PRESA D'ATTO DI UNA REALTÀ INNOVATIVA NEI LINFOMI INDOLENTI

MACROREGIONALE EMILIA-ROMAGNA

Bologna, Aemilia Hotel, 19 ottobre 2024

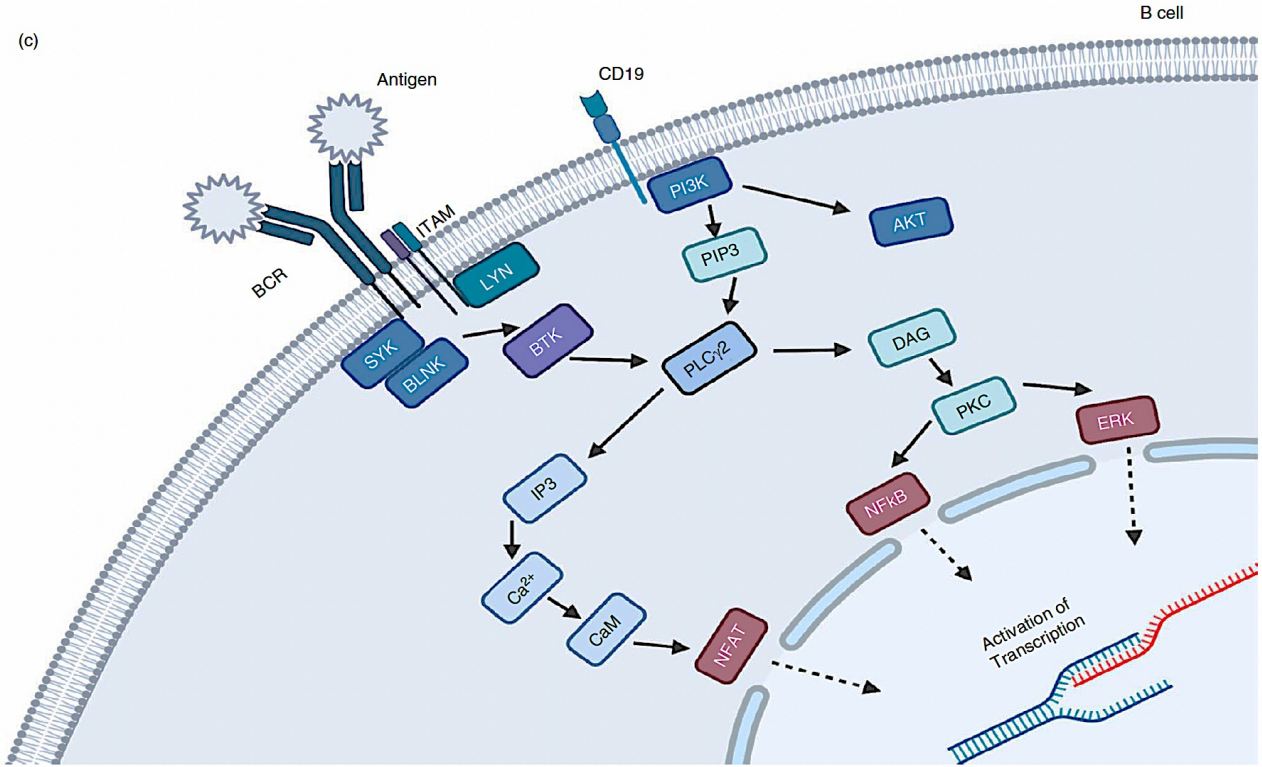
Il punto di vista del farmacologo

Romano Danesi
Università degli Studi di Milano

Disclosures

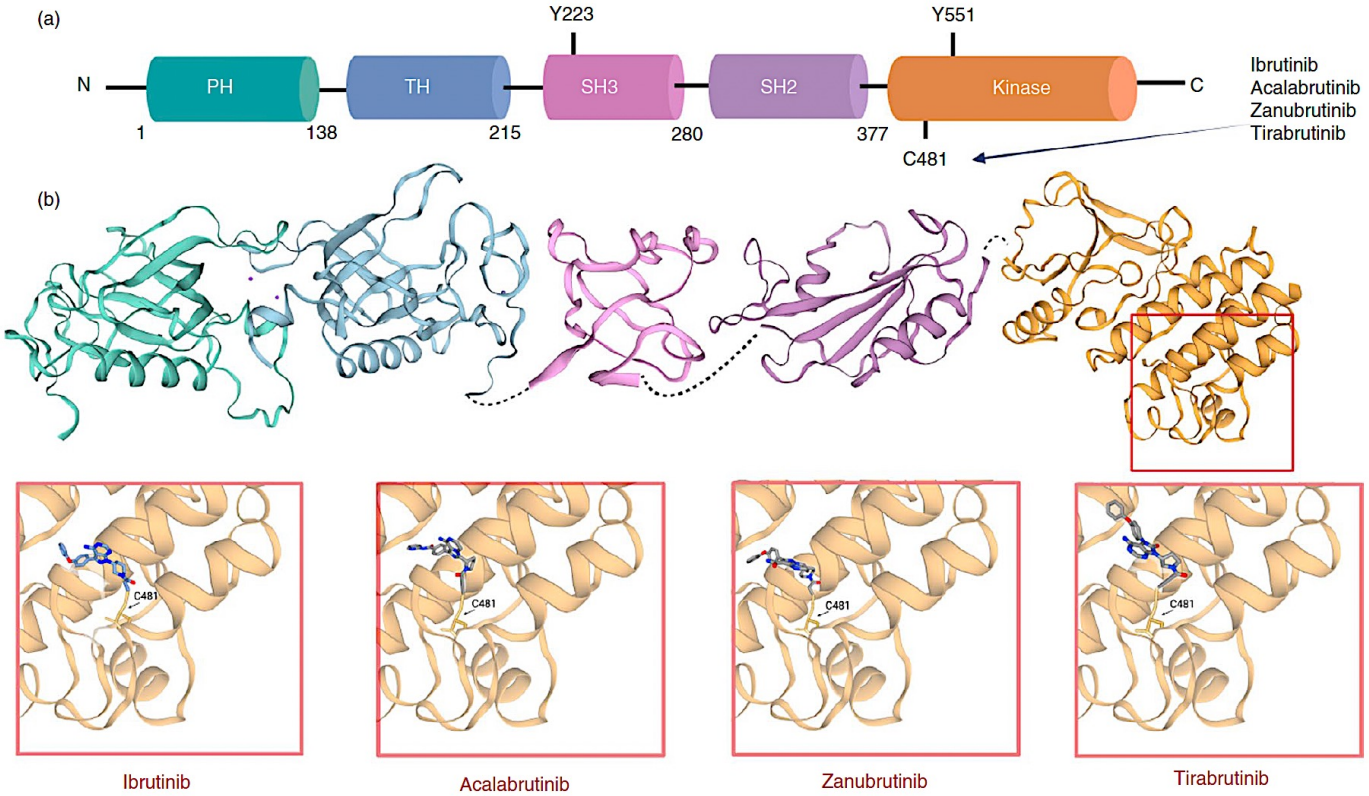
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
MSD			X		X		
Eisai			X		X	X	
AstraZeneca	X		X		X	X	
BeiGene					X		
Janssen	X		X		X		
Novartis			X		X		
Lilly			X		X		
Incyte			X		X		
AB Science			X				

The role of BTK in B cell proliferation



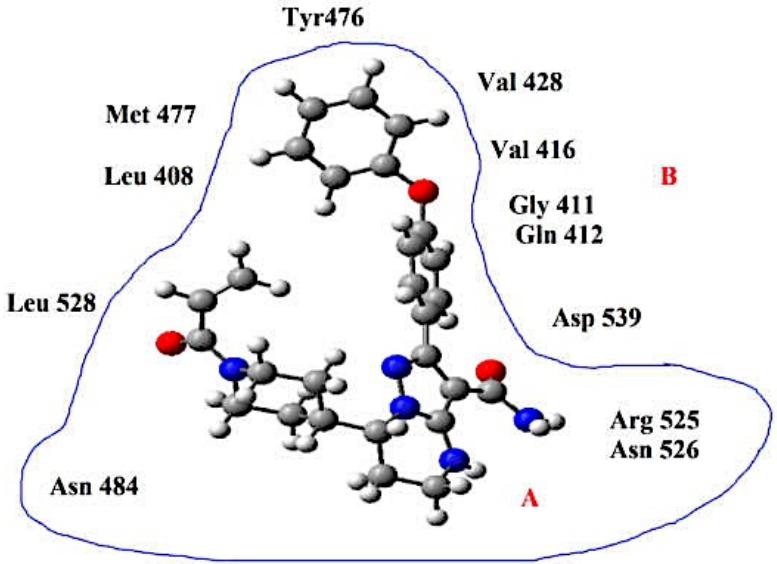
Charlotte McDonald et al. Immunology. 2021;164:722–736

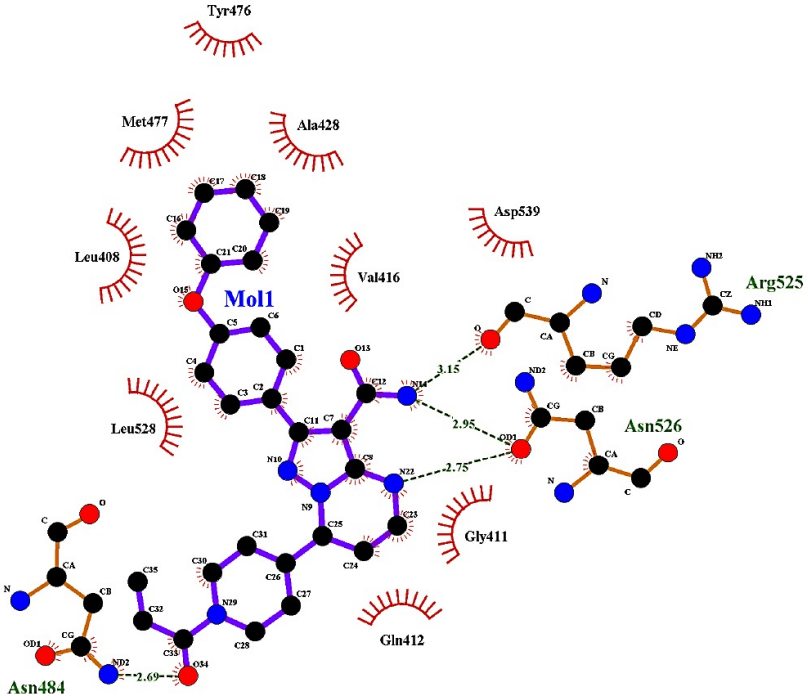
Molecular interaction of covalent inhibitors with BTK



Charlotte McDonald et al. Immunology. 2021;164:722–736

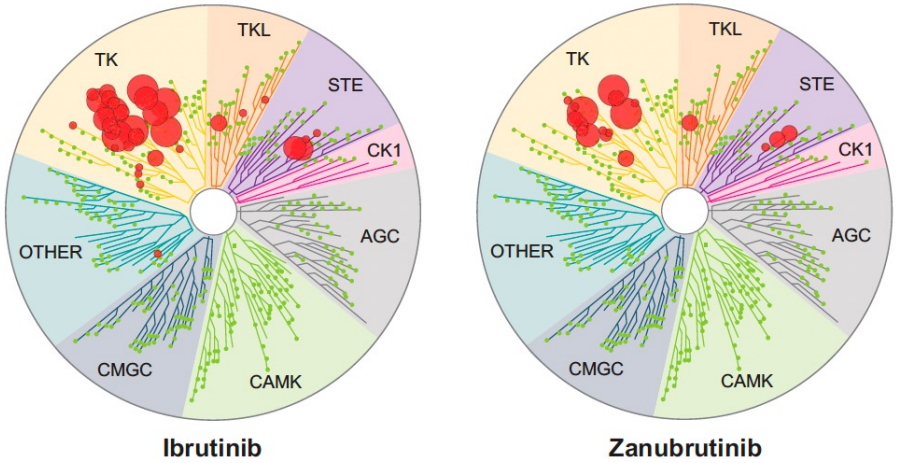
Schematic 2D diagram of zanubrutinib bound to BTK and details of the interaction with the hydrophobic pocket





Mahani NM et al. DOI: https://dx.doi.org/10.4314/bcse.v36i2.19

Kinase profiling at concentrations of 100 x IC_{50} based on BTK IC_{50}



	Zanubrutinib 71 nM		Ibrutinib 32 nM	
1	BLK	99.9	BLK	100.2
2	ERBB4/HER4	99.1	BMX/ETK	99.7
3	TXK	98.5	ERBB4/HER4	99.5
4	BMX/ETK	98.1	TXK	98.8
5	BTK	95.1	TEC	98
6	TEC	79.3	BTK	97.2
7	BRK	63.9	FGR	95.7
8	FGR	53.1	YES/YES1	92.9
9	EGFR	43.3	LCK	91.2
10	LCK	40.6	ITK	84.3
11	YES/YES1	37.1	HCK	93
12	CSK	28.8	CSK	81
13	STK33	23.7	EGFR	76.5
14	BMPR2	22.6	FYN	66.9
15	AXL	22.4	ERBB2/HER2	61.9
16	HCK	21.9	SRMS	61
17	PKCd	20.9	JAK3	58.7
18	FLT3	20.5	LYN	52.3
19	MEKK1	20.1	c-Src	46.1
20	ITK	19.1	FLT3	41.8
21	MSK2/RPS6KA4	19	BRK	41.6
22	ERN1/IRE1	17.9	ABL2/ARG	40.4
23	MNK2	17.8	WNK1	32.5
24	FRK/PTK5	17.8	MNK2	32.4

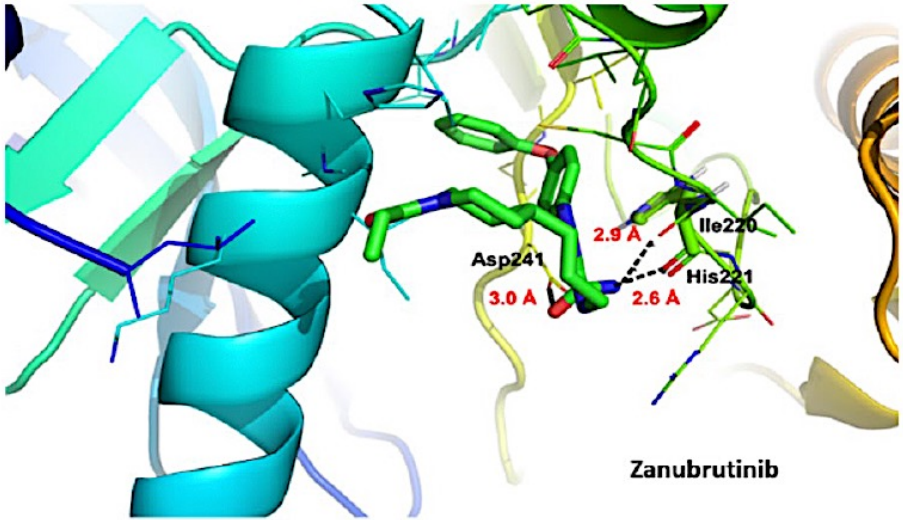
Tam CS et al. Blood Cancer Journal 2023;13:141

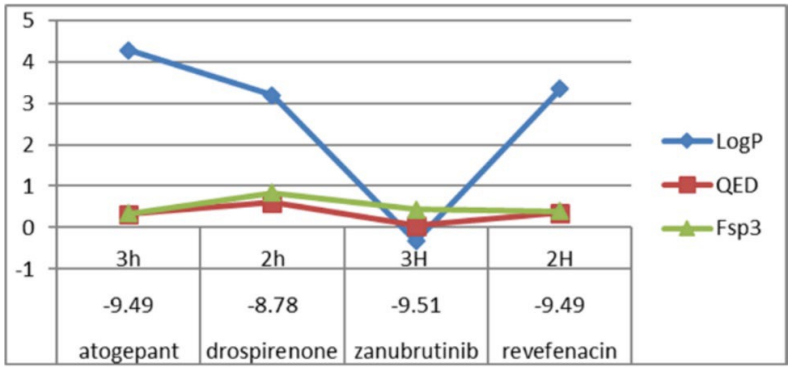
BTK inactivation kinetic parameters for ibrutinib and zanubrutinib

Compound	K_I (nM)	k_{inact} (s^{-1})	k_{inact}/K_I ($M^{-1}s^{-1}$)
Ibrutinib	54 ± 49	0.027 ± 0.025	$47.7 \times 10^4 \pm 1.48 \times 10^4$
Zanubrutinib	126 ± 59	0.033 ± 0.013	$27.9 \times 10^4 \pm 0.08 \times 10^4$

Podoll T et al. J Pharmacol Exp Ther 384:173–186, 2023

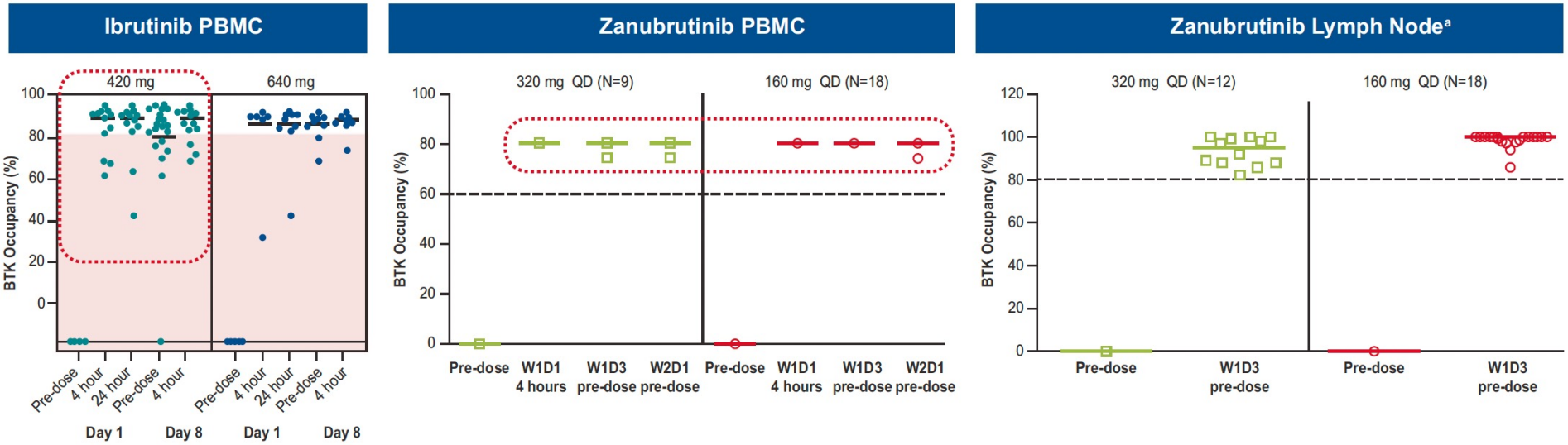
Molecular docking outcomes of zanubrutinib against 1Y6A region of VEGFR2 – increased cardiovascular safety





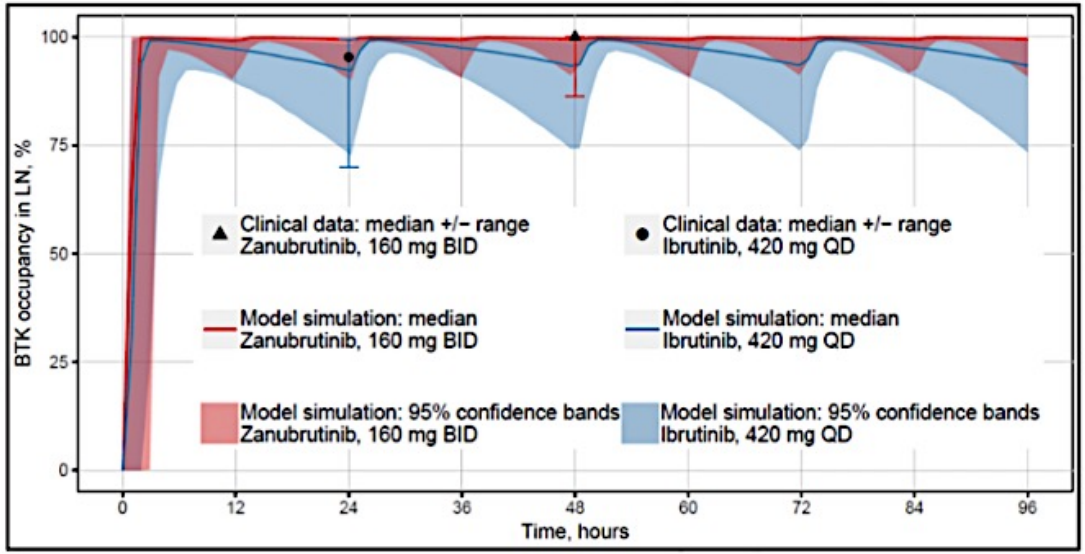
Vidya Sagar Jerra et al. Medical Oncology (2024) 41:198

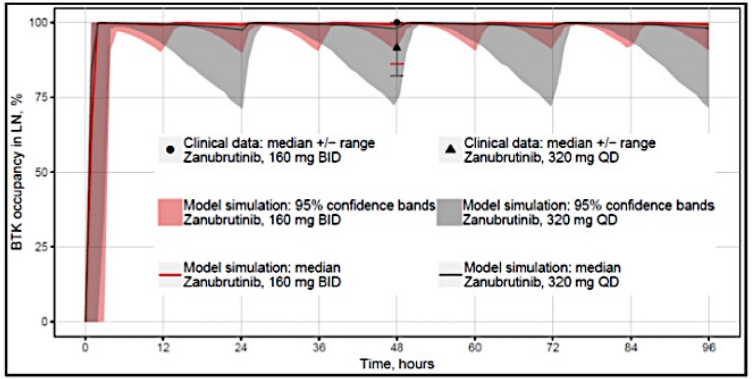
Zanubrutinib BTK occupancy in PBMC and in lymph nodes by dose regimens relative to those of ibrutinib



Tam CS et al. Blood Cancer Journal 2023;13:141

BTK occupancy of zanubrutinib vs ibrutinib and of zanubrutinib 160 mg BID vs. 320 mg QD (systems pharmacology model)

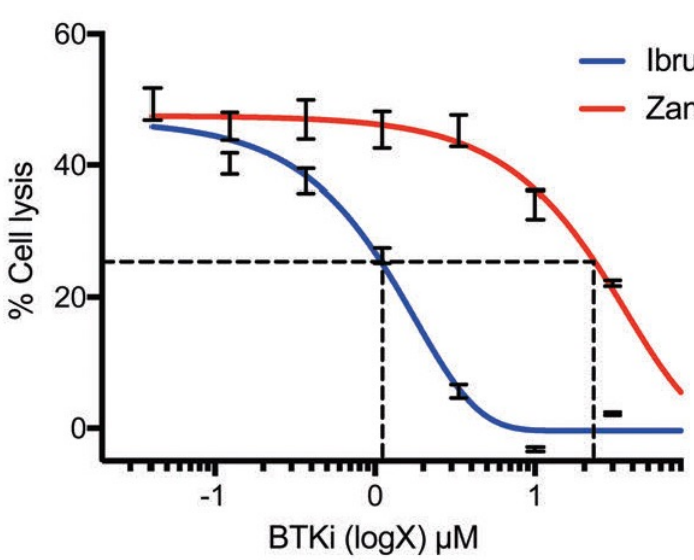




Srikumar Sahasranaman et al. http://doi.org/10.1182/blood-2019-129133

Zanubrutinib spares NK effector function

Mino MCL cells and NK92MI cells were co-seeded and treated with vehicle or various concentrations of BTK inhibitors



		IC50 (nM)		
Targets	Assays	Ibrutinib	Zanurutinib	Zanu/Ibru
BTK	BTK-pY223	3.5	1.8	0.5
	Rec-1 proliferation	0.34	0.36	1.1
	BTK occupation	2.4	2.2	0.9
ITK	ITK occupation	130	3290	25
	p-PLCγ1	77	3477	45
	IL-2 production	260	2536	9.8

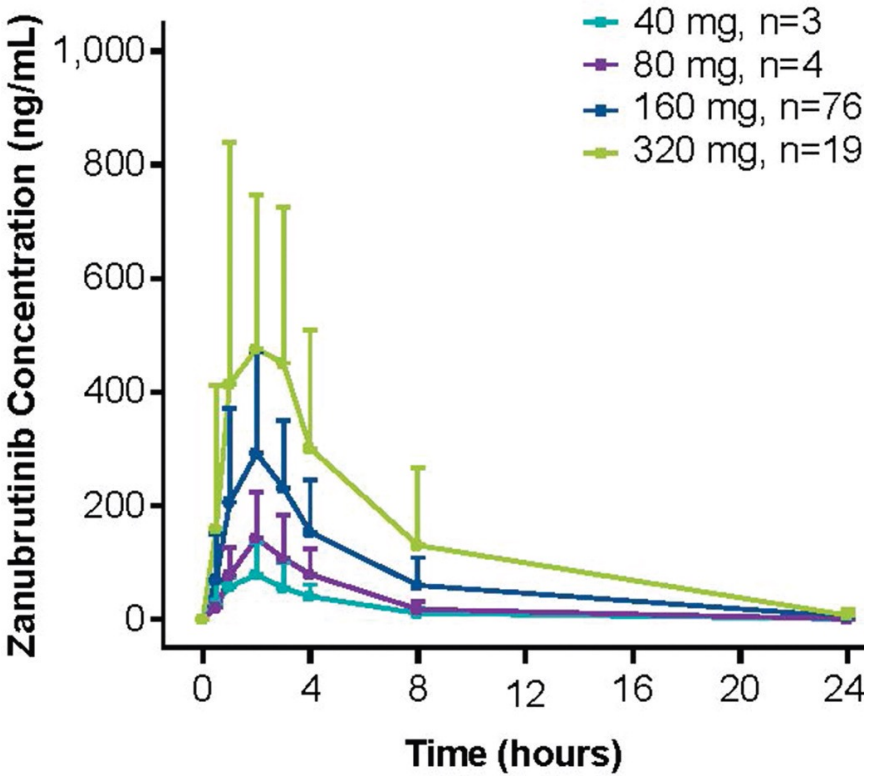
Thijs W.H. Flinsenberg et al. Haematologica 2020; 105:e76

Pharmacokinetic characteristics

- Zanubrutinib PK properties were unaffected by factors including renal (estimated glomerular filtration rate ≥30 mL/min) and mild/moderate hepatic impairment (Child-Pugh class A or B)
- With appropriate dose reductions, it could be administered with moderate or strong CYP3A inhibitors.
- Zanubrutinib can be administered concurrently with proton pump inhibitors (PPI)/acid-reducing agents without restriction.
- Zanubrutinib has high volume of distribution (approximately 880 L), high AUC/IC50, and half-life of 2-4 h.
- Pharmacokinetics is not saturable

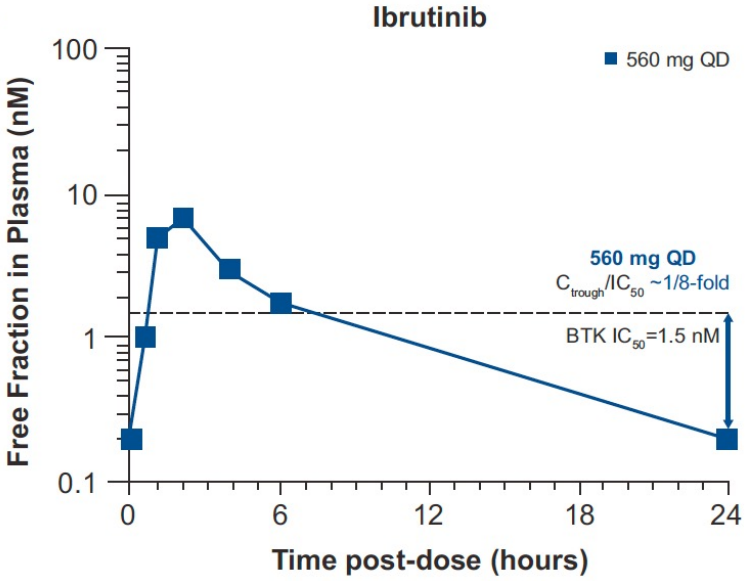
Tam CS et al. Blood Cancer Journal 2023;13:141; Tam CS et al. Expert Review of Clinical Pharmacology, 2021;14:1329-1344

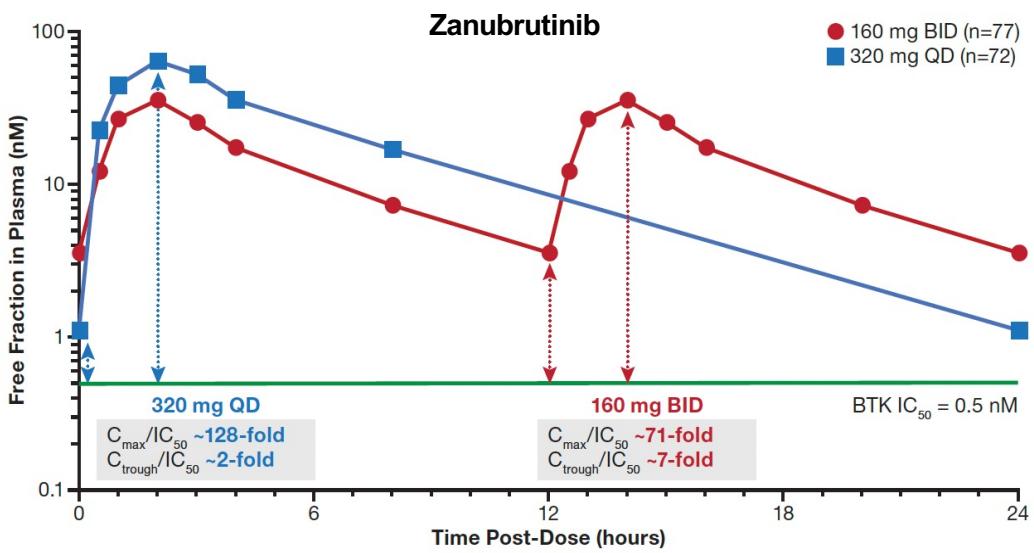
Dose-proportional increase in drug levels



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

Pharmacokinetics and AUIC of ibrutinib and zanubrutinib





Tam CS et al. Blood Cancer Journal 2023;13:141

Ying C. Oua et al. Leukemia & Lymphoma DOI: 10.1080/10428194.2021.1929961

Comparison of PK parameters of BTKi

Parameter	Ibrutinib	Acalabrutinib	Zanubrutinib
Absolute bio-availability	< 10%	25%	45–50%[b]
Half-life	4–13 h	1–2 h	2–4 h
Metabolism	Predominantly via CYP3A	Predominantly via CYP3A	Predominantly via CYP3A
Excretion	Faeces, 80%; urine, < 10%	Faeces, 84%; urine, 12%	Faeces, 87%; urine, 8%

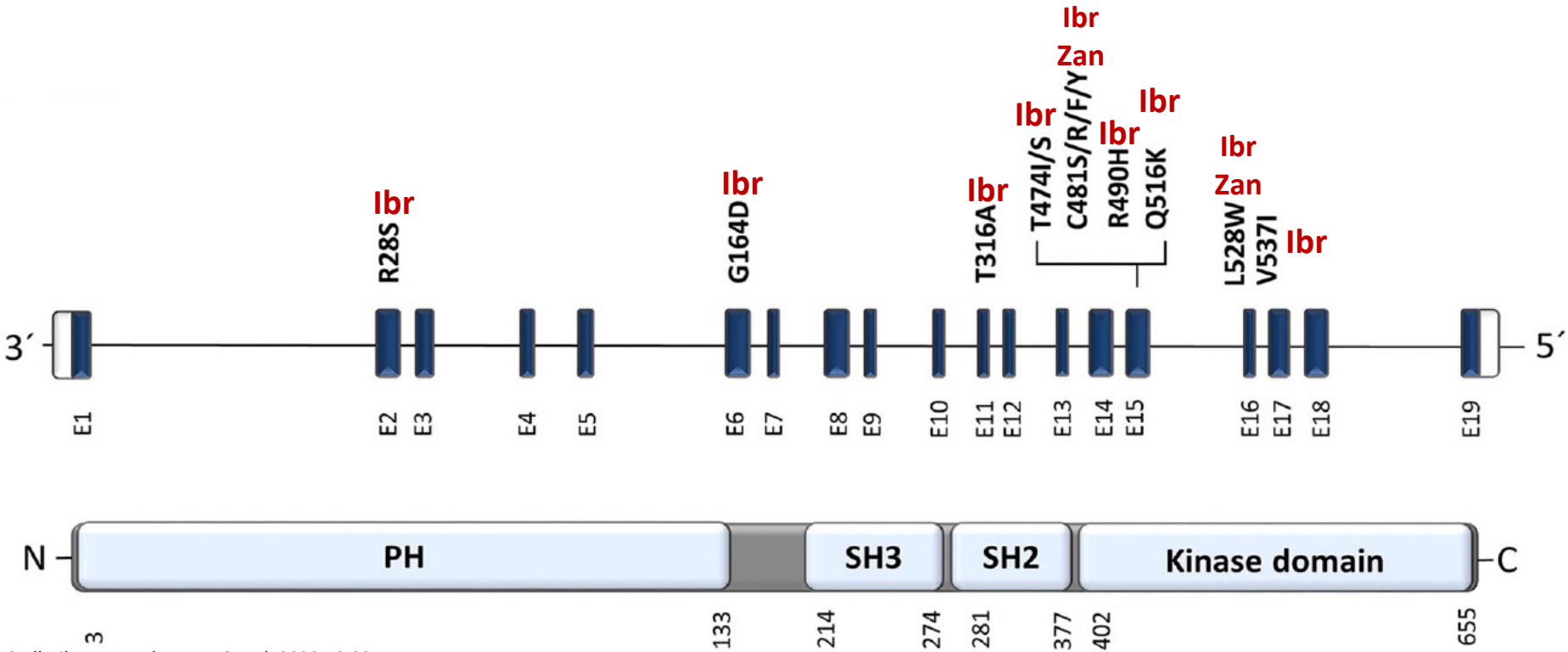
Matt Shirley. Targeted Oncology (2022) 17:69–84

A comparative look to PK and PD

	Zanubrutinib	Ibrutinib
FDA-approved dose	160 mg BID or 320 mg QD	420 or 560 mg QD
IC_{50} against BTK (nM)	0.5	1.5
Potency of major active metabolite against BTK	Not applicable	~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
$AUC_{0\text{-}24hr}$(CV %) ng-hr/mL	160 mg BID: 2,295 (37 %) 320 mg QD: 2,180 (41 %)	420 mg QD: 707-1,159 (50 % - 72 %) 560 mg QD: 865-978 (69 % - 82 %)
fu $AUC_{0\text{-}24hr}$(nM-hr)	160 mg BID: 278 320 QD: 267	420 mg QD: 37-60 560 mg QD: 46-51
Plasma exposure of major active metabolite	Not applicable	1- to 2.8-fold higher than parent AUC
Median BTK occupancy in PBMC at trough (%)	160 mg BID: 100 320 mg QD: 100	420 mg to 820 mg QD: >90
Median BTK occupancy in lymph node at trough (%)	160 mg BID: 100 320 mg QD: 94	420 mg QD: >90
P-gp and brain penetration	Weak P-gp substrate Brain penetration data in patients available	Not a P-gp substrate Brain penetration data in patients available

https://memoinoncology.com/esh-cll/esh-cll-2022-satellite-symposium-inhibition-of-brutons-tyrosine-kinase-btk-a-key-approach-to-managing-and-treating-cll-patients/

BTK resistance mutations



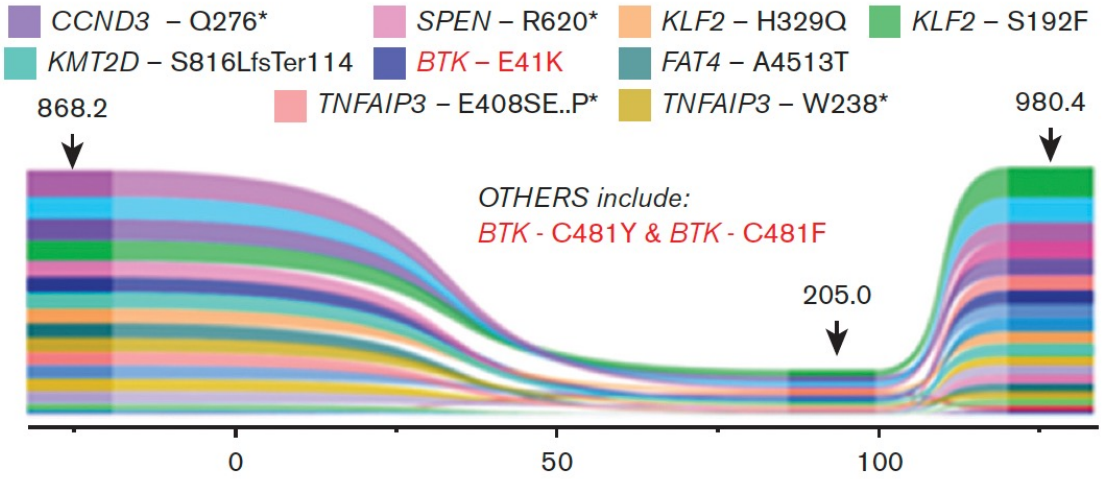
Sedlarikova L et al. Front. Oncol. 2020;10:894
Shazia Nakhoda et al. Br J Haematol 2023; 200(2): 137–149

Detection of ctDNA mutations (C481) and evolution during zanubrutinib therapy

MZ03 (SPLENIC)

Progressive Disease

hGE/mL plasma	Day -26	Day 86	Day 127
BTK – E41K	504.0	83.1	449.1
BTK – C481Y	*BD*	11.4	8.9
BTK – C481F	*BD*	2.2	63.3
TNFAIP3 – W238*	449.9	59.2	237.2
TNFAIP3 – E408SE..P*	438.1	45.1	471.2
KMT2D – S816LfsTer114	497.4	78.9	379.5



Piers Blombery et al. Blood Advances 2023;7:3531-3539

Conclusions

- Zanubrutinib is a BTK inhibitor with high selectivity and potency.
- First generation BTKi suppresses NK-cell cytotoxicity, most likely due to off-target inhibition of ITK, while zanubrutinib spares NK activity.
- Zanubrutinib has favorable pharmacokinetics.
- Multiparametric pharmacologic assessment suggests that zanubrutinib challenges the limit of second generation BTKi.