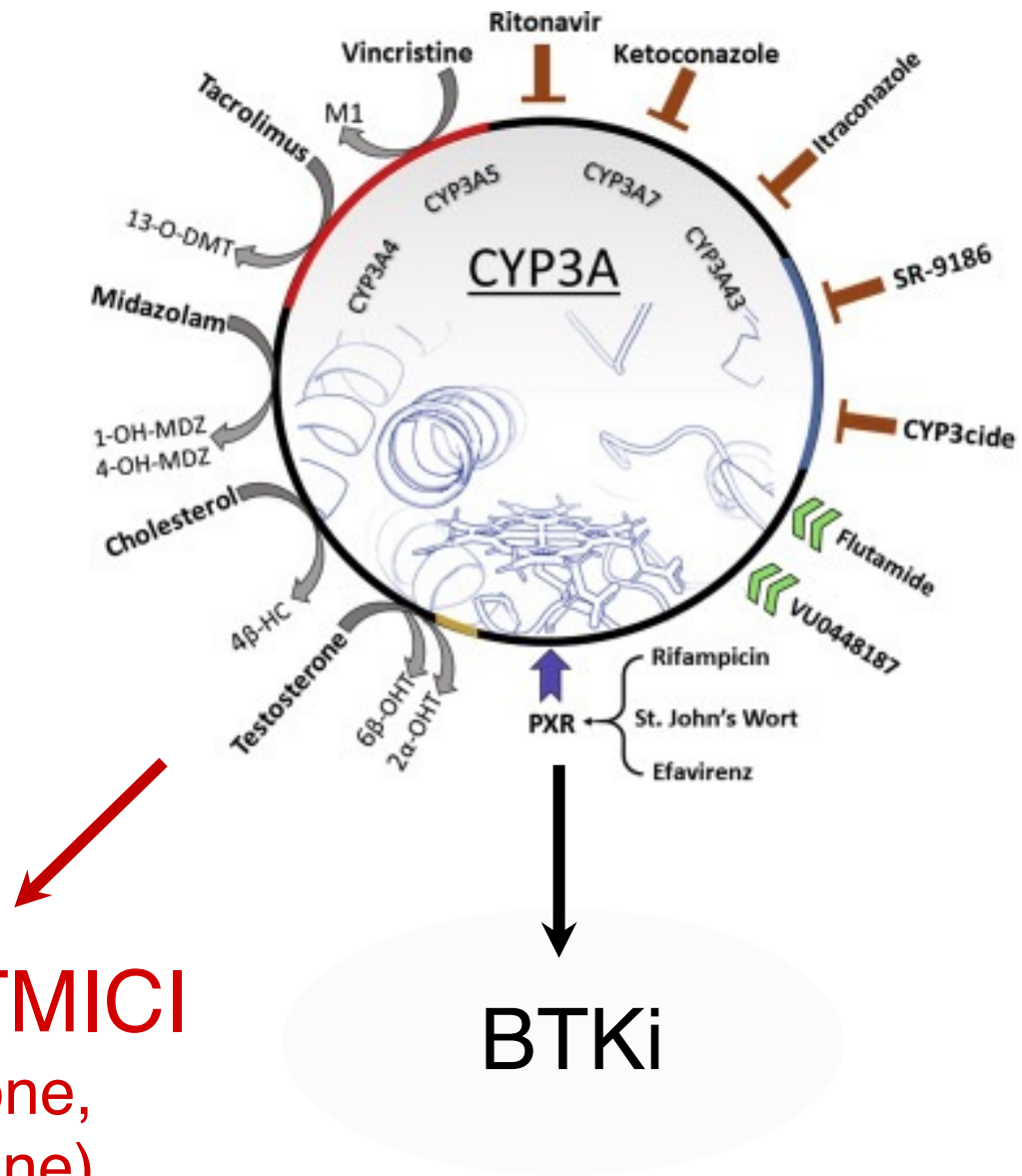
1. TAILOR YOUR AGENDA TO DRUG CHARACTERISTICS



2. TAILOR YOUR CHOICES TO DDI RISK



ANTIARITMICI
(amiodarone,
propafenone)



DESETIL-AMIODARONE

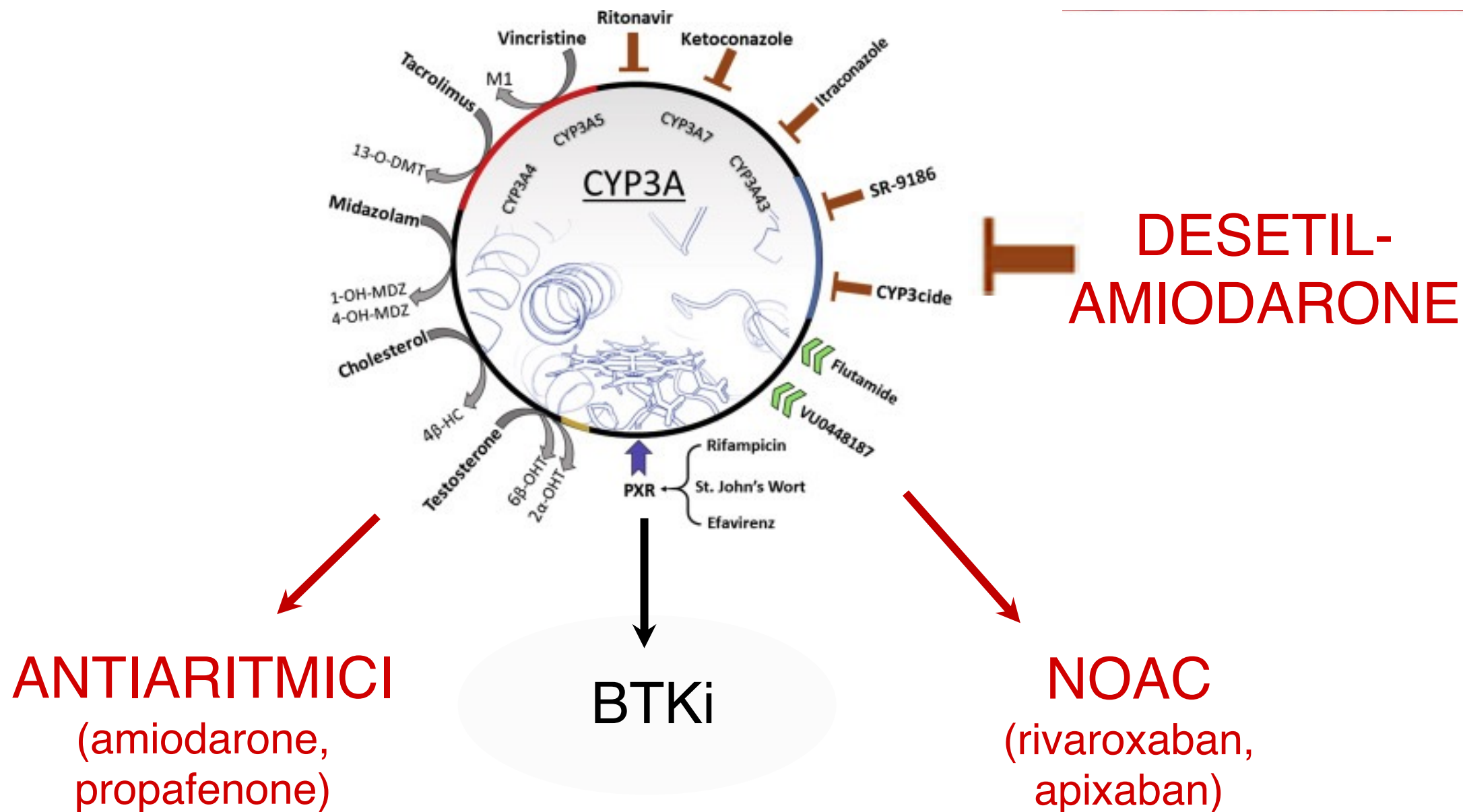
BTKi

Concomitant Treatment with Ibrutinib and Amiodarone Causing Reversible Heart Failure Syndrome

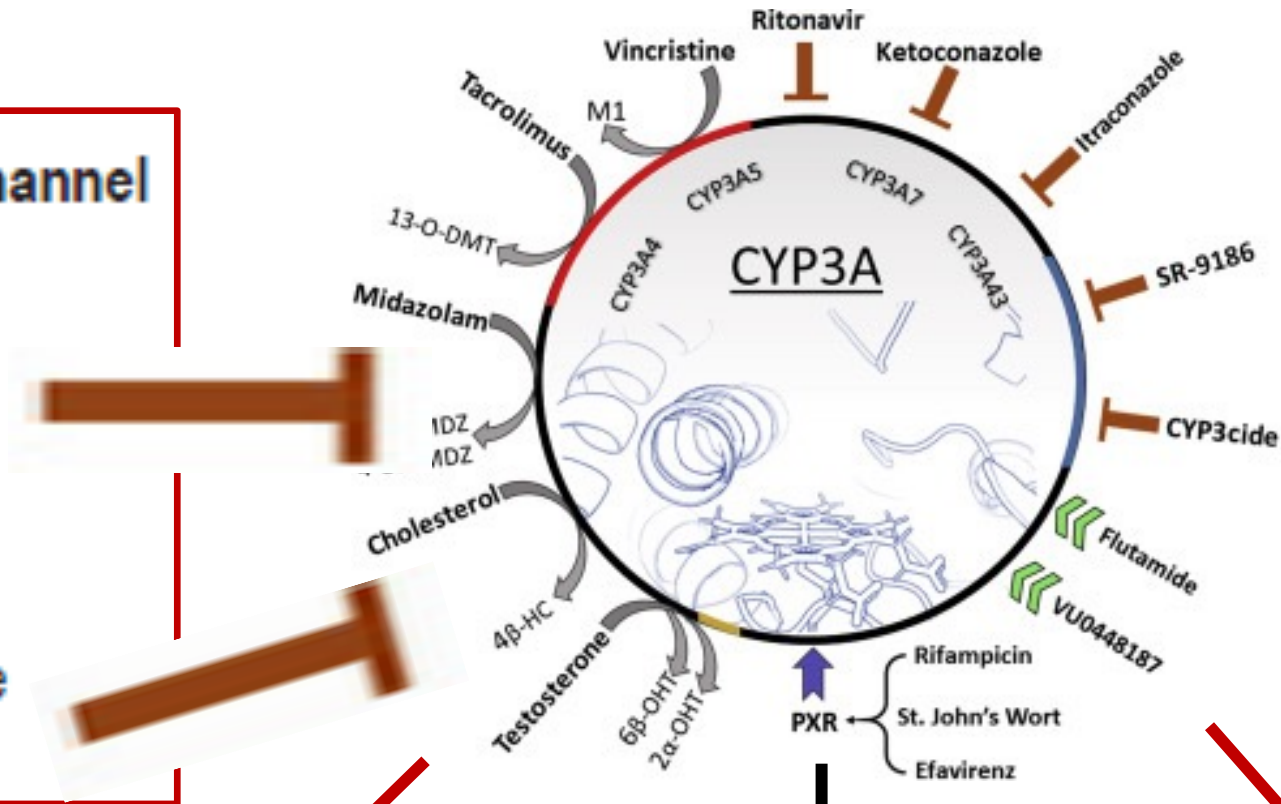
Yishay Wasserstrum MD^{1,3}, Pia Raanani MD^{2,3}, Ran Kornowski MD^{1,3} and Zaza Iakobishvili MD PhD^{1,3}

¹Department of Cardiology, Rabin Medical Center (Beilinson Campus) and ²Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel

³Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel



Calcium channel blockers
Amlodipine
Diltiazem
Felodipine
Nifedipine
Nisoldipine
Nitrendipine
Verapamil



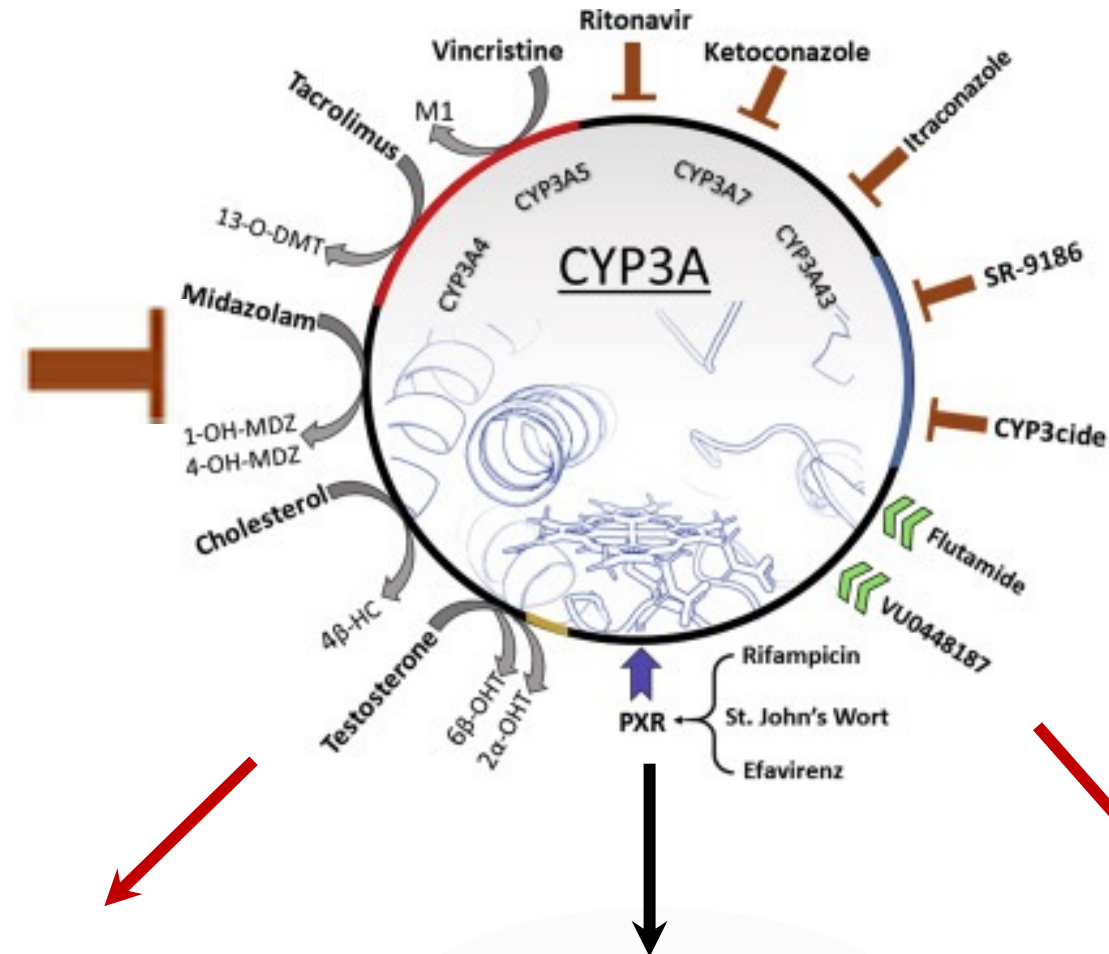
DESETIL-AMIODARONE

ANTIARITMICI
(amiodarone, propafenone)

BTKi

NOAC
(rivaroxaban, apixaban)

ANTIFUNGINI
(>>triazolici)



DESETIL-AMIODARONE

ANTIARITMICI
(amiodarone,
propafenone)

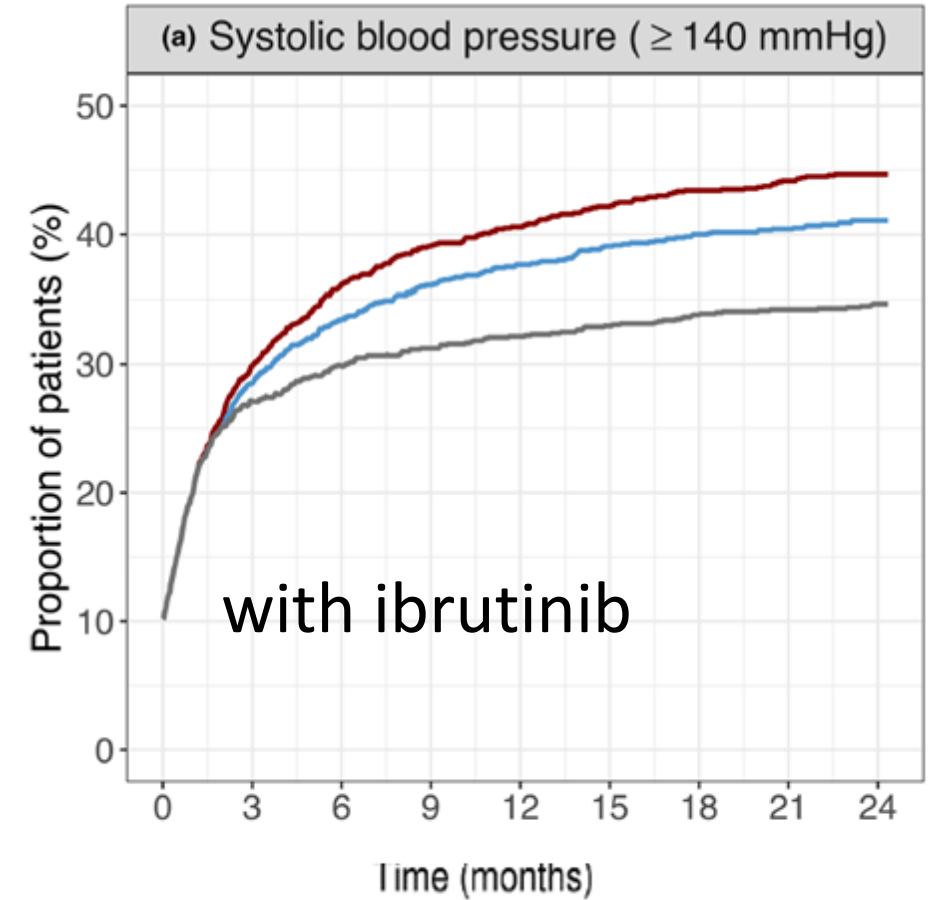
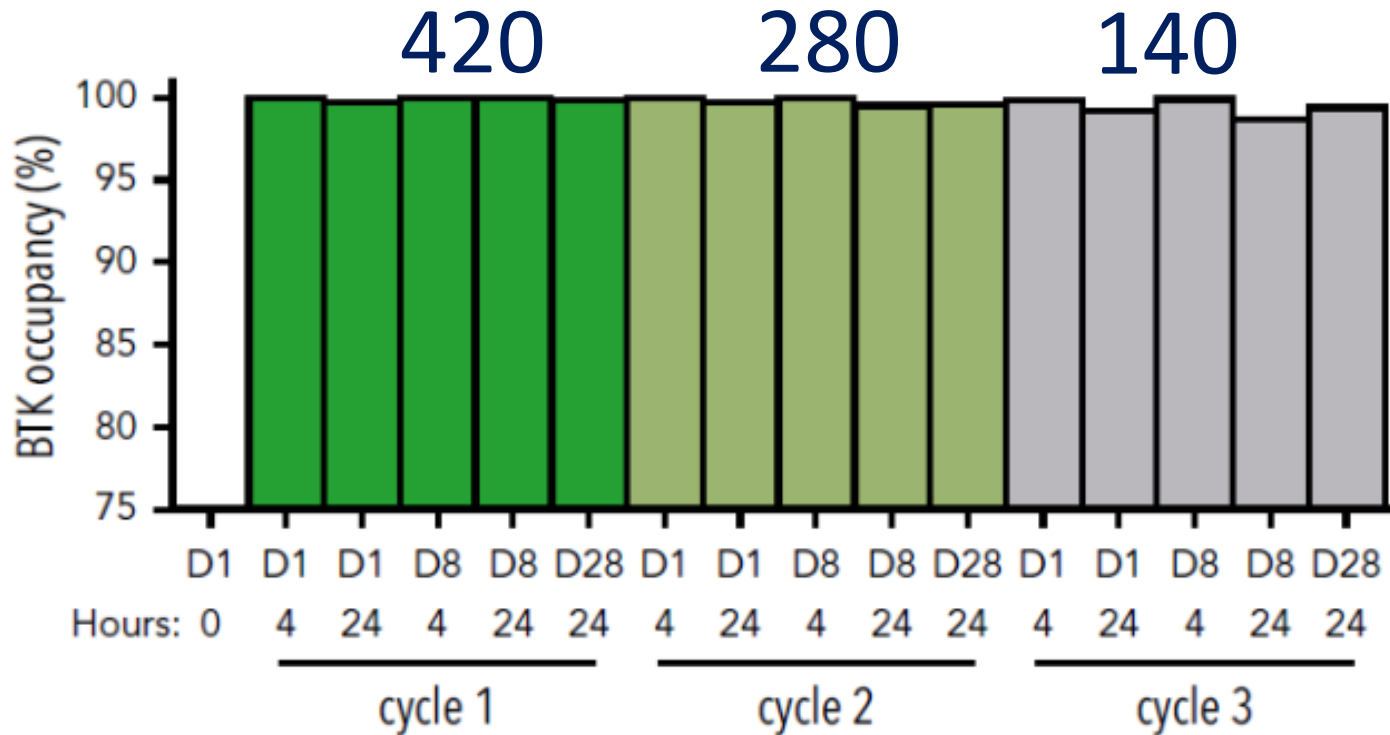
BTKi

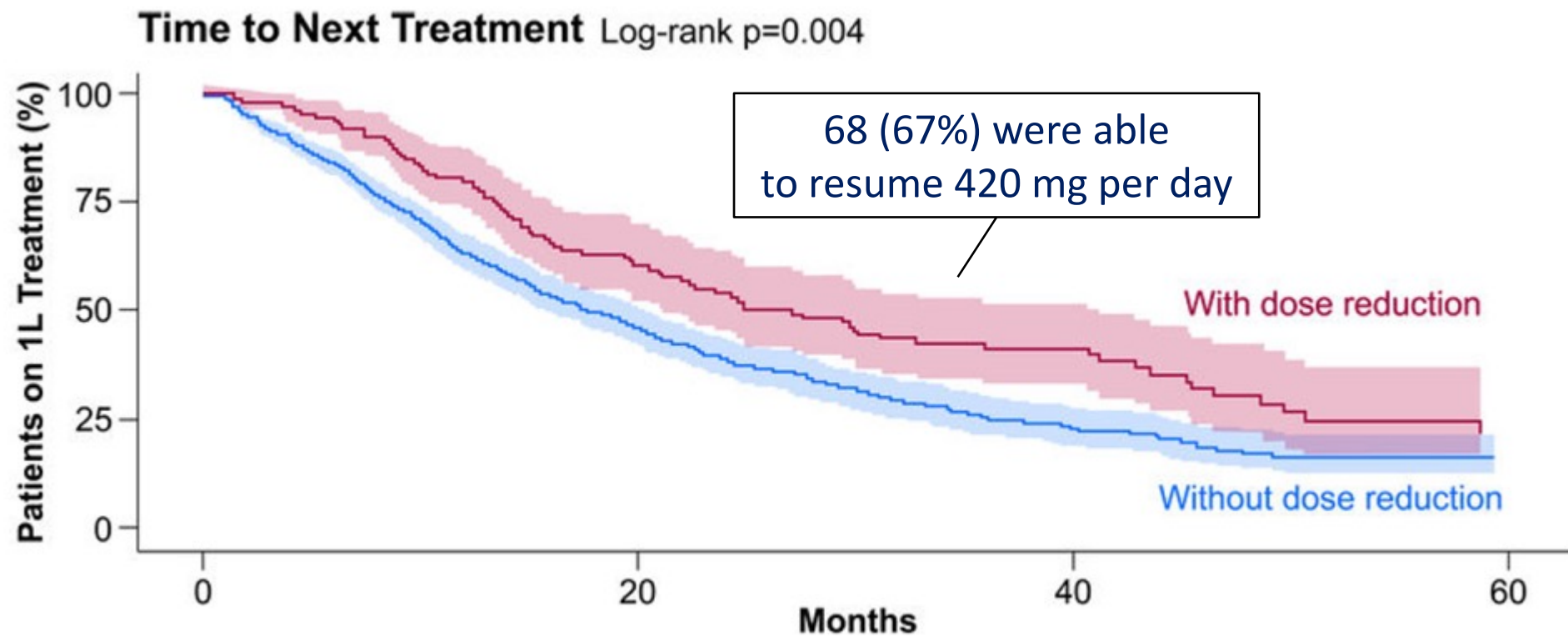
NOAC
(rivaroxaban,
apixaban)



Co-administered CYP3A Inhibitor	Increase in $C_{\max}$	
	<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%

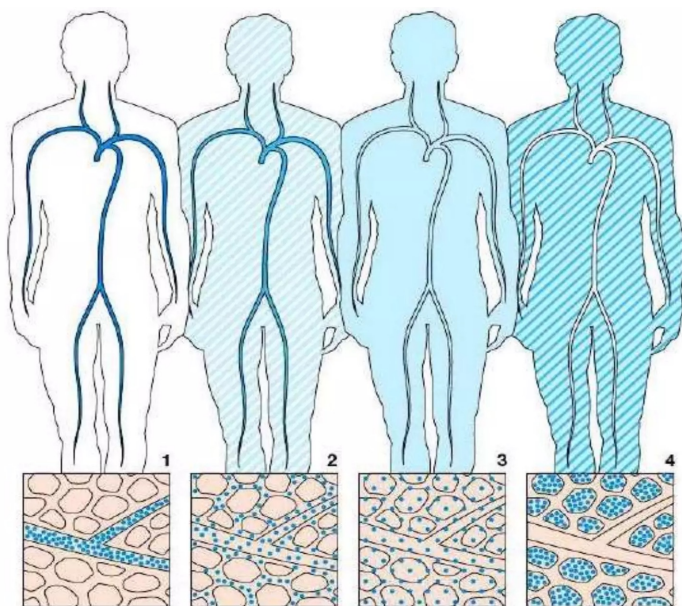
3. DOSE REDUCTIONS





Blood 142 (2023) 269–270

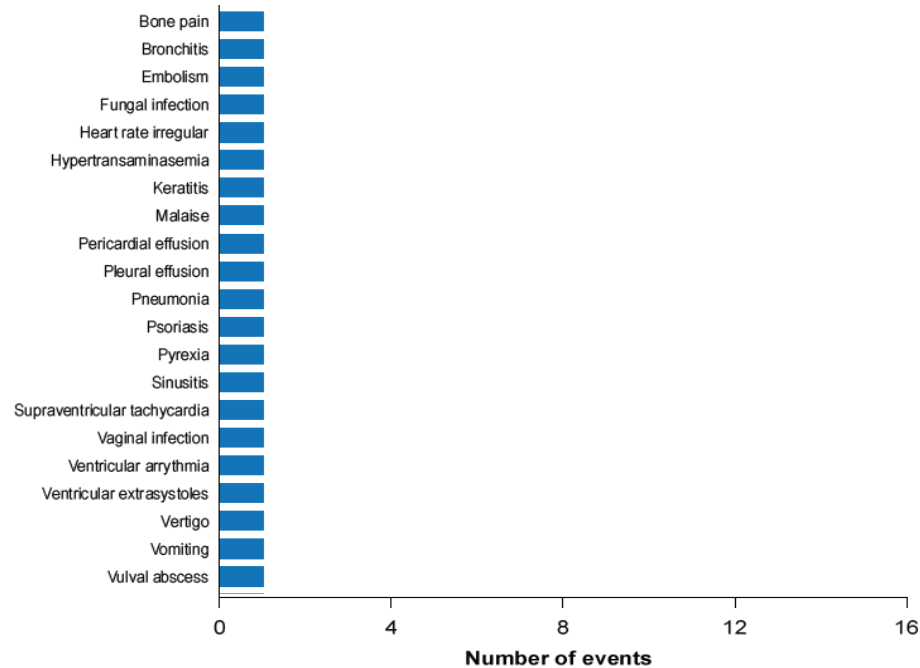
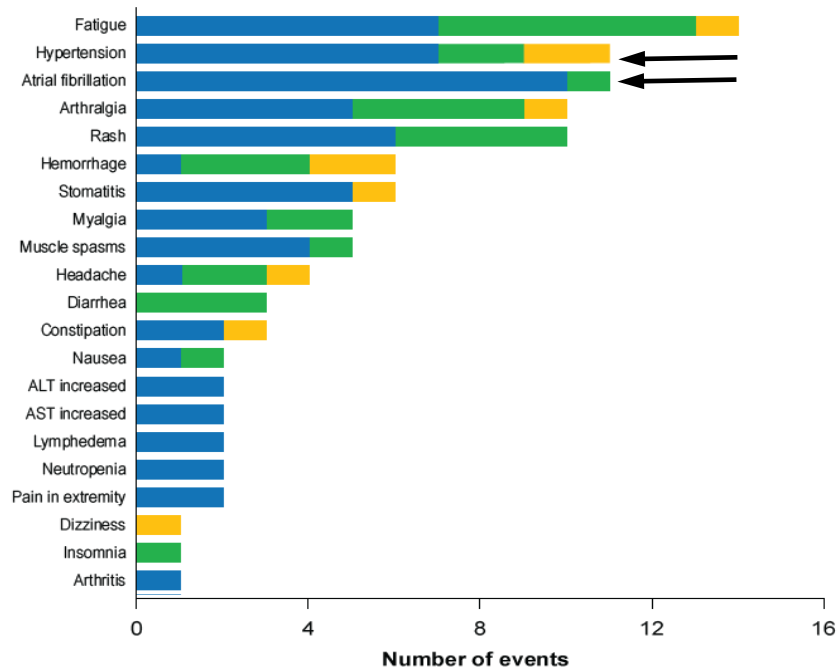
3. DOSE REDUCTIONS: A CAUTIONARY NOTE



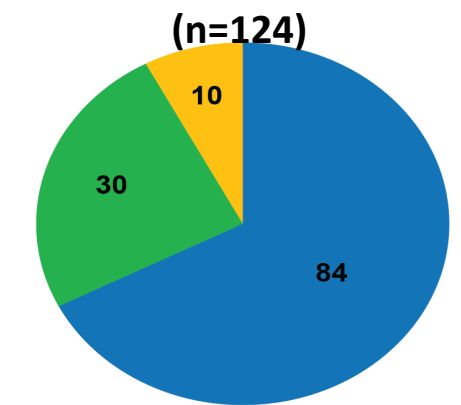
BTKi	Vd (L)
Ibrutinib	683
Acalabrutinib	723
Zanubrutinib	881

Blood Lymph Cancer: Targets Ther 2023,13: 67–76;
Expert Opin Drug Metab Toxicol. 2016,12: 1381–1392;
J Clin Pharmacol 2022, 62: 812–822

4. SWITCH TO ANOTHER BTKi



Total Intolerance Events



- Did not recur
- Recurred at lower grade
- Recurred at same grade
- Recurred at higher grade^a

ZANUBRUTINIB

BGB-3111-215

UPDATED SAFETY AND EFFICACY RESULTS OF ZANUBRUTINIB IN PATIENTS WITH B-CELL MALIGNANCIES WHO ARE INTOLERANT OF IBRUTINIB AND/OR ACALABRUTINIB

Shadman M et al. Poster presented at the 2023 European Hematology Association 2023 conference; abstract number: P683

SOME CONCLUSIONS

- Class effects
- Pharmacologically manageable with due caution
- Surveillance, dose reductions, switch to another BTKI
- Adesso tocca al cardiologo