

**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

ROMA

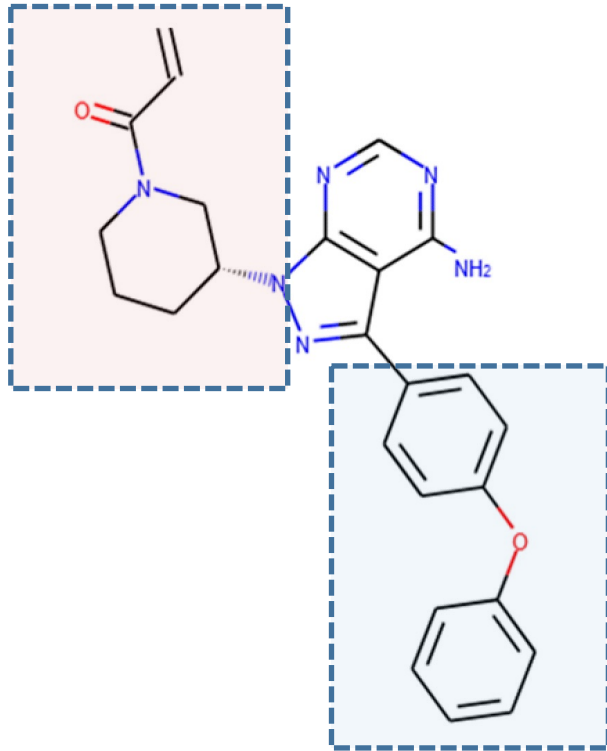
19 Giugno 2024

UNAHOTELS Decò

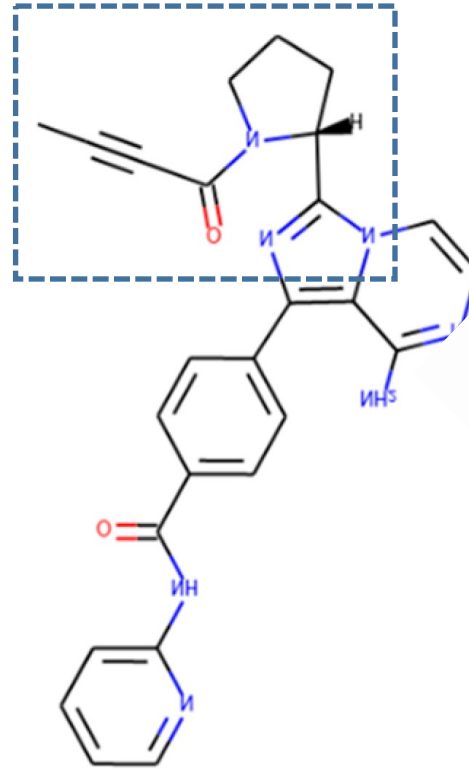
DISCLOSURES

Company name	Honoraria	Research funding	Advisory boards	Speakers' bureau
Janssen Italy				X
Incyte Italy		X	X	X
BeiGene Italy			X	X
Servier Italy	X			
Astellas EU		X		

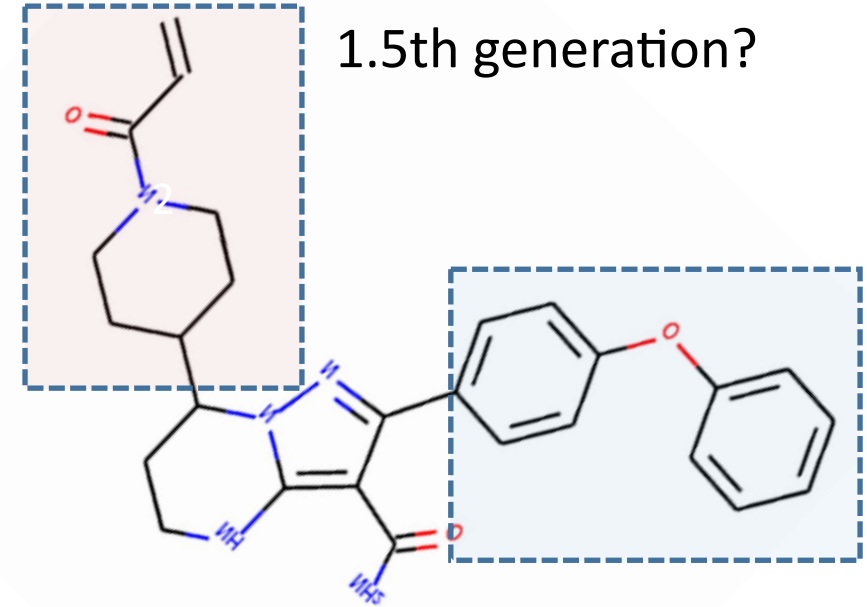
IBR, ACA and ZAN are covalent BTKi



IBRUTINIB
1st generation

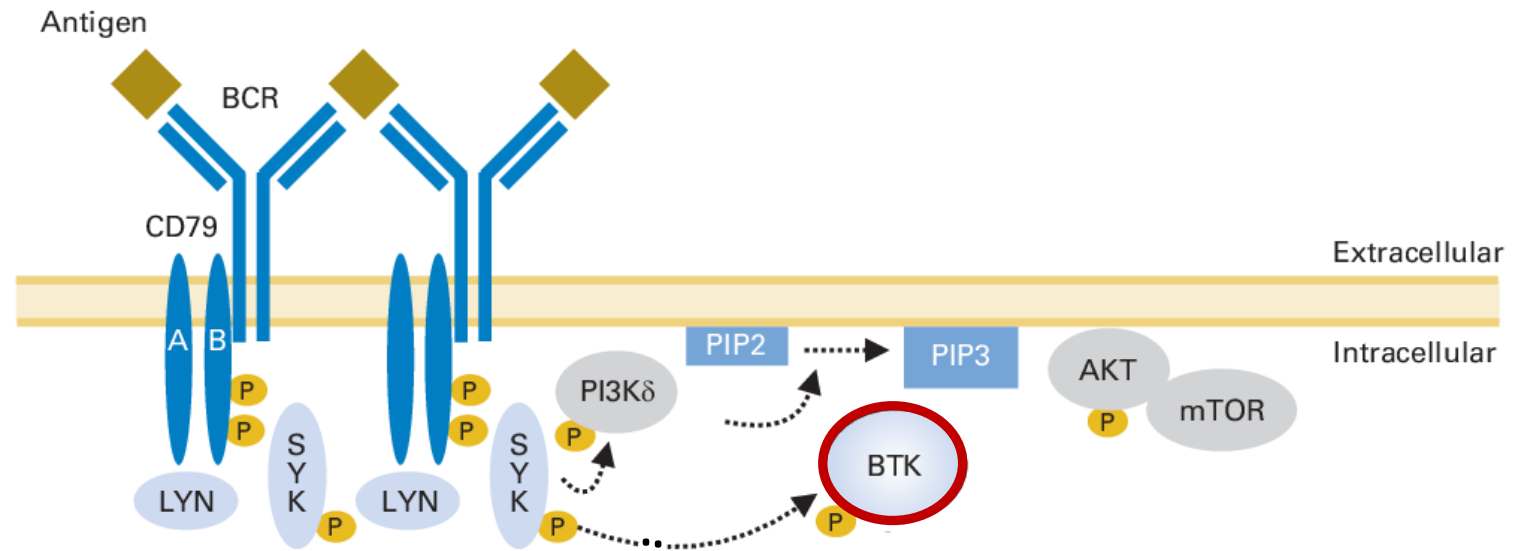
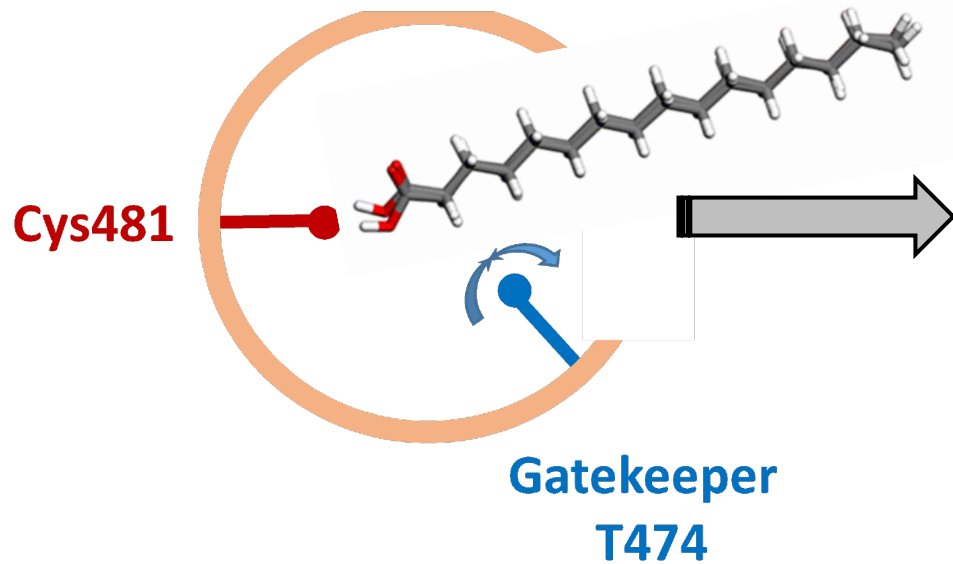
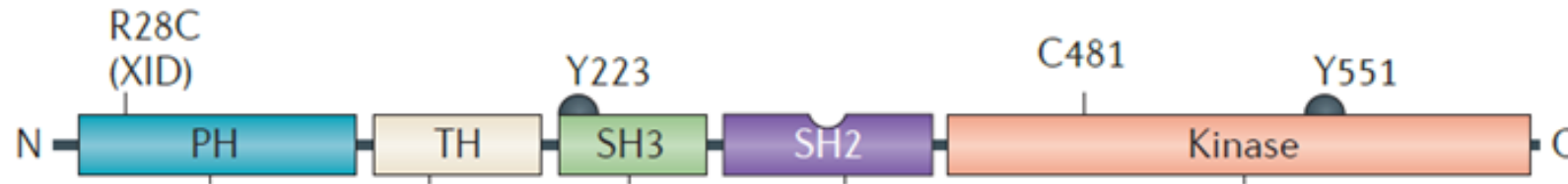


ACALABRUTINIB
2nd generation

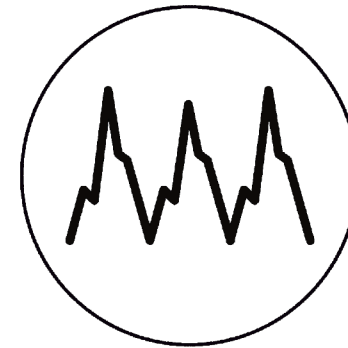
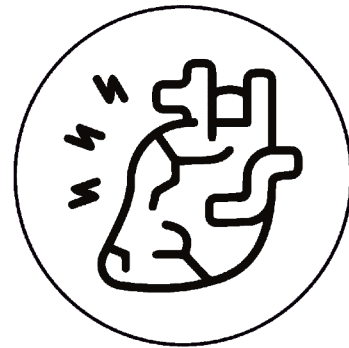
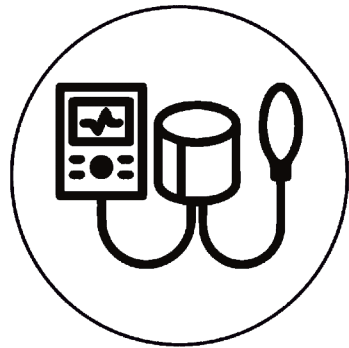


ZANUBRUTINIB
2nd or 3d
generation?

IBR, ACA and ZAN BIND TO CYS481 IN THE KINASE DOMAIN OF BTK



CV EFFECTS ASSOCIATED WITH COVALENT BTKI



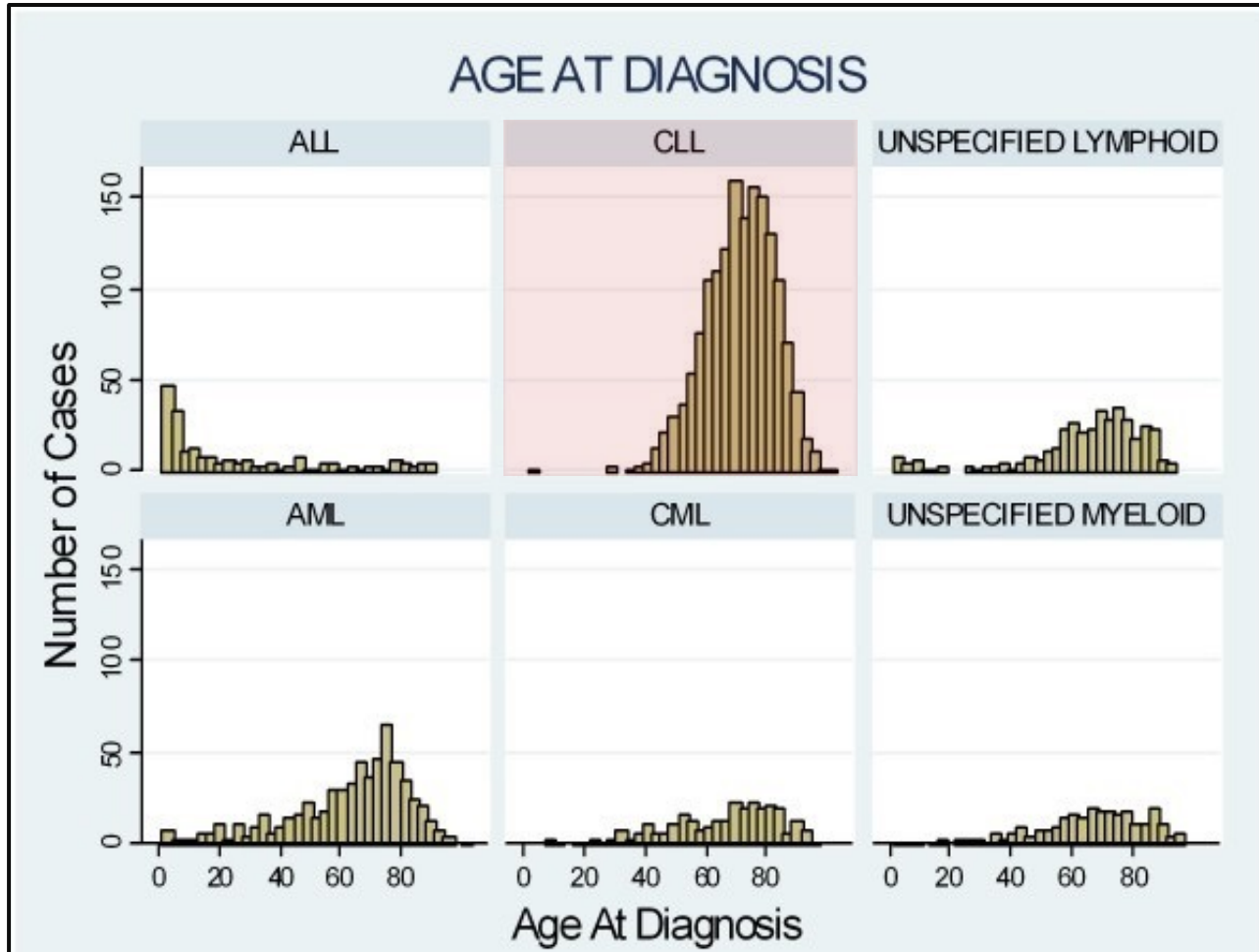
CV EFFECTS ASSOCIATED WITH COVALENT BTKI

- Most likely *off target* effects
- 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

- Target promiscuity
- Mode of action
- **CLASS EFFECTS**

THE CLL PATIENT

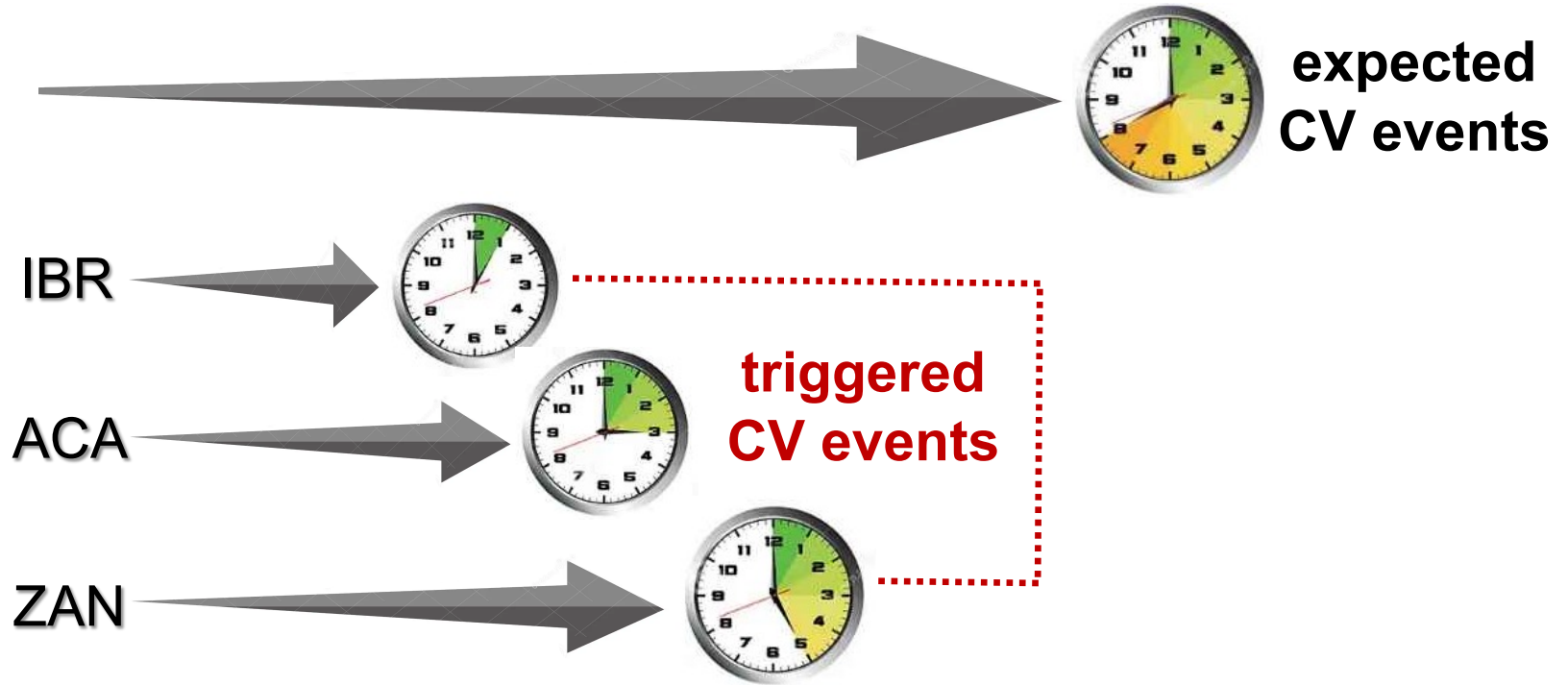


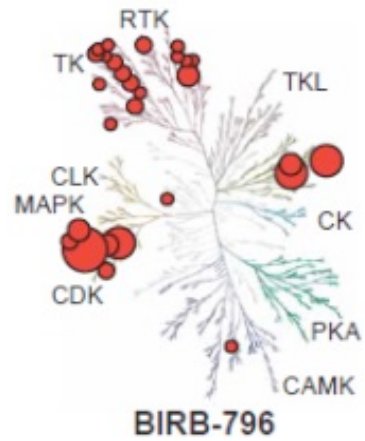
Pre-existing or
expected CV
morbidity

BTKi: MORE OF TRIGGERS THAN CAUSATIVE AGENTS

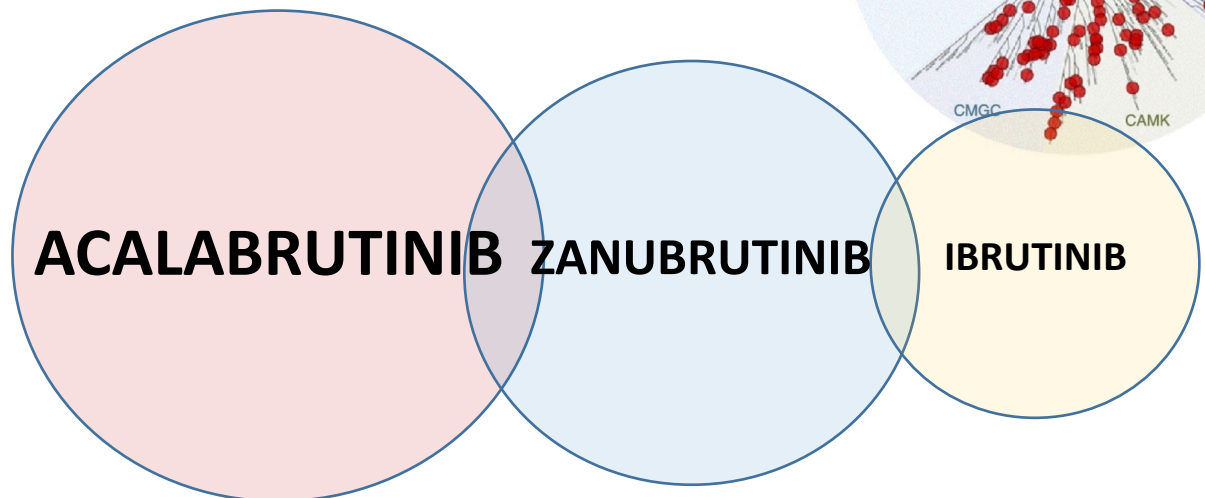


at-risk patient





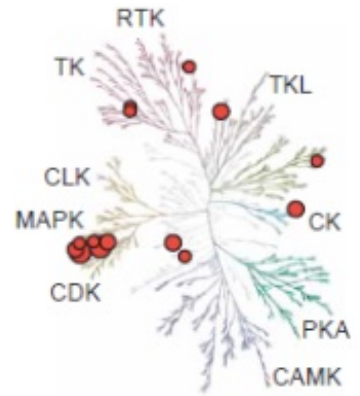
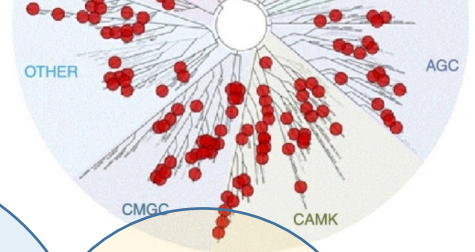
BIRB-796



Podoll et al. JPET 2023;384:173-186.



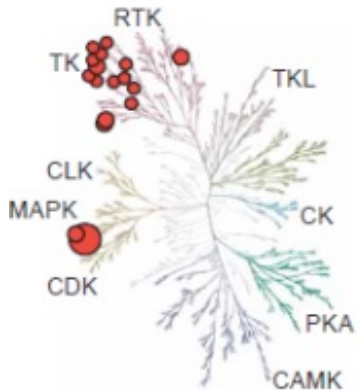
SELECTIVITY



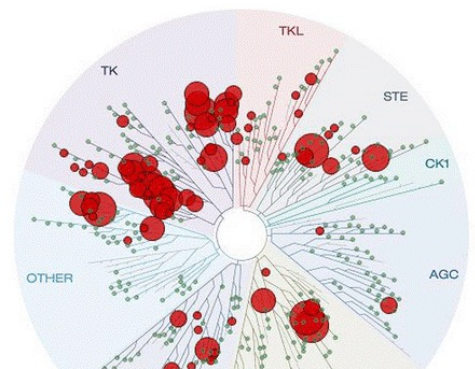
SB202190

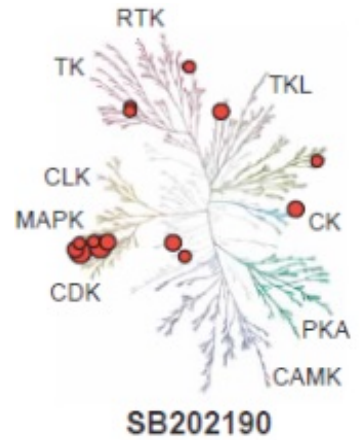
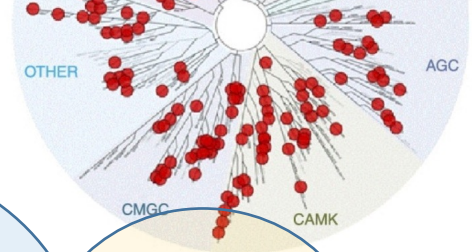
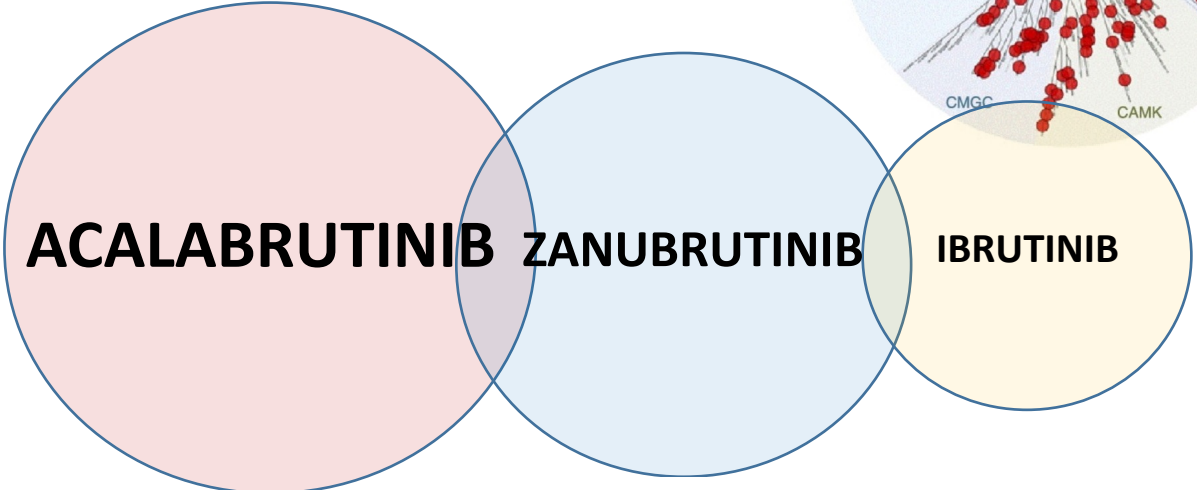
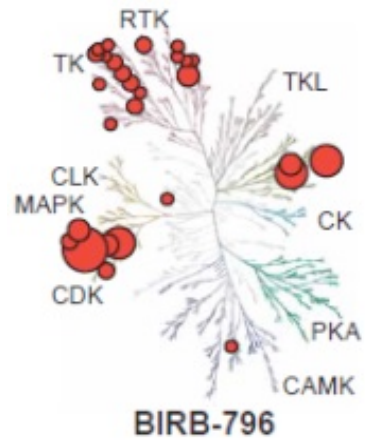


SB

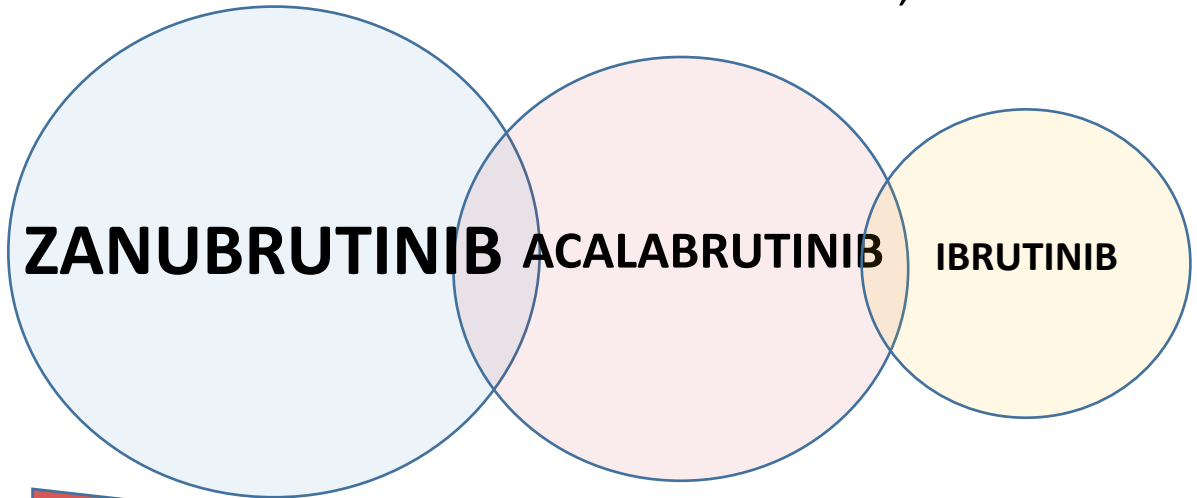


VX-745

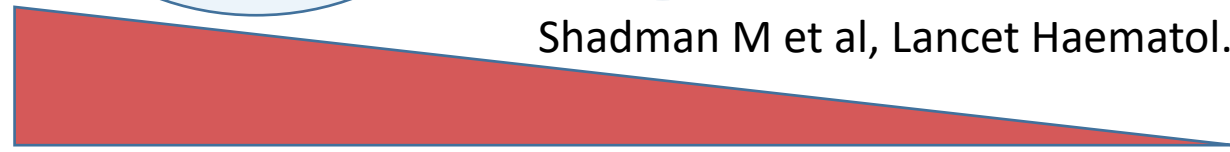
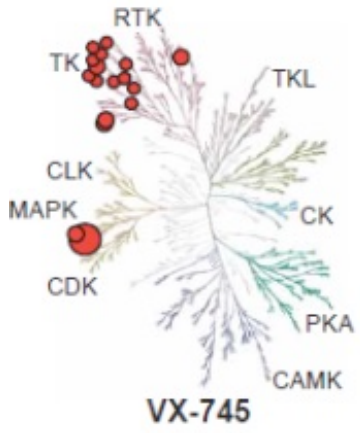




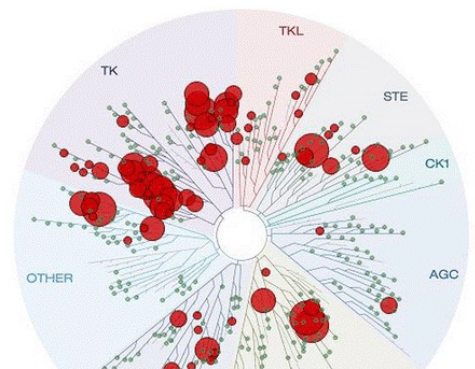
Podoll et al. JPET 2023;384:173-186.



Shadman M et al, Lancet Haematol. 2022



SELECTIVITY



A CAUTIONARY NOTE

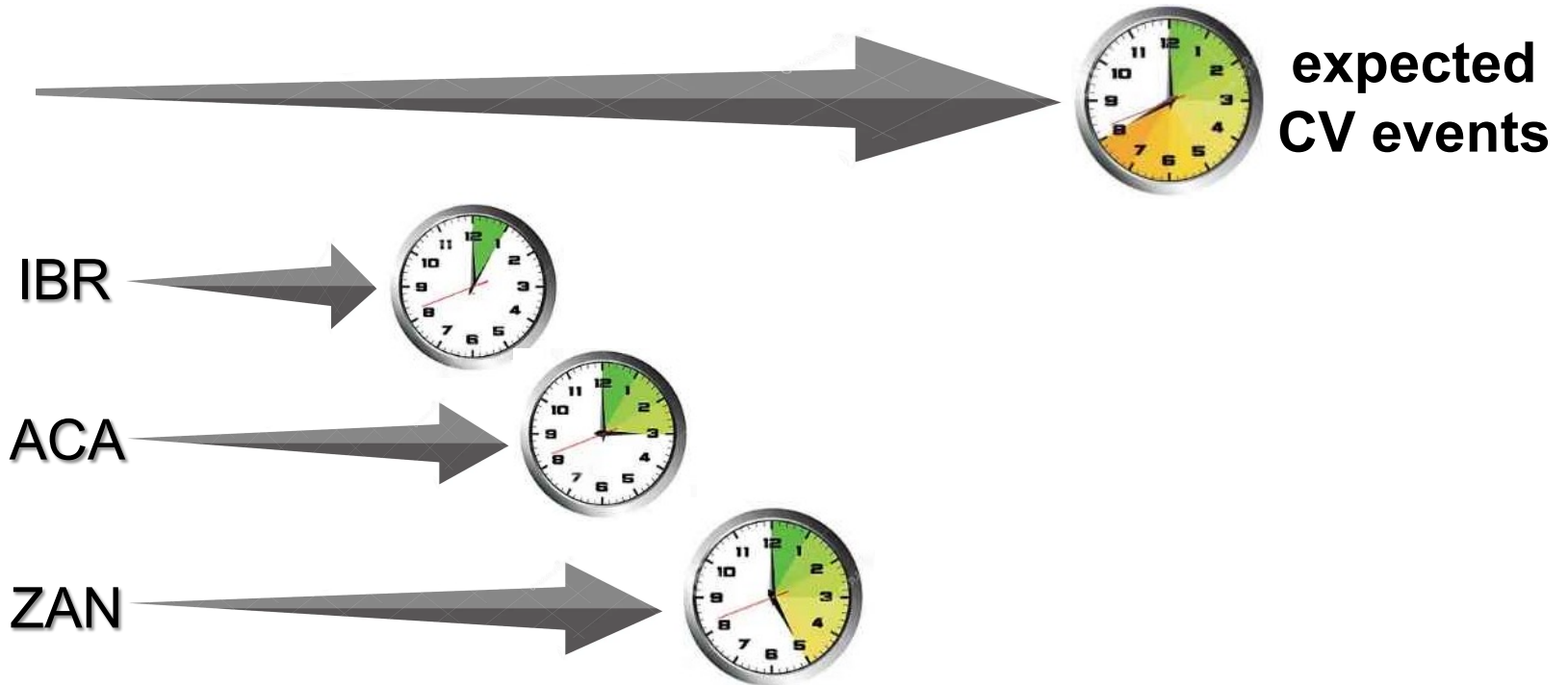
Reported selectivity (from high to low)	IC ₅₀ (μ M)	K _i * (μ M)	BTKi in the assay (μ M)	Selectivity conditions	
				vs IC ₅₀	vs K _i
acalabrutinib	0.005	0.181	1	●	●
ACP-5862†	0.005	0.188	1	●	●
zanubrutinib	0.0005	0.126	1	●	●
ibrutinib	0.0015	0.054	1	●	●
zanubrutinib	0.00071	0.126	0.071	●	●
acalabrutinib	0.0240	0.181	2.400	●	●
ibrutinib	0.00032	0.054	0.032	●	●
ACP-5862†	0.0630	0.188	6.300	●	●

Minotti, Blood Adv (comm. *in press*)

FORGET ABOUT SELECTIVITY BUT WATCH THE CLOCK

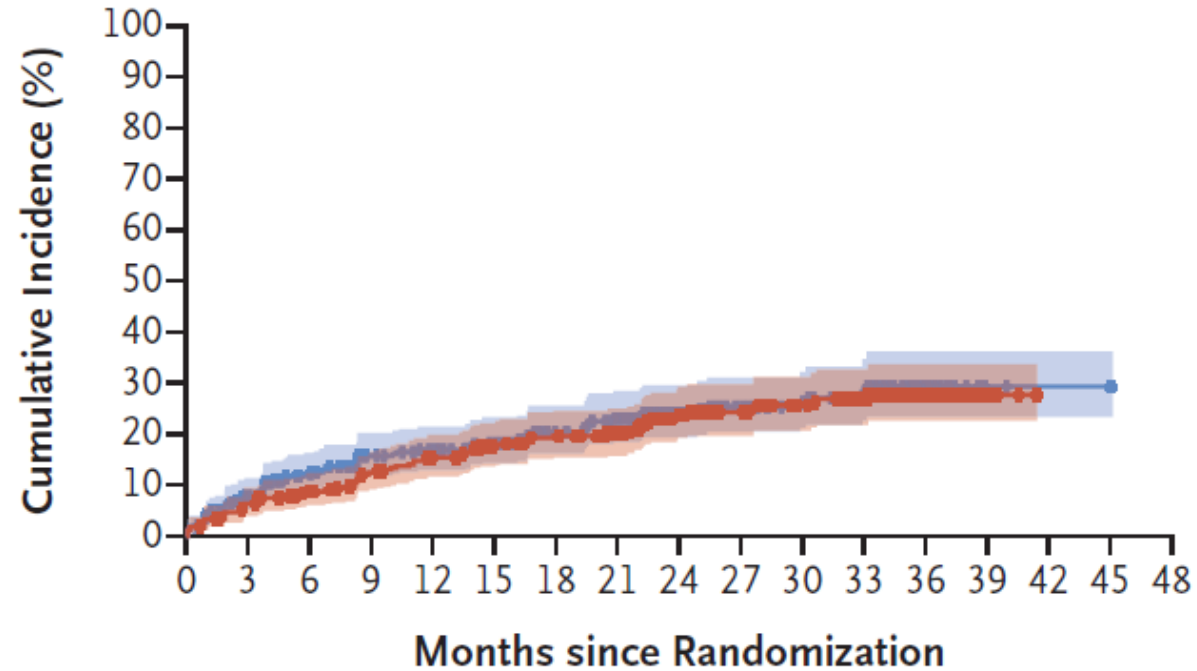


at-risk patient



Minotti, Blood Adv (comm. *in press*)

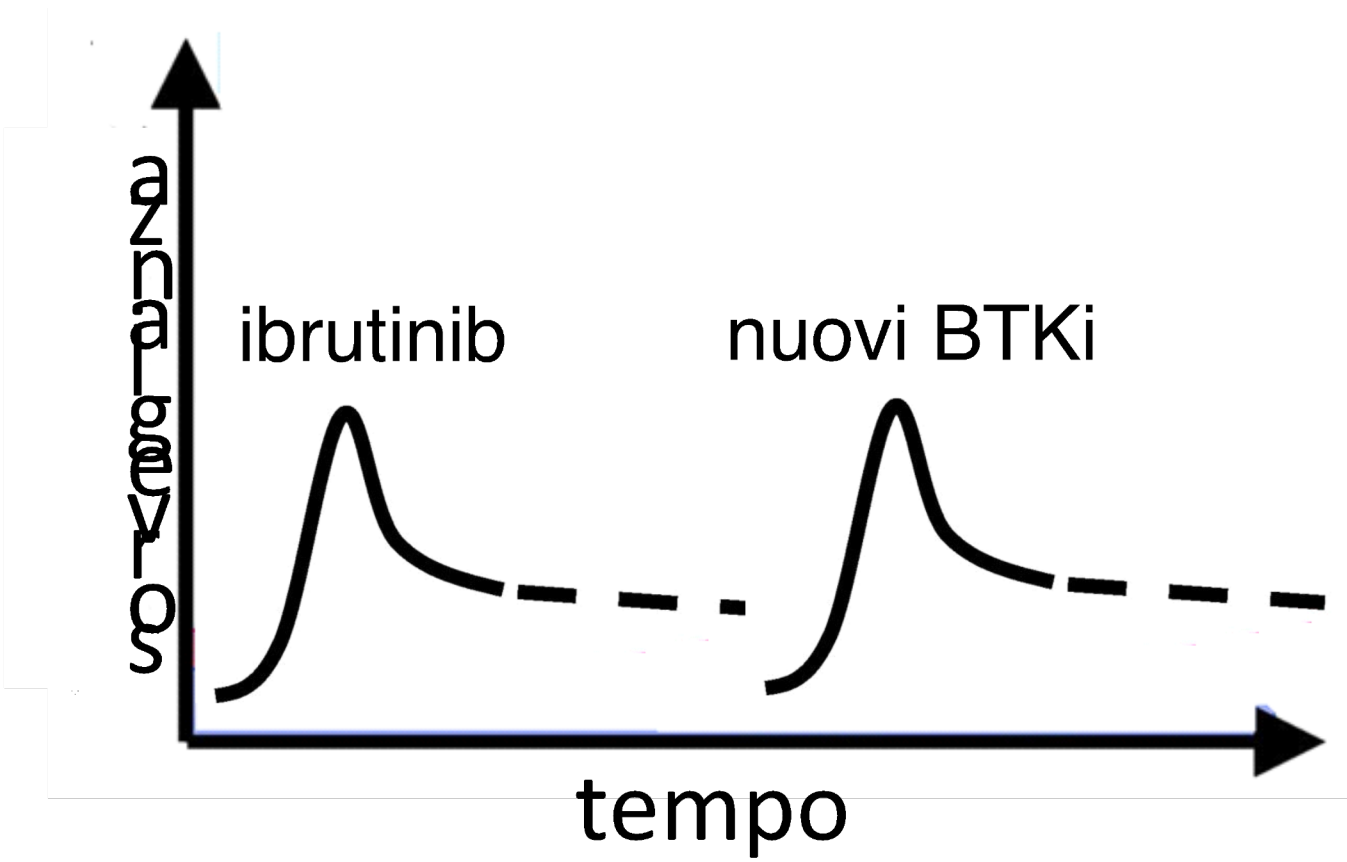
THE ALPINE CASE



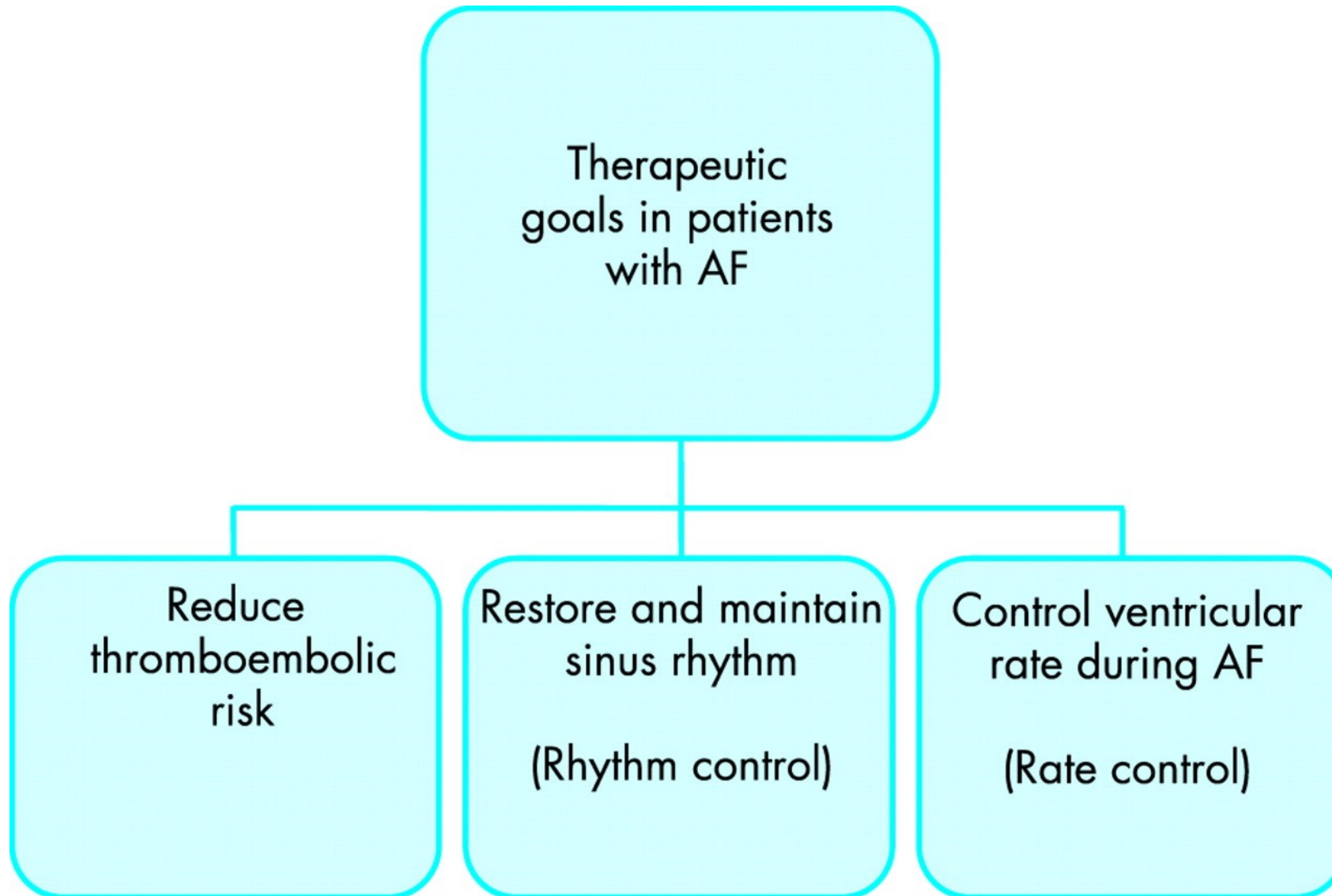
N ENGL J MED 388;4 NEJM.ORG JANUARY 26, 2023

HOW TO MANAGE CLASS EFFECTS OF BTKi

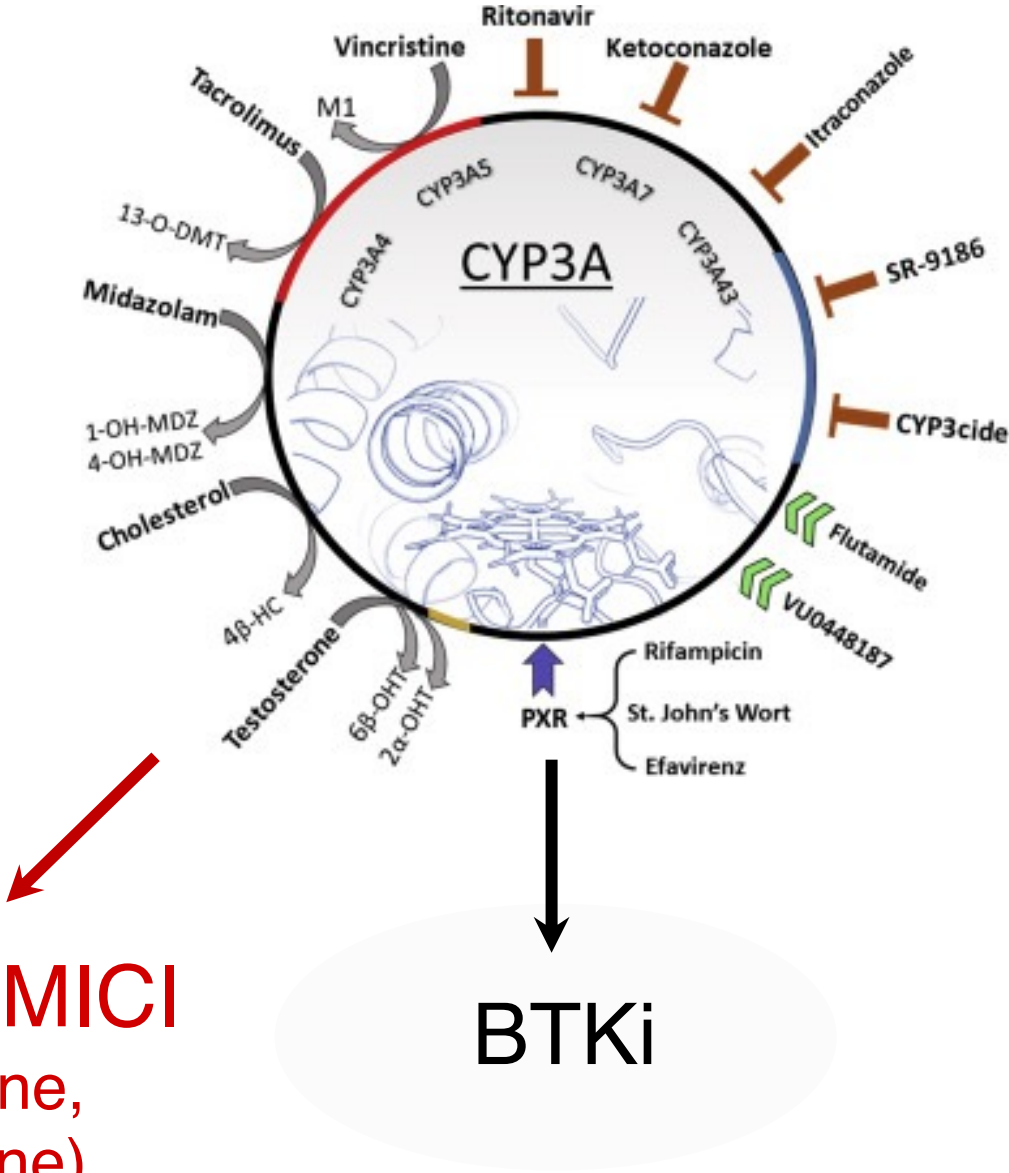
1. TAILOR YOUR AGENDA TO DRUG CHARACTERISTICS



2. TAILOR YOUR CHOICES TO DDI RISK



ANTIARITMICI
(amiodarone,
propafenone)



DESETIL-AMIODARONE

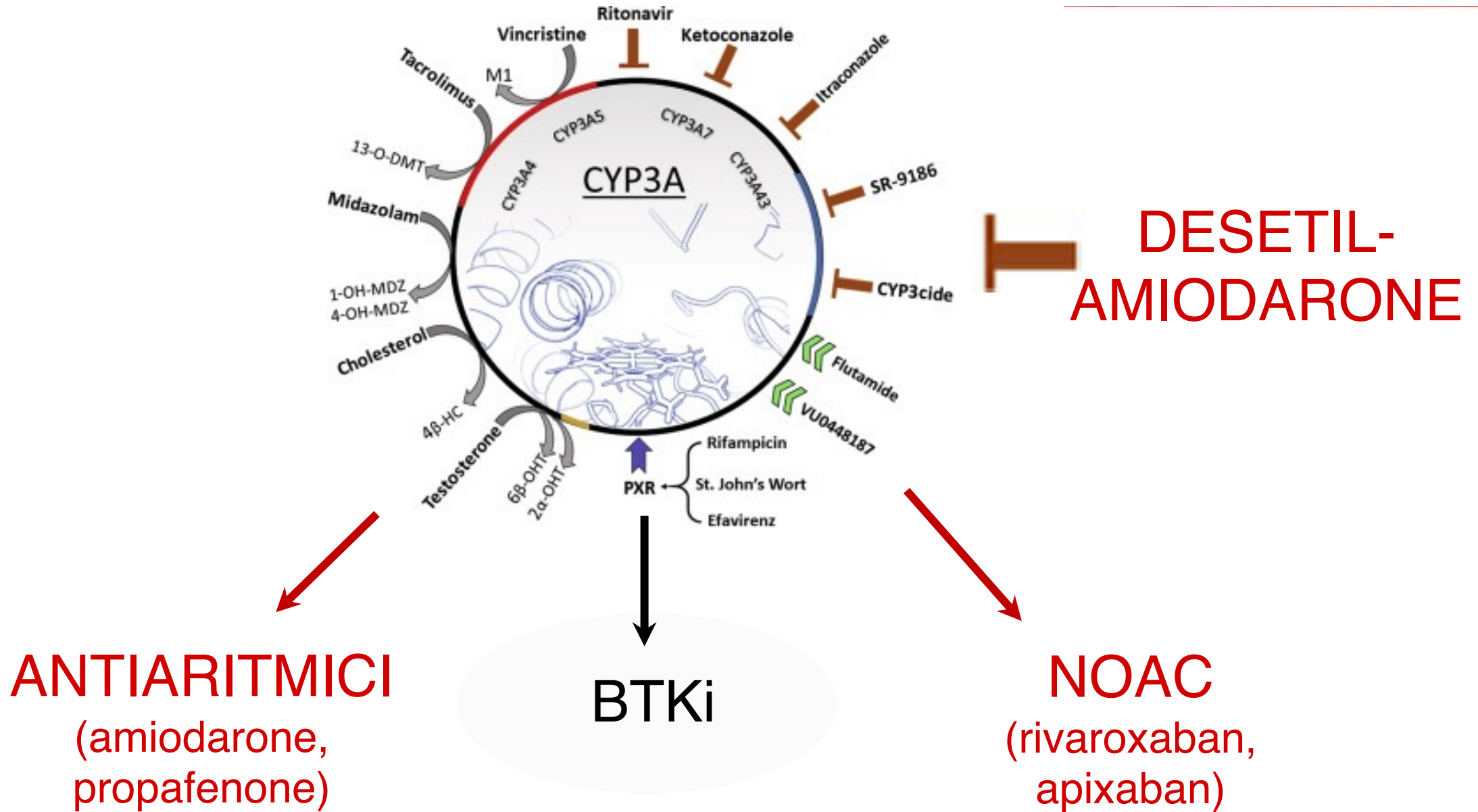
BTKi

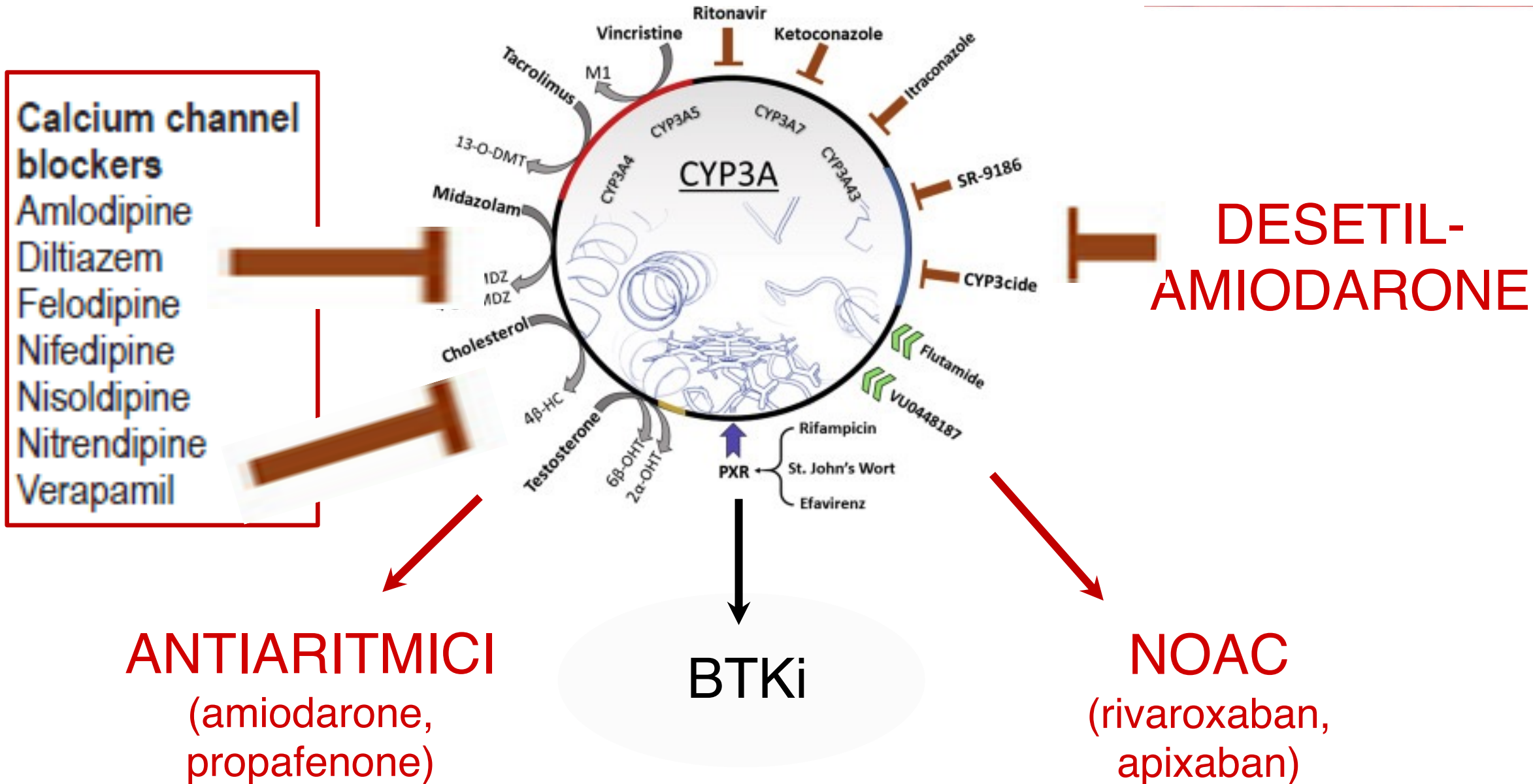
Concomitant Treatment with Ibrutinib and Amiodarone Causing Reversible Heart Failure Syndrome

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

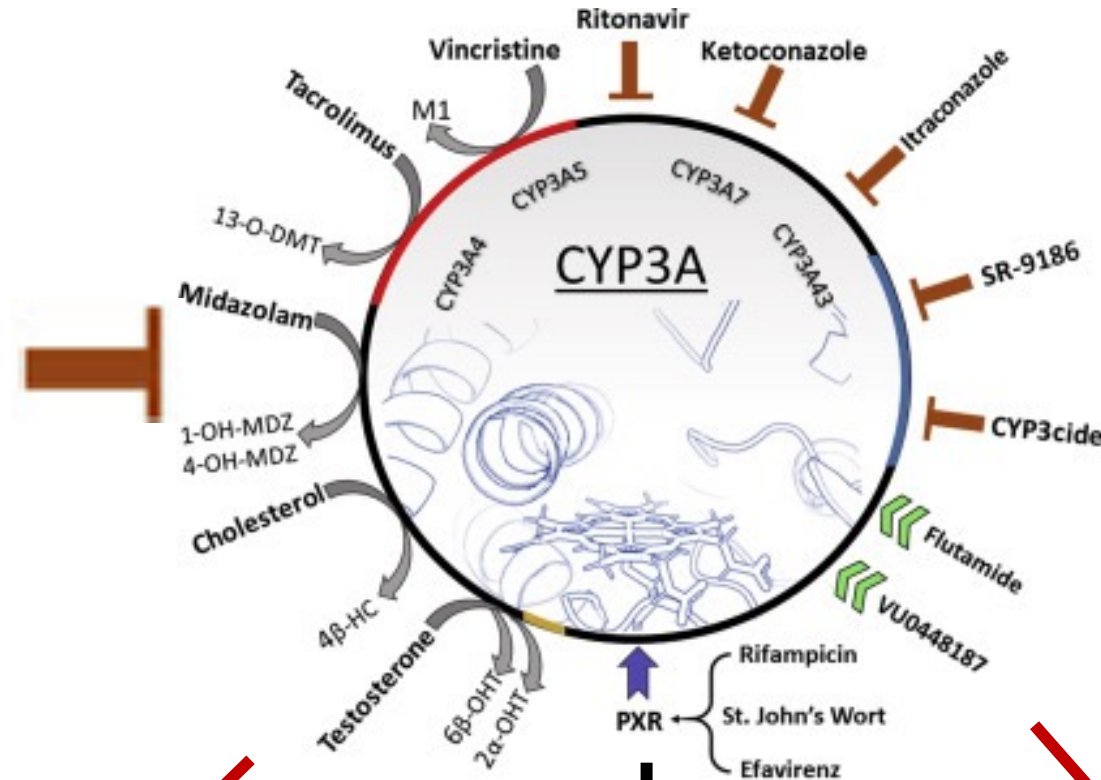
¹Department of Cardiology, Rabin Medical Center (Beilinson Campus) and ²Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel

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





ANTIFUNGINI
(>>triazolici)



DESETIL-AMIODARONE

ANTIARITMICI
(amiodarone, propafenone)

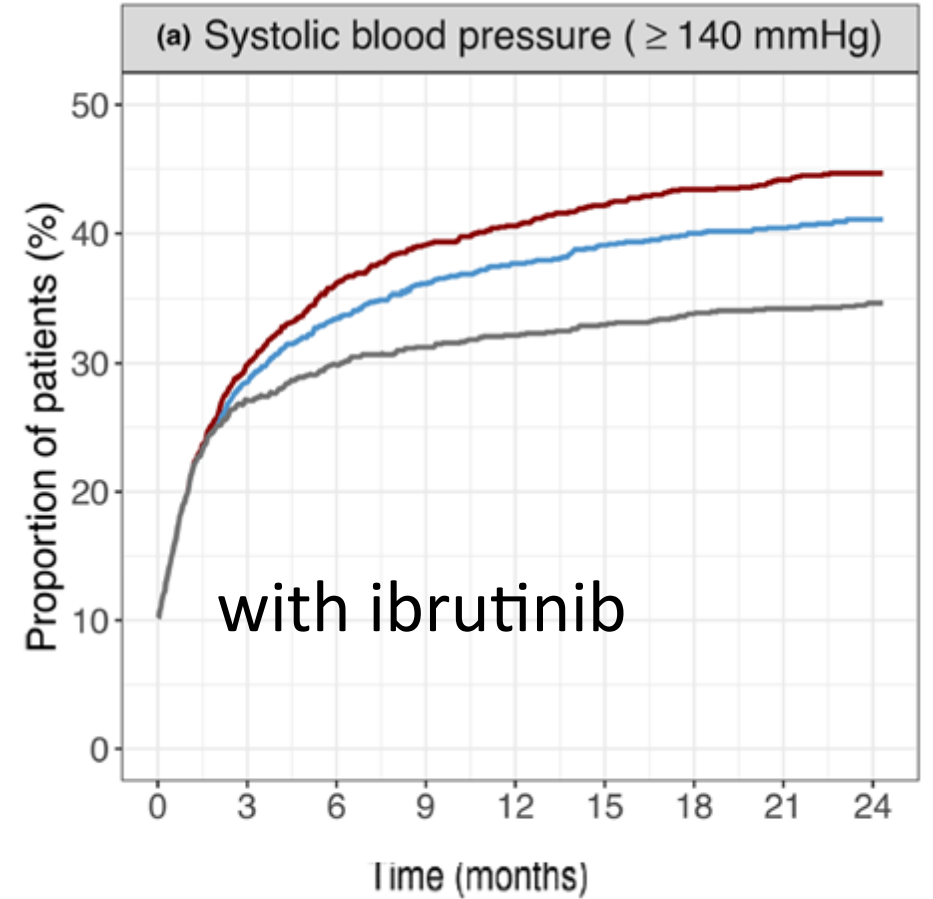
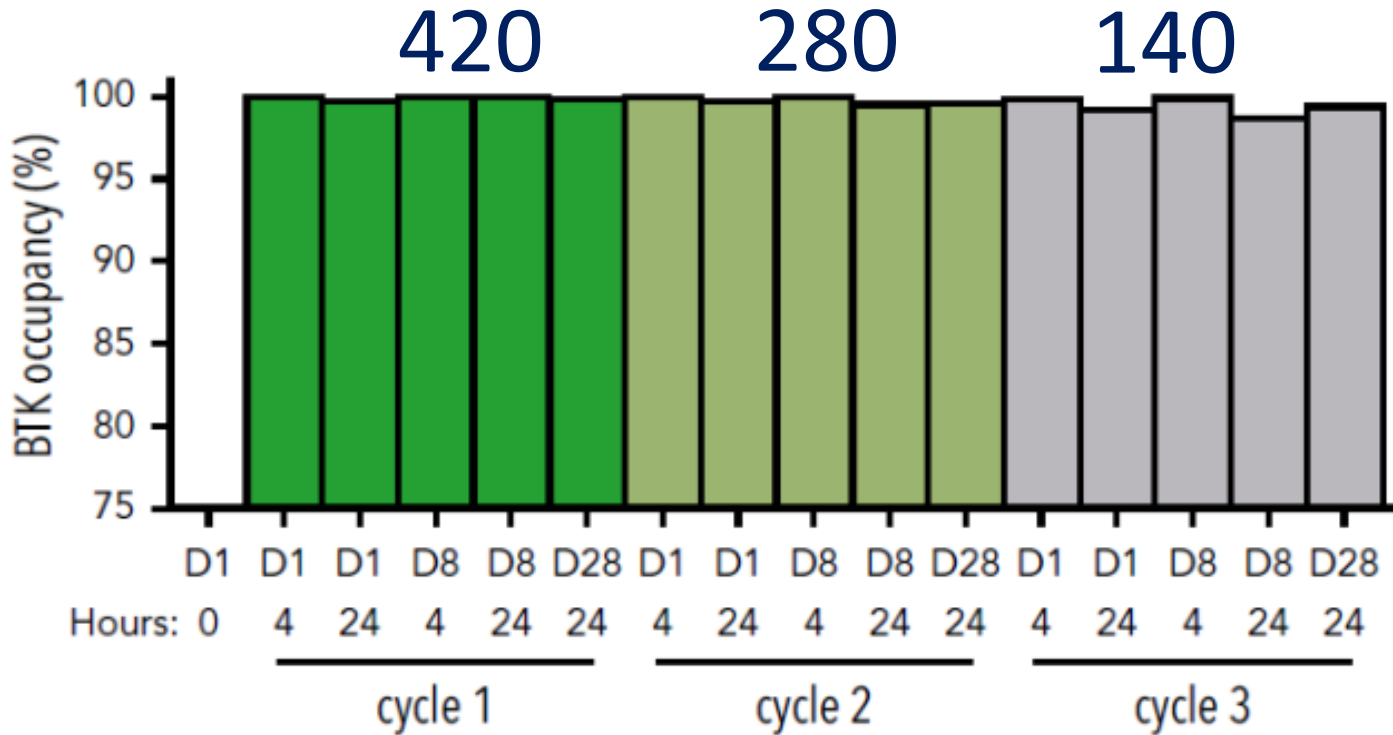
BTKi

NOAC
(rivaroxaban, apixaban)

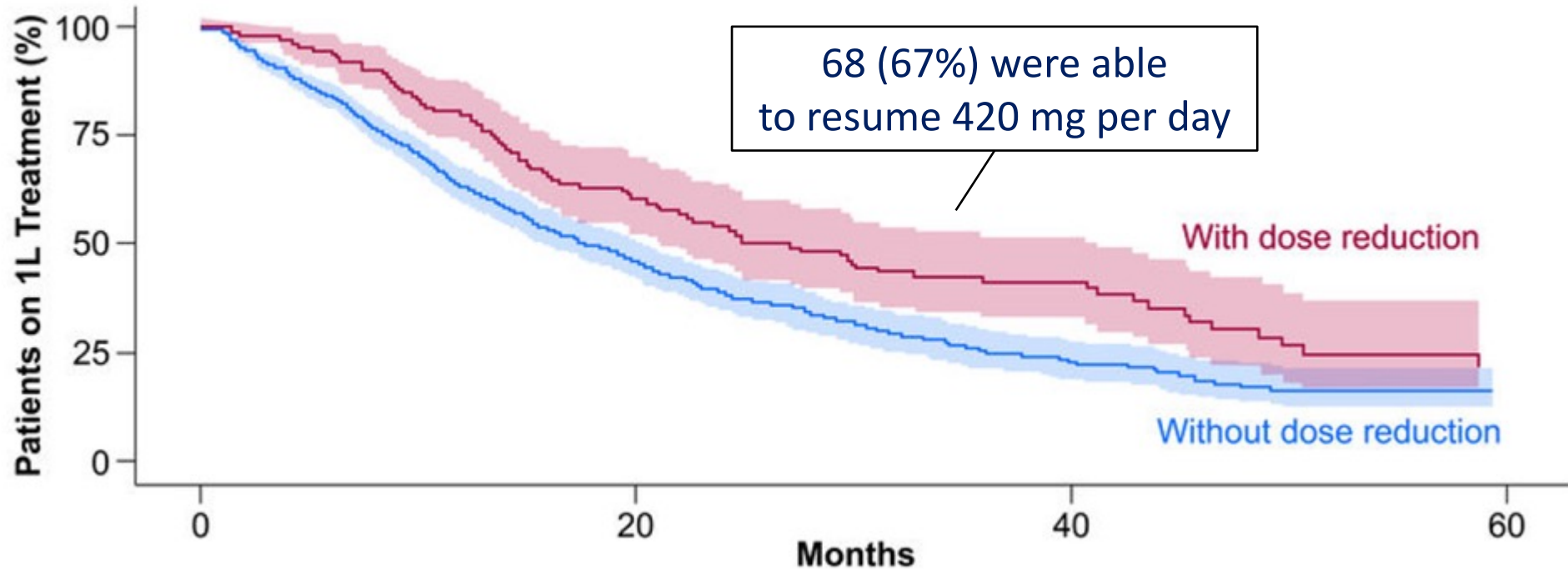


Co-administered CYP3A Inhibitor	Increase in C_{max}	
		<i>Observed</i>
Itraconazole (200 mg once daily)	157%	
		<i>Predicted</i>
Clarithromycin (250 mg twice daily)	175%	
Diltiazem (60 mg three times daily)	151%	

3. DOSE REDUCTIONS

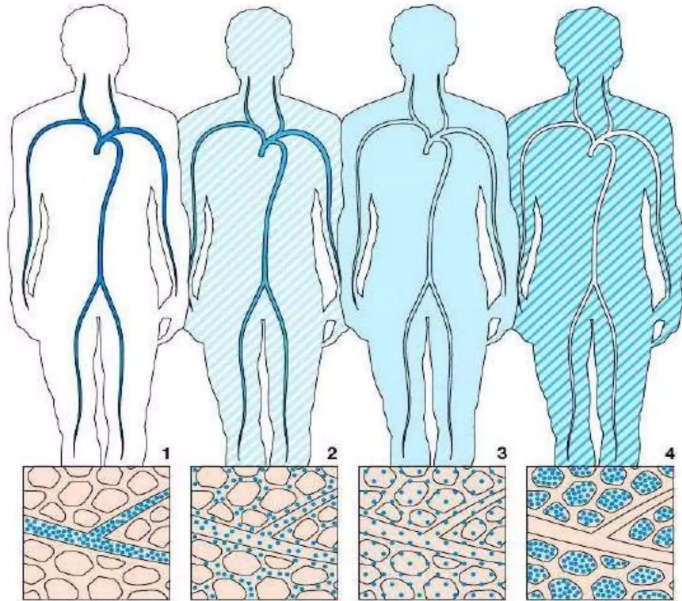


Time to Next Treatment Log-rank p=0.004



Blood 142 (2023) 269–270

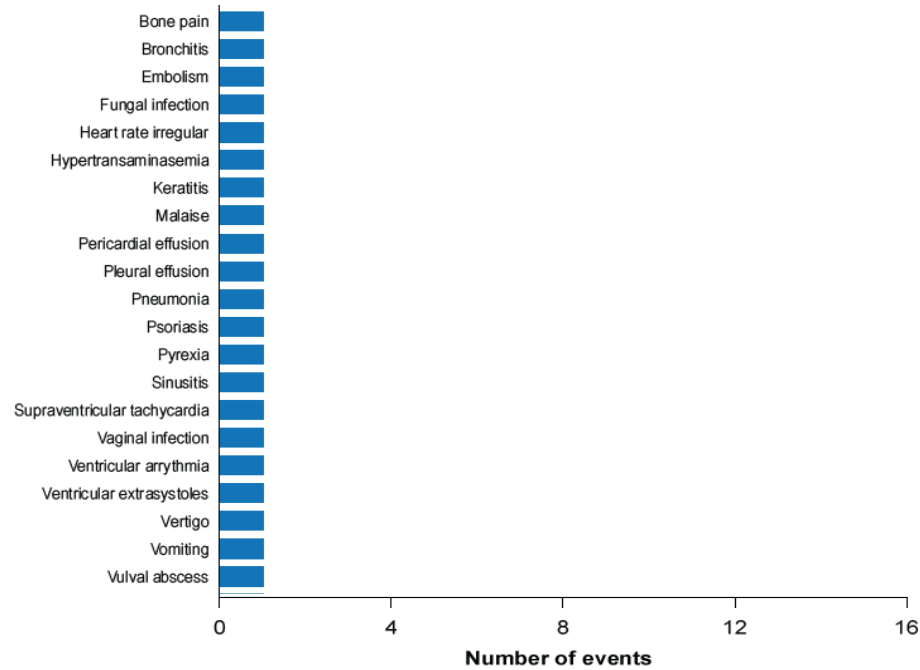
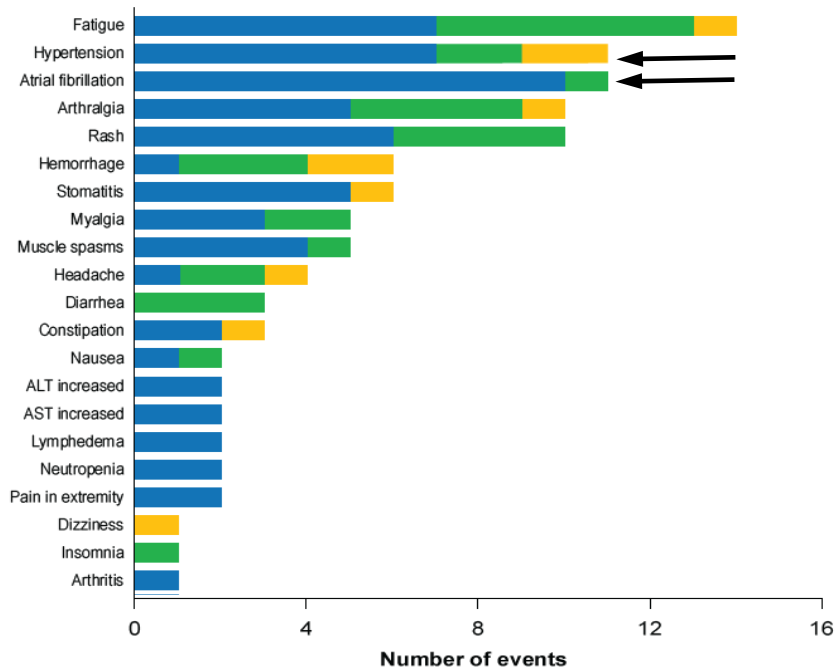
3. DOSE REDUCTIONS: A CAUTIONARY NOTE



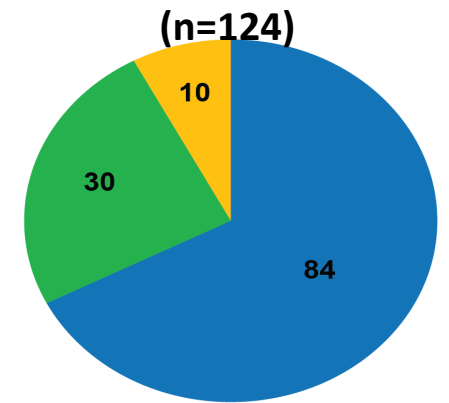
BTKi	Vd (L)
Ibrutinib	683
Acalabrutinib	723
Zanubrutinib	881

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 (n=124)



- 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