HOT NEWS

NELLE SINDROMI LINFOPROLIFERATIVE:
inarrestabile dinamicità

Zanubrutinib è di seconda o terza generazione?

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PALERMO

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Hotel NH Palermo

Disclosures

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BeiGene					X		
Janssen	X		X		X		
Novartis			X		X		
Lilly			X		X		
Incyte			X		X		
AB Science			X				

Someone has already given an answer

EXPERT REVIEW OF CLINICAL PHARMACOLOGY
2021, VOL. 14, NO. 11, 1329–1344
https://doi.org/10.1080/17512433.2021.1978288

Taylor & Francis
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DRUG PROFILE

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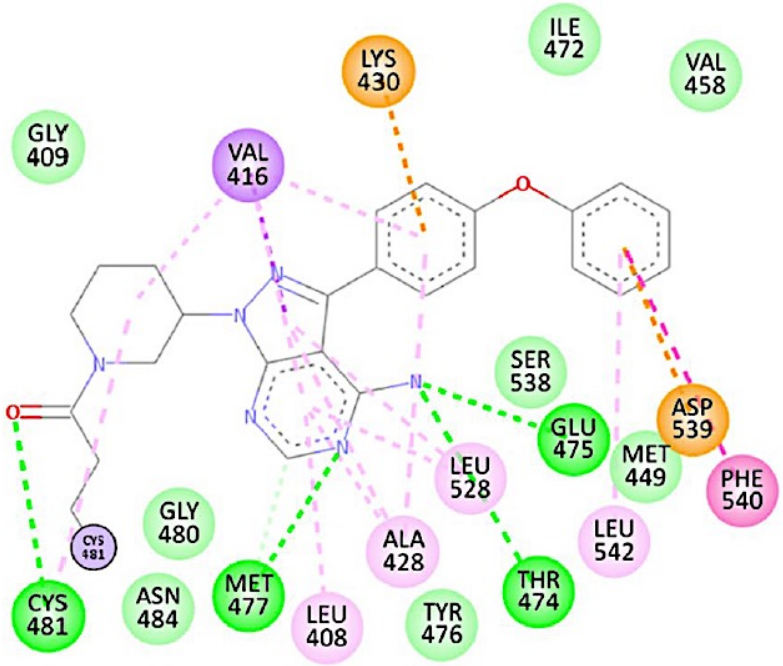
Clinical pharmacology and PK/PD translation of the second-generation Bruton's tyrosine kinase inhibitor, zanubrutinib

Constantine S. Tam [a,b,c,d], Ying C. Ou[e], Judith Trotman[f,g] and Stephen Opat[h,i]

The challenges of increasing the generation

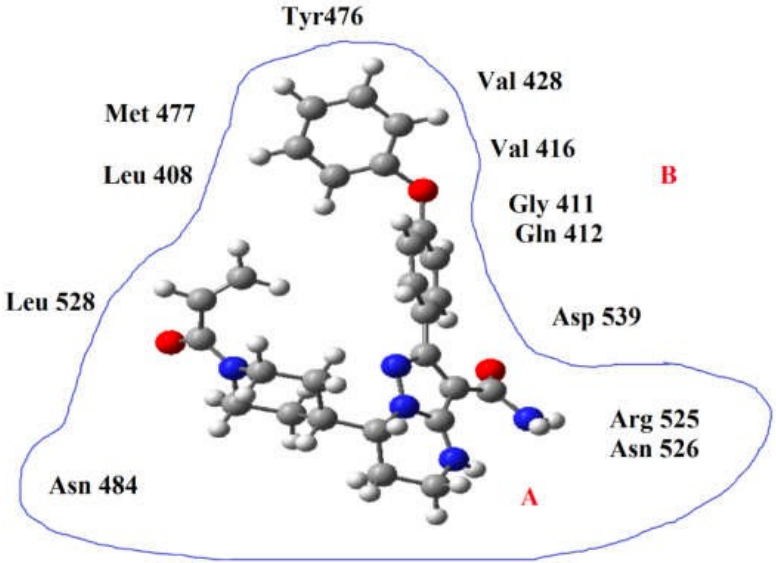
Pharmacodynamics

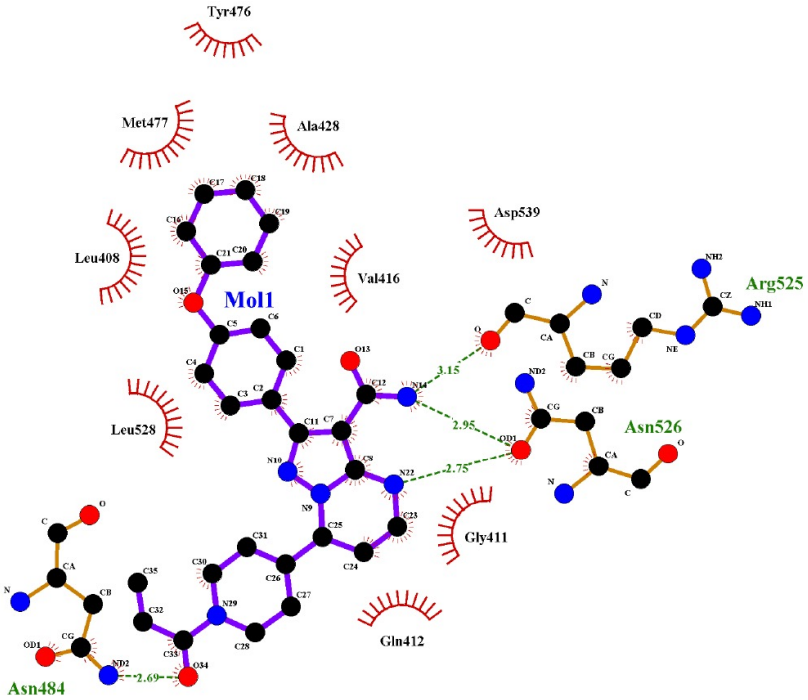
2D diagram of BTK interaction with ibrutinib



Mohammed Alrouji et al. Scientific Reports 2023;13:17684

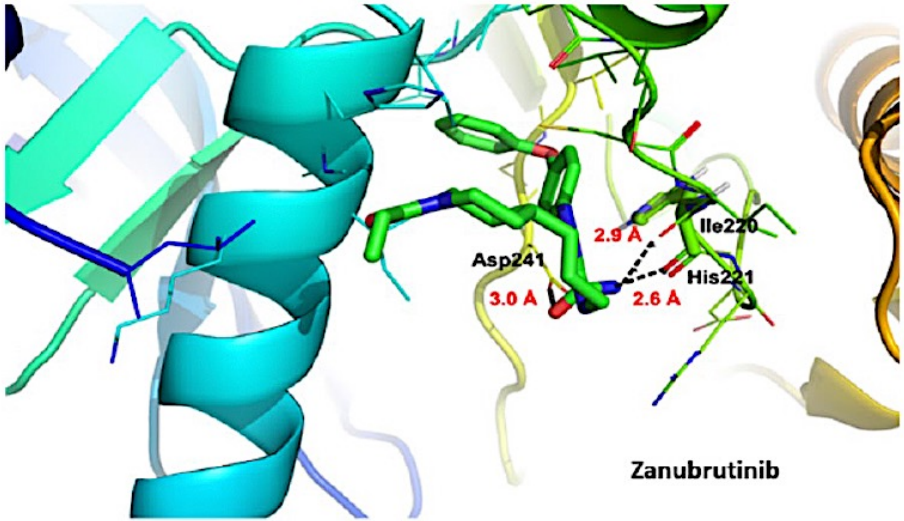
Schematic 2D diagram of zanubrutinib bound to BTK and details of the interaction with the hydrophobic pocket

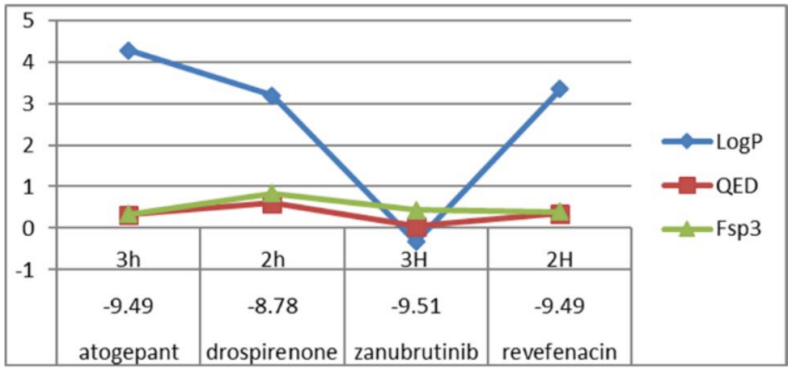




Mahani NM et al. DOI: https://dx.doi.org/10.4314/bcse.v36i2.19

Molecular docking outcomes of zanubrutinib against 1Y6A region of VEGFR2





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

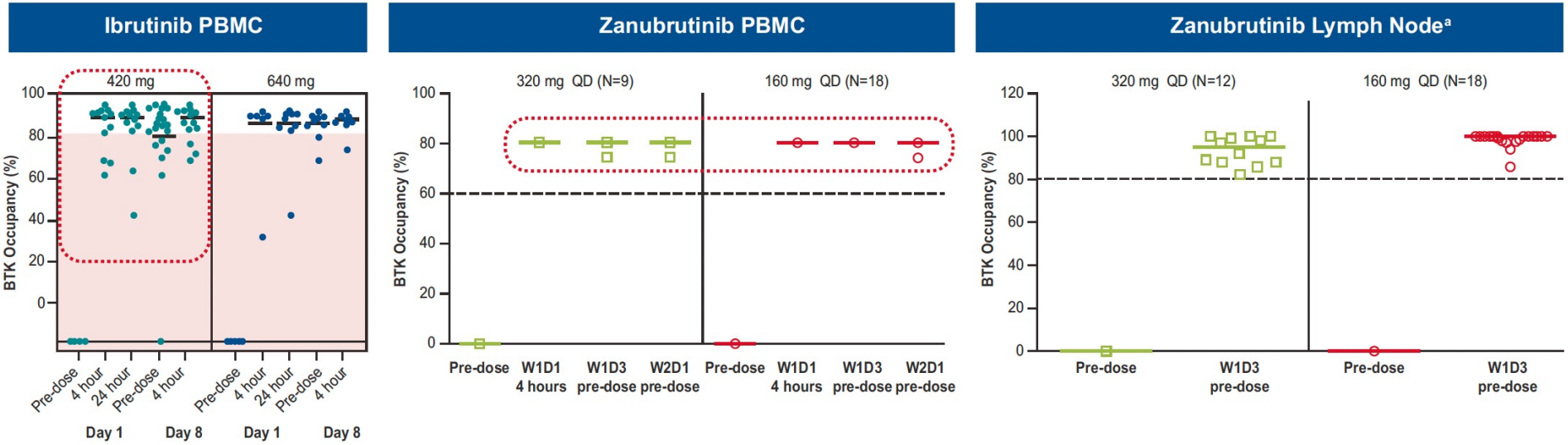
Kinase profiling at concentrations of 100 x IC_{50} based on BTK IC_{50}

Targets with >50% inhibition are highlighted in red

	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

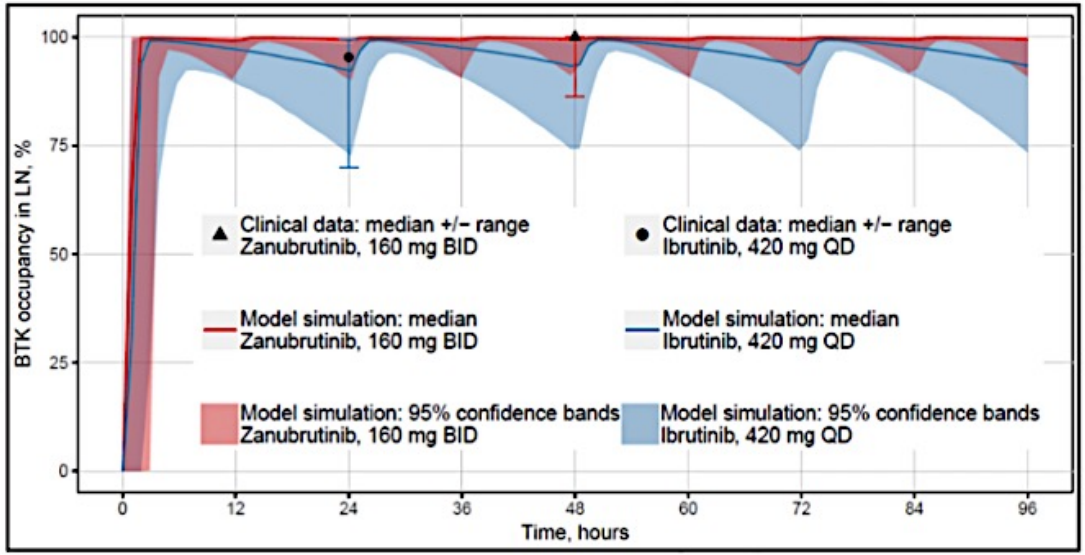
Tam CS et al. Blood Cancer Journal 2023;13:141

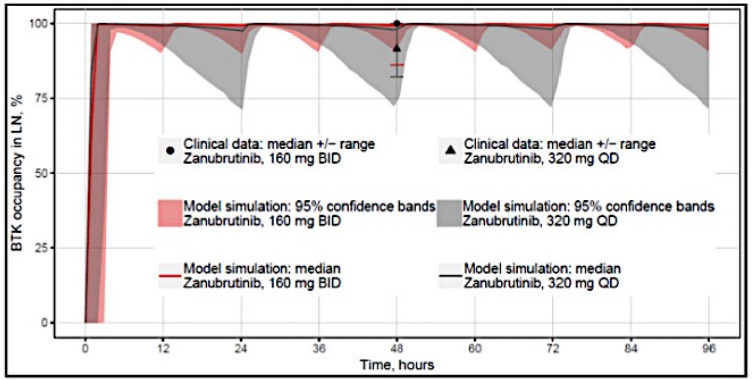
Zanubrutinib BTK occupancy in PBMC and in lymph nodes by dose regimens relative to those of ibrutinib



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)

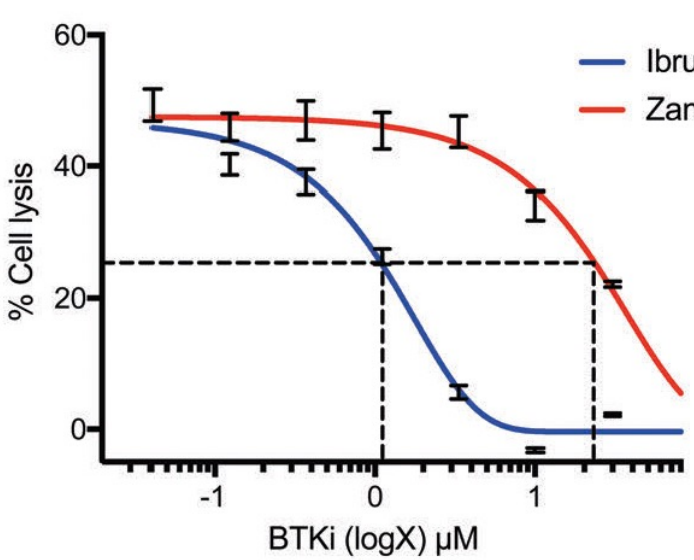




Srikumar Sahasranaman et al. http://doi.org/10.1182/blood-2019-129133

Zanubrutinib spares NK effector function

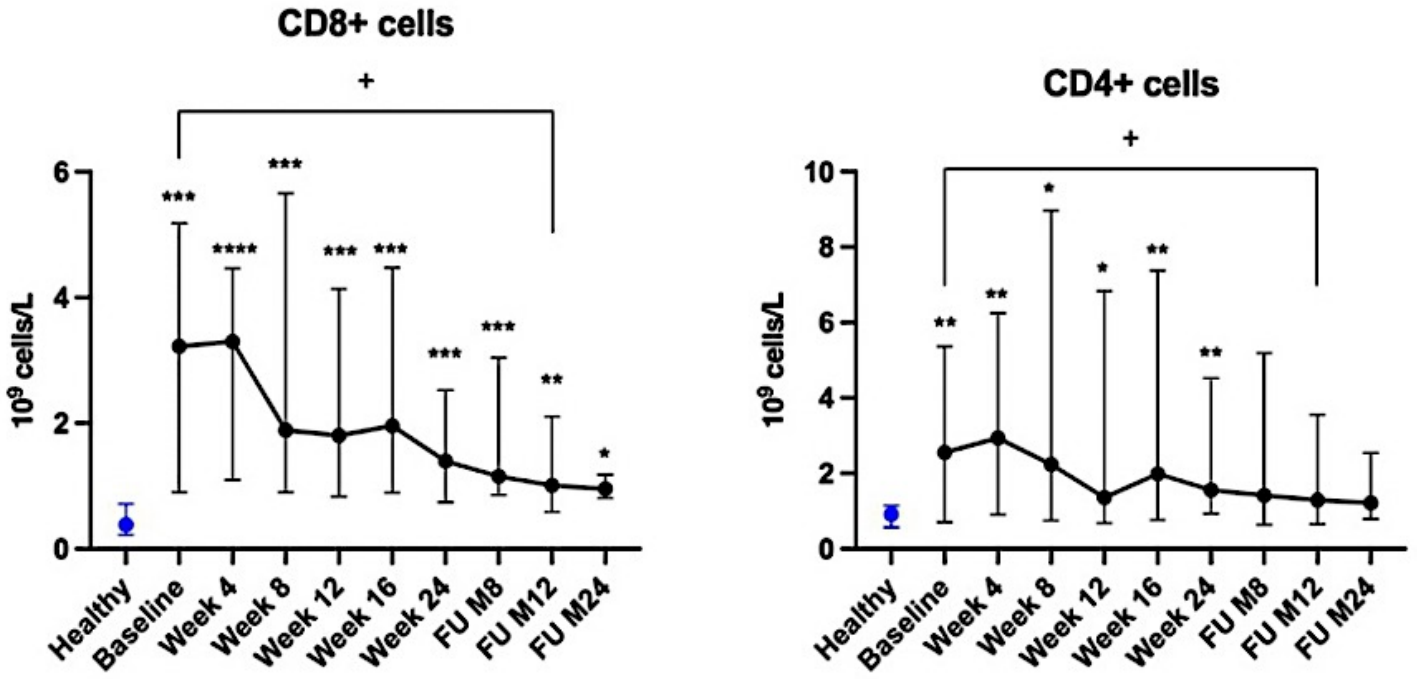
Mino MCL cells and NK92MI cells were co-seeded and treated with vehicle or various concentrations of BTK inhibitors



		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

The reduction of the tumor burden drives changes in the T-cell profile of CLL patients treated with zanubrutinib



Maria Andersson et al. HemaSphere, 2023;7(S3):1082-1084

The challenges of increasing the generation

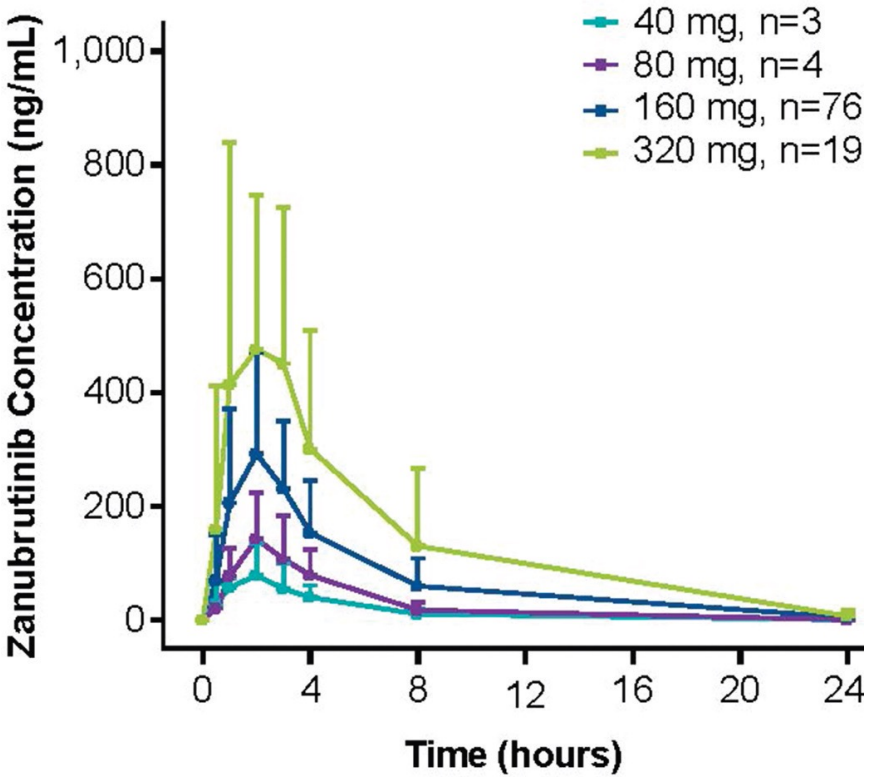
Pharmacokinetics

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

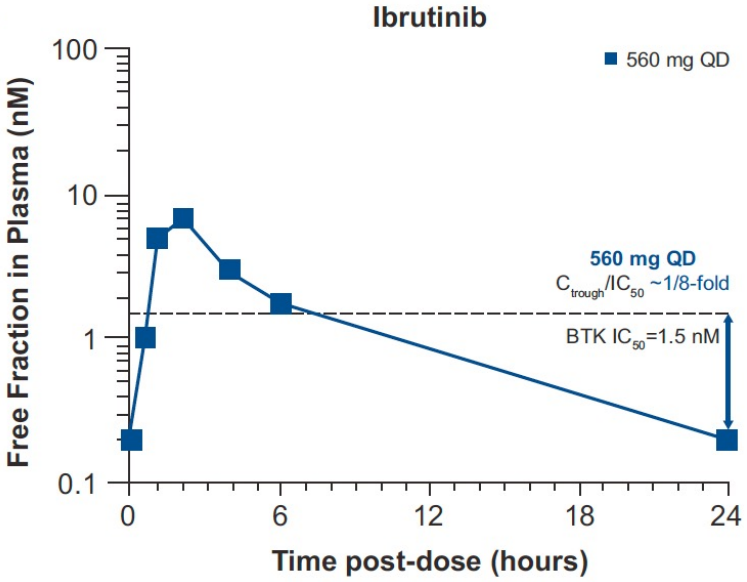
Tam CS et al. Blood Cancer Journal 2023;13:141; Tam CS et al. Expert Review of Clinical Pharmacology, 2021;14:1329-1344

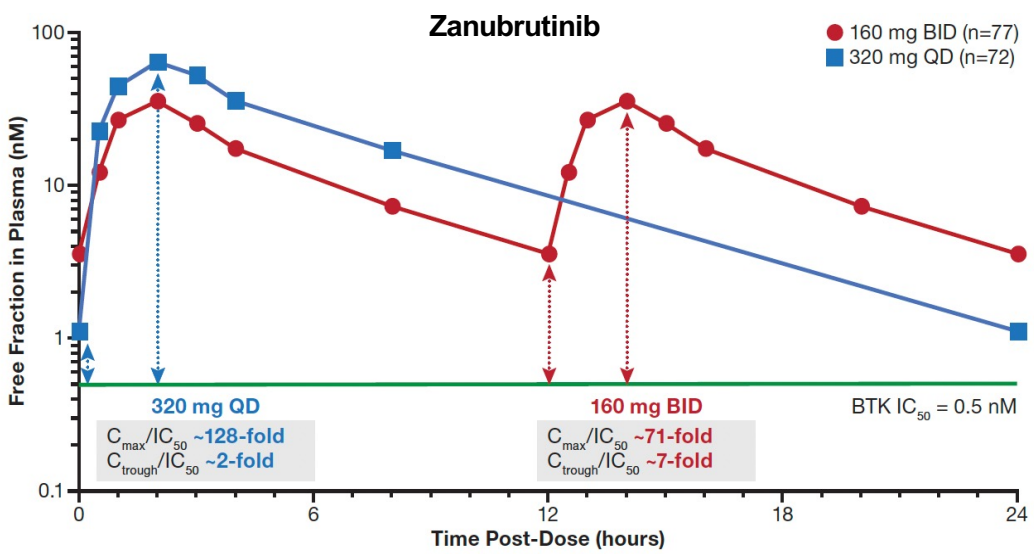
Dose-proportional increase in drug levels



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

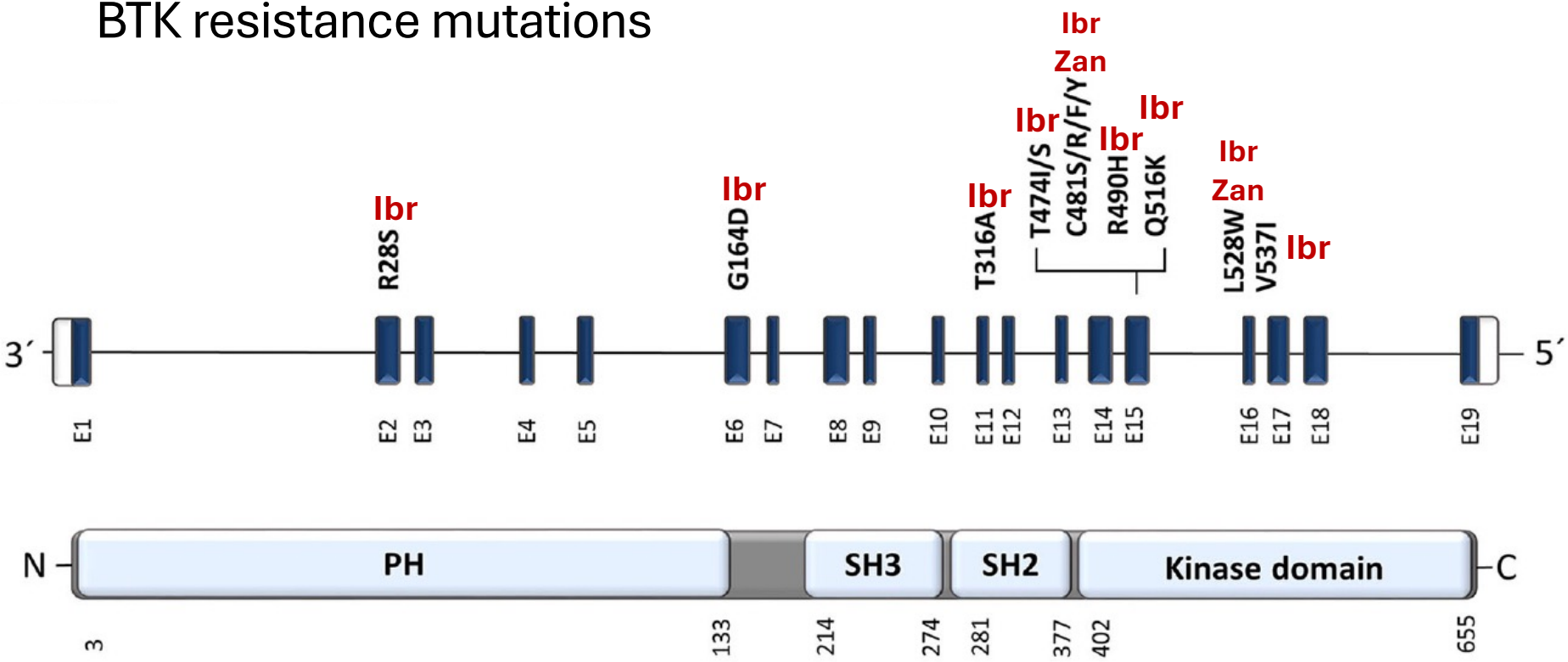
Parameter	Ibrutinib	Acalabrutinib	Zanubrutinib
Absolute bio-availability	< 10%	25%	45–50%[b]
Half-life	4–13 h	1–2 h	2–4 h
Metabolism	Predominantly via CYP3A	Predominantly via CYP3A	Predominantly via CYP3A
Excretion	Faeces, 80%; urine, < 10%	Faeces, 84%; urine, 12%	Faeces, 87%; urine, 8%

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

Resistance mutations

Do they really matter?

BTK resistance mutations



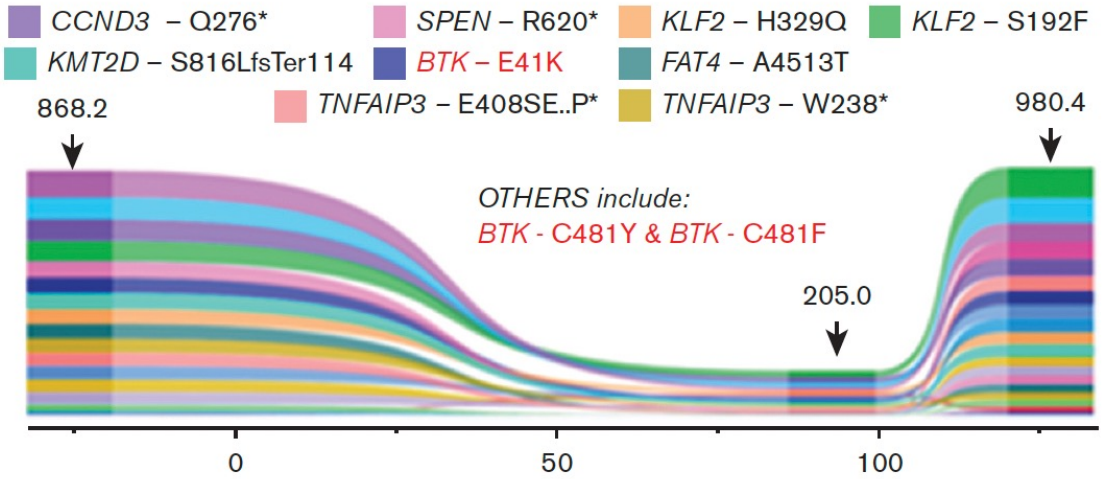
Sedlarikova L et al. Front. Oncol. 2020;10:894
Shazia Nakhoda et al. Br J Haematol 2023; 200(2): 137–149

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.