Farmacologia

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Disclosures of NAME SURNAME

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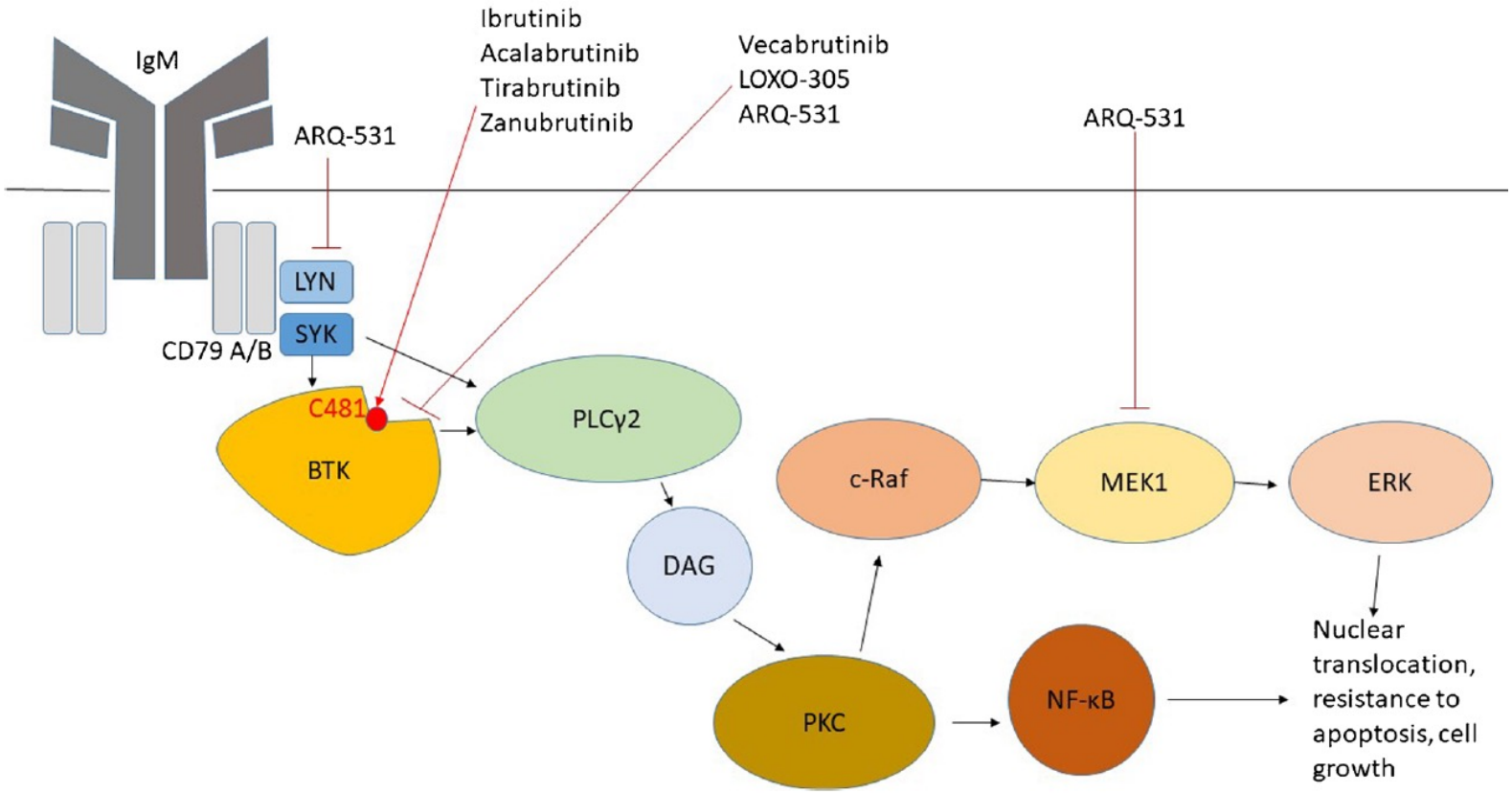
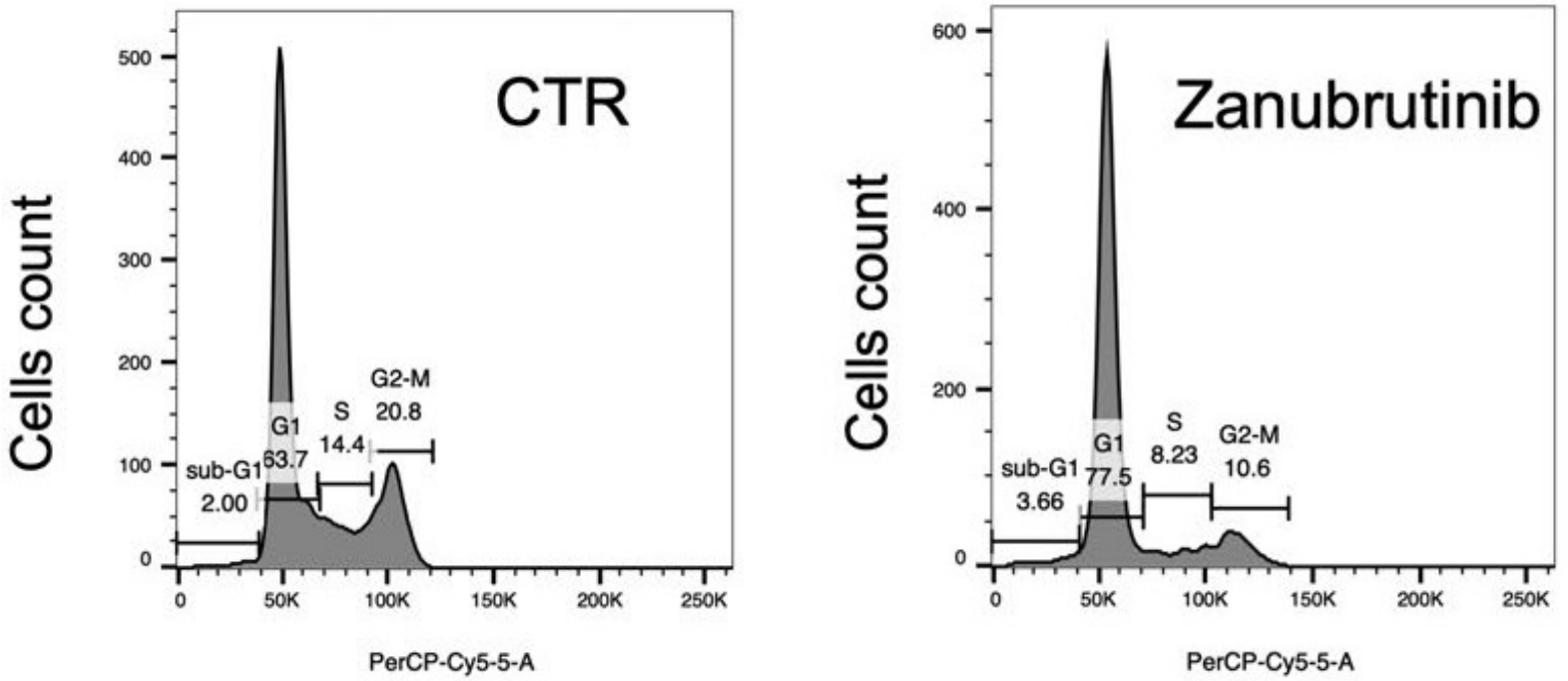
Eisai					X	X	
AstraZeneca					X	X	
Beigene					X		
Janssen					X		
Novartis					X		
Lilly					X		
Incyte					X		
AB Science			X				

Mechanism of action of BTK inhibitors



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

Cell cycle distribution after treatment with zanubrutinib



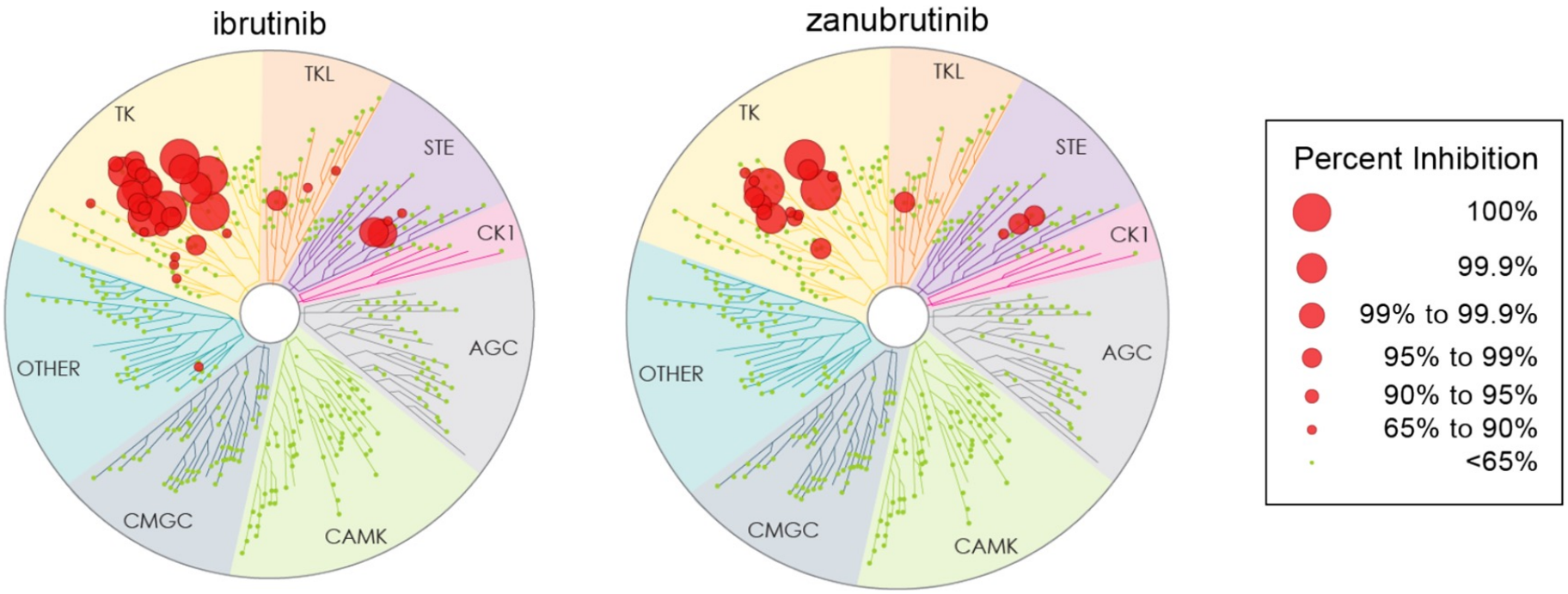
Tarantelli C et al. Haematologica 2019; 104:e307

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

Kinome profiling at 1 μM of ibrutinib and zanubrutinib



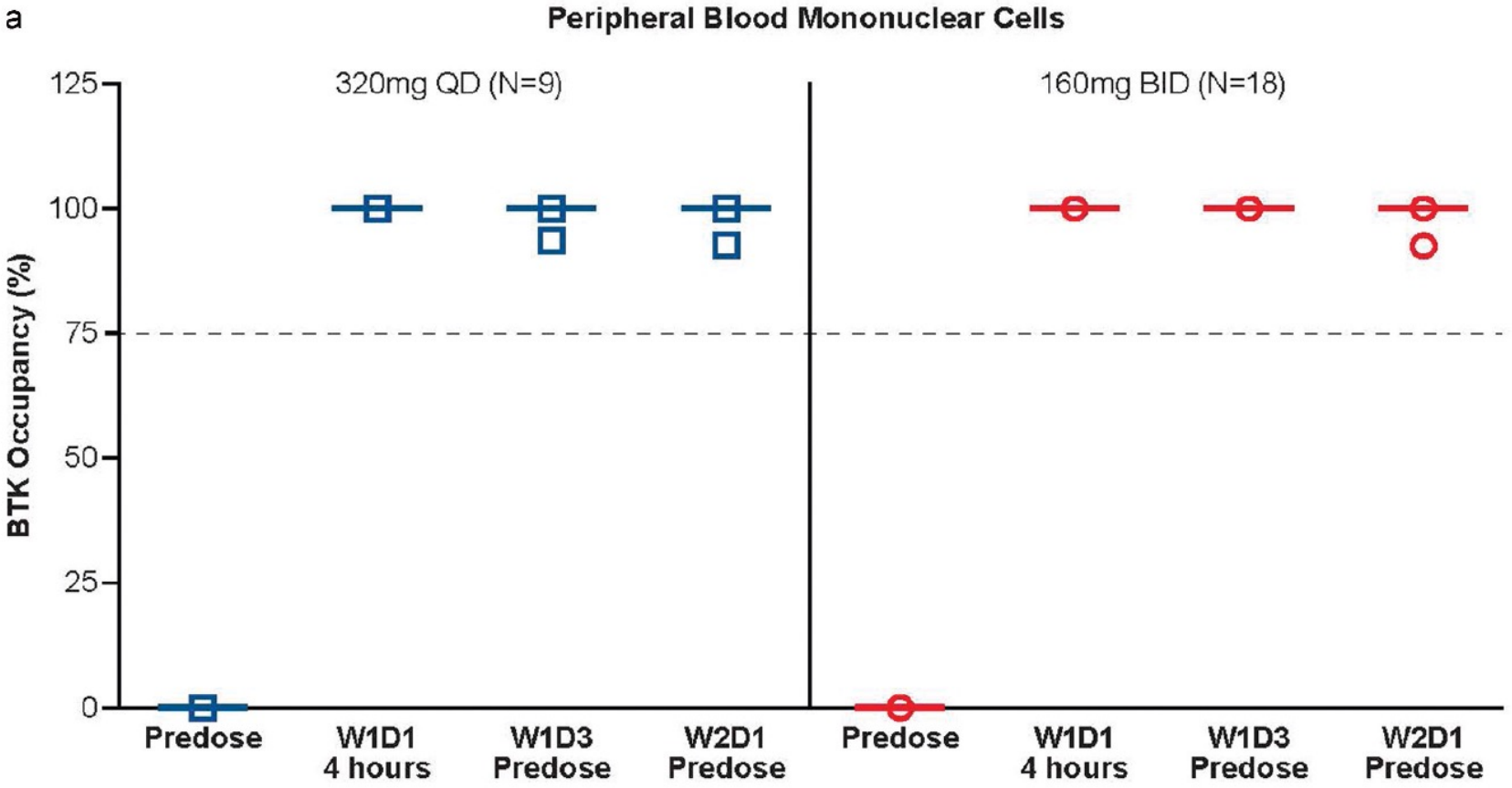
Kaptein A et al. Blood (2018) 132 (Supplement 1) : 1871

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**

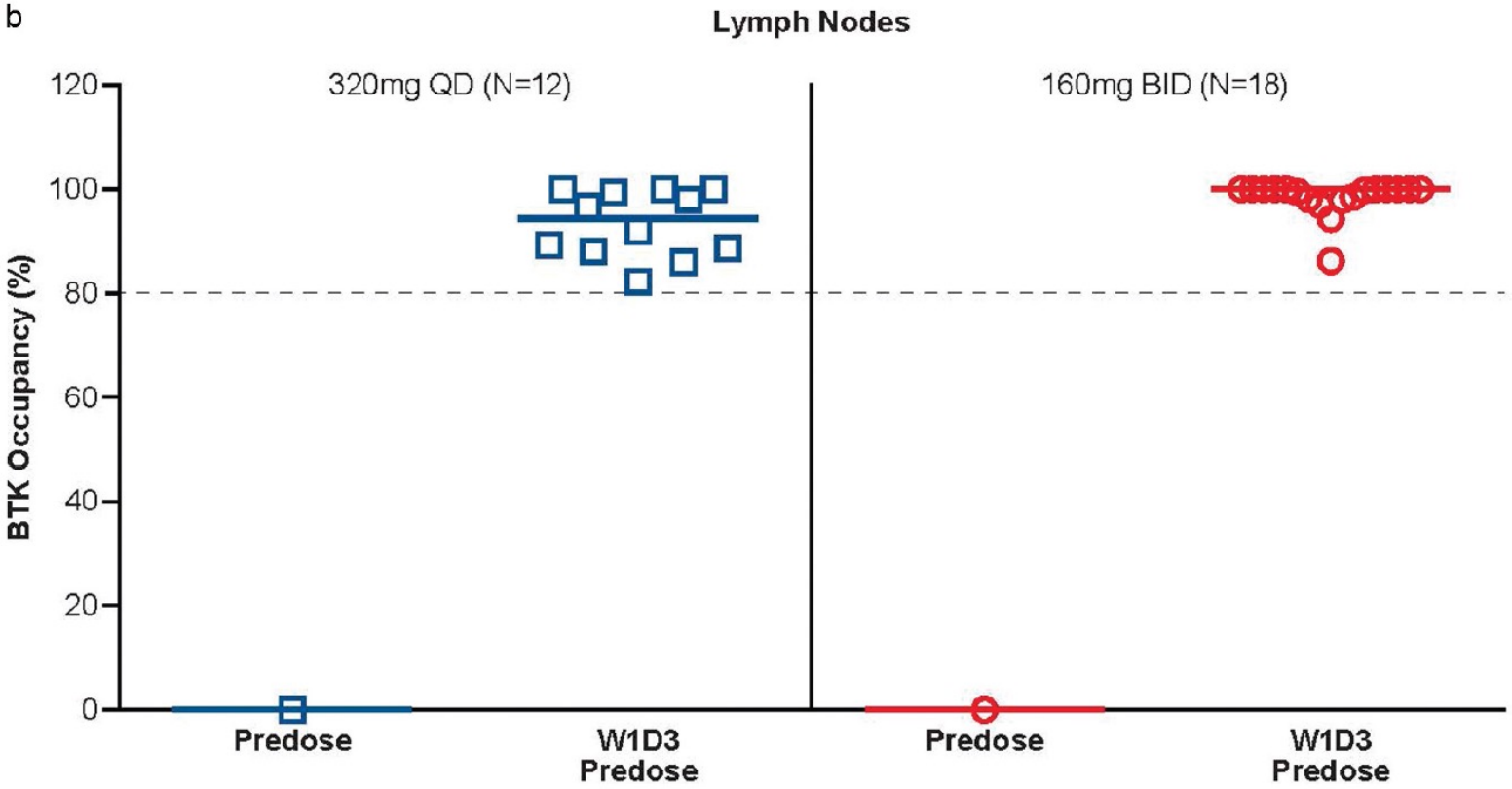
Tam CS et al. Expert Review of Clinical Pharmacology 2021;14:11,1329-1344

Zanubrutinib BTK occupancy in PBMC by dose regimen



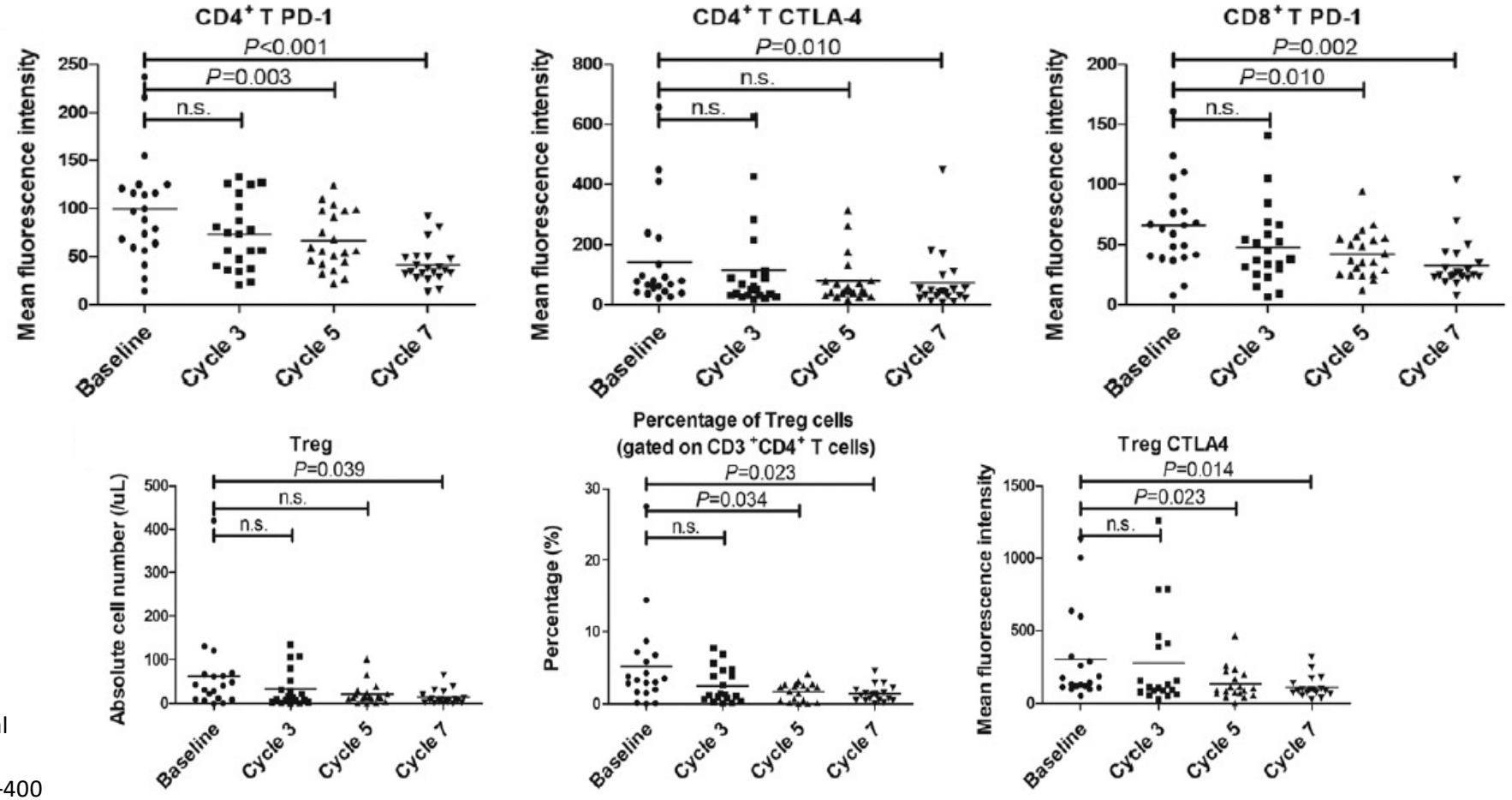
Tam CS et al. Blood 2019;134(11):851-859
Tam CS et al. Expert Review of Clinical Pharmacology 2021;14:11,1329-1344

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

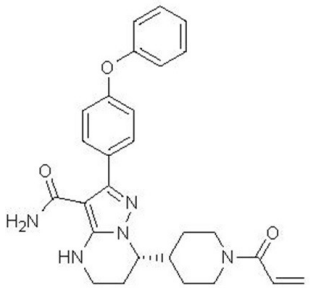
Dynamics of T cells and their subsets changes during zanubrutinib treatment



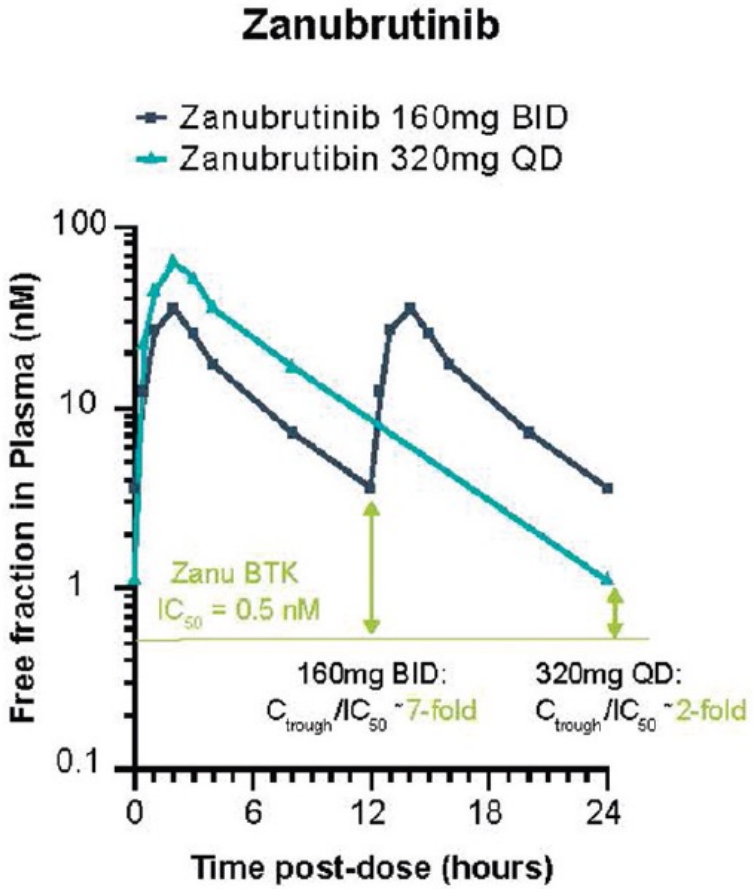
Zou Y-X et al. Hematological Oncology 2019;37:392–400

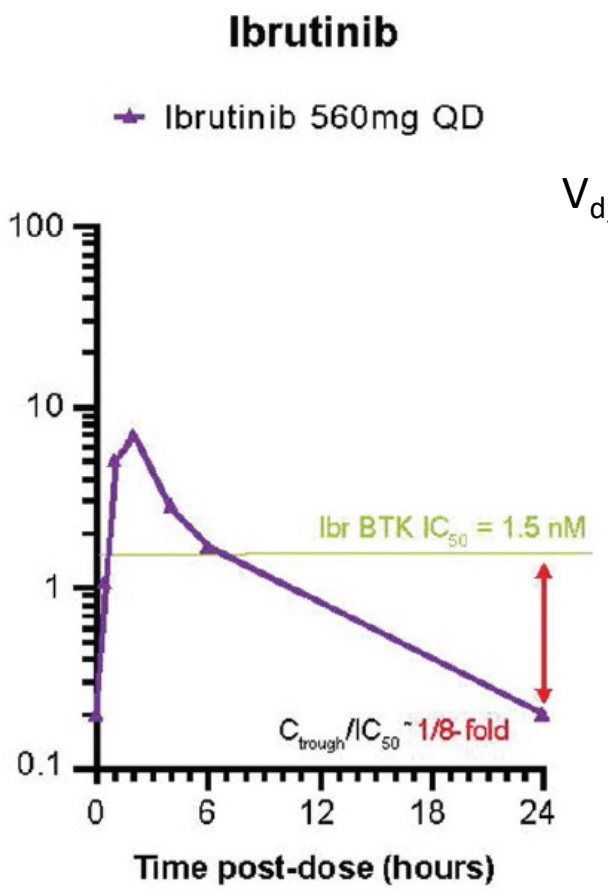
Free drug concentration time profiles relative to IC50 of BTK

Vp/F: 345 L

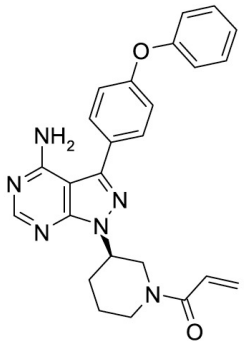


Zanubrutinib





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

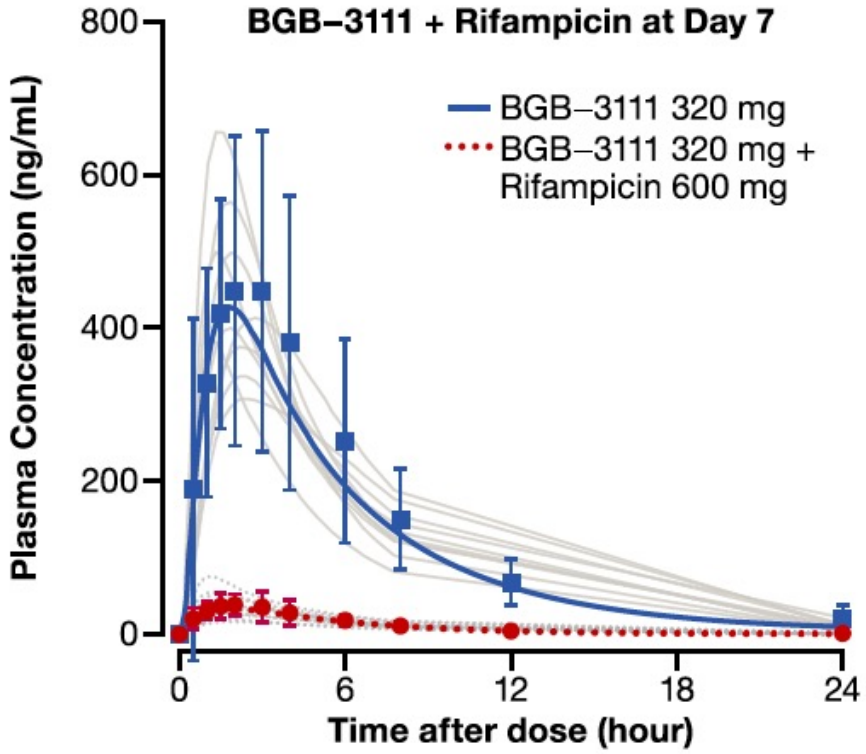


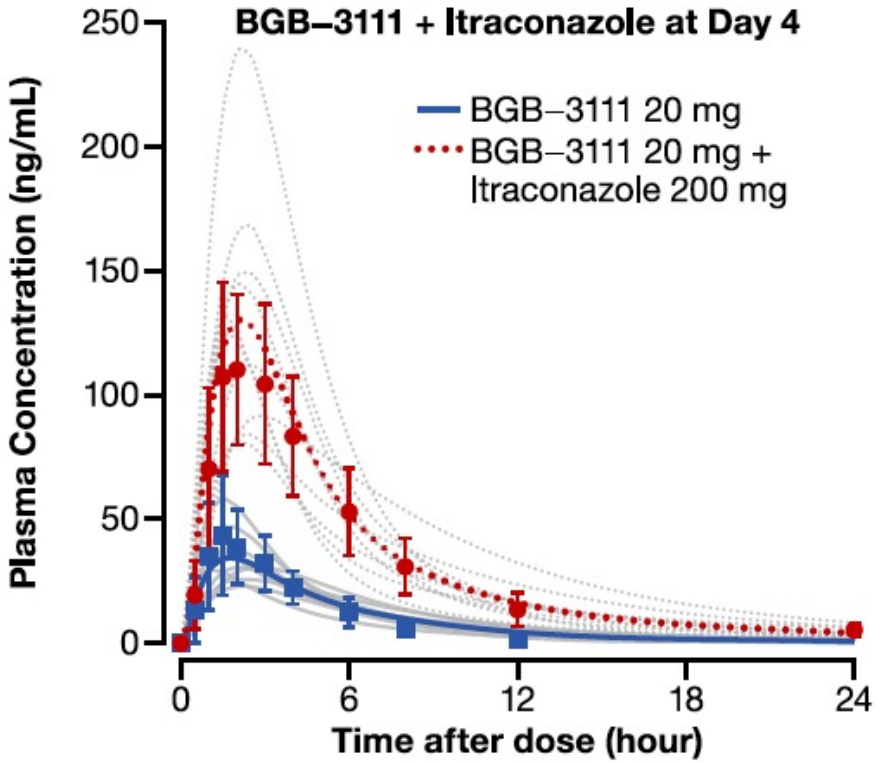
Ibrutinib

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

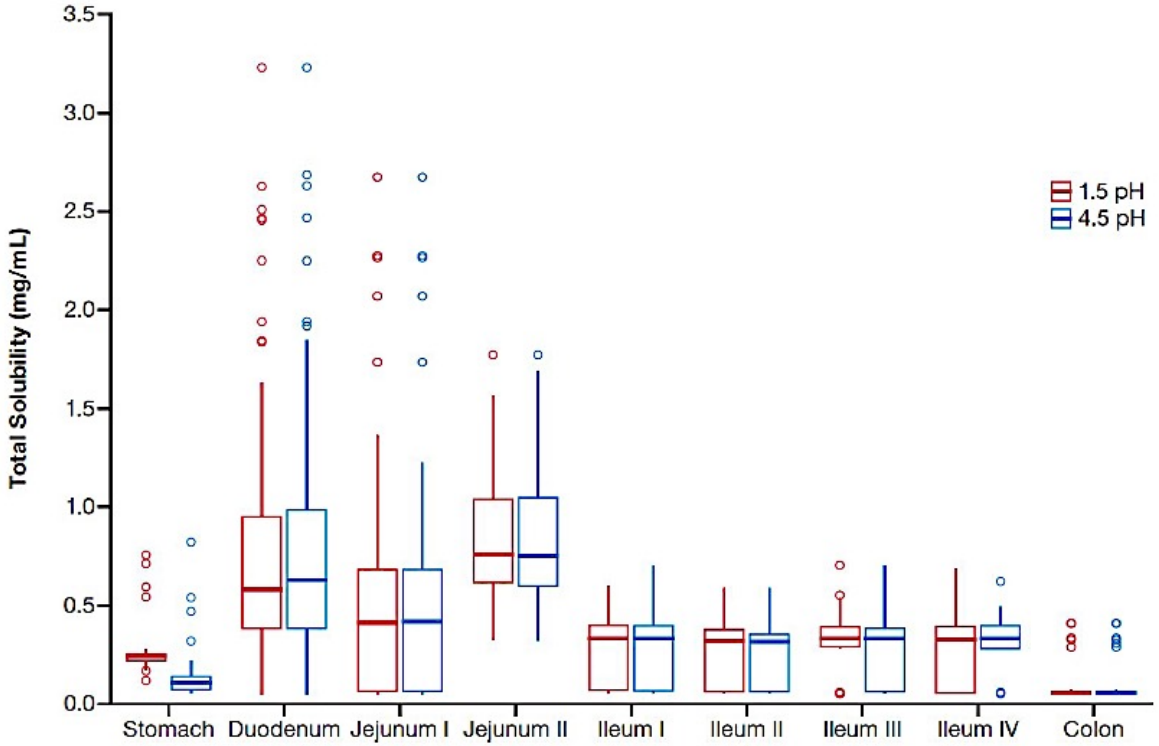
Marostica E et al. Cancer Chemother Pharmacol. 2015;75:111–21

DDI of zanubrutinib with CYP3A4 modulators





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



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

Drug-drug interactions of ibrutinib

Tyrosine kinase inhibitor	Generate/ Undergo	Drug-drug interaction	Study	Mechanism	Consequences	Recommendations
Ibrutinib	Undergoes	Ketoconazole	Healthy subjects	Strong CYP3A4 inhibition	Augmentation of ibrutinib AUC and Cmax by 29-fold and 24-fold respectively	Association should be avoided. Ibrutinib dose interruption or modification is warranted when treatment of a patient on ibrutinib requires administration of strong or moderate CYP3A inhibitors.
		Verapamil	Case report	CYP3A4 inhibition	Patient admitted because of severe diarrhea	Ibrutinib was discontinued for 5 days. Verapamil was stopped. as an alternative antihypertensive drug was prescribed (lercanidipine)
		Strong CYP3A4 inducers	Healthy subjects	Strong CYP3A4 induction	Ibrutinib plasma concentration is decreased by 92% and AUC by 90%	Avoid strong CYP3A4 inducers. Alternative drugs must be proposed.

Gay C et al. Hematological Oncology 2017;35:259–280.

Drug-drug interactions of zanubrutinib and ibrutinib

	Zanubrutinib	Ibrutinib
Food Effect		
Clinical Data (Low or high-fat meal)	No clinically meaningful impact on PK	C_{max}: 2- to 4-fold increase AUC: 2-fold increase
Label recommendation	Dose with or without food	Dose with or without food
Use with CYP3A inhibitors		
Clinical Data	Itraconazole increased AUC 3.8-fold (Fasted, HV)	Ketoconazole increased AUC 24-fold (Fasted, HV) Voriconazole (strong CYP3A inhibitor) increased steady state Cmax of ibrutinib by 6.7-fold and AUC by 5.7-fold (non-fasted, patients).
Label recommendation	Strong CYP3A inhibitor: Dose reduction to 80 mg QD Moderate inhibitors: dose reduction to 80 mg BID	Avoid strong CYP3A inhibitors except for posaconazole and voriconazole. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib Moderate CYP3A inhibitor: dose reduction to 280 mg once daily
Use with CYP3A inducers		
Clinical Data: With potent CYP 3A Inducer rifampin	Reduced AUC by 13.5-fold	Reduced AUC by >10-fold
Label recommendation	Avoid moderate and strong CYP3A inducers	Avoid moderate and strong CYP3A inducers

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

Drug-disease and drug-drug interactions of zanubrutinib and ibrutinib

	Zanubrutinib	Ibrutinib
Use with ARA including PPI		
Clinical DDI Data:	No clinically meaningful impact on PK	No clinically meaningful impact on PK
Label recommendation	No restriction	No restriction
Hepatic impairment		
Clinical data	AUC relative to subjects with normal liver function: Mild: 111% Moderate: 121% Severe: 160%	AUC relative to subjects with normal liver function: Mild: 270% Moderate: 820% Severe: 980%
Label recommendation	Severe: 80 mg BID Mild/Moderate: No dosage modification	Severe: Avoid Moderate: Dose reduction to 70 mg QD Mild: Dose reduction 140 mg QD
Renal impairment		
Clinical data	Mild and moderate renal impairment ([CLcr] ≥ 30 mL/min) had no influence on the exposure	Mild and moderate renal impairment ([CLcr] > 25 mL/min) had no influence on the exposure
Label Recommendation	Mild/moderate renal impairment (CLcr ≥ 30 mL/min): No dose modification	NA

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

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.