Farmacologia

Romano Danesi

UO Farmacologia clinica e Farmacogenetica

Università di Pisa

TORINO

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Disclosures of Romano Danesi

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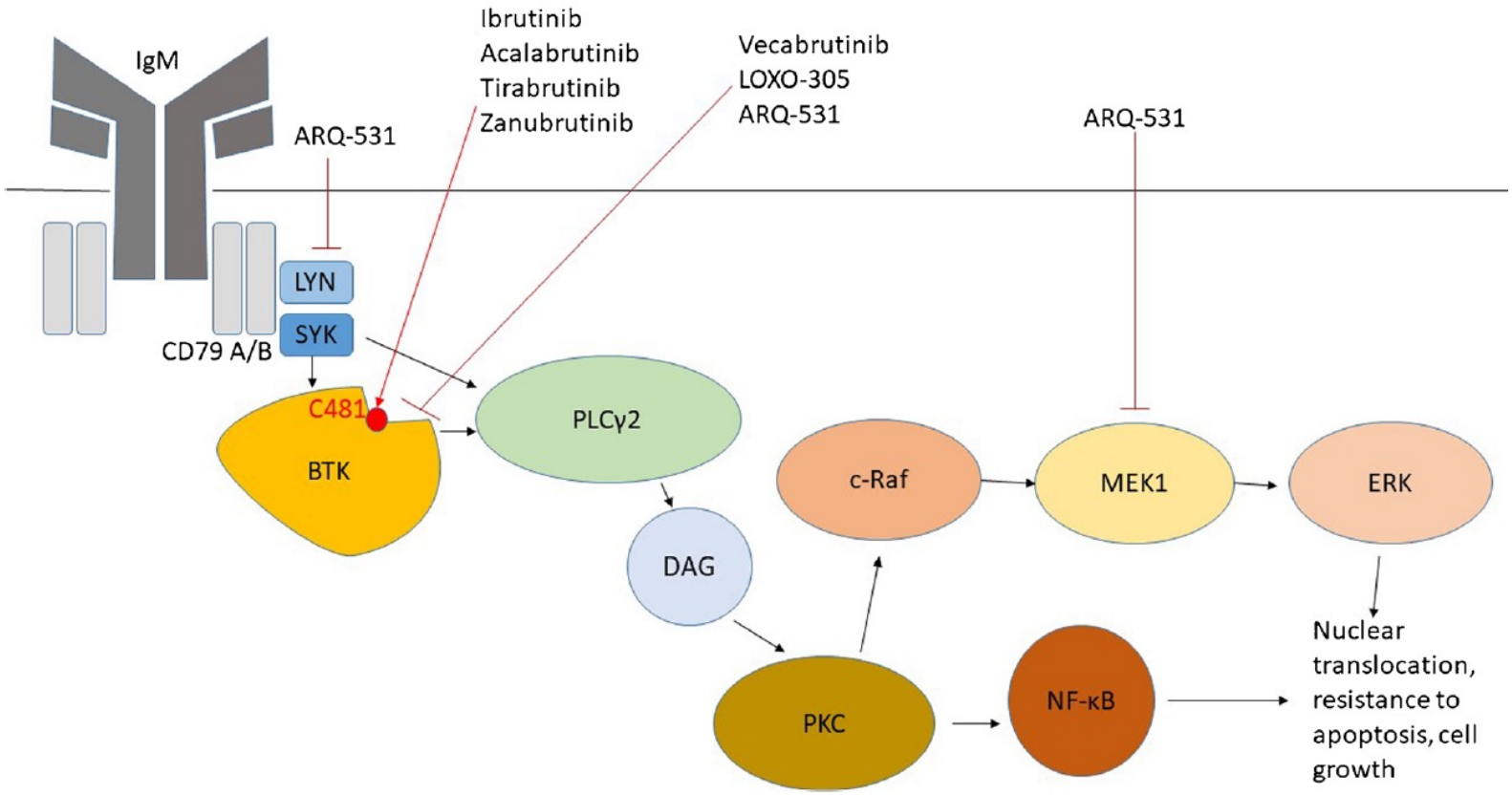
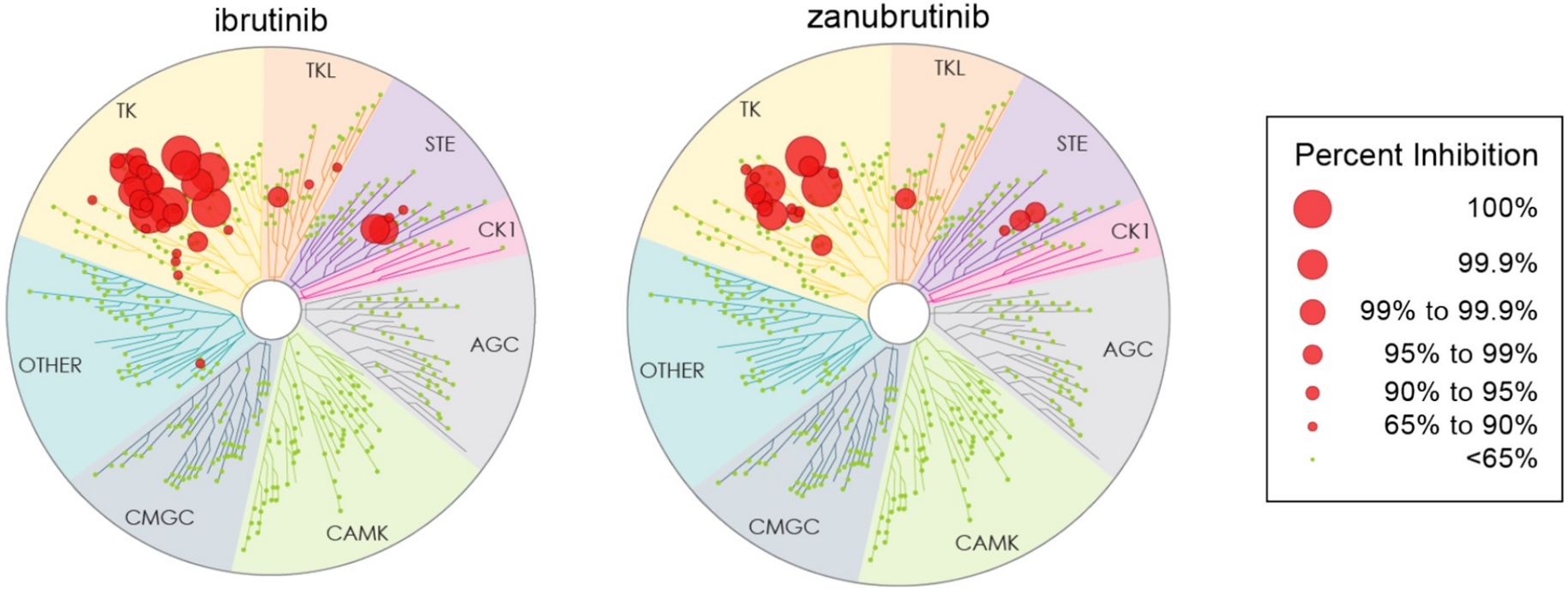
Eisai			X		X	X	
AstraZeneca	X		X		X	X	
Beigene					X		
Janssen	X		X		X		
Novartis			X		X		
Lilly			X		X		
Incyte			X		X		
AB Science			X				

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

IC_{50} of BTK and members of the TEC protein kinase family by ibrutinib and zanubrutinib

Kinase	Ibrutinib IC_{50} (nM)[a]	Zanubrutinib IC_{50} (nM)[b]
BLK	0.1 + 0.0	1.13[c]
BMX	0.8 ± 0.1	0.62[c]
BTK	1.5	0.3 ± 0.06
EGFR	5.3 ± 1.3	2.6 ± 1.0[c]
ERBB2	6.4 ± 1.8	530 ± 273
ERBB4	3.4 ± 1.4	1.58[c]
ITK	4.9 ± 1.25	56 ± 12
JAK3	32 ± 15.0	580 ± 21
TEC	10 ± 2.0	2.0 ± 0.8
TXK	2.0 ± 0.3	2.95[c]

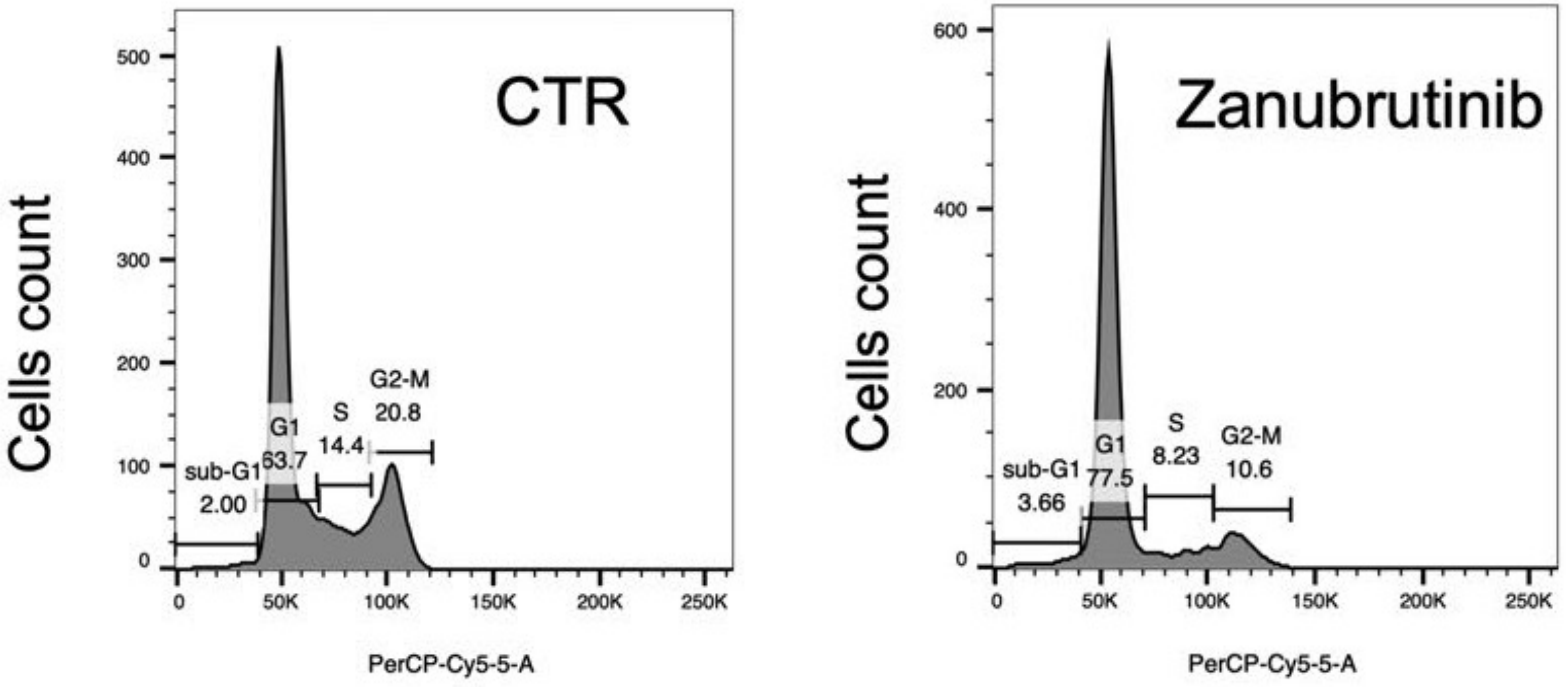
O'Brien SM et al. Front Oncol 2021,11:720704

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**

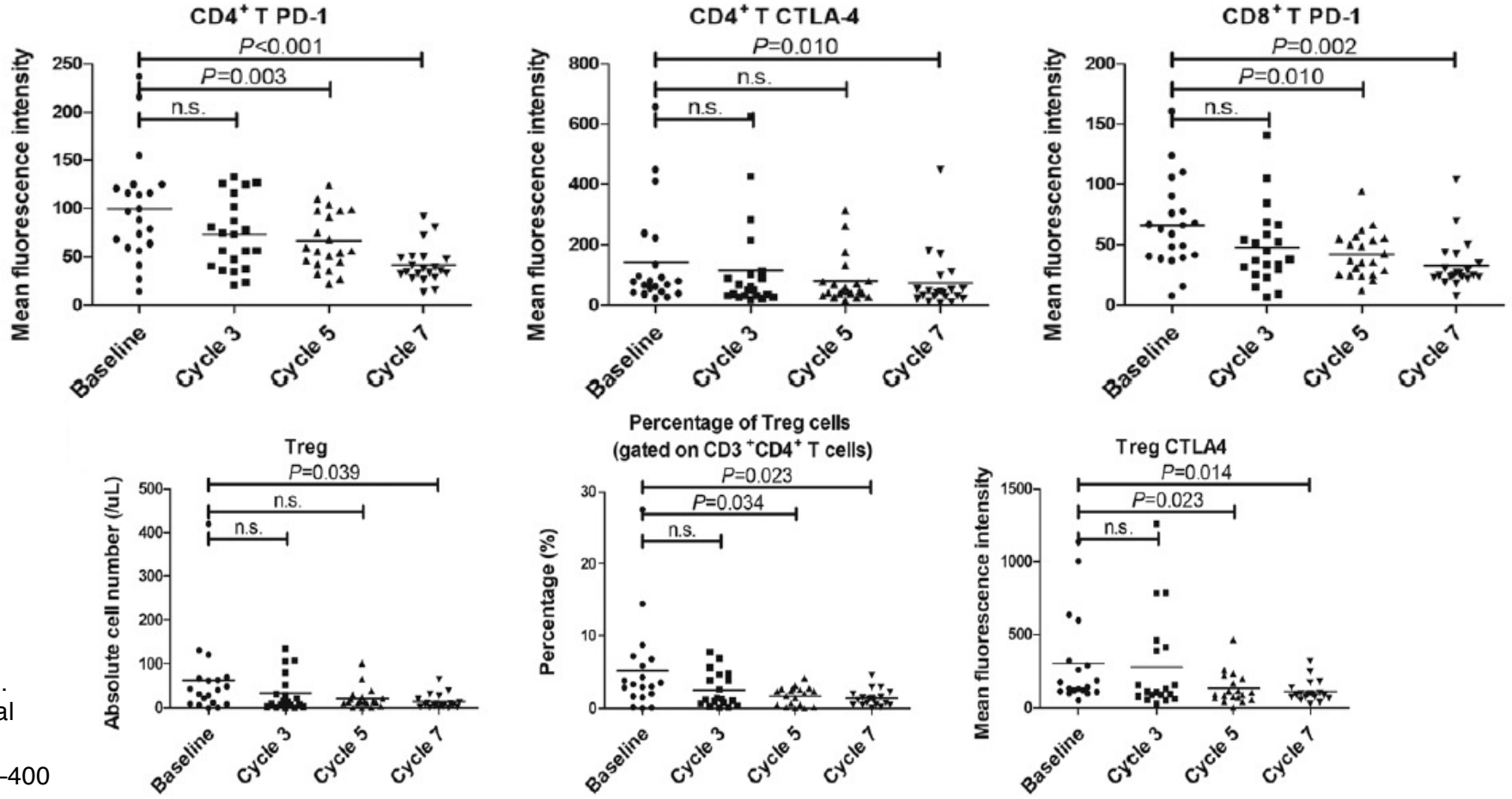
Tam CS et al. Expert Review of Clinical Pharmacology 2021;14:11,1329-1344

Cell cycle distribution after treatment with zanubrutinib



Tarantelli C et al. Haematologica 2019; 104:e307

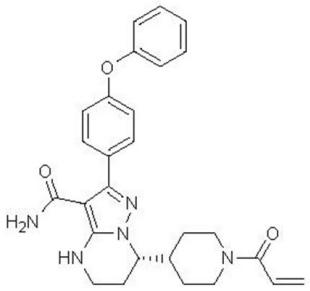
Dynamics of T cells and their subsets changes during zanubrutinib treatment



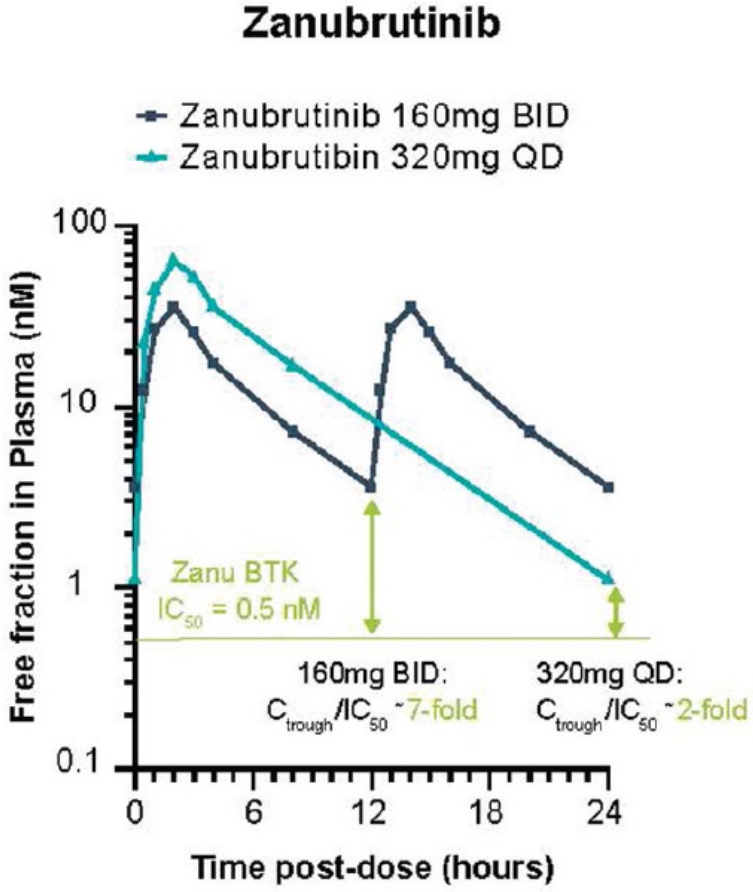
Zou Y-X et al. Hematological Oncology 2019;37:392–400

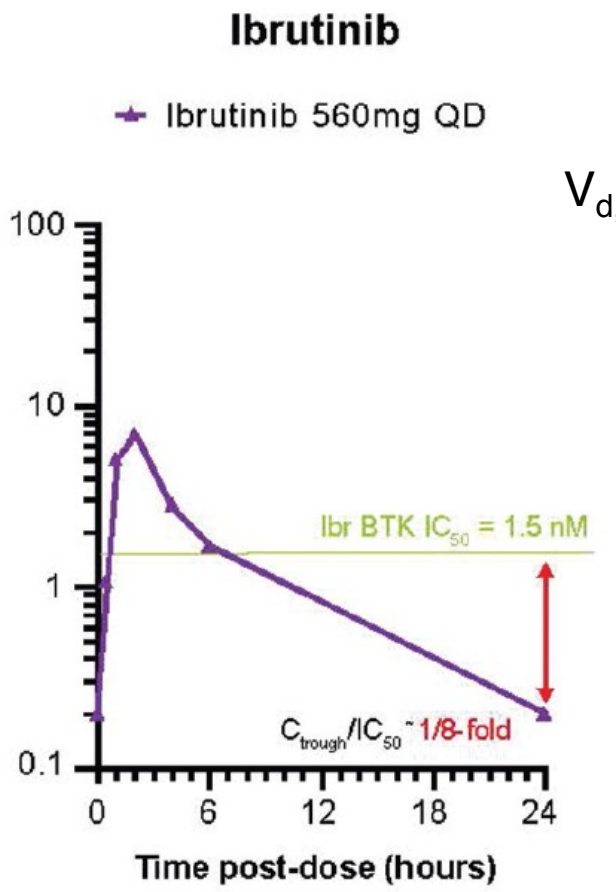
Free drug concentration time profiles relative to IC50 of BTK

Vp/F: 345 L

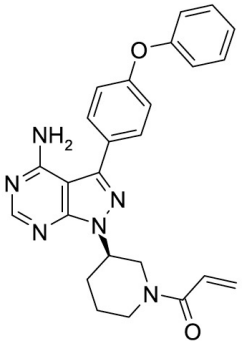


Zanubrutinib





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

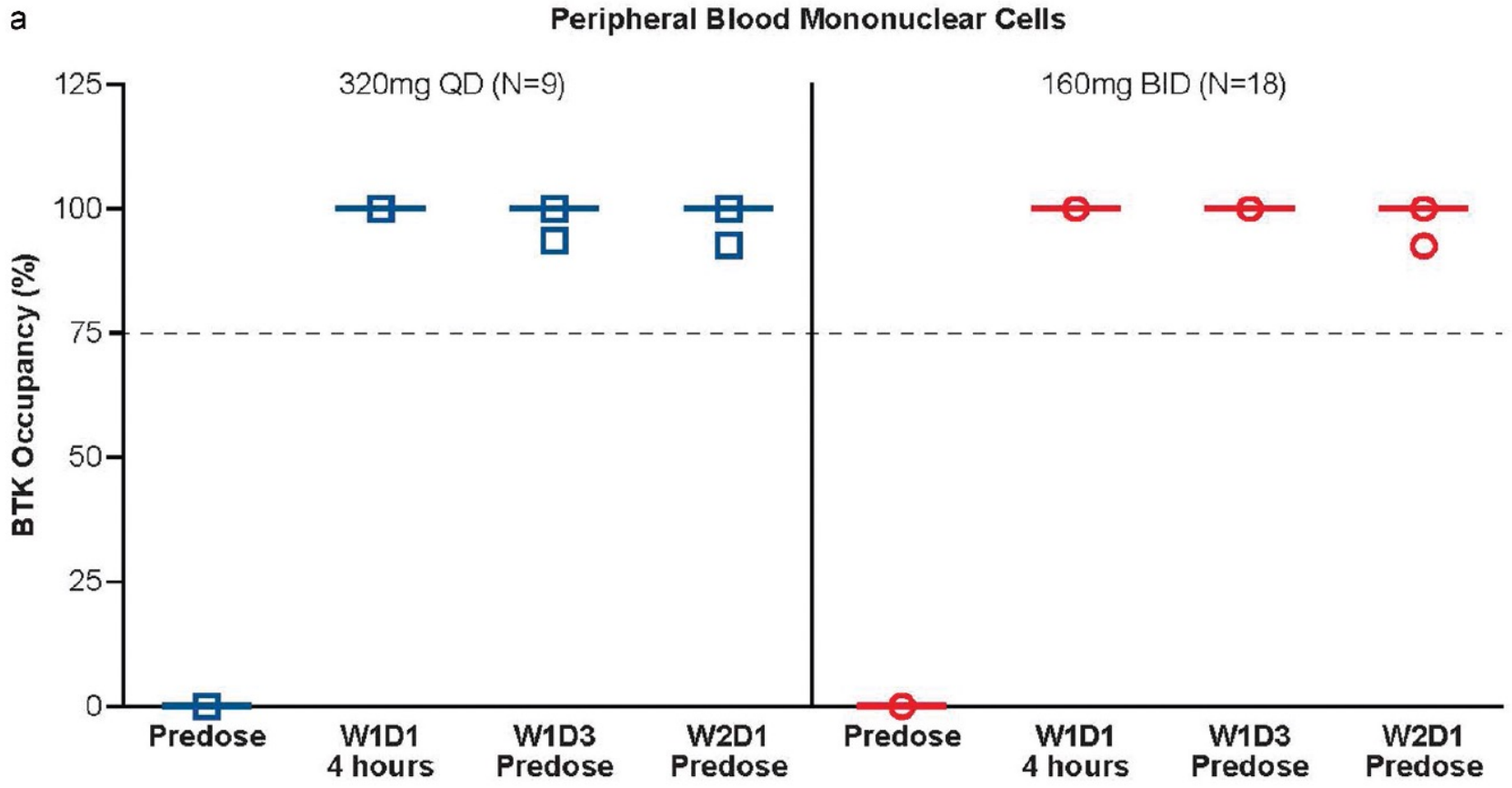


Ibrutinib

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

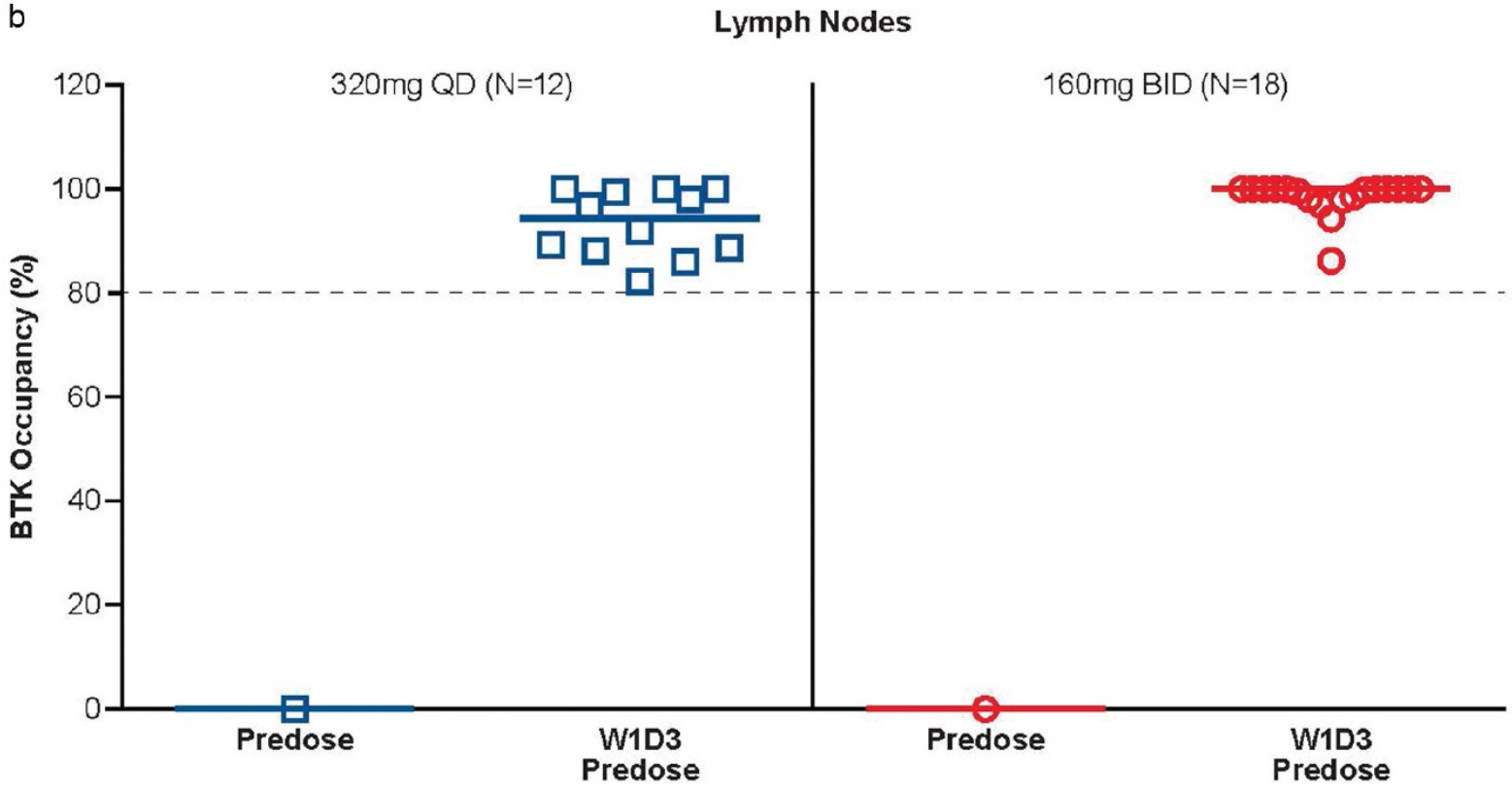
Marostica E et al. Cancer Chemother Pharmacol. 2015;75:111–21

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



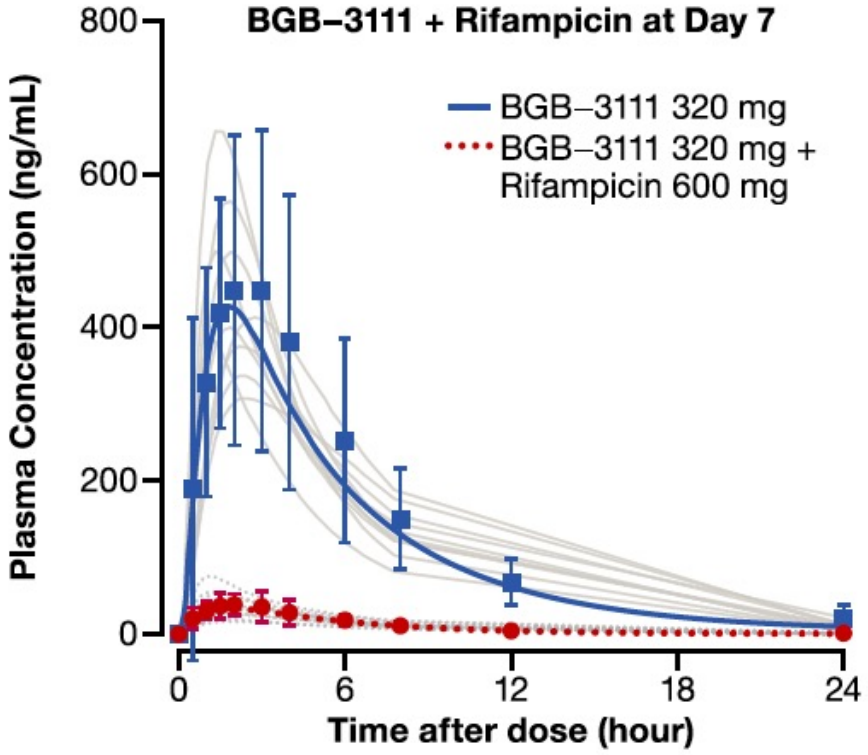
Tam CS et al. Blood 2019;134(11):851-859
Tam CS et al. Expert Review of Clinical Pharmacology 2021;14:11,1329-1344

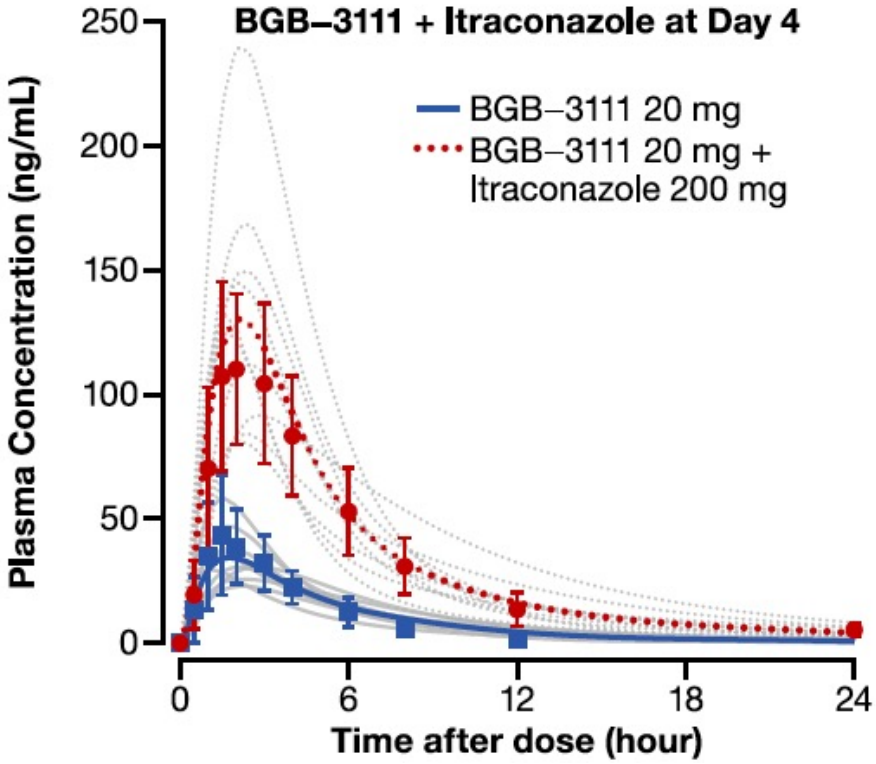
Pharmacologic characteristics of zanubrutinib and ibrutinib

	Zanubrutinib	Ibrutinib
Approved indications	MCL, WM*	MCL, CLL, and WM. MZL chronic graft versus host disease (cGVHD)
FDA approved dose	160 mg BID or 320 mg QD	420 or 560 mg QD
IC_{50} against BTK (nM) [24]	0.5	1.5
Potency of major active metabolite against BTK	NA	~15-fold less potent compared to the parent molecule
Half-life (hr)	~2 to 4	~4 to 6
Plasma protein binding (%)	~94%	97.3% – 97.7% [15]
$AUC_{0\text{-}24hr}$ (CV%) ng·hr/mL	160 mg BID: 2295 (37%) 320 mg QD: 2180 (41%)	420 mg QD: 707–1159 (50%-72%) 560 mg QD: 865–978 (69%-82%)
fu. $AUC_{0\text{-}24hr}$ (nM·hr)	160 mg BID: 278 320 mg QD: 267	420 mg QD: 37–60 560 mg QD: 46–51
Plasma exposure of major active metabolite	NA	1- to 2.8-fold higher than parent AUC [15]
Median BTK occupancy in PBMC at trough	320 mg QD:100% 160 mg BID: 100%	420 mg to 820 mg QD: >90% [30,33]
Median BTK occupancy in lymph node at trough	320 mg QD: 94% 160 mg BID: 100%	420 mg QD: >90% [16]
Pgp and brain penetration	Weak P-gp substrate Brain penetration data in patients available	Not a P-gp substrate Brain penetration data in patients available
Major enzyme involved	CYP3A	CYP3A

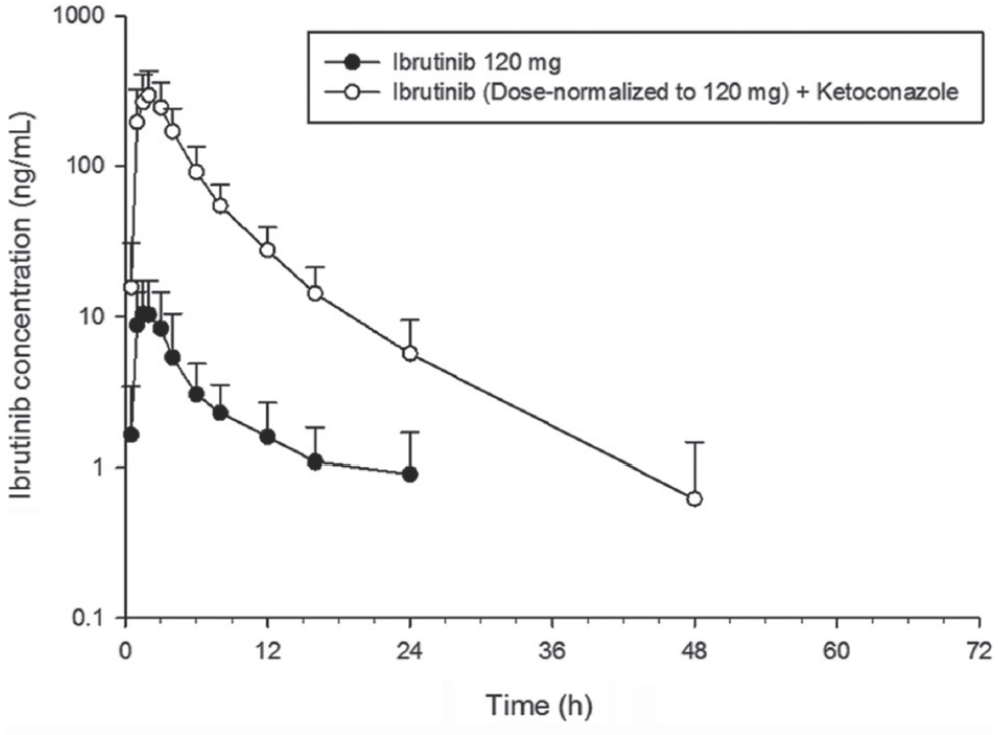
Tam CS et al. Expert Review of Clinical Pharmacology 2021;14:11,1329-1344

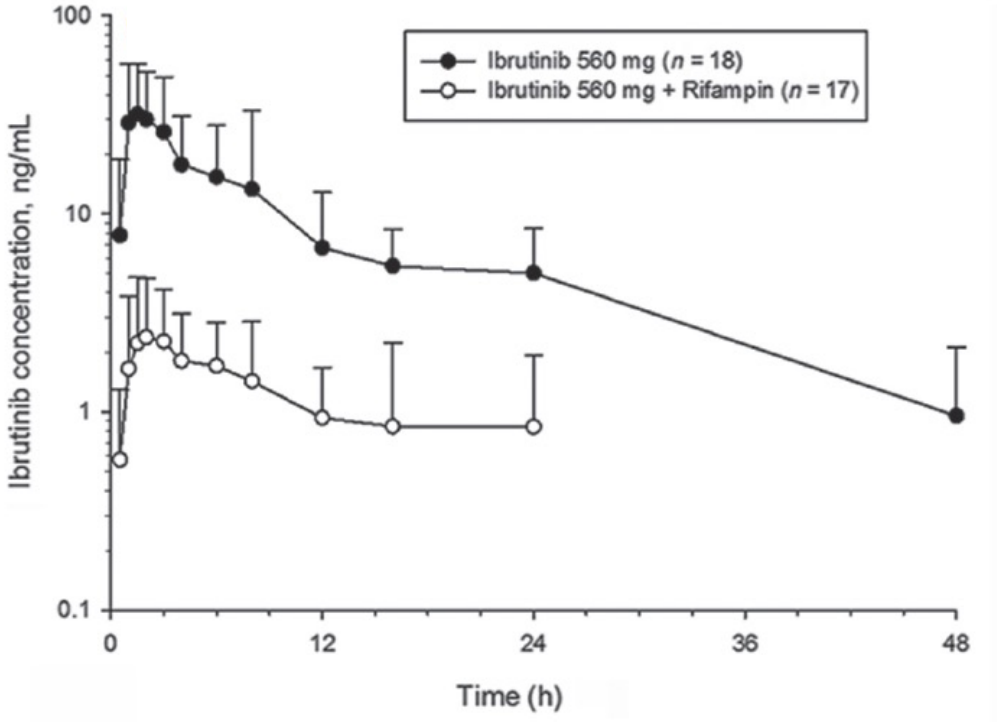
DDI of zanubrutinib with CYP3A4 modulators





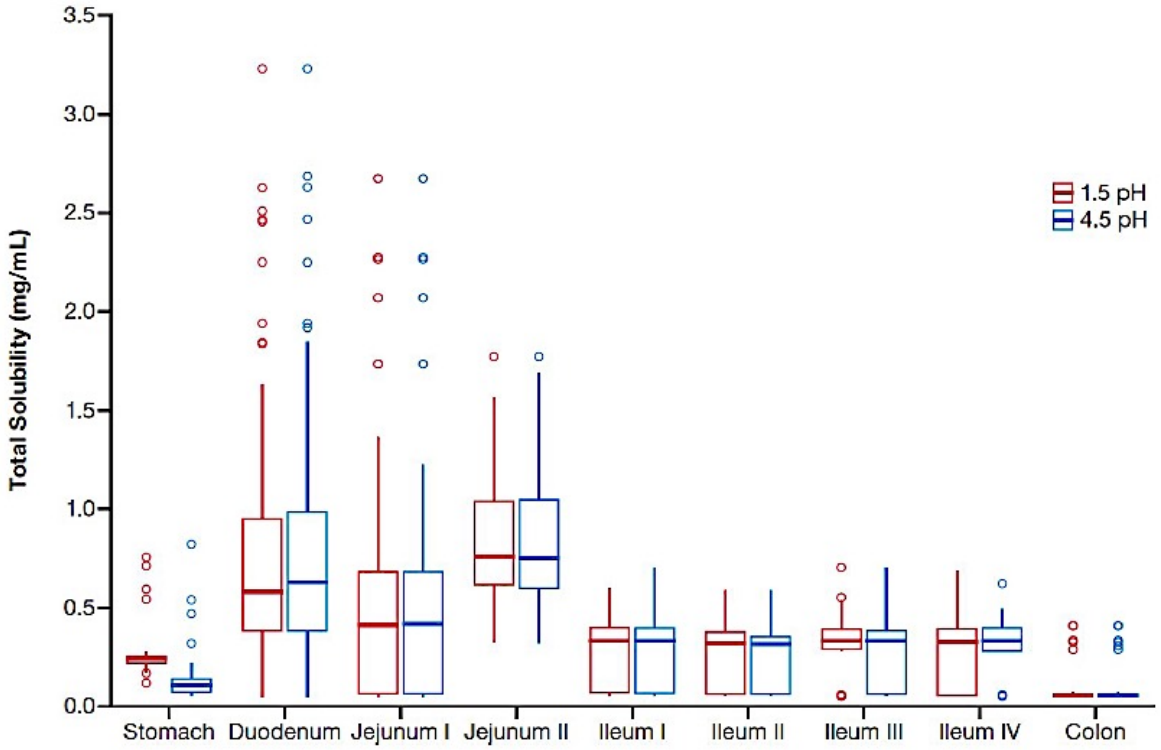
DDI of ibrutinib with CYP3A4 modulators





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

Predicted effect of gastric pH values (pH=1.5 and 4.5) on solubility



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

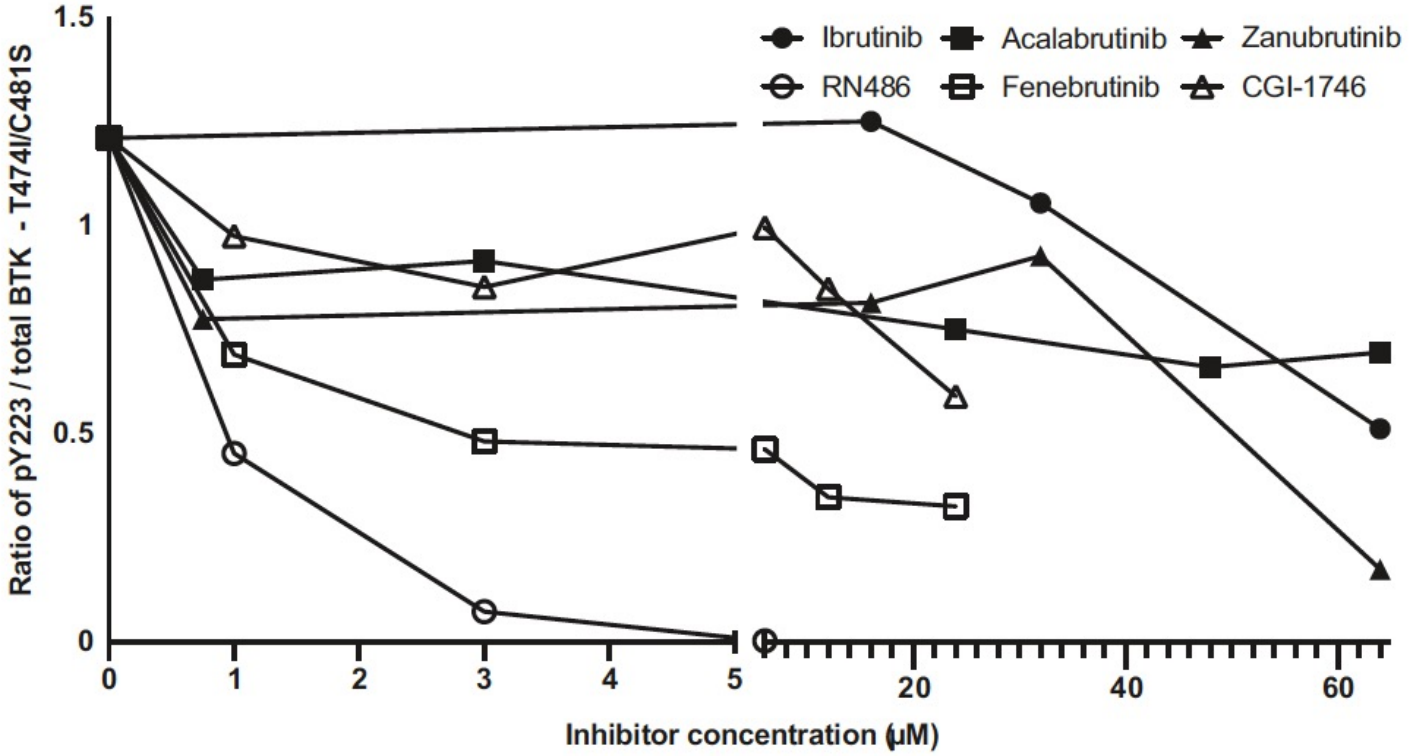
Wang K et al. CPT Pharmacometrics Syst Pharmacol 2021;10:441–454

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 an oral inhibitor of Bruton's tyrosine kinase designed for greater target selectivity and higher therapeutic exposures than the first-in-class BTK inhibitor 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.