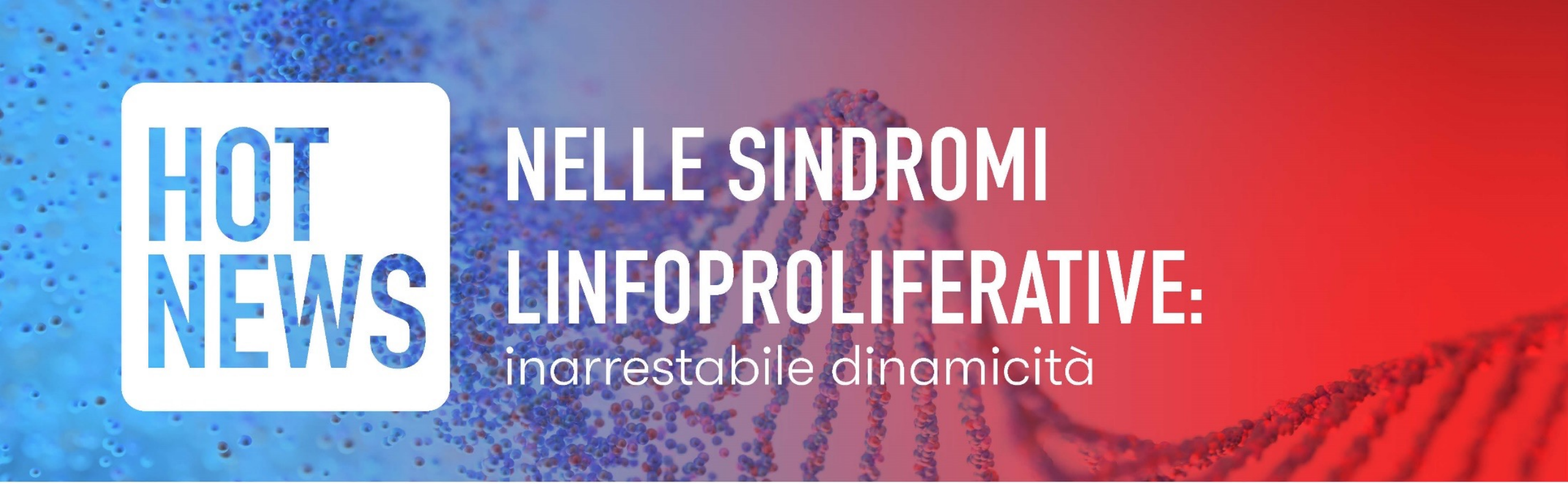


La tossicità cardiologica dei BTKi e l'impatto sull'aspetto della gestione terapeutica: il punto di vista del farmacologo clinico

Giorgio Minotti

Università e Fondazione Policlinico Campus Bio-Medico di Roma

GENOVA

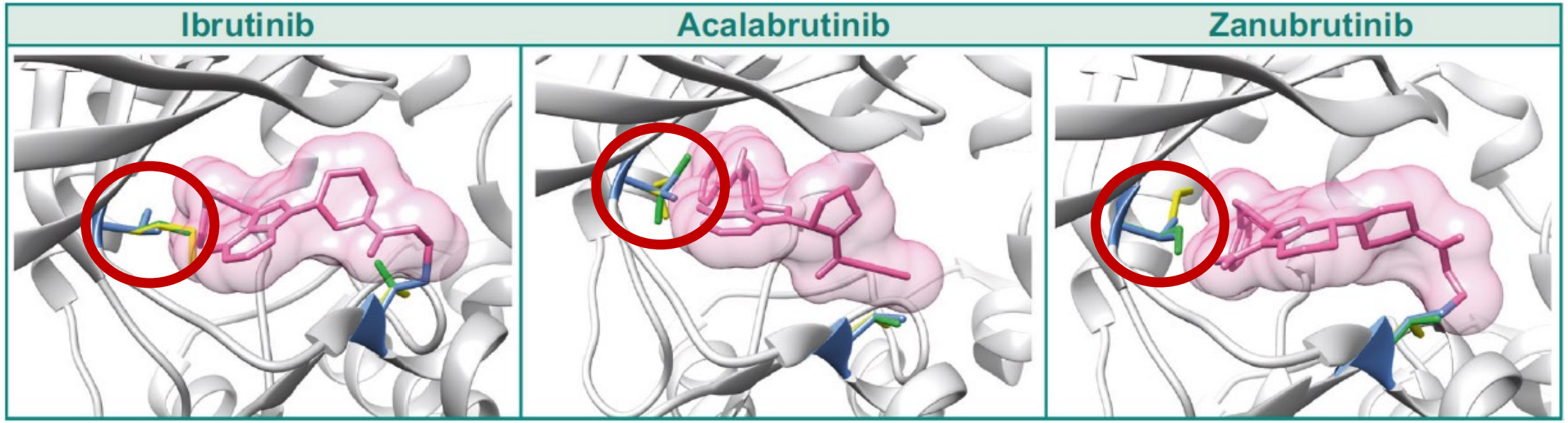
17 Luglio 2024

NH Collection Genova Marina

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		

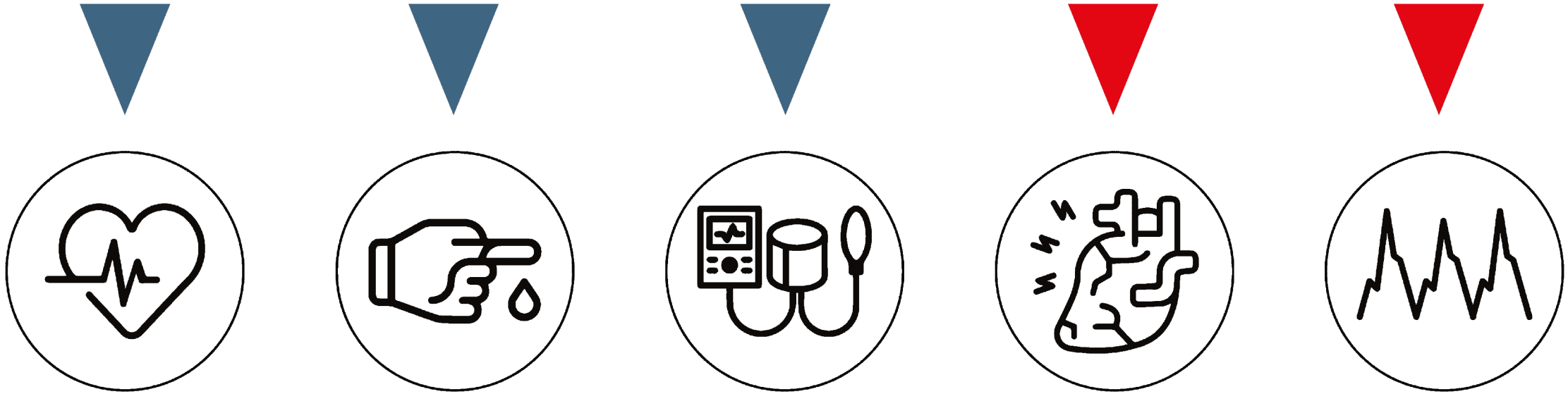
They all bind to Cys 481 in the kinase domain of BTK



Leukemia (2021) 35:1317–1329
https://doi.org/10.1038/s41375-021-01123-6

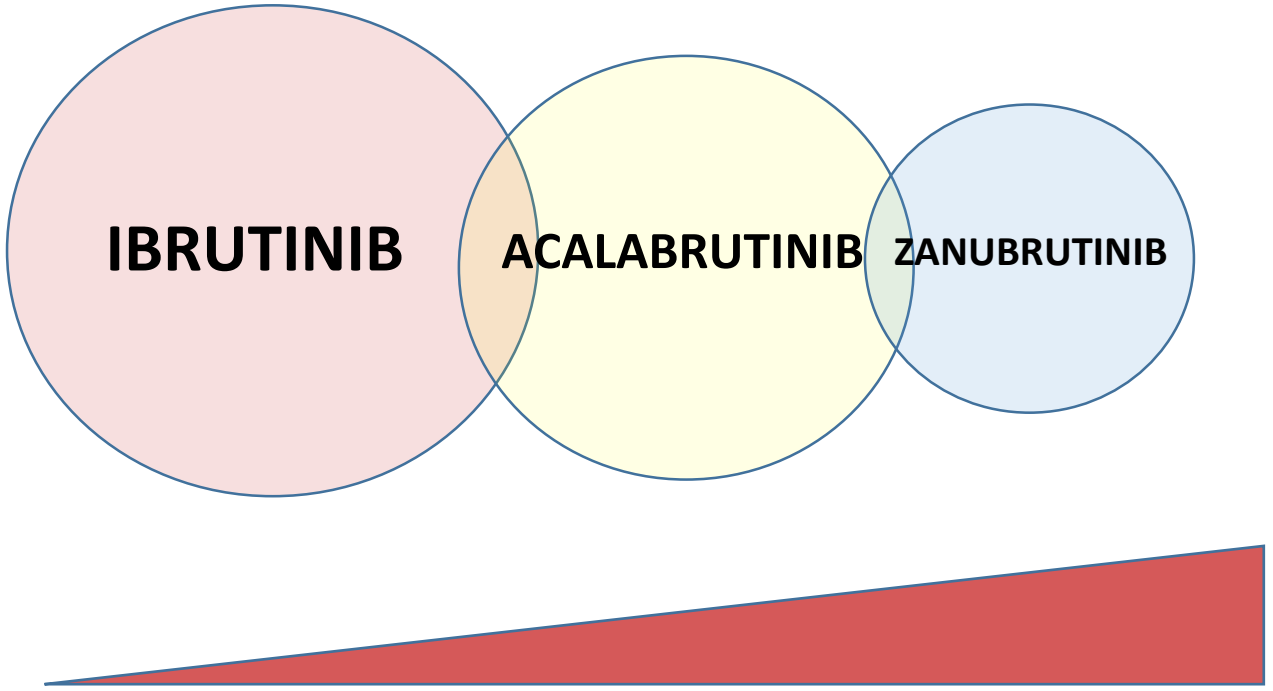
- BTK highly homologous to many other kinases (including members of TEC and Src super families)
- Cys481 in 9 other kinases (including HER2/HER4)
- Druggable cysteines in >200 other kinases

CV EFFECTS ASSOCIATED WITH COVALENT BTKi



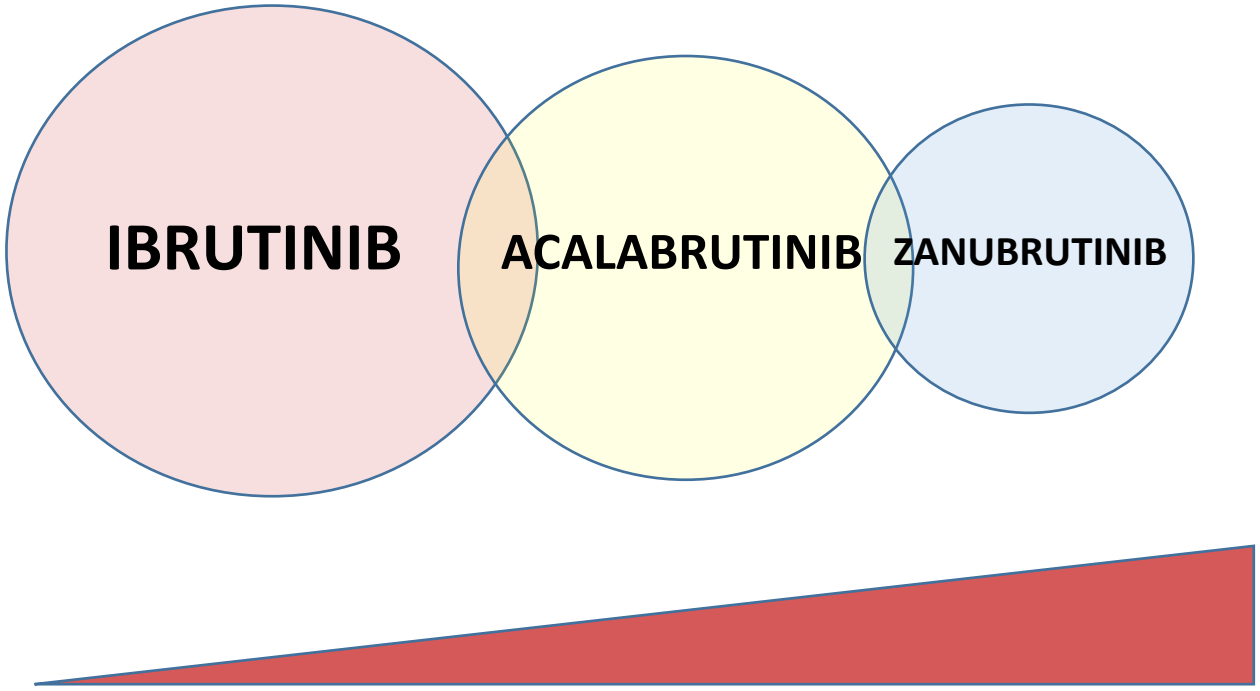
Likely *off target* effects, certainly *class effects*

WHO DOES MORE?



Shadman M et al, Lancet Haematol. 2022

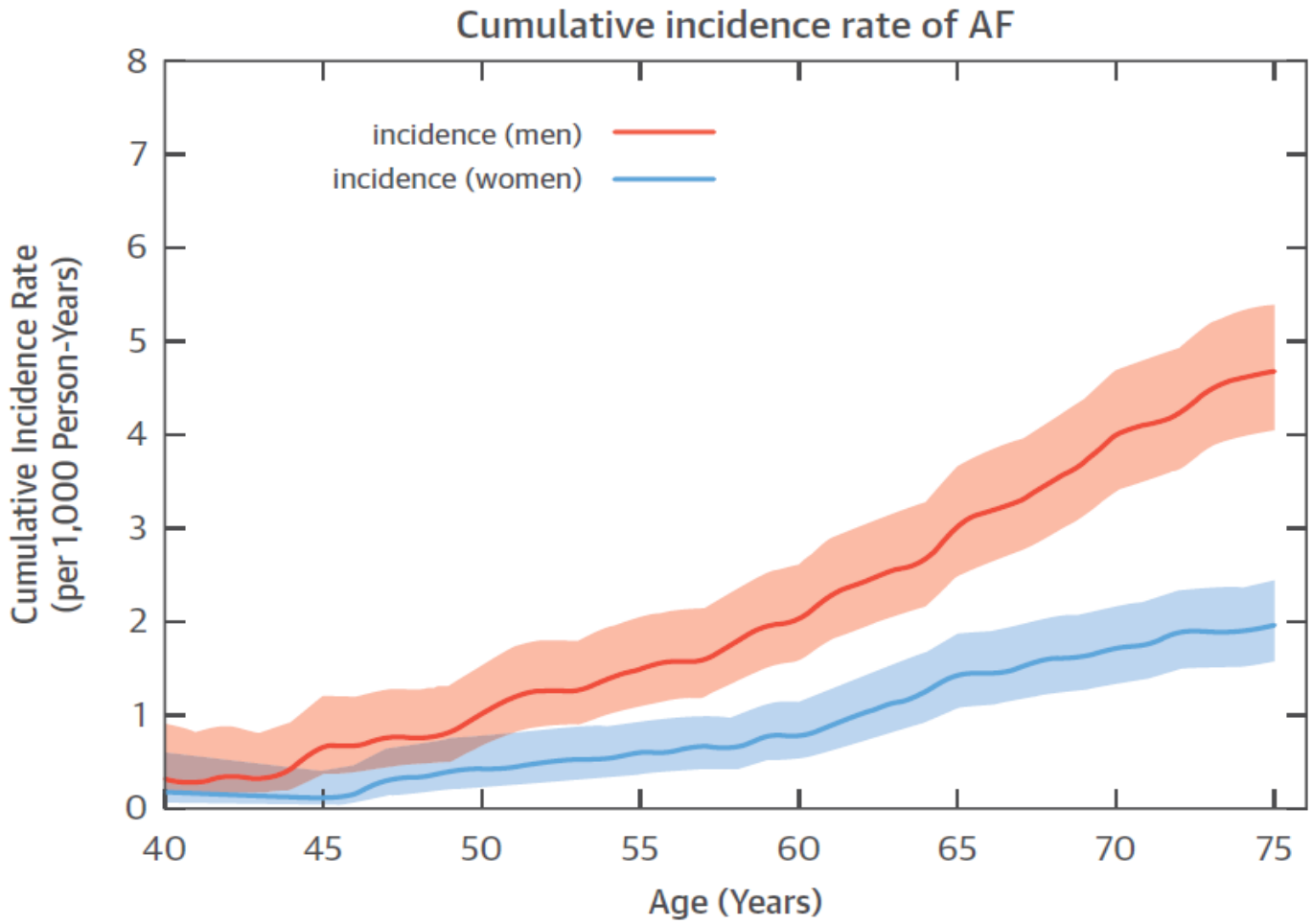
WHO DOES MORE?



Shadman M et al, Lancet Haematol. 2022

THE PATIENT

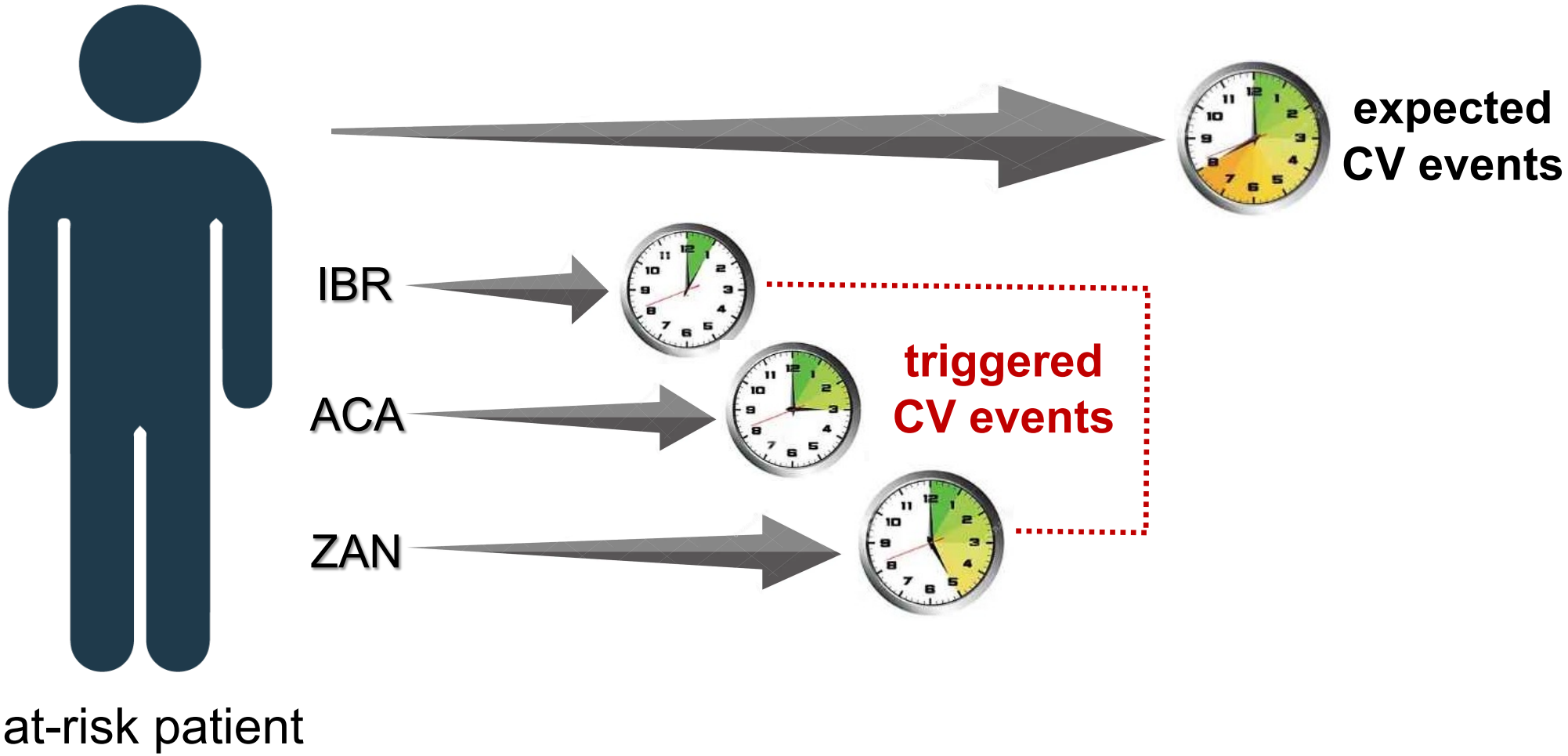
Age, pre-existing or expected CV morbidities



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

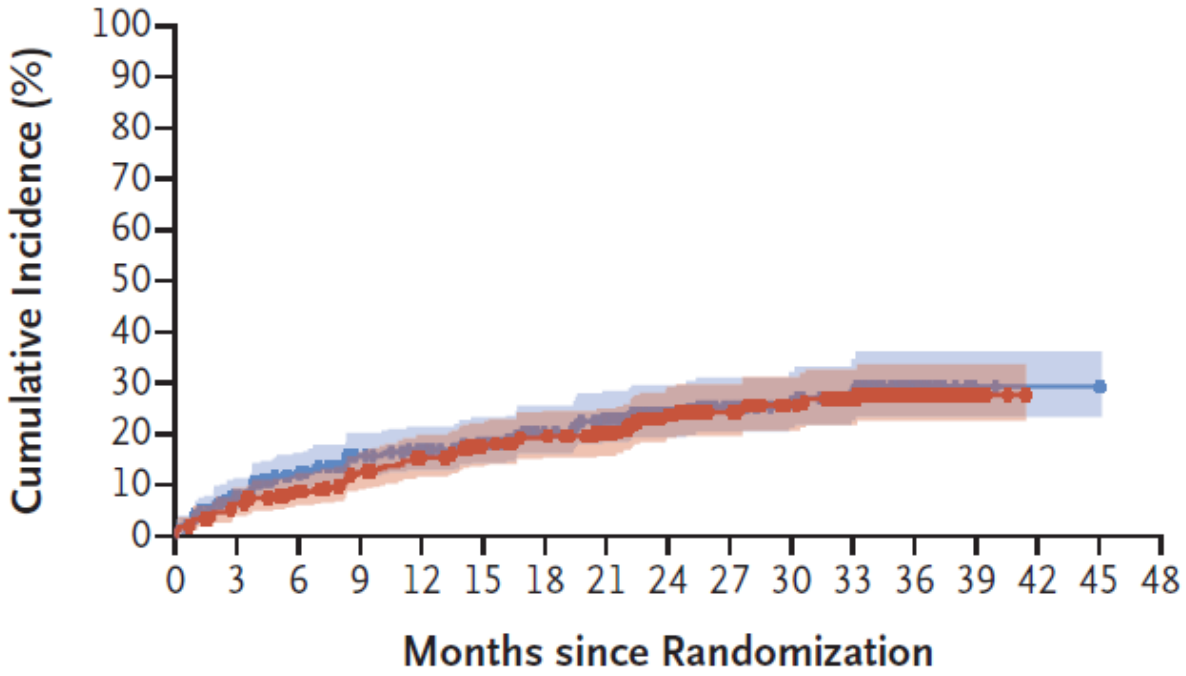
blood advances

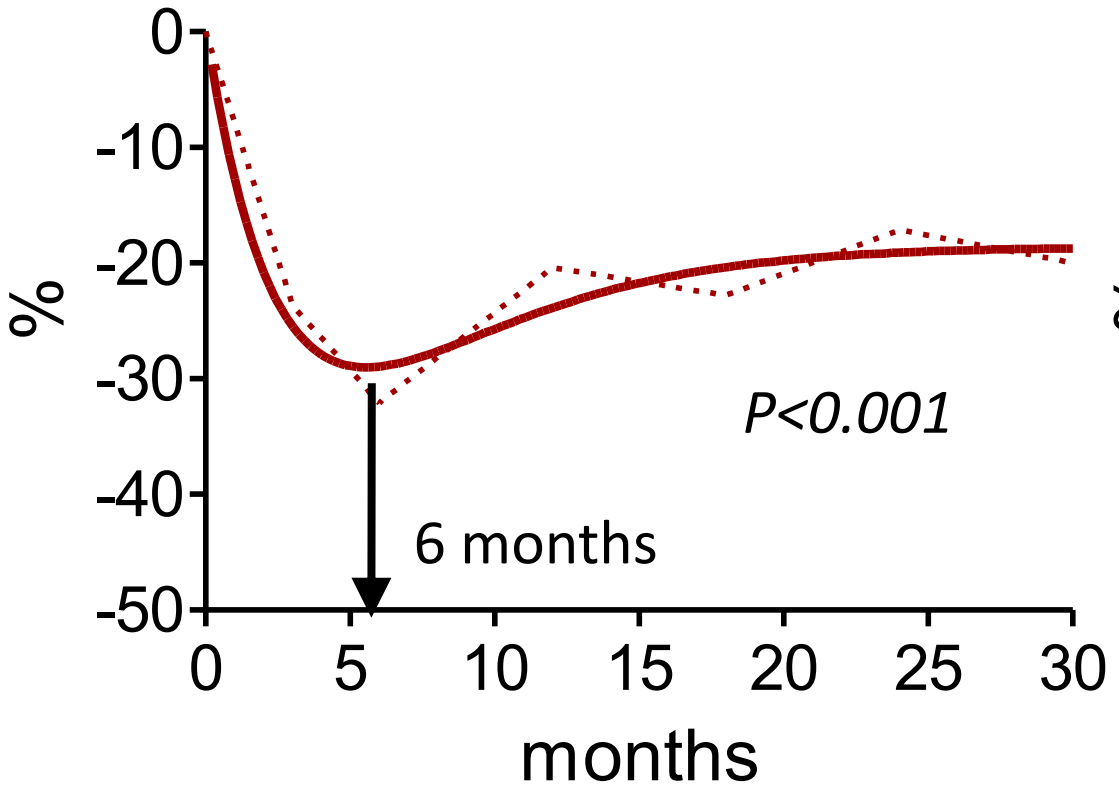
Cardiovascular toxicity of Bruton tyrosine kinase inhibitors: forget about selectivity but watch the clock

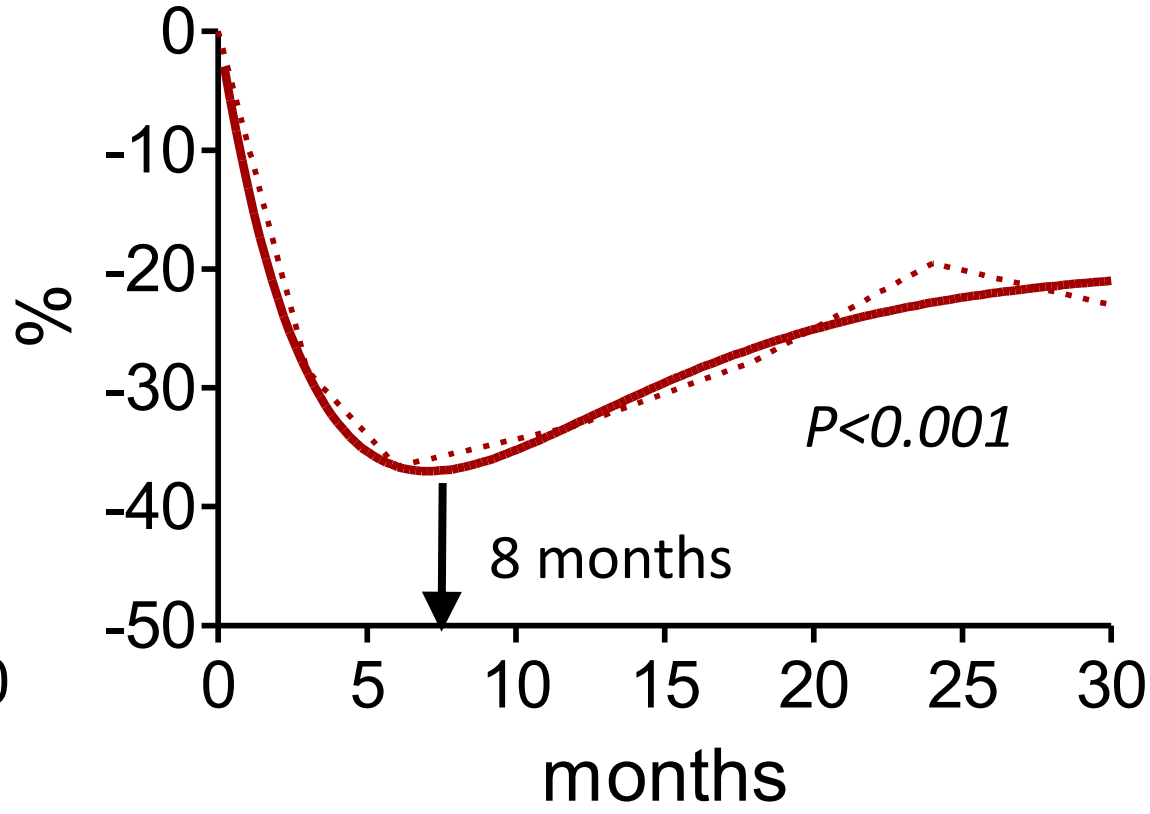


Minotti, Blood Adv 2024

THE ALPINE CASE







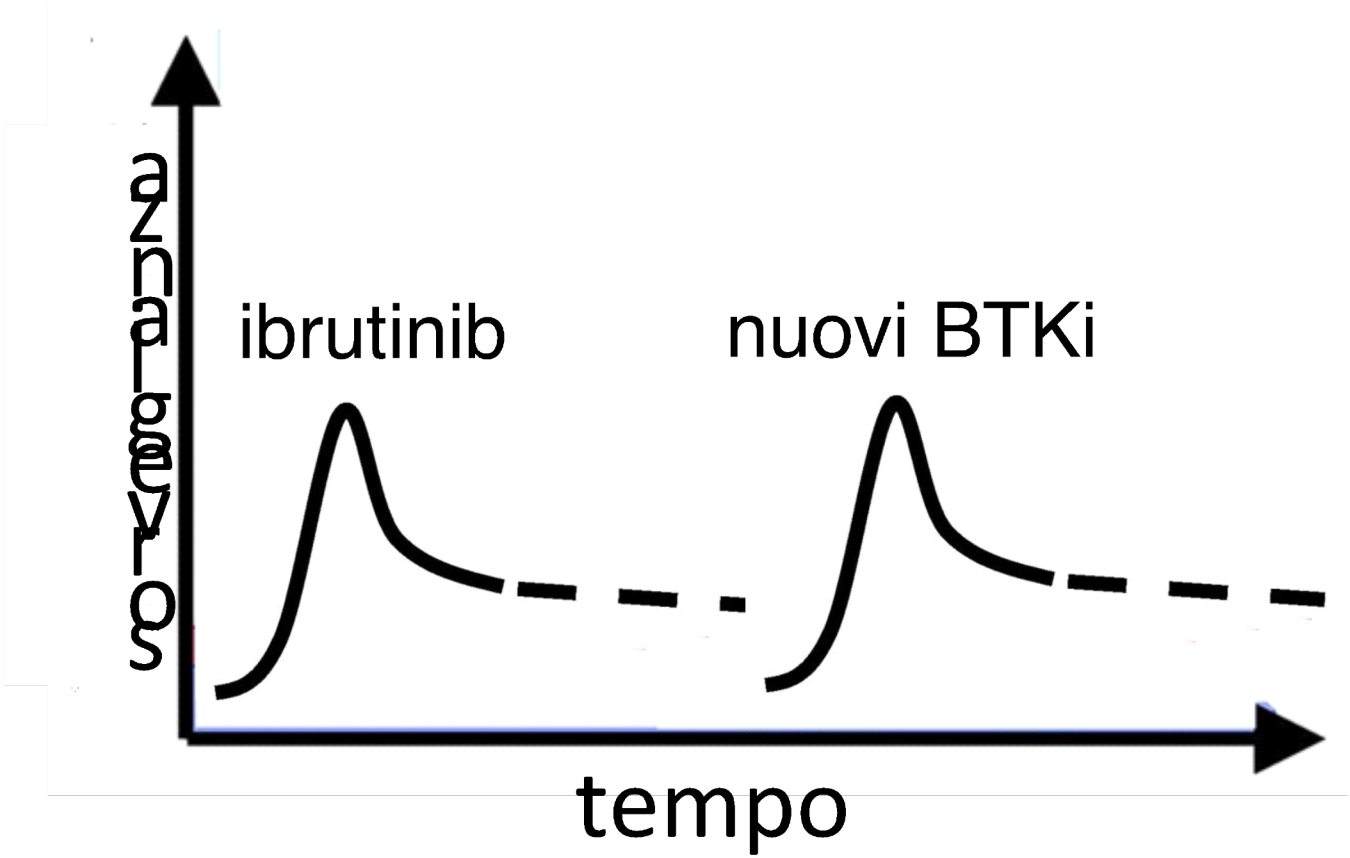
Over the first 6 months therapy, ZAN associates with ~30% reduction of initiating new anti-HTN compared with IBR

Over the first 8 months therapy, ZAN associates with >35 reduction of **initiating a new class of anti-HTN** compared with IBR

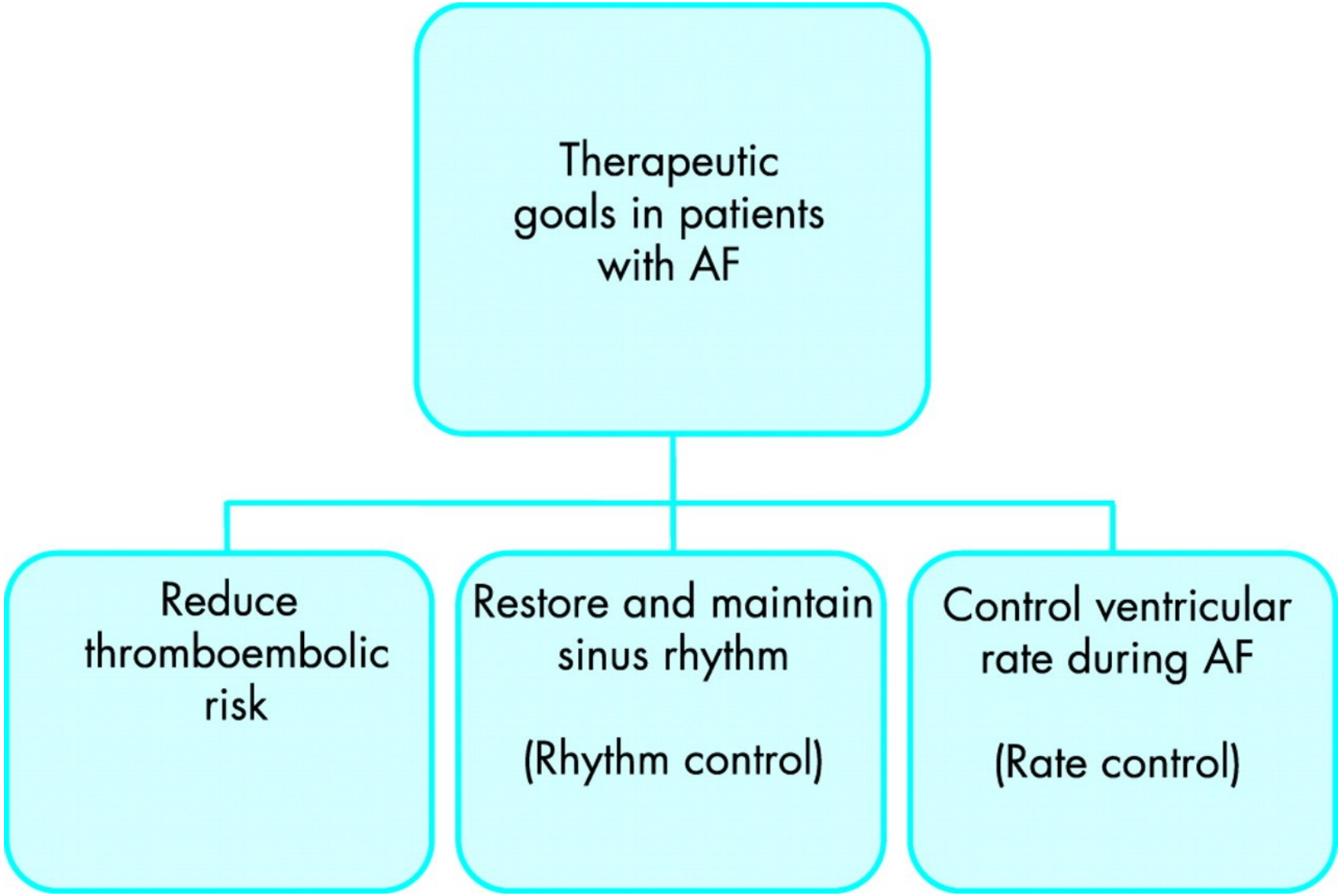
GM elab. of Ramirez et al., ASCO 2024 e19016

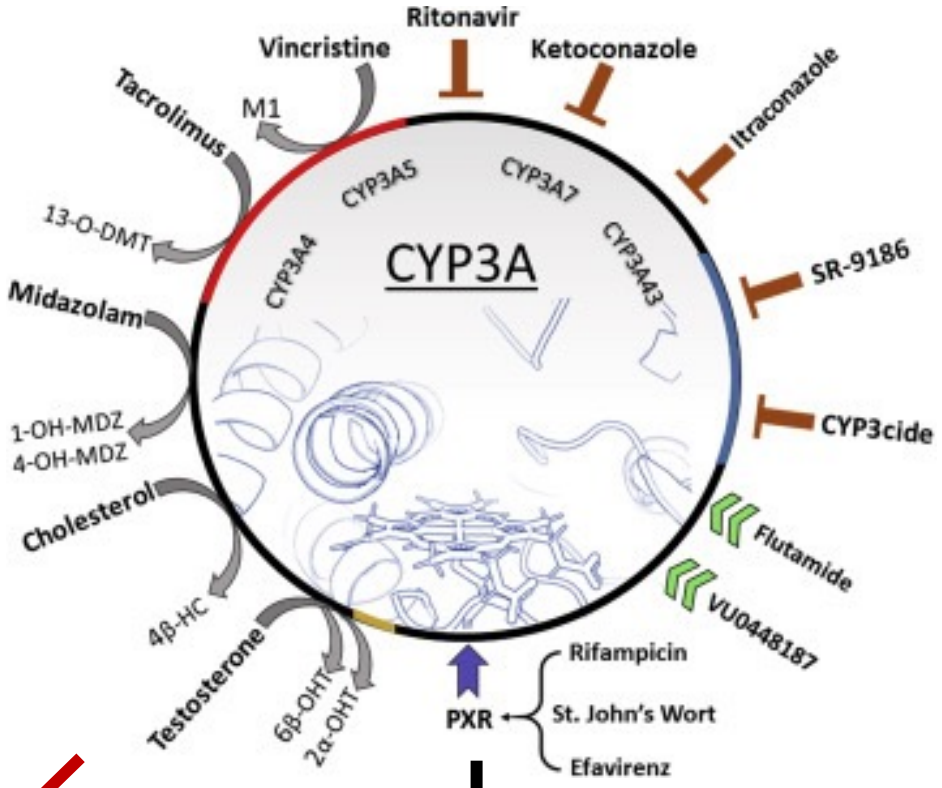
HOW TO MANAGE *CLASS EFFECTS* OF BTKi

1. TAILOR YOUR AGENDA TO DRUG CHARACTERISTICS



2. TAILOR YOUR CHOICES TO DDI RISK





DESETIL-AMIODARONE

ANTIARITMICI
(amiodarone, propafenone)

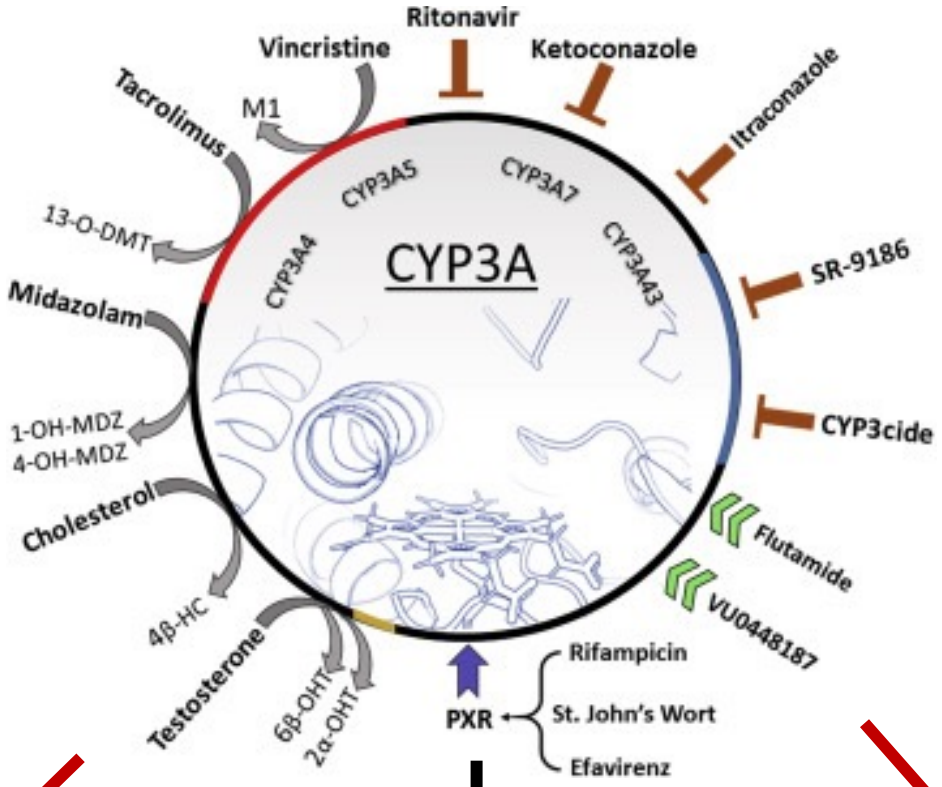
BTKi

IMAJ • VOL 18 • JULY 2016

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]

[1]Department of Cardiology, Rabin Medical Center (Beilinson Campus) and [2]Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel
[3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel



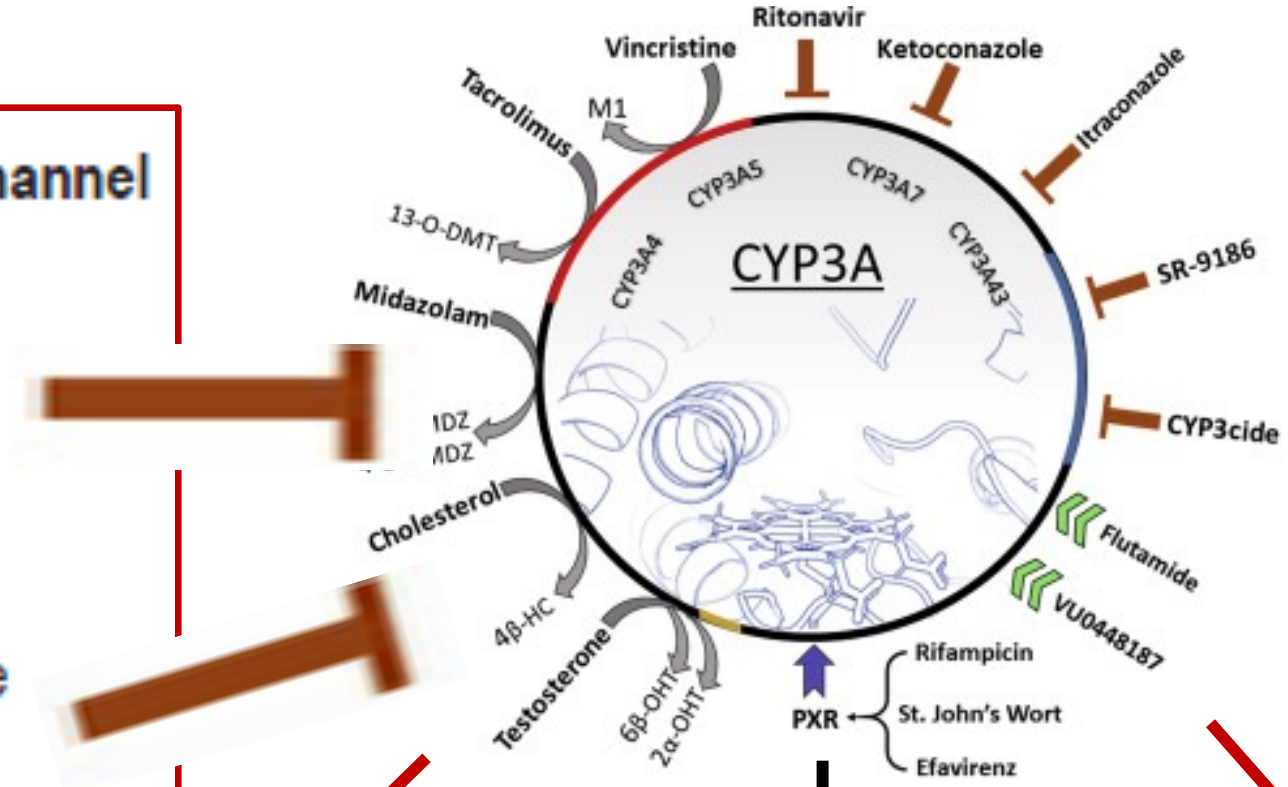
DESETIL-AMIODARONE

ANTIARITMICI
(amiodarone, propafenone)

BTKi

NOAC
(rivaroxaban, apixaban)

Calcium channel blockers
Amlodipine
Diltiazem
Felodipine
Nifedipine
Nisoldipine
Nitrendipine
Verapamil



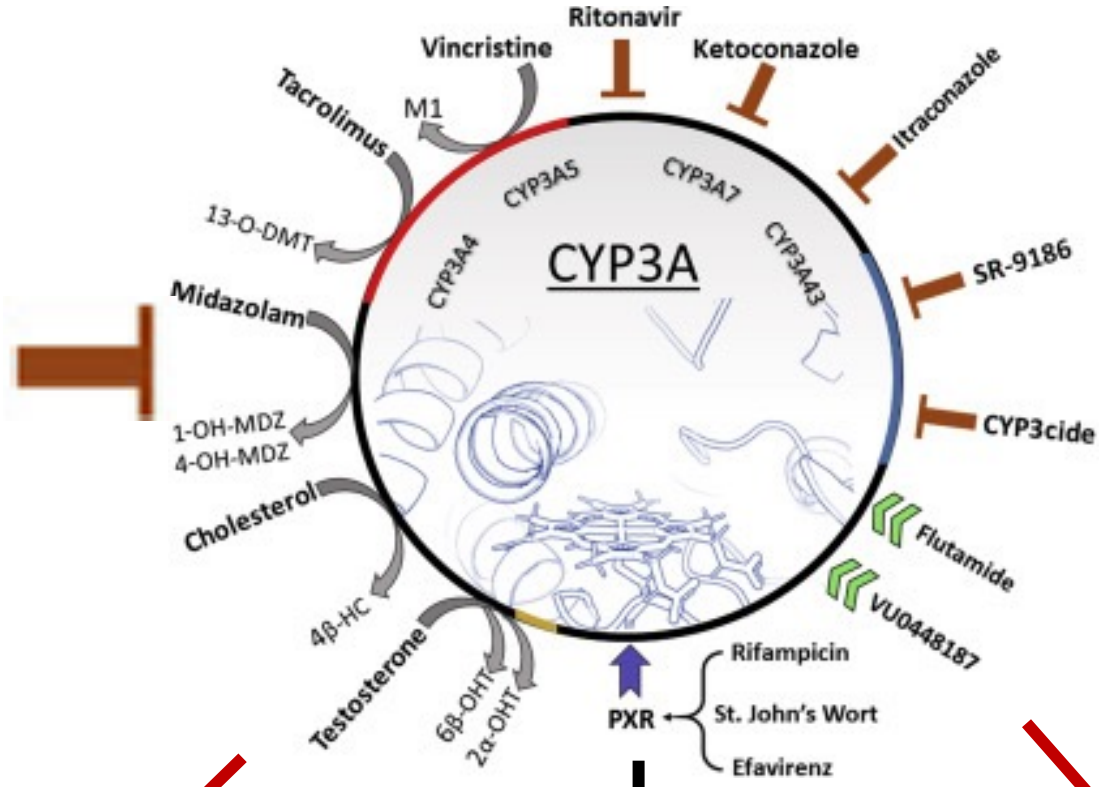
DESETIL-AMIODARONE

ANTIARITMICI
(amiodarone, propafenone)

BTKi

NOAC
(rivaroxaban, apixaban)

ANTIFUNGINI
(>>triazolici)



DESETIL-
AMIODARONE

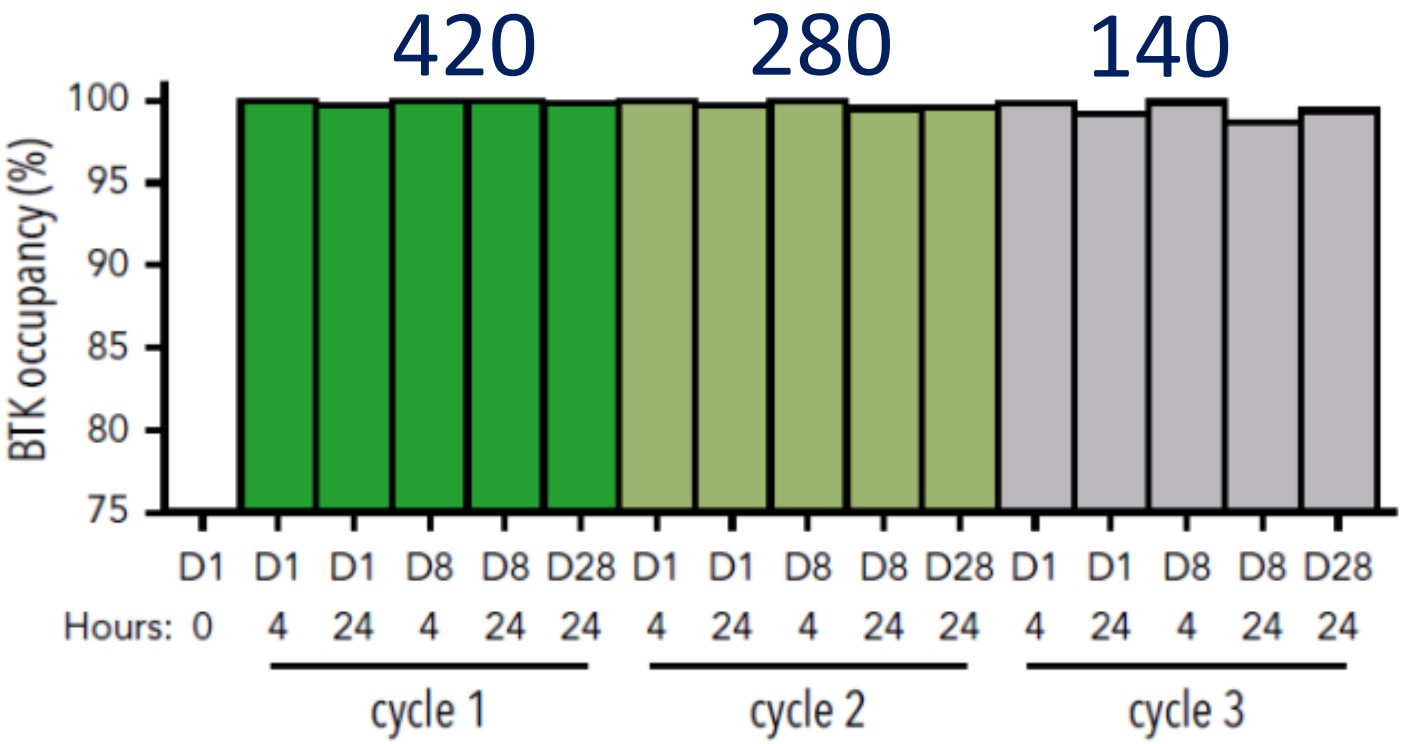
ANTIARITMICI
(amiodarone,
propafenone)

BTKi

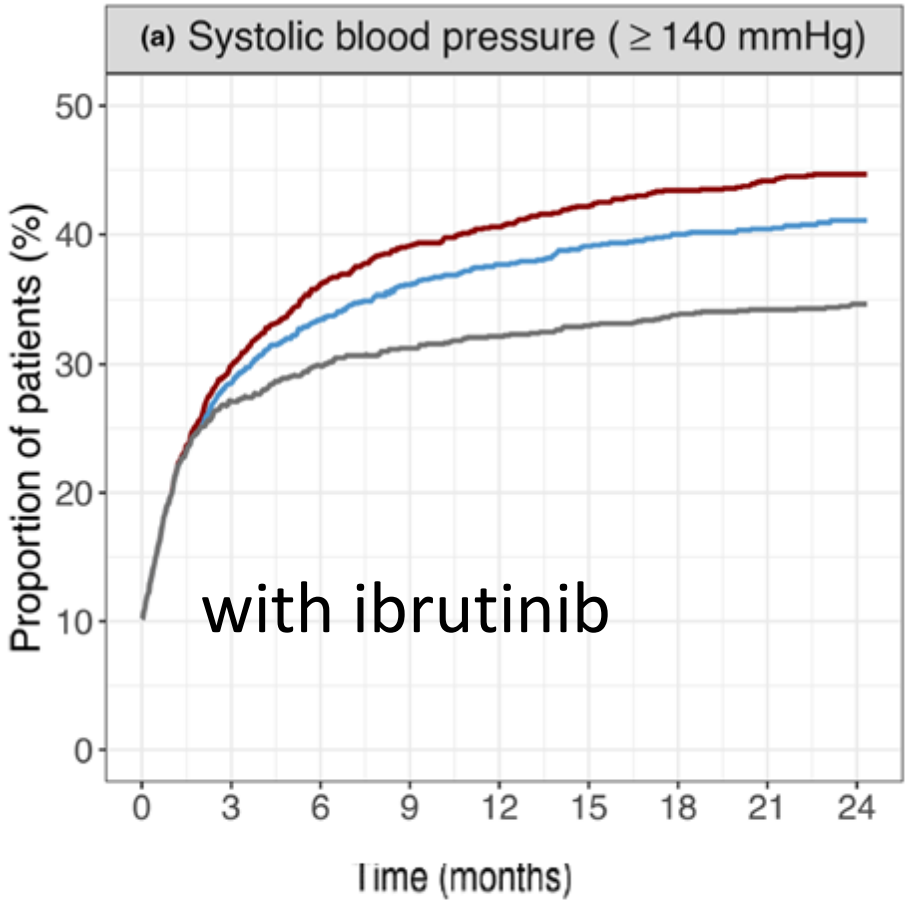
NOAC
(rivaroxaban,
apixaban)

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

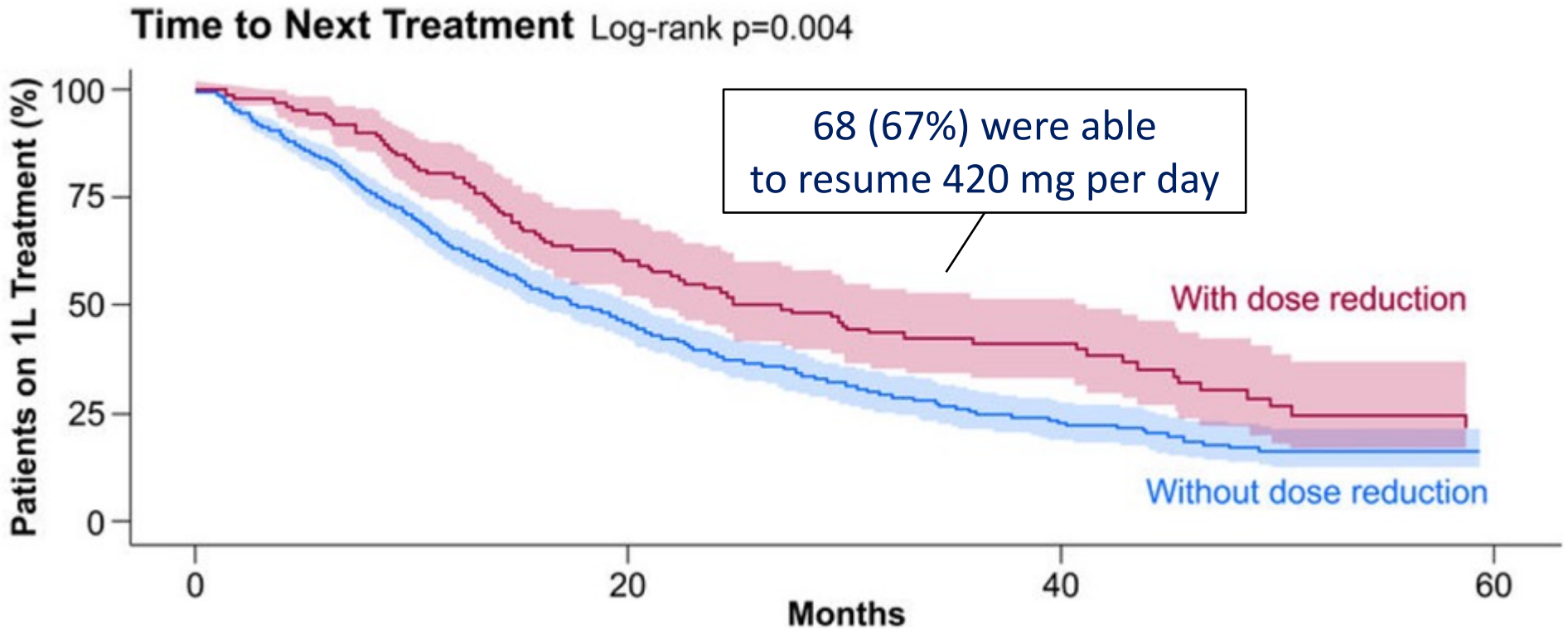
3. DOSE REDUCTIONS



blood® 22 NOVEMBER 2018 | VOLUME 132, NUMBER 21

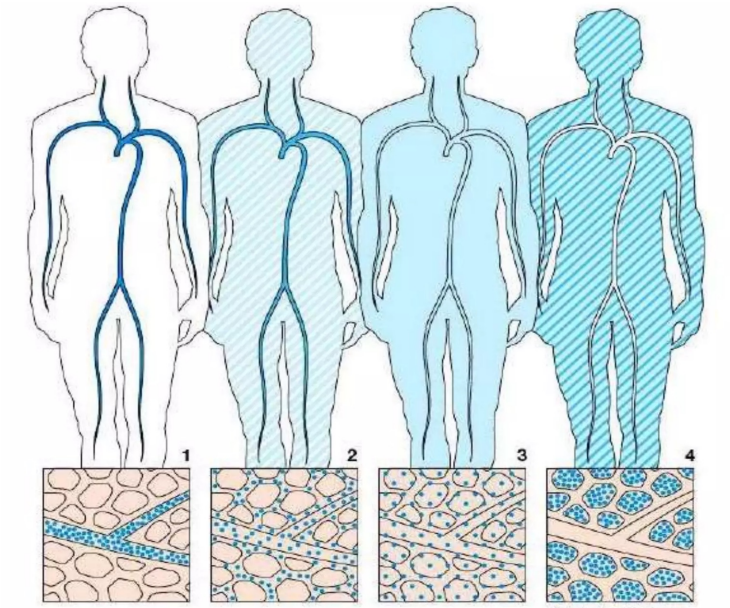


CPT Pharmacometrics Syst Pharmacol 2023;12:1305–1318.



Blood 142 (2023) 269–270

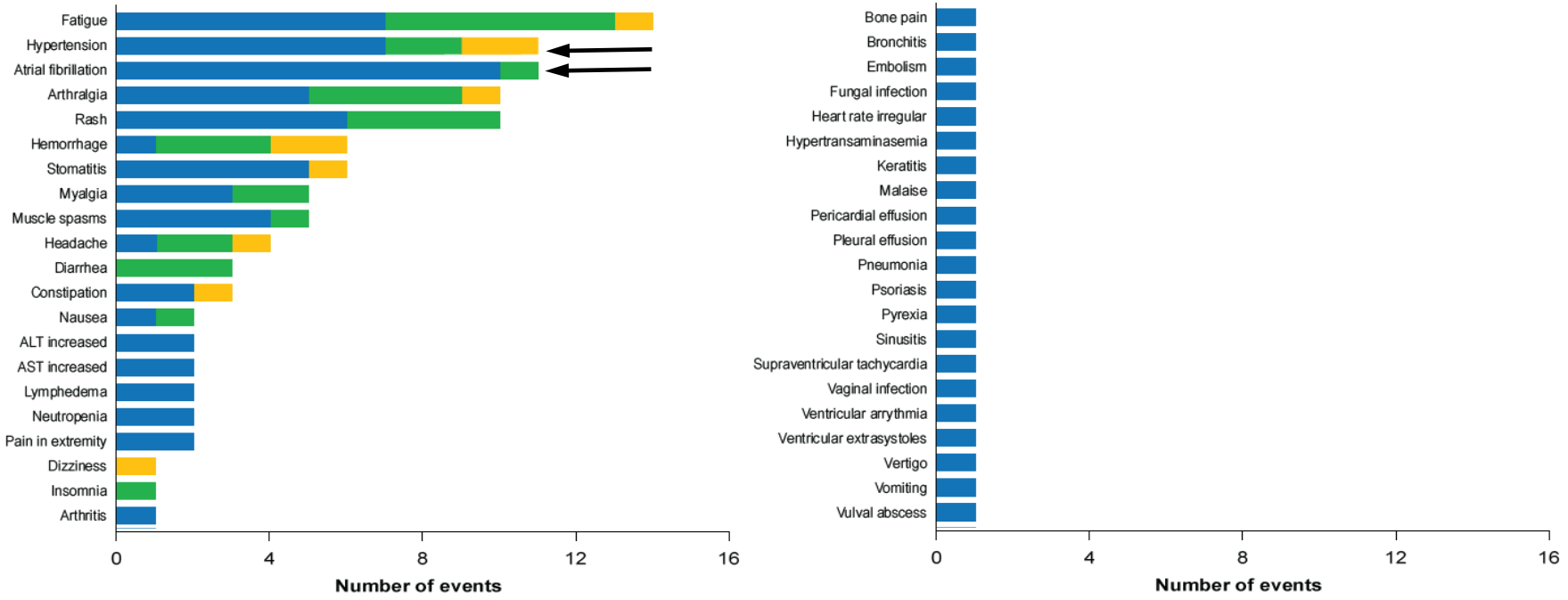
3. DOSE REDUCTIONS: A CAUTIONARY NOTE

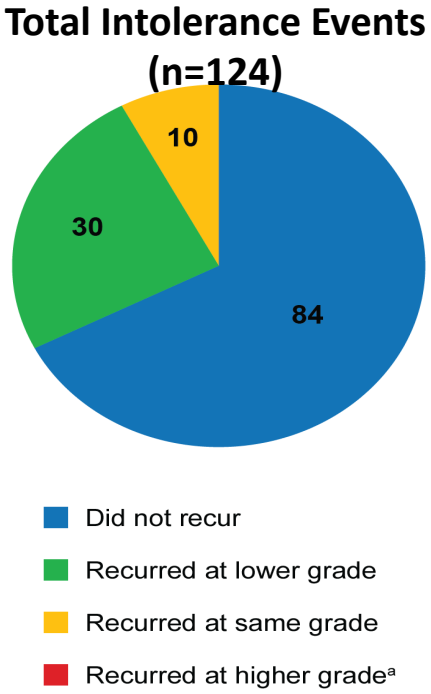


BTKi	Vd (L)
Ibrutinib	683
Acalabrutinib	723
Zanubrutinib	881

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





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