Non-C481 Mutations and Next Generation BTK Inhibitors

Constantine (Con) Tam

Disclosure of Constantine TAM

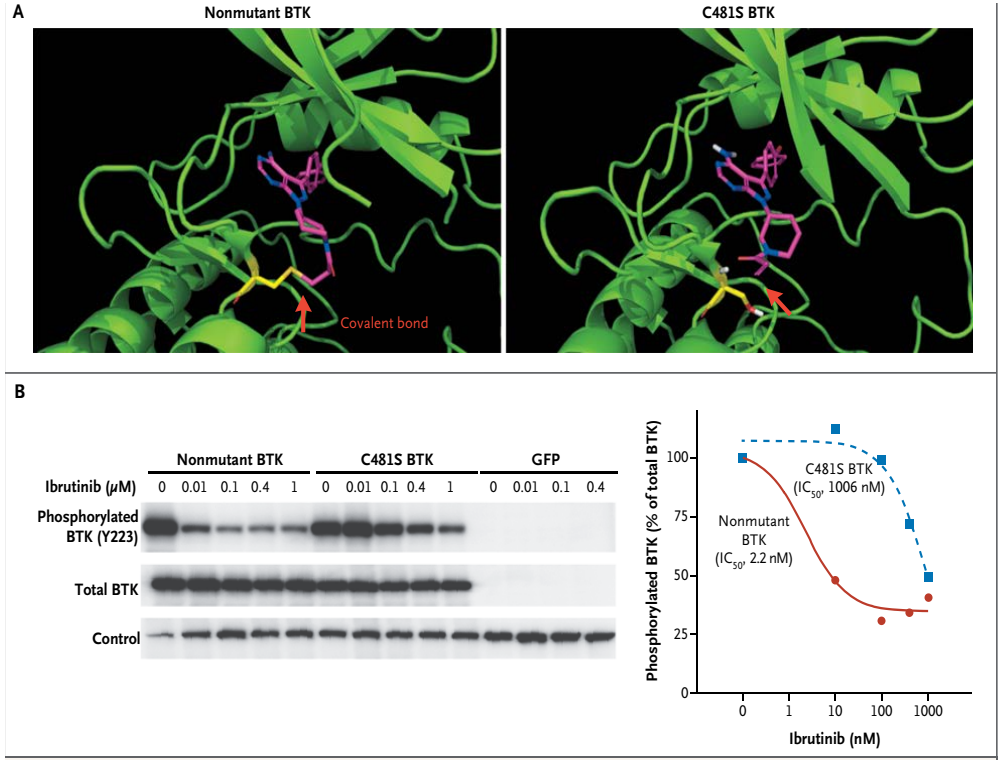
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen	x					x	
AbbVie	x					x	
BeiGene	x					x	
LOXO						x	
AstraZeneca						x	

Resistance Mutations to Ibrutinib

ID	Type of Relapse	BTK mutation	PLCγ2 mutation
605*	CLL	no	R665W
1694	CLL	C481F	no
883	CLL	C481S	no
934	CLL	C481S	D1140G
1602*	CLL	C481S	no
1140*	CLL	C481S	R665W, L845F, S707Y
1151	CLL	C481S	no
62	CLL	---	---
1314	CLL	---	---
1716	CLL	C481S	no
1833	CLL	C481S	no
2	CLL	no	R665W, S707P, S707F, R742P, L845fs

Woyach JA *et al* N Engl J Med, 2014

Maddocks *et al* JAMA Oncol, 2015



Furman RR *et al*, N Engl J Med, 2014

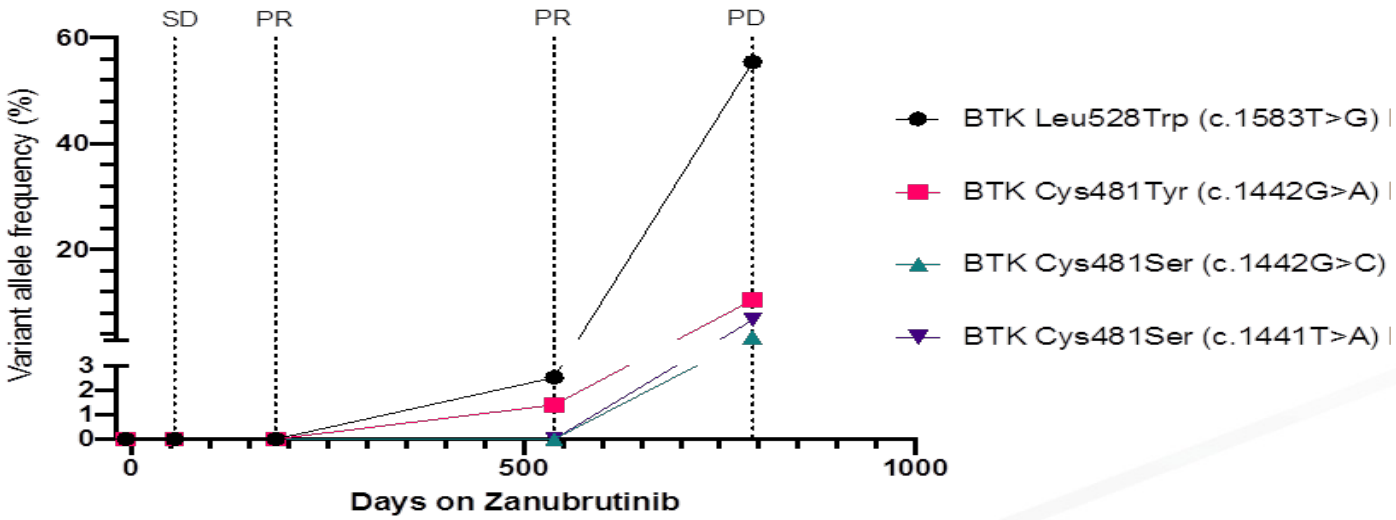
BTK Leu528Trp - a Potential Secondary Resistance Mechanism Specific for Patients with Chronic Lymphocytic Leukemia Treated with the Next Generation BTK Inhibitor Zanubrutinib

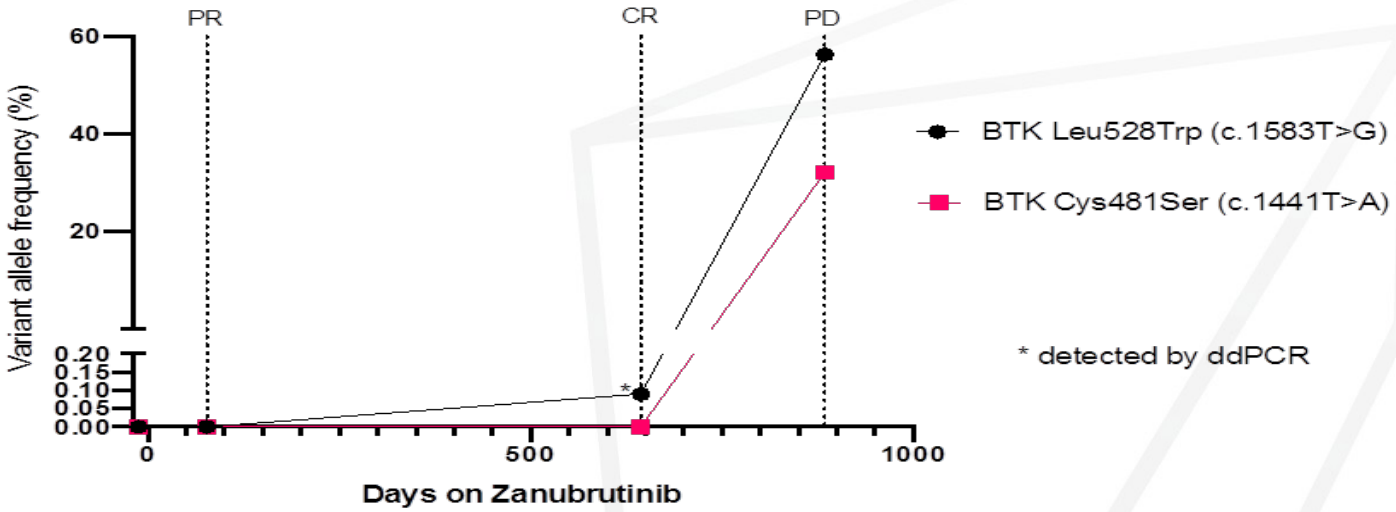
Sasanka M. Handunnetti*, Chloe Pek Sang Tang*, Tamia Nguyen, Xing Zhou, Ella Thompson, Hanzi Sun, Haimei Xing, Bo Zhang, Yin Guo, Lesley Ann Sutton, Paolo Ghia, Richard Rosenquist, Lydia Scarfo, Silvia Bonfiglio, John F. Seymour, Mary Ann Anderson, Andrew W. Roberts, David C.S. Huang, Ye Liu, Chan Y. Cheah, David A. Westerman, Paul Sung-Hao Yeh, Constantine S. Tam and Piers Blombery

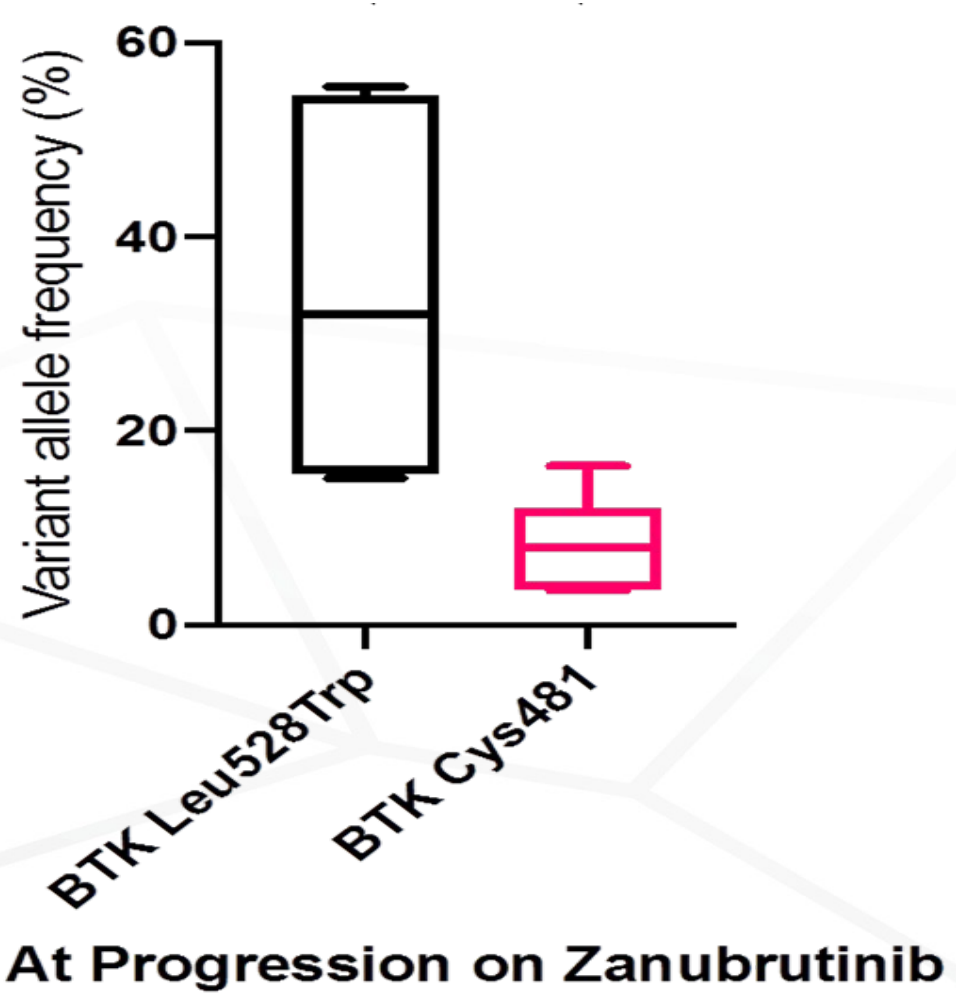
*contributed equally to the research

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

Leu528Trp is detectable in zanubrutinib treated patients before clinical CLL progression

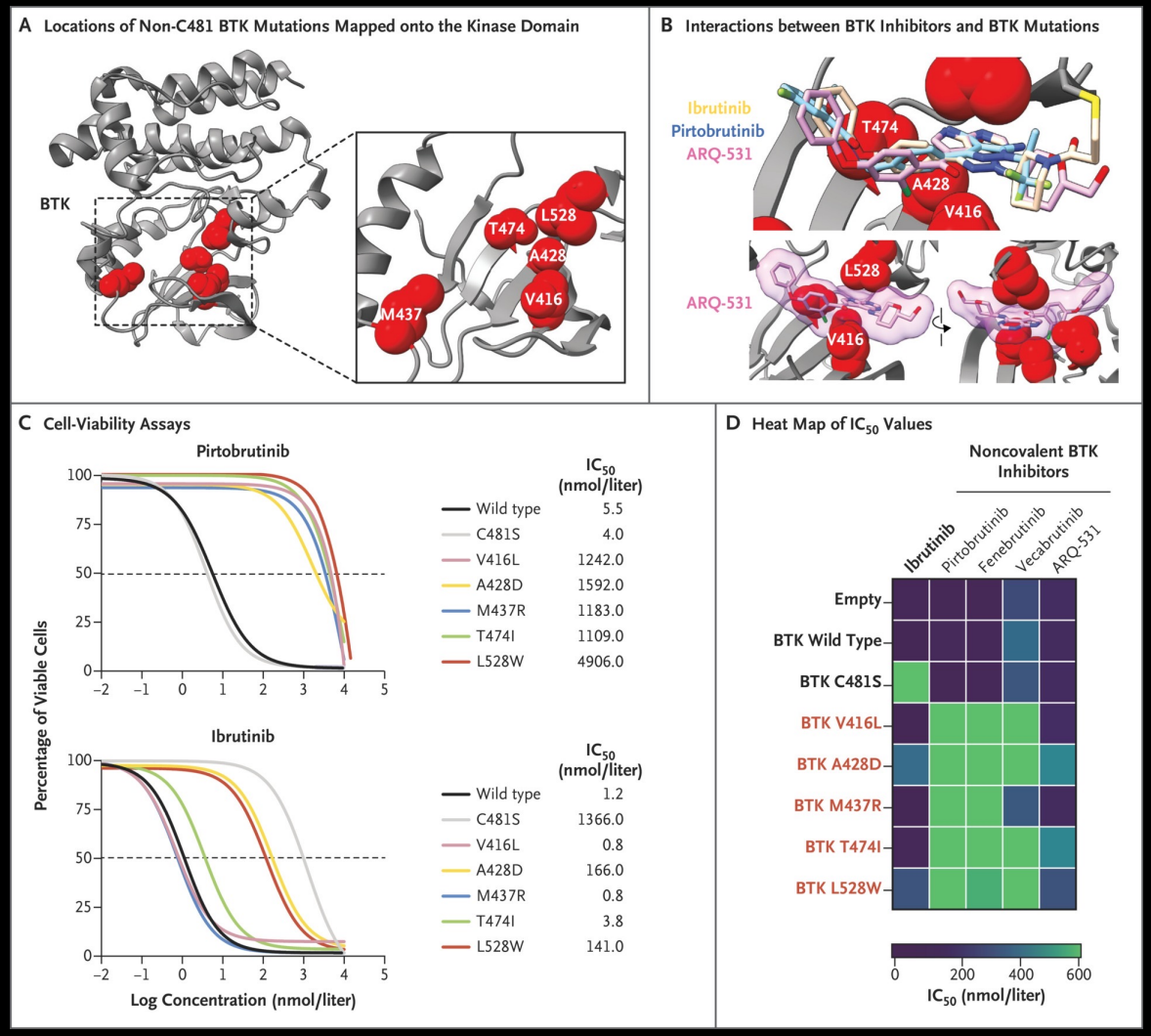






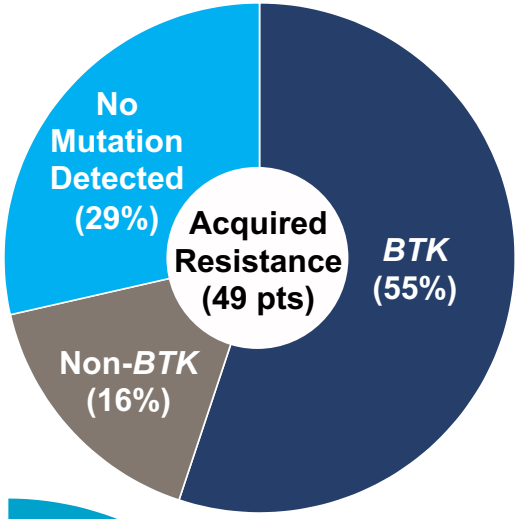
BTK Leu528Trp and Cys481 mutations are present in different cells in zanubrutinib progressors

Resistance to BTK Inhibitors Conferred by BTK Mutations Outside the C481 Residue.

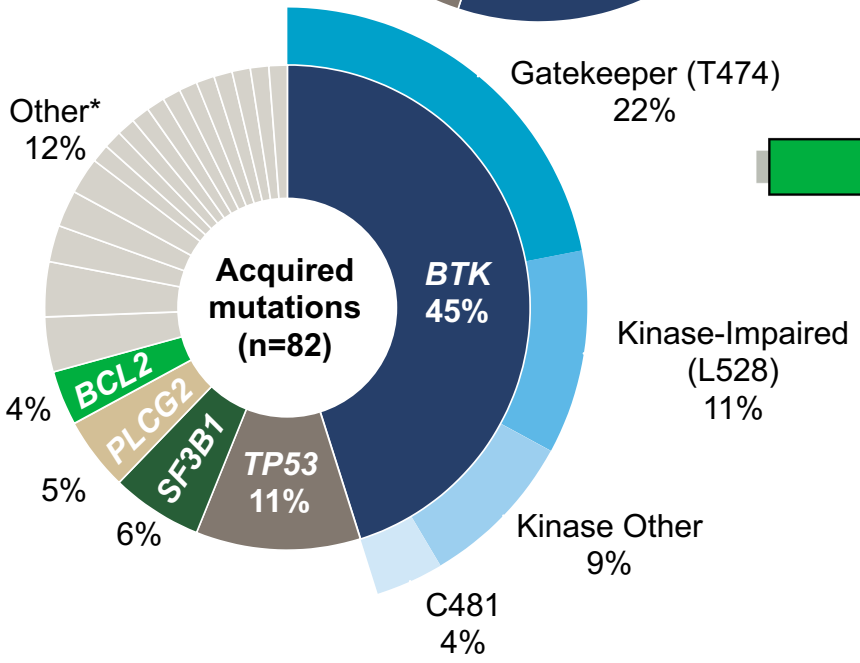


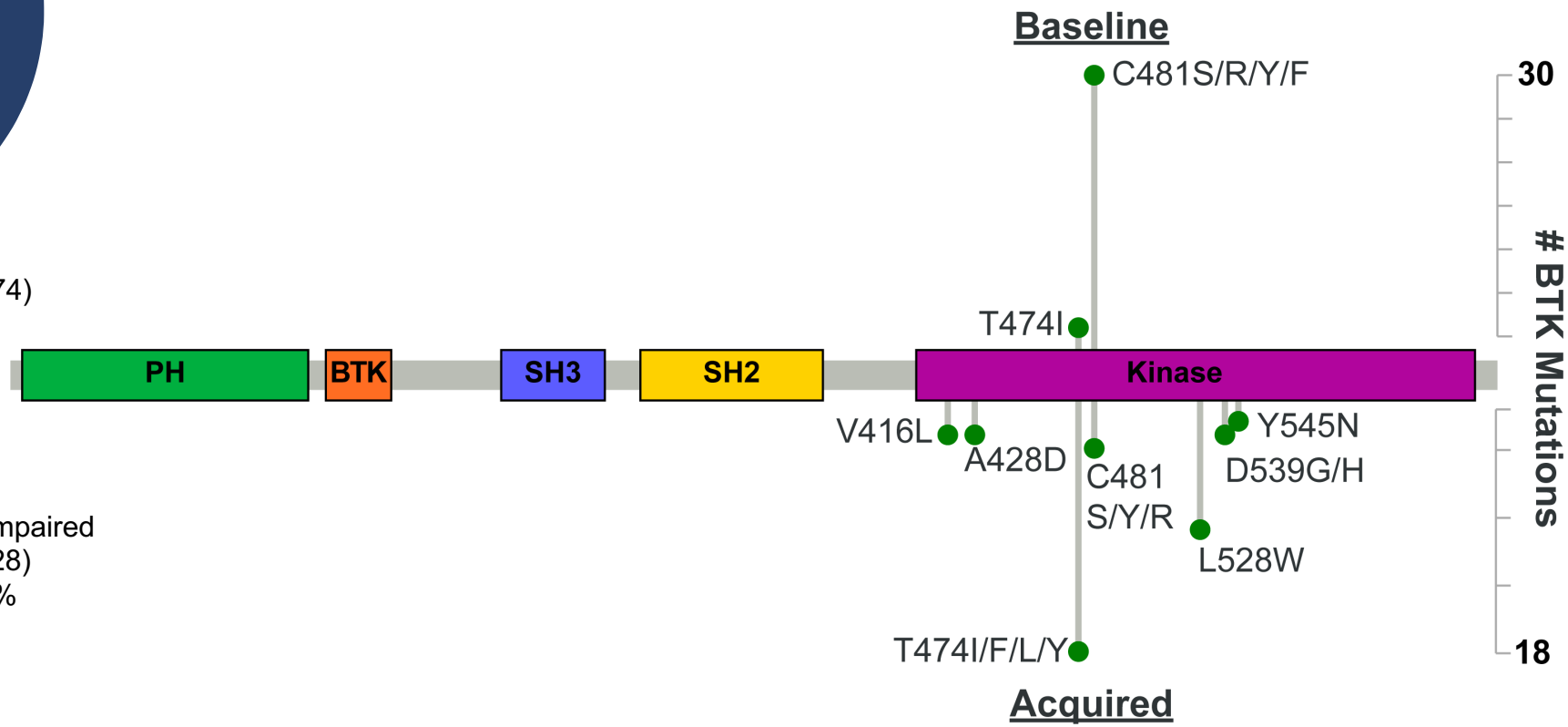
Wang E et al. N Engl J Med 2022;386:735-743

Acquired Resistance to Pirtobrutinib Converged Around On-target *BTK* Mutations (Non-C481)



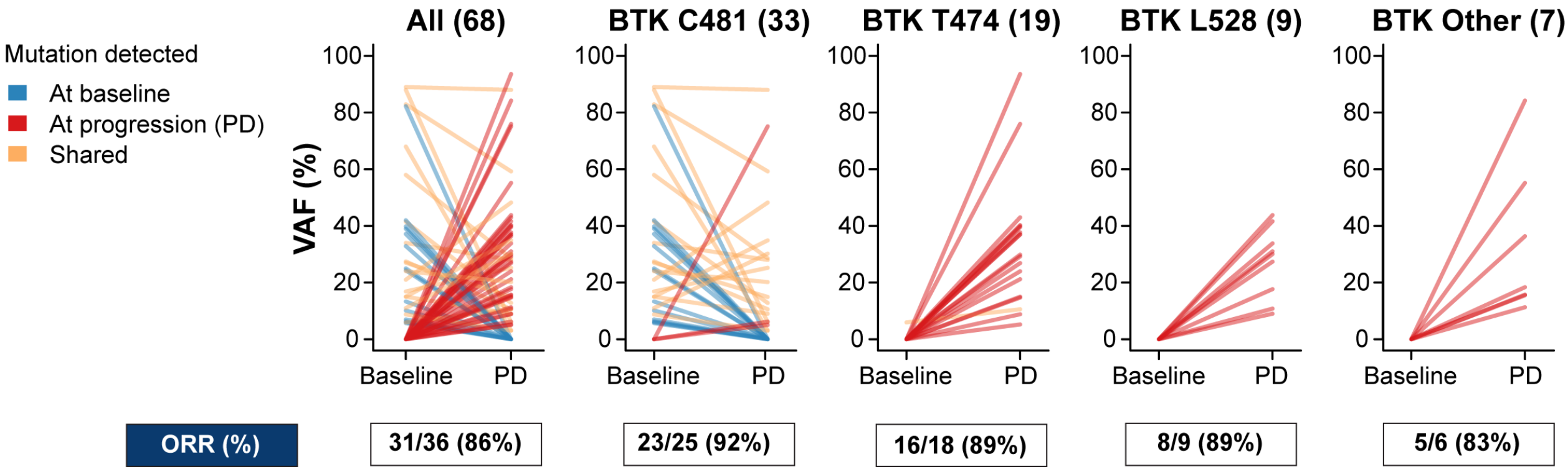
- 71% (35/49) of patients had at least one acquired mutation at progression
- Total of 82 acquired mutations in 35 patients





*Others: *APC, ATM, CDKN2A, CDKN2B, EP300, ERBB3, IRF4, KIT, KMT2C, NOTCH1, NRAS, NTRK1, PIK3CG, RB1, SMARCA4, TNFAIP3, XPO1.*

Majority of *BTK* Acquired Mutations were *BTK* T474, L528



- Decrease/clearance of C481 clones observed at progression on pirtobrutinib in 92% (22/24) patients[a]
- *BTK* C481R/S/Y, T474, L528, other kinase mutations arose at/near progression (n=27 patients[a])
- ORR and time on treatment were similar across groups regardless of the acquired BTK mutation

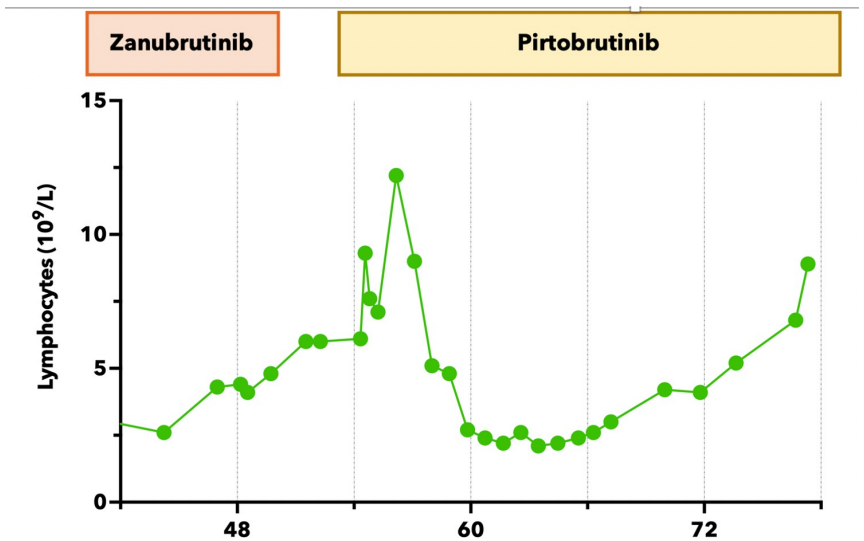
[a]Number of mutations is higher than number of patients because patients had multiple BTK mutations. [b]9 patients acquired multiple *BTK* mutations. VAF, variant allele frequency; VUS, variants of unknown significance; PD, at progressive disease.

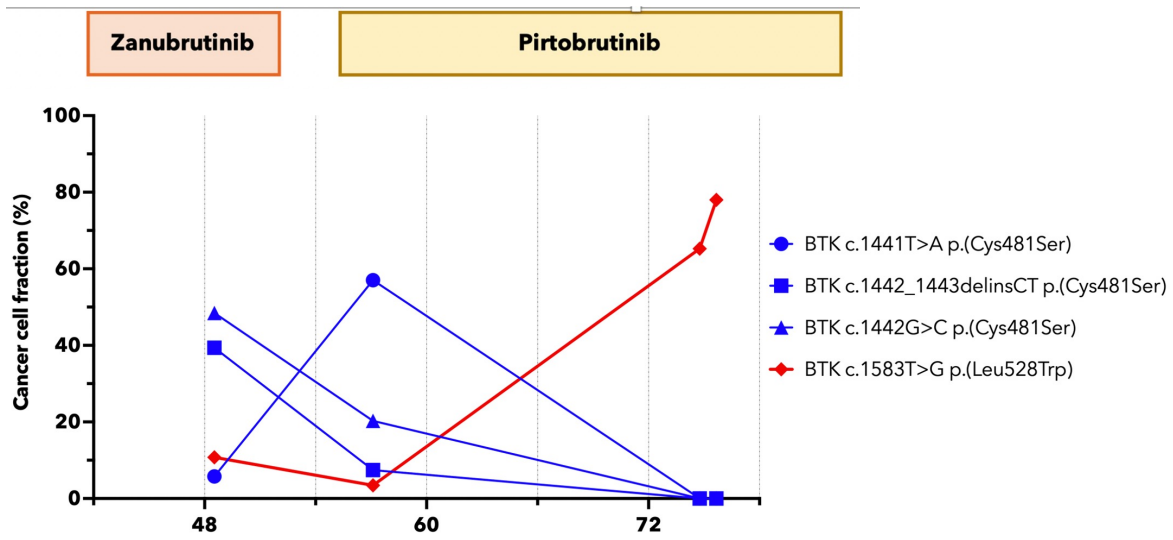
STIMULUS REPORT

blood advances

Enrichment of BTK Leu528Trp mutations in patients with CLL on zanubrutinib: potential for pirtobrutinib cross-resistance

Piers Blombery,[1,2] Ella R. Thompson,[1,2] Thomas E. Lew,[1-3] Ing Soo Tiong,[1] Rory Bennett,[1] Chan Y. Cheah,[4] Katharine Louise Lewis,[4] Sasanka M. Handunnetti,[1] Chloe Pek Sang Tang,[1] Andrew Roberts,[1-3] John F. Seymour,[1,2] and Constantine S. Tam[1,2]



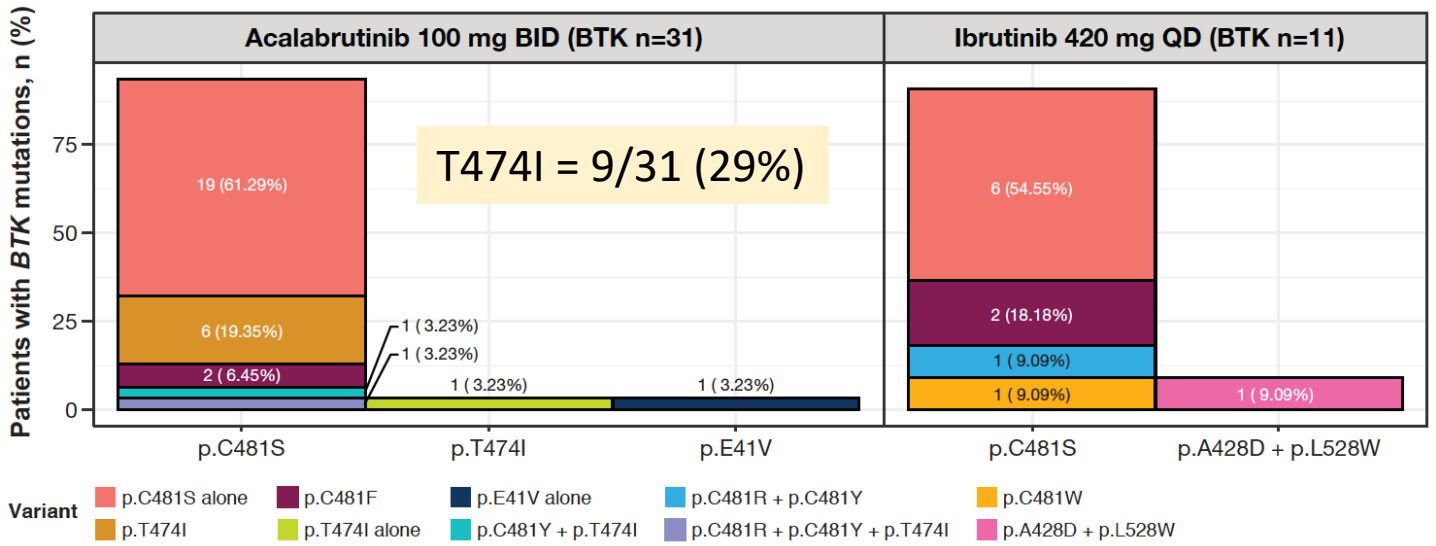


Woyach ASH 2019; Rogers Haematologica 2021; Sun ASH 2022; Blombery Blood Adv 2022; Wang NEJM 2022; Dhami Sci Signal 2022; Woyach JCO 2017; Landau Nat Comm 2017; Quinquenel Blood 2019; Estupinan Leukemia 2021; Byrd NEJM 2013; Song BJH 2022; Mato Lancet 2021; Naeem ASH 2022; Gomez Blood 2023

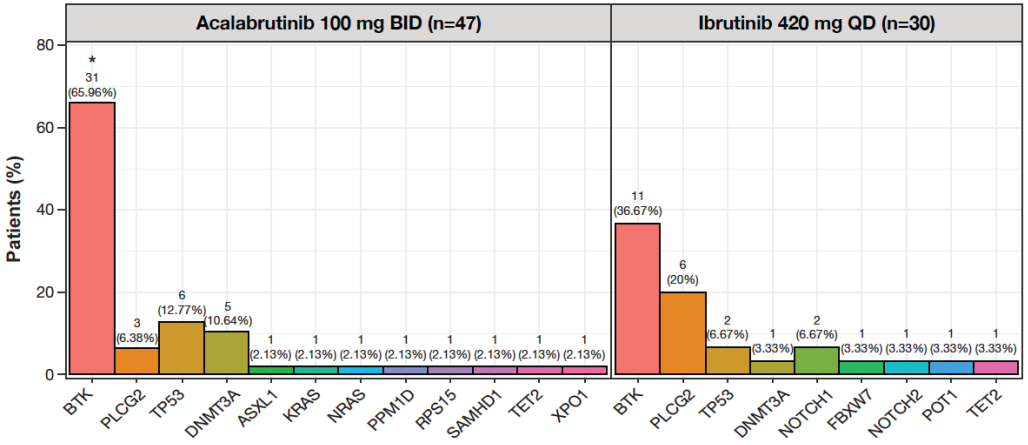
Characterization of Mechanisms of Resistance in Previously Treated Chronic Lymphocytic Leukemia From a Head-to-Head Trial of Acalabrutinib Versus Ibrutinib

Jennifer A. Woyach[1], Daniel Jones[2], Wojciech Jurczak[3], Tadeusz Robak[4], Arpad Illés[5], Arnon P. Kater[6], Paolo Ghia[7], John C. Byrd[8], John F. Seymour[9], Susan Long[10], Nehad Mohamed[2], Gary De Jesus[11], Richard Lai[11], Gerjan de Bruin[12], Anna Butturini[11], Simon Rule[13], Veerendra Munugalavadla[11]

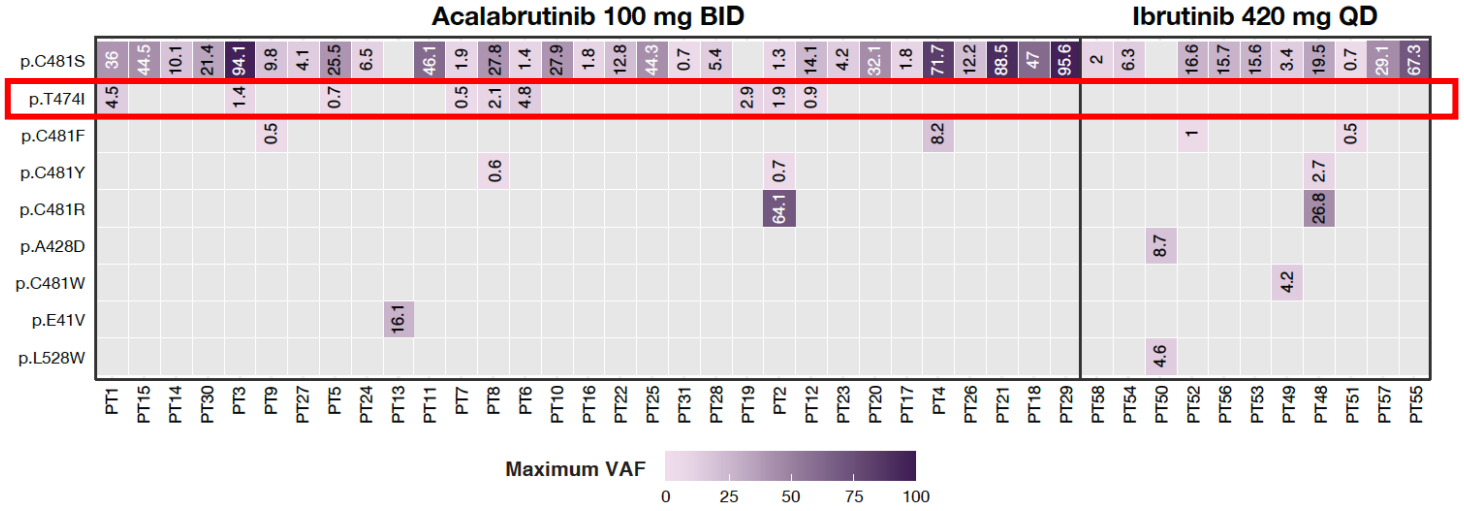
Acalabrutinib Arm Associated with T474I "Gatekeeper" Mutations…



BTK Mutations Dominate CLL Progression in Both Arms



… However T474I Mutations Tend to be Low VAF



BTK Mutations (Oct 2023)

Drug	Resistant Mutations	Has In-Vitro Activity Against
Ibrutinib	C481S in >90% (Rare – D43H, C481 kinase dead, A428D, L528W, T474I)	L528W, T474I/L, C481 kinase dead (via HCK), V416L/M, A428D
Acalabrutinib	C481S, C481 kinase dead, T474I, E41V	L528W
Zanubrutinib	C481S, C481 kinase dead, L528W, A428D	T474I, V416L/M
Pirtobrutinib	C481 kinase dead, L528W, V416L, T474I/F/L/Y, A428D, M477I, M437R, D539G/H, Y545N	C481S

*C481 Kinase Dead = C481F, C481Y, C481W, C481G, C481R. C481T is catalytically active (Hamasy Leukemia 2017)

Woyach ASH 2019; Rogers Haematologica 2021; Sun ASH 2022; Blombery Blood Adv 2022; Wang NEJM 2022; Dhami Sci Signal 2022; Woyach JCO 2017; Landau Nat Comm 2017; Quinquenel Blood 2019; Estupinan Leukemia 2021; Byrd NEJM 2013; Song BJH 2022; Mato Lancet 2021; Naeem ASH 2022; Gomez Blood 2023; Brown ASH 2023; Brown EHA 2023; Woyach ICML 2023; Ahn IWCLL 2023; Qi Blood Advances 2023.