Farmacologia

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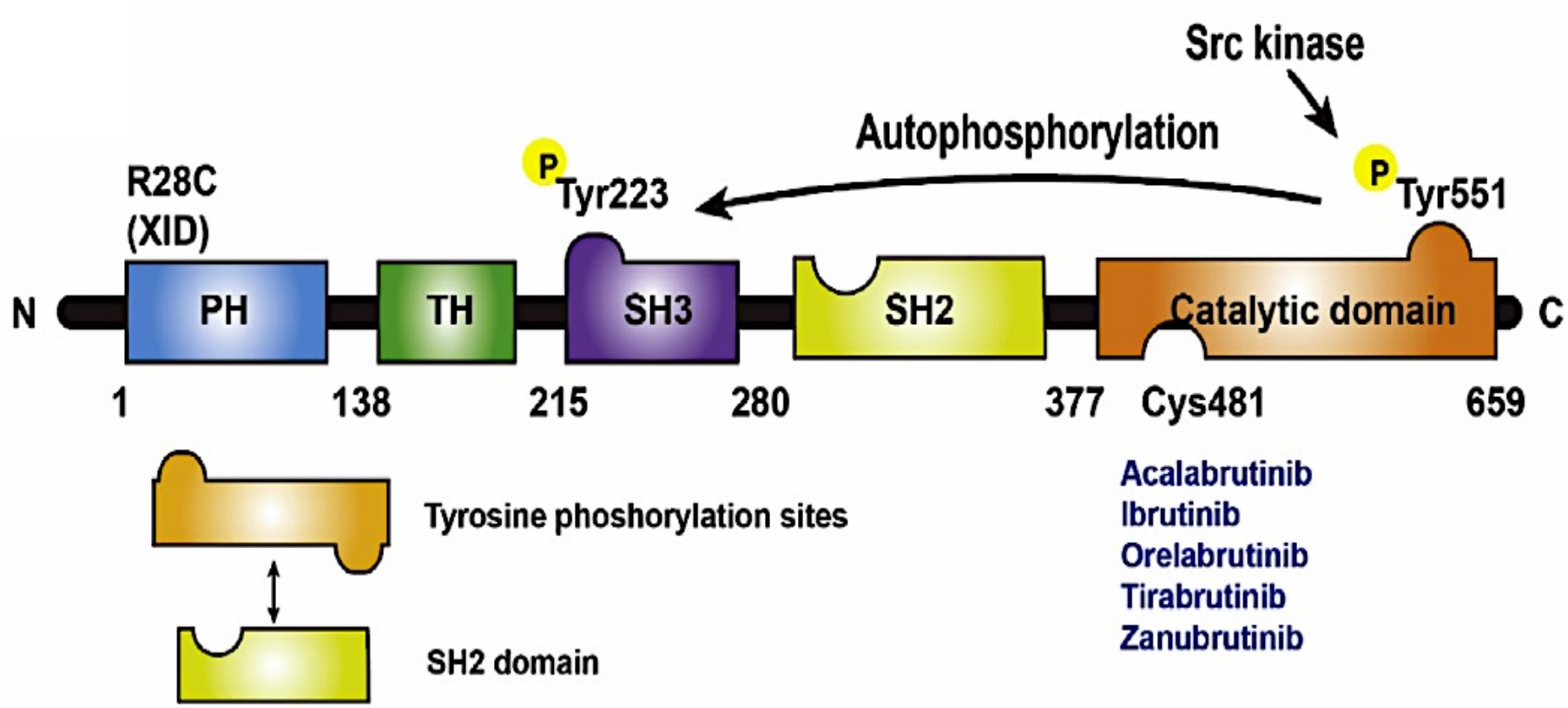
27 Aprile 2022

HILTON MILAN

Disclosures of Romano Danesi

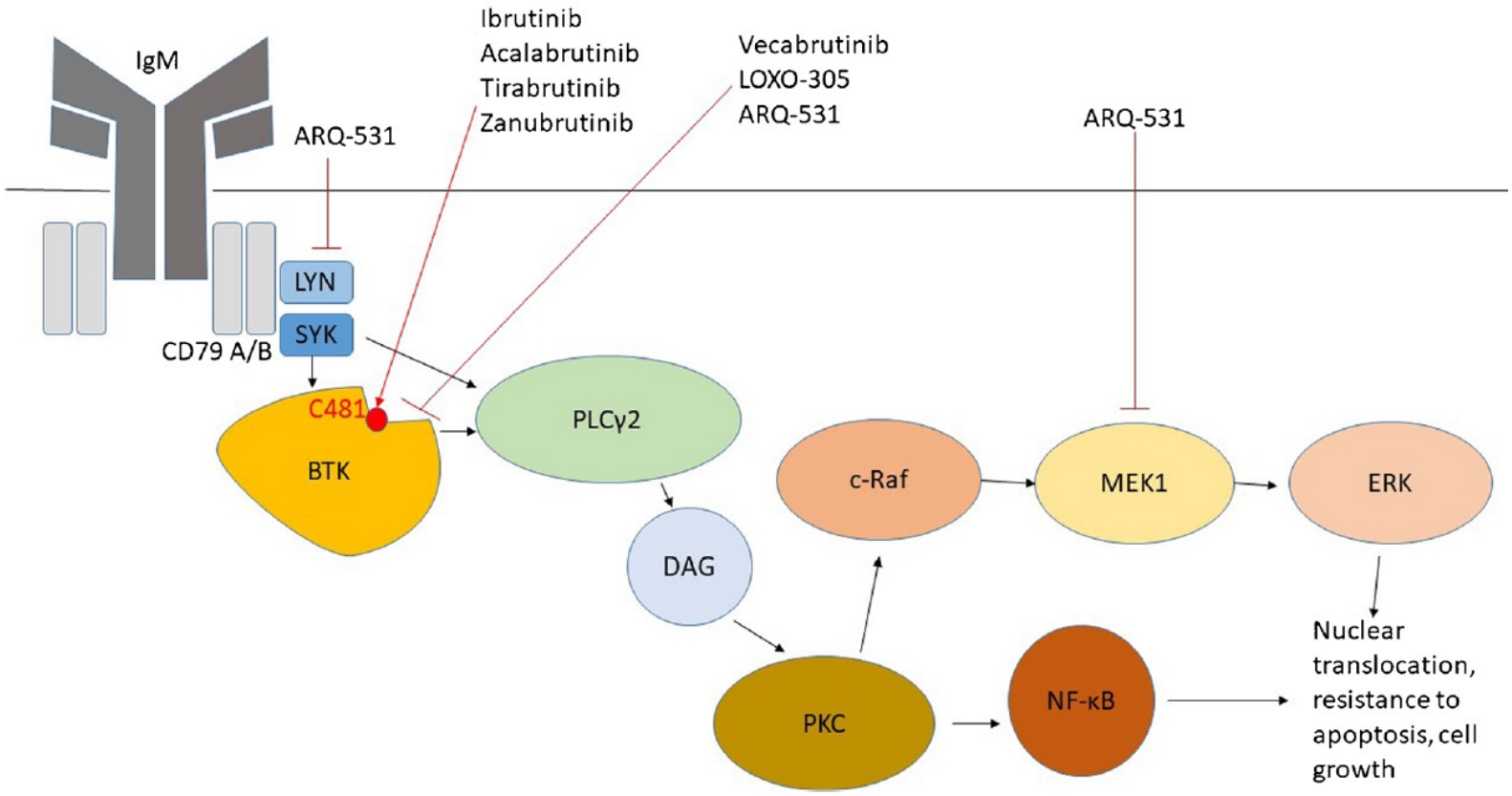
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
MSD			X		X		
Eisai			X		X	X	
AstraZeneca	X		X		X	X	
Beigene					X		
Janssen	X		X		X		
Novartis			X		X		
Lilly			X		X		
Incyte			X		X		
AB Science			X				

Structure of BTK



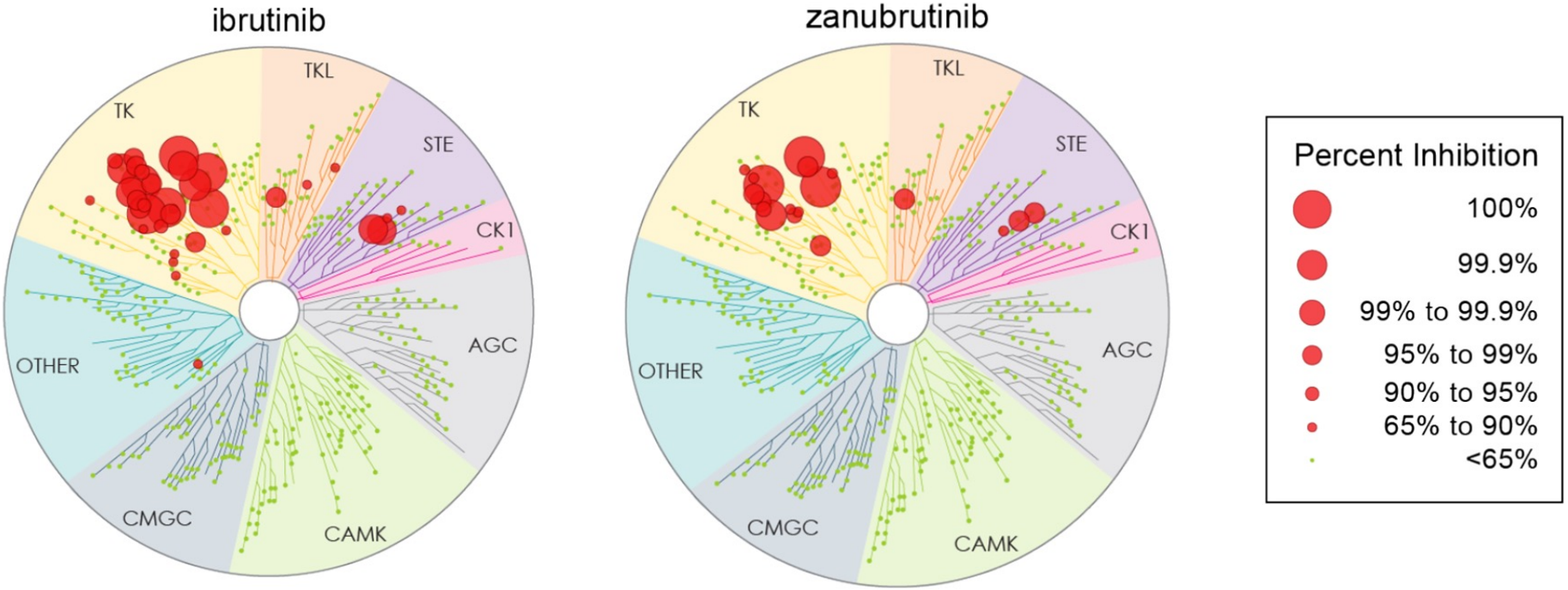
Liu J et al. Eur J Med Chem 217 (2021) 113329

Mechanism of action of BTK inhibitors



Bond DA, Woyach JA. Curr Hematol Malig Rep (2019) 14:197–205

Kinome profiling at 1 μM of ibrutinib and zanubrutinib



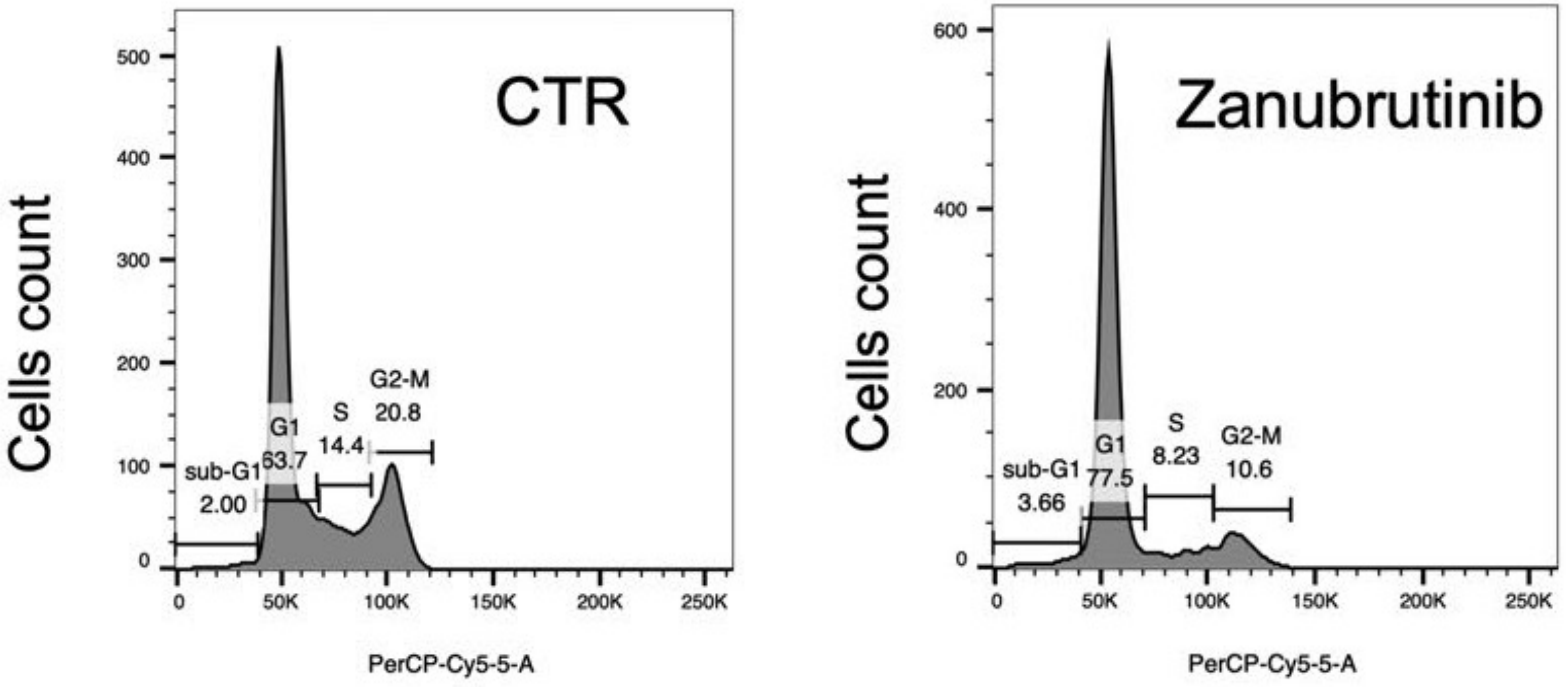
Kaptein A et al. Blood (2018) 132 (Supplement 1) : 1871

Selectivity of zanubrutinib and ibrutinib on selected kinases

	Relative to BTK IC_{50} (0.3/0.5 nM)	Relative to BTK IC_{50} (1.5 nM)
Kinase[a]	Zanubrutinib selectivity	Ibrutinib selectivity[b]
EGFR	**42**	3.5
ITK	**100**	3.3
TEC	**88**	6.7
HER2	**176**	4.3
HER4	**13.8**	2.3
BMX	2.8	0.5
TXK	4.4	1.3
BLK	5.0	0.1
JAK3	**2754**	**21**

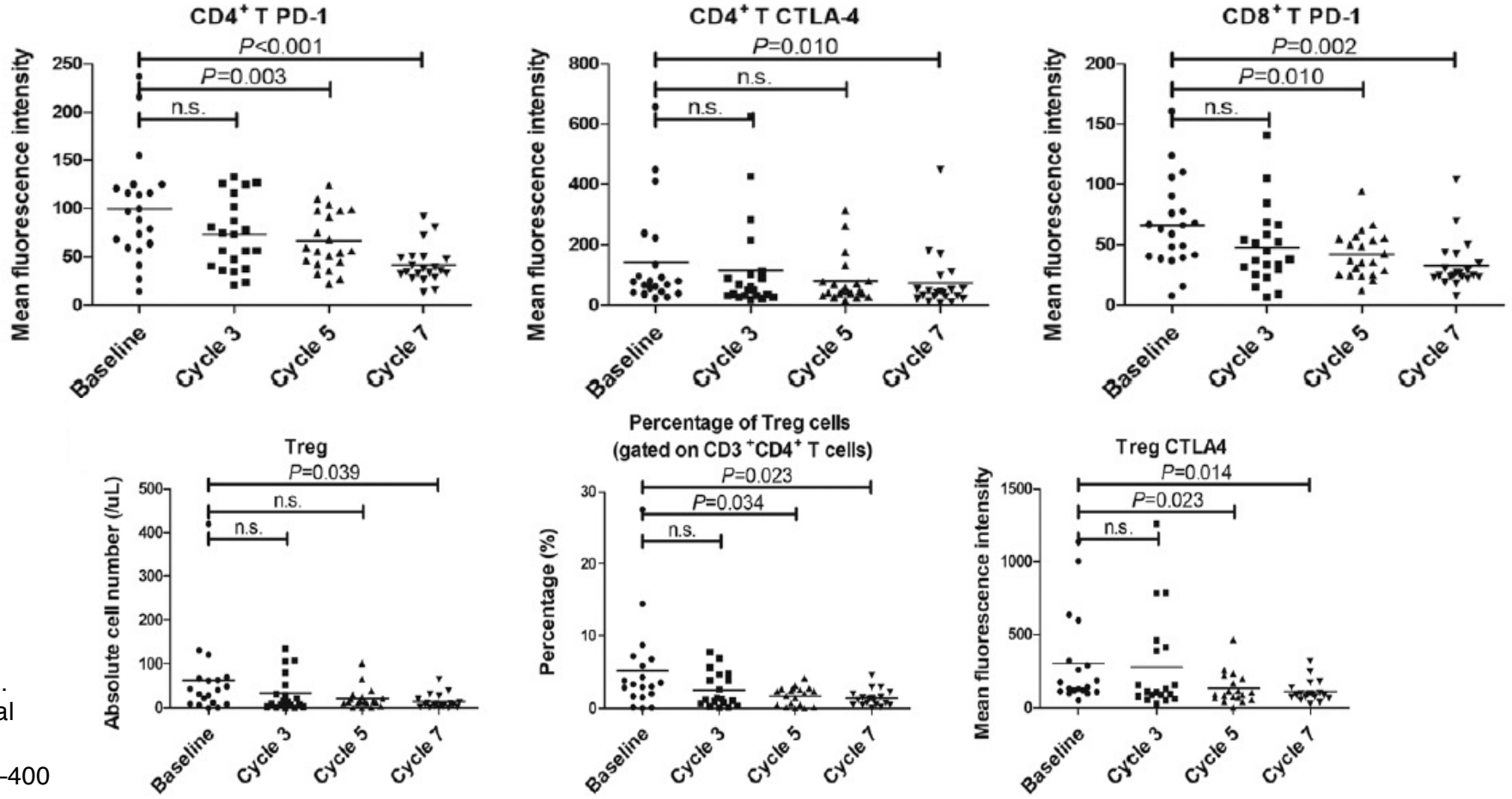
Tam CS et al. Expert Review of Clinical Pharmacology 2021;14:11,1329-1344

Cell cycle distribution after treatment with zanubrutinib



Tarantelli C et al. Haematologica 2019; 104:e307

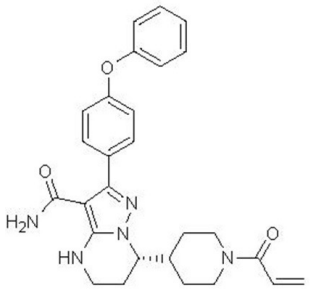
Dynamics of T cells and their subsets changes during zanubrutinib treatment



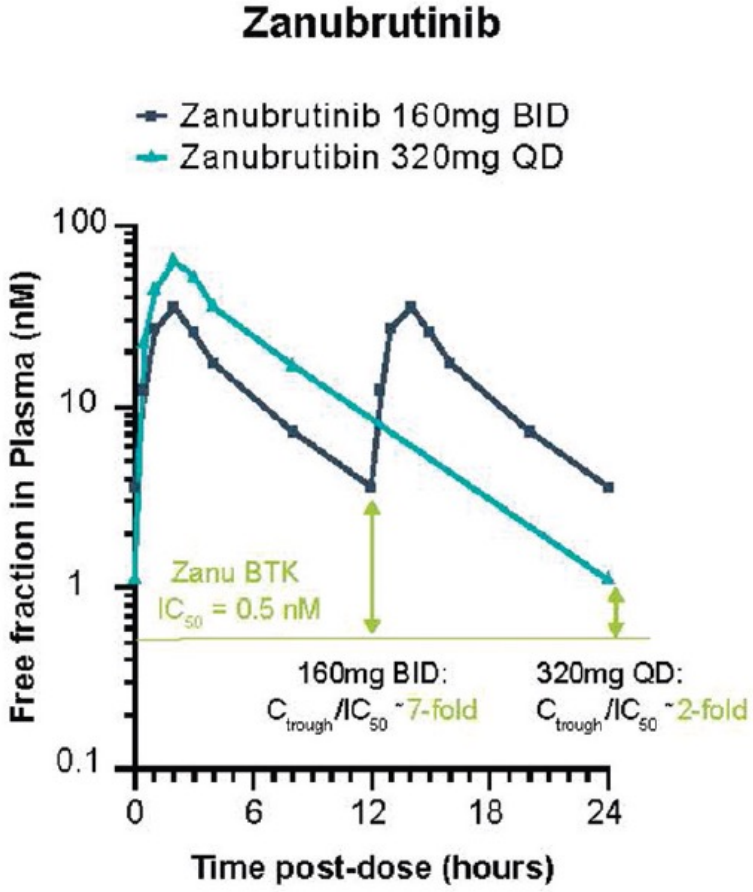
Zou Y-X et al. Hematological Oncology 2019;37:392–400

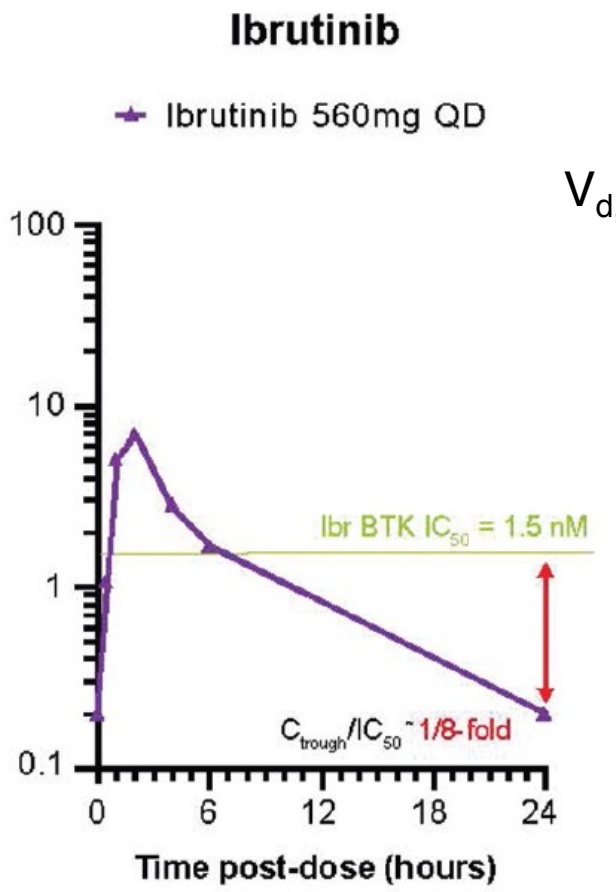
Free drug concentration time profiles relative to IC50 of BTK

Vp/F: 345 L

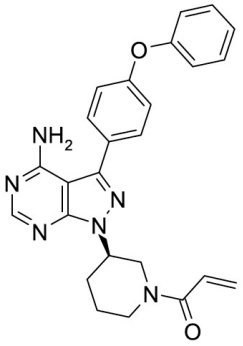


Zanubrutinib





$V_{d,ss}/F$: 10000 L

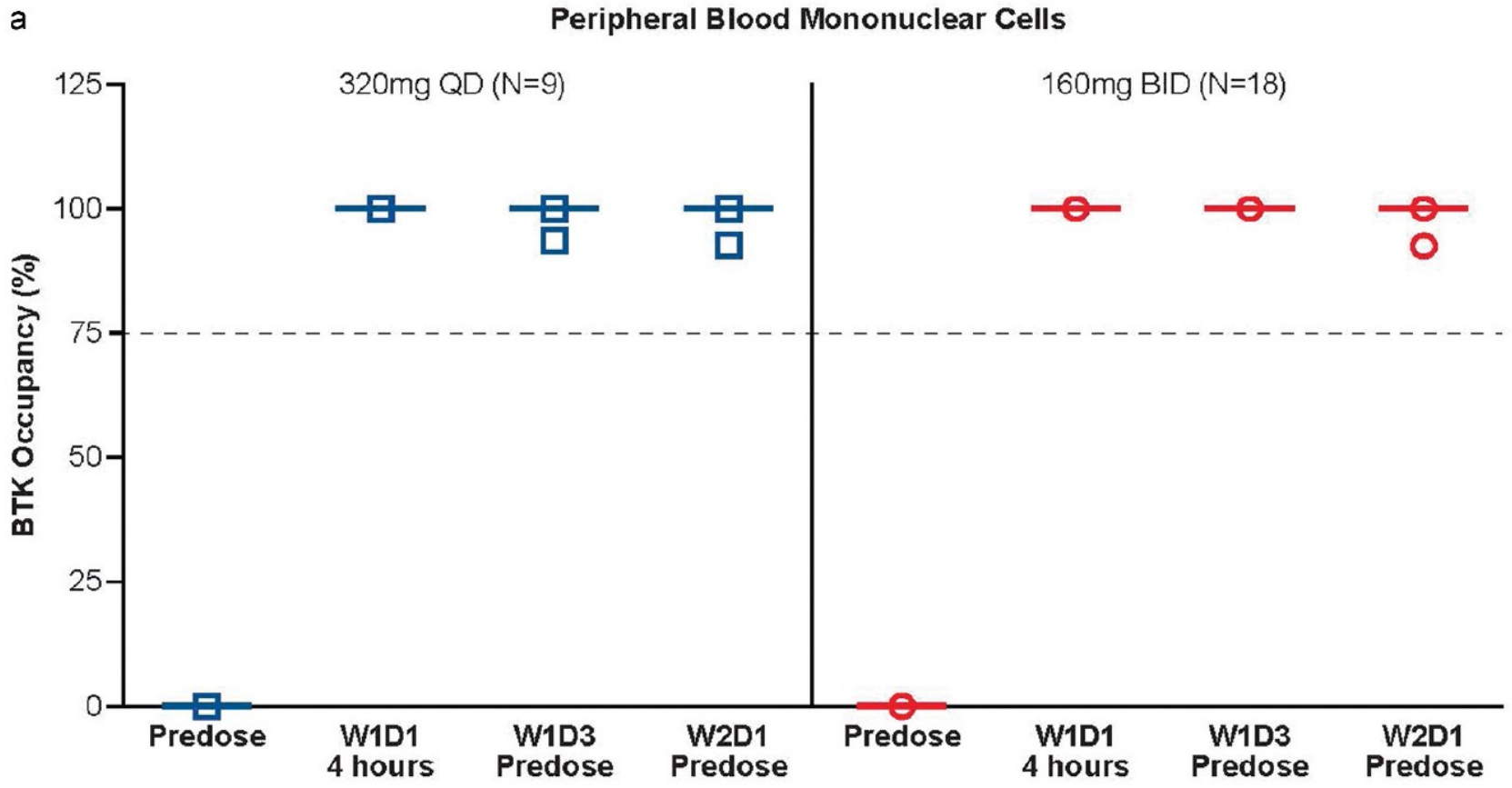


Ibrutinib

Tam CS et al. Expert Review of Clinical Pharmacology 2021;14:11,1329-1344

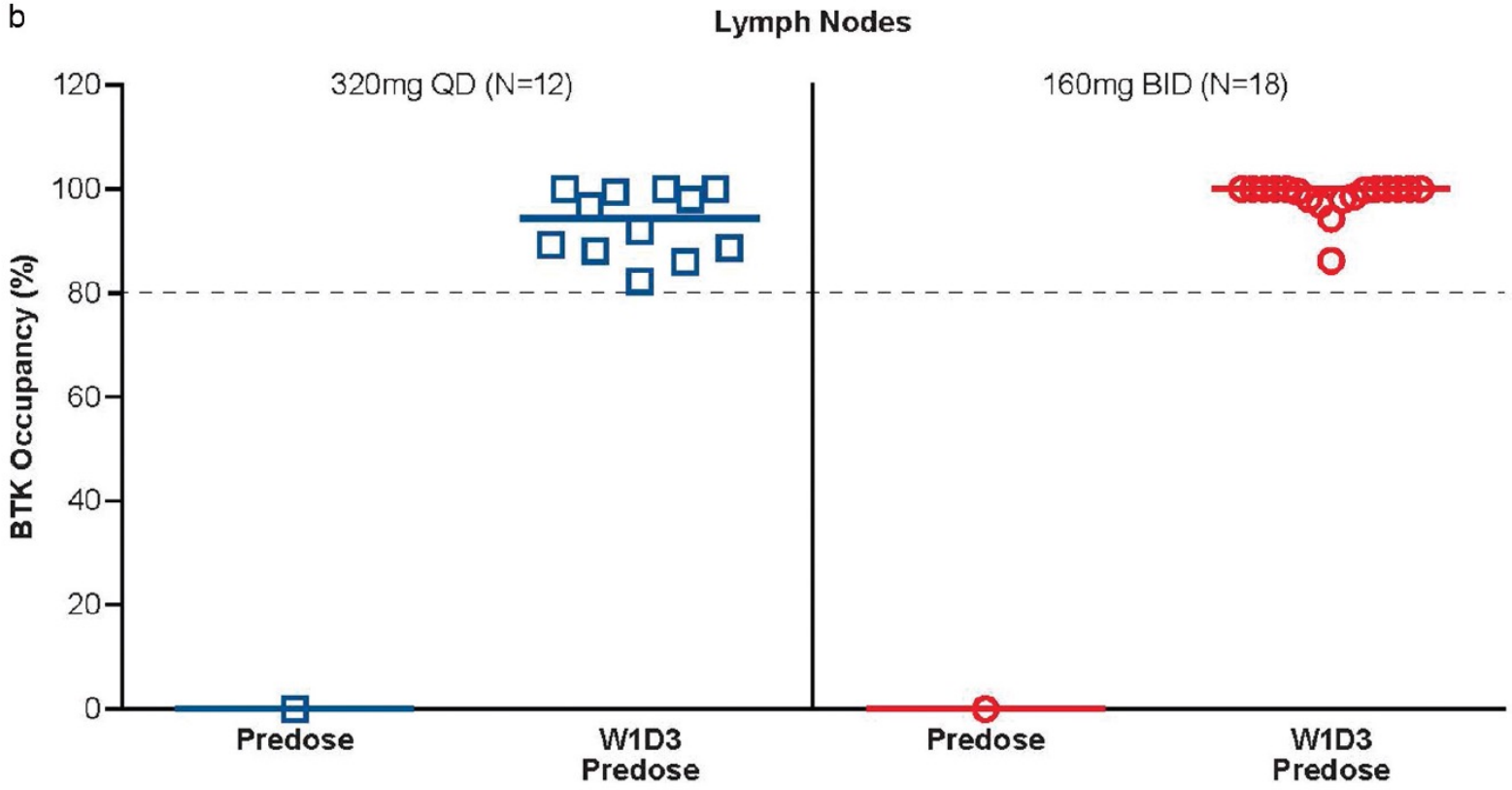
Marostica E et al. Cancer Chemother Pharmacol. 2015;75:111–21

Zanubrutinib BTK occupancy in PBMC by dose regimen



Tam CS et al. Blood 2019;134(11):851-859
Tam CS et al. Expert Review of Clinical Pharmacology 2021;14:11,1329-1344

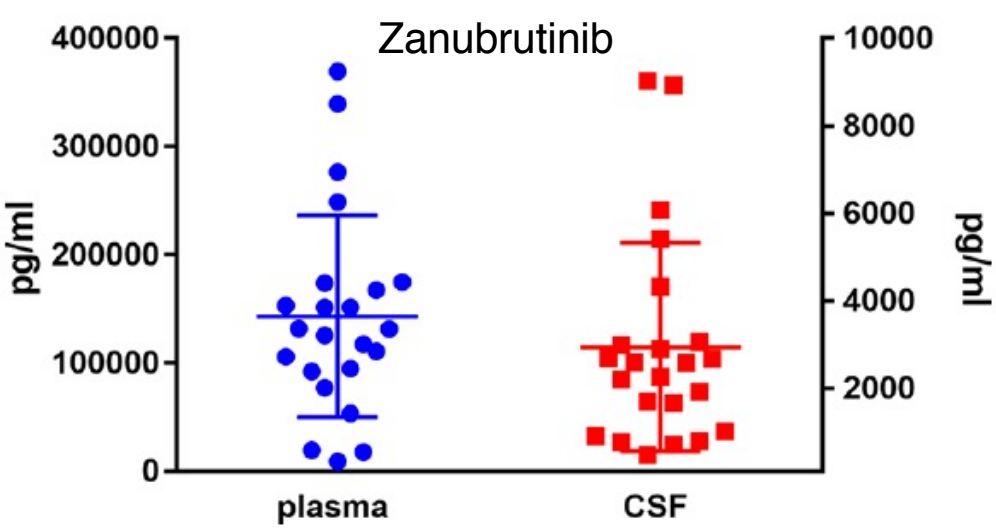
Zanubrutinib BTK occupancy in lymph nodes by dose regimen

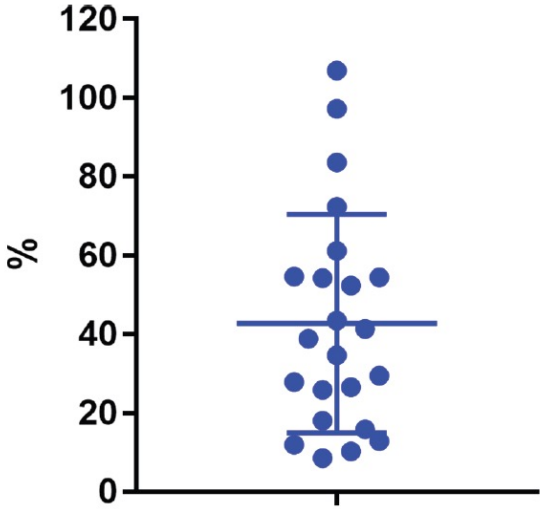


Tam CS et al. Blood 2019;134(11):851-859
Tam CS et al. Expert Review of Clinical Pharmacology 2021;14:11,1329-1344

Plasma and CSF levels of ibrutinib and zanubrutinib

	Ibrutinib			Zanubrutinib
Dose(mg)	560mg qd	700mg qd	840mg qd	160mg bid
Mean Plasma(ng/ml)	53.7	217.4	875.6	143.2
Mean CSF (ng/ml)	0.62	0.87	0.59	2.94

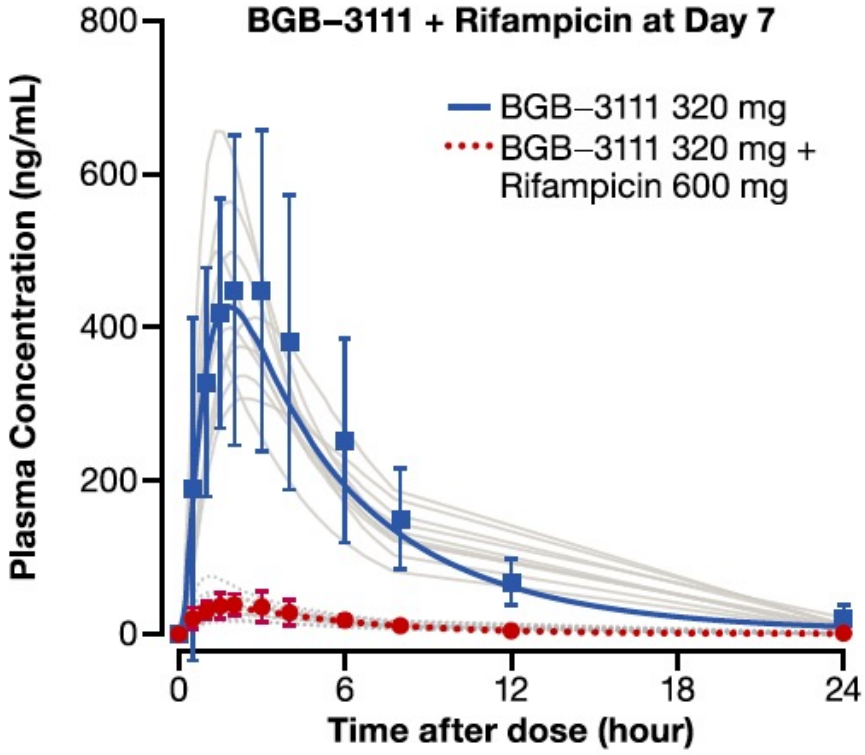


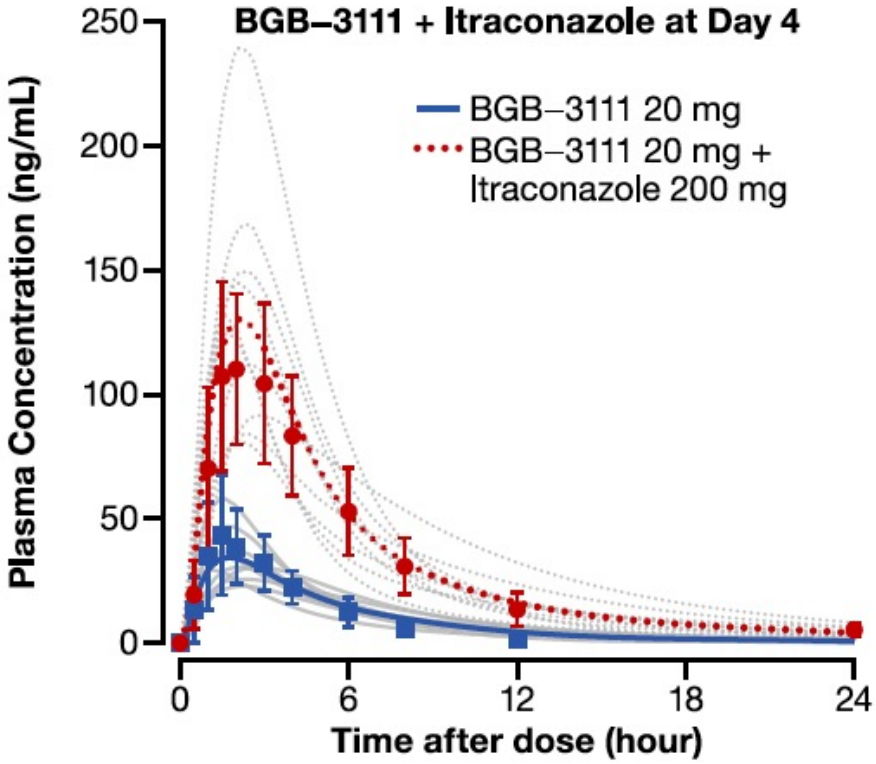


Corrected CSF/plasma ratios of zanubrutinib

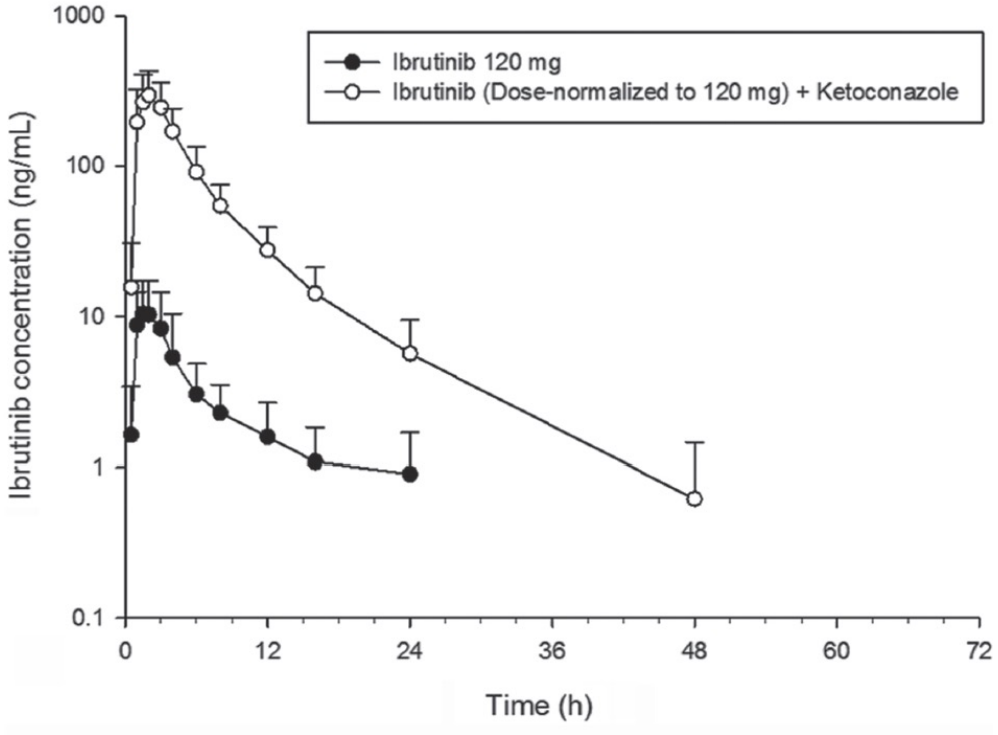
Zhang Y et al. Front Oncol 2021;11:760405

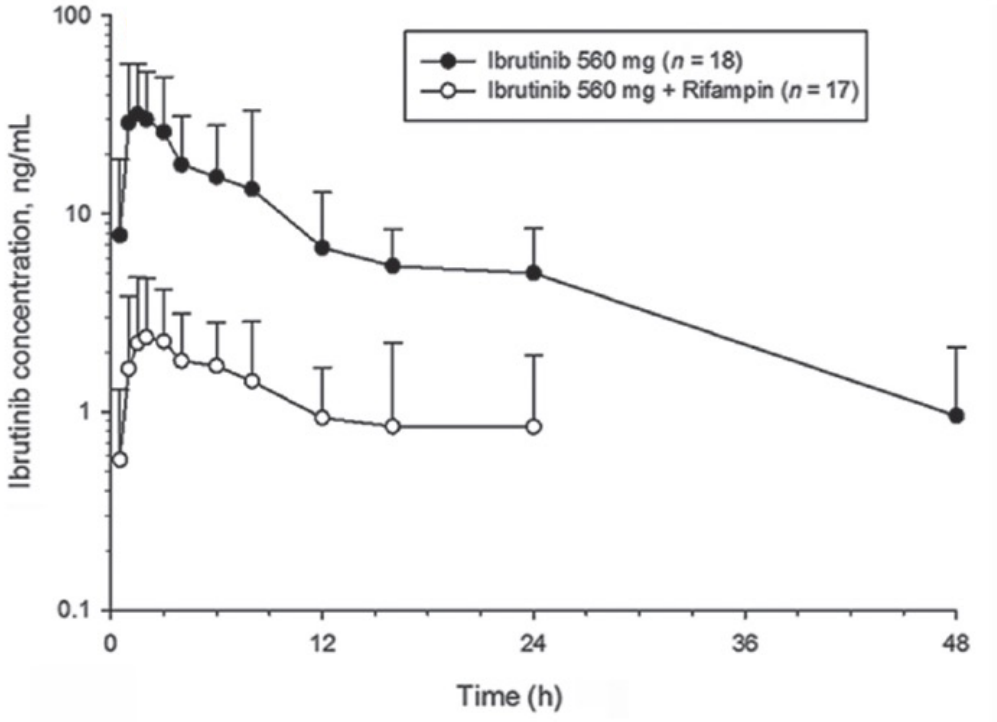
DDI of zanubrutinib with CYP3A4 modulators





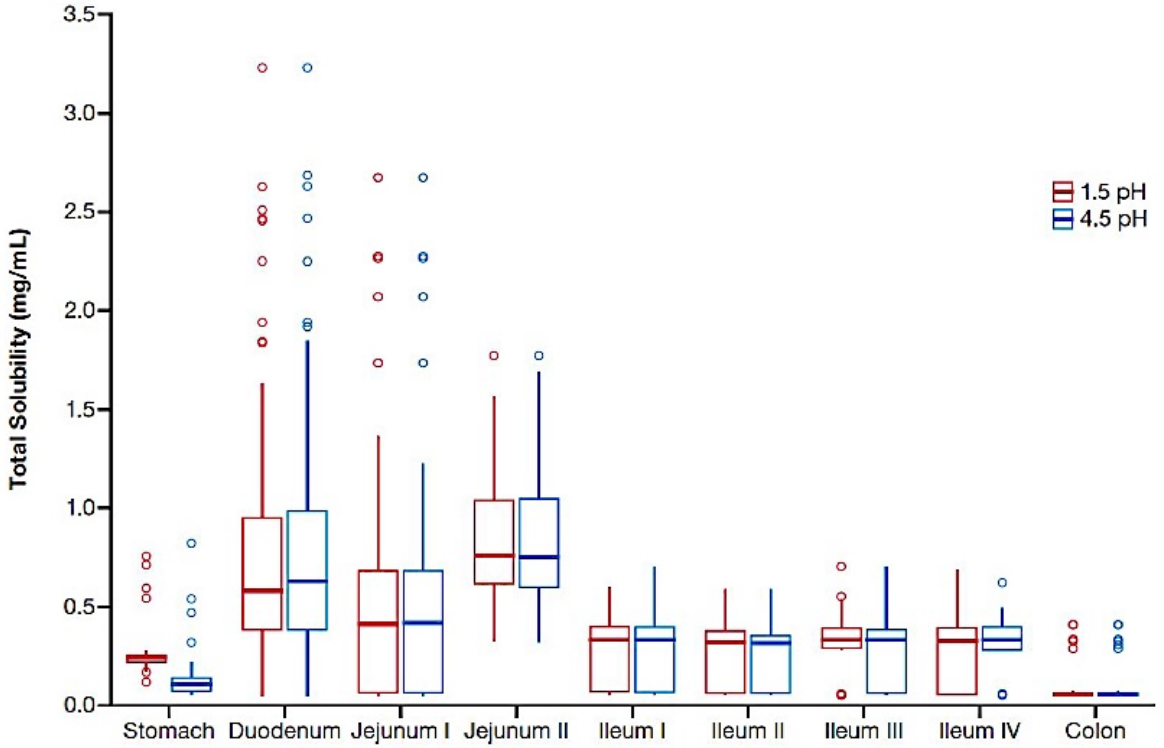
DDI of ibrutinib with CYP3A4 modulators





de Jong J et al. Pharma Res Per, 3(4), 2015, e00156

Effect of gastric pH values on solubility and PK of zanubrutinib



Wang K et al. CPT Pharmacometrics Syst Pharmacol 2021;10:441–454

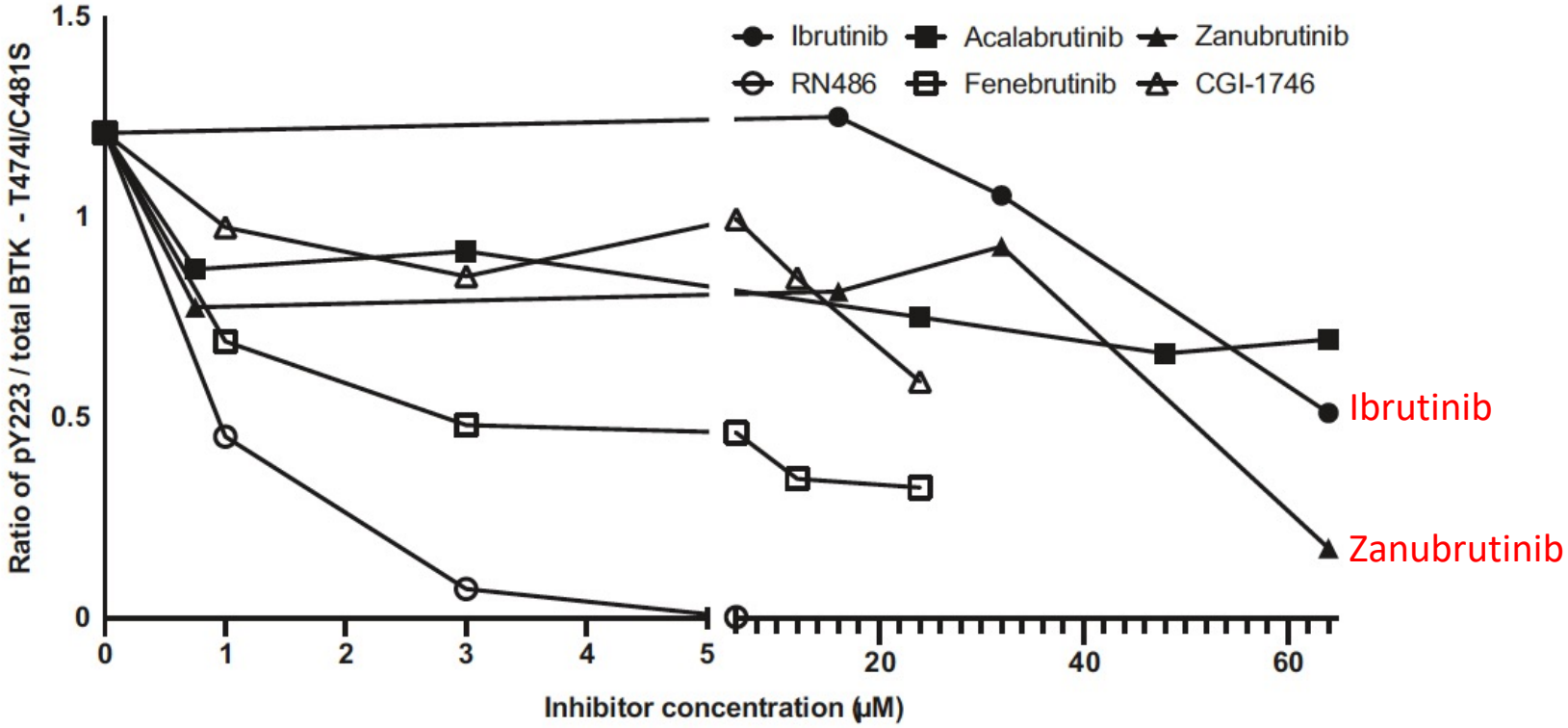
PK Parameters	pH=1.5	pH=4.5	Ratio
C_{max}, ng/mL (95%CI)	238.39 (206.79-274.81)	232.40 (201.07-268.60)	1.03
$AUC_{0\text{-}24hr}$, ng*hr/mL (95%CI)	1444.15 (1308.28-1594.13)	1456.12 (1320.47-1605.70)	0.99

Effects of ibrutinib on BTK activity in single and double variants

	BTK residue single variants				BTK residues double variants	
	T474E T474V T474L **T474I** T474Q **T474S**	T474A T474N	T474P	T474M	T474A/C481S T474S/C481S	T474I/C481S T474M/C481S T474M/C481T
BTK activity	normal	weak	absent	normal	weak	normal
Ibrutinib inhibitory conc. (μM)	0.5	0.5	—	≥ 4	0.5	> 64

Estupiñán HY et al. Leukemia (2021) 35:1317–1329

Comparison of ibrutinib on mechanisms of resistance with second-generation BTK inhibitors



Estupiñán HY et al. Leukemia (2021) 35:1317–1329

Conclusions

- Zanubrutinib is has greater target selectivity and therapeutic exposures than ibrutinib.
- Zanubrutinib forms an irreversible, covalent bond at Cys481 within the adenosine triphosphate-binding pocket of BTK.
- The greater selectivity of zanubrutinib as well as its PK/PD profiles translates into clinically impactful benefits, including improved dosing flexibility, safety, and efficacy.