9° WORKSHOP
IN EMATOLOGIA TRASLAZIONALE

DELLA SOCIETÀ ITALIANA DI EMATOLOGIA SPERIMENTALE

Bologna, Aula "G. Prodi", 19-20 maggio 2025

Resistance to BTK inhibitors in CLL

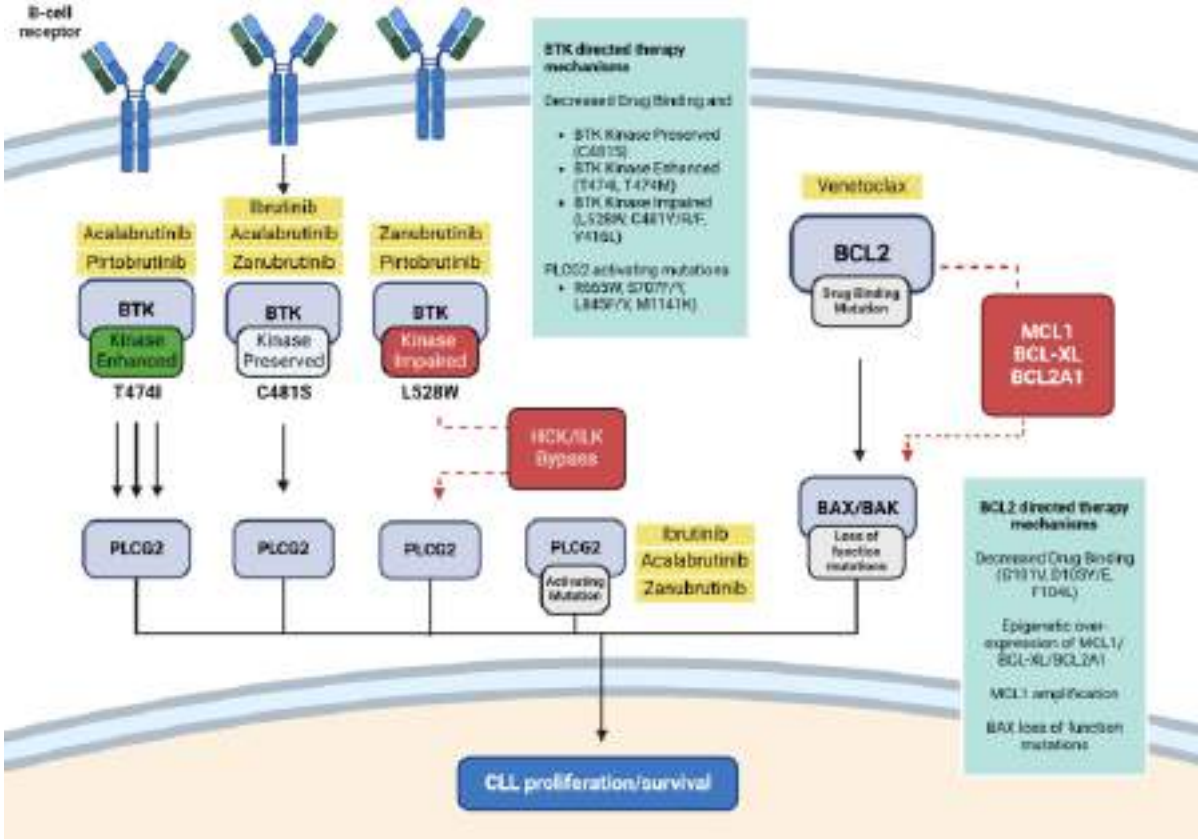
Lydia Scarfò

Università Vita Salute and IRCCS Ospedale San Raffaele, Milano

Disclosures di Lydia Scarfò

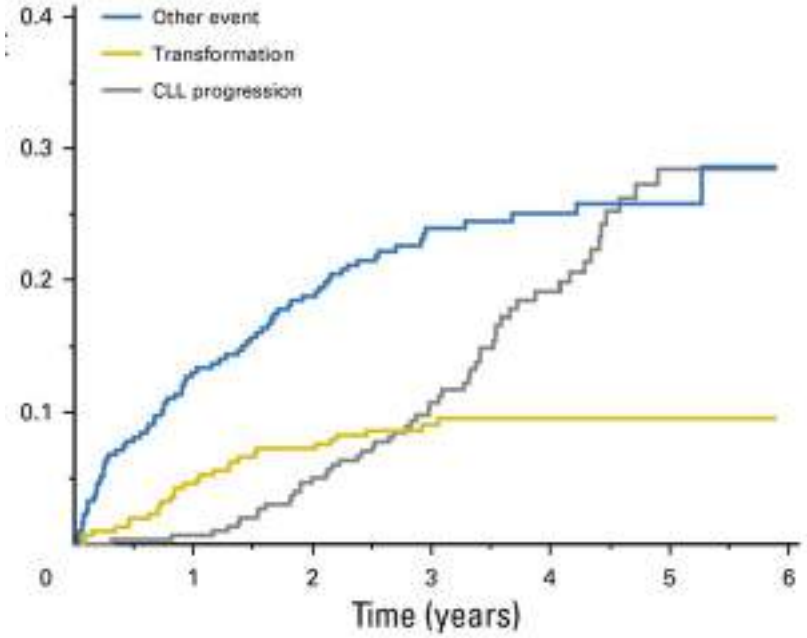
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie			X			X	
AstraZeneca			X			X	
BeOne			X			X	
Johnson & Johnson			X			X	
Lilly			X			X	
Merck			X				X

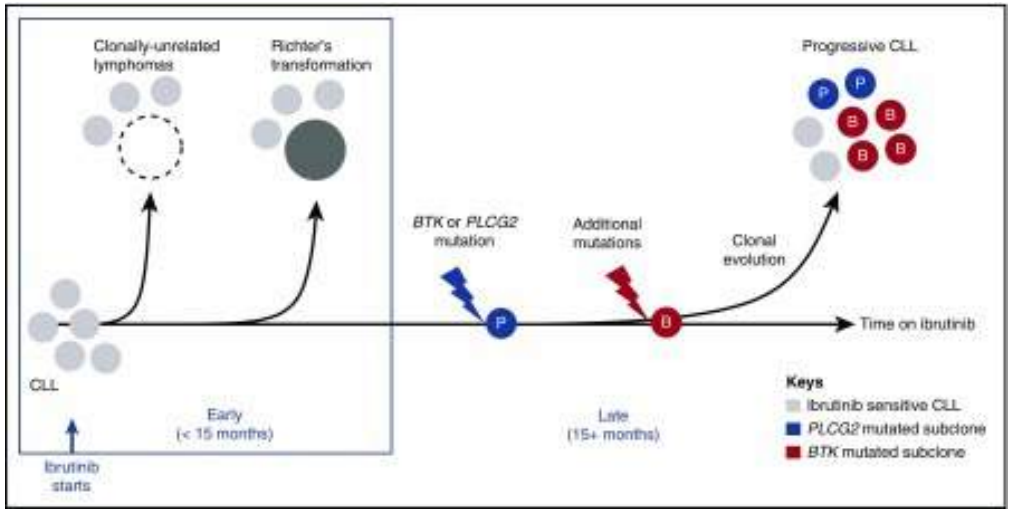
BTK-dependent signaling pathways in CLL



Blombery P et al. Accepted for publication

CLL Progression on Ibrutinib and Resistance Mutations

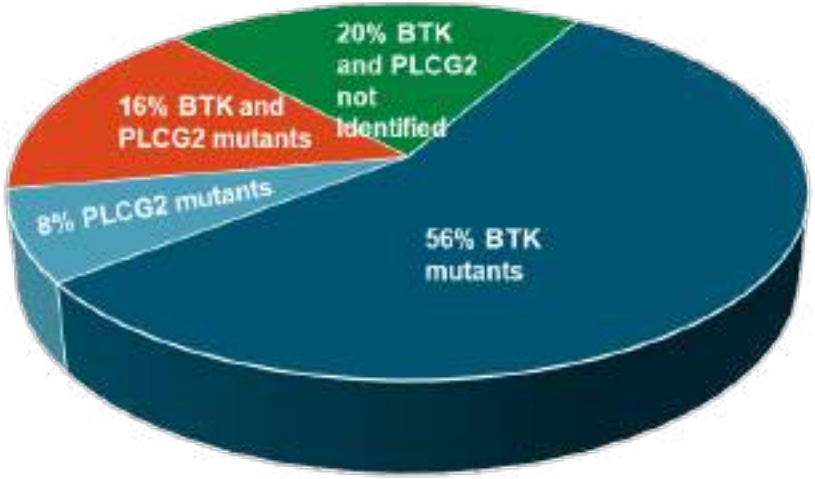


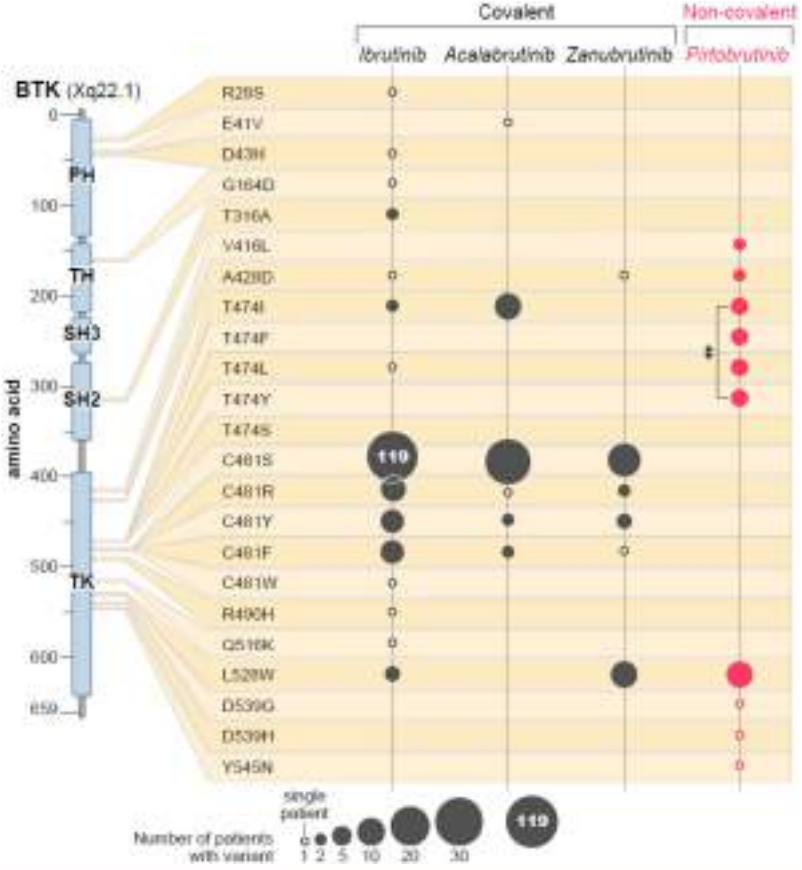


Ibrutinib discontinuation due to PD, intolerance or RT.
Resistance mutations occur up to 15 months before manifestation of clinical progression.

Wiestner A. Haematologica. 2021; Ahn IE, et al. Blood 2017

BTK Mutations associate with Resistance

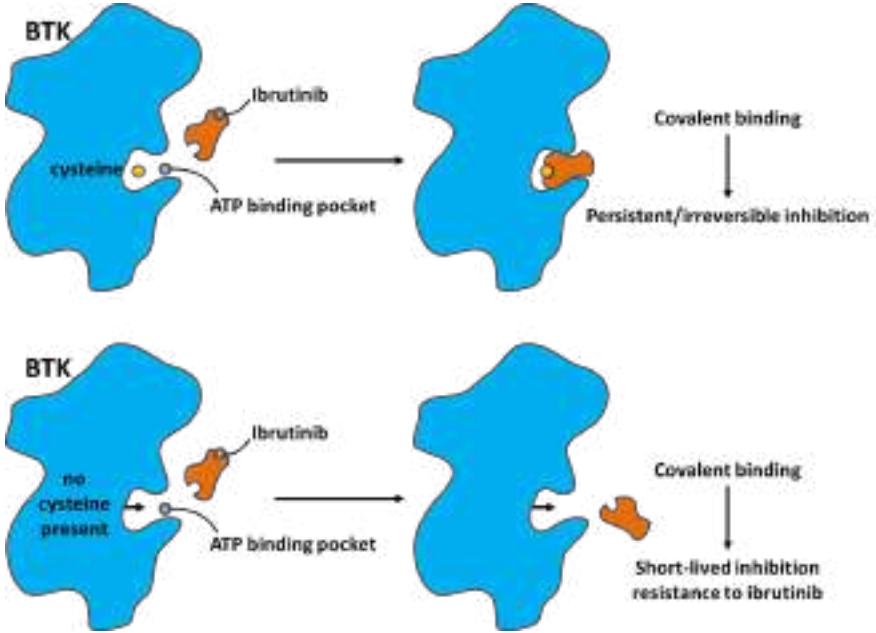


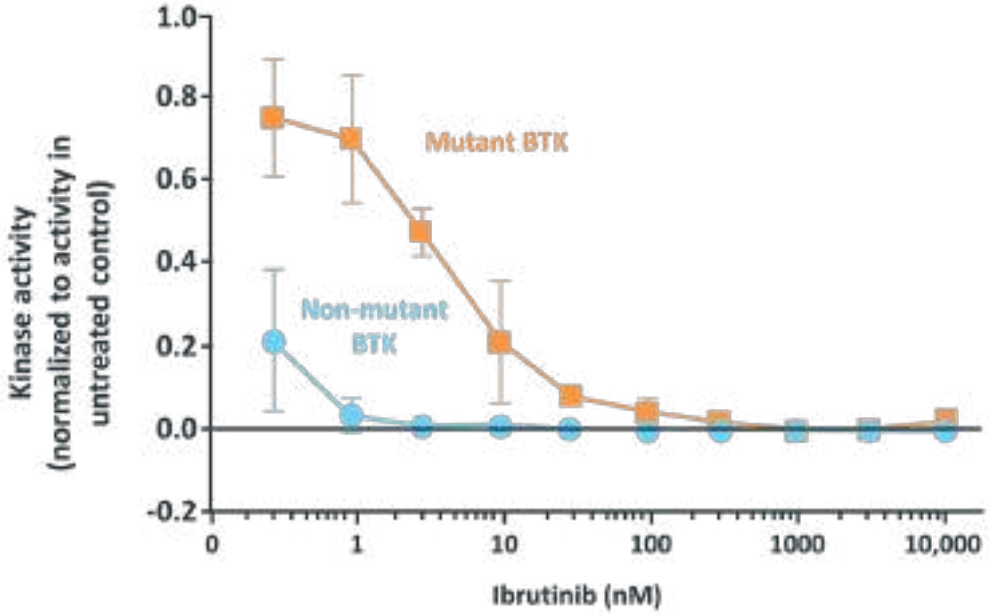


Early studies showed high prevalence of *BTK* mutations in patients with CLL progressing on ibrutinib

Gruessner C et al, Leuk &Lymph 2025

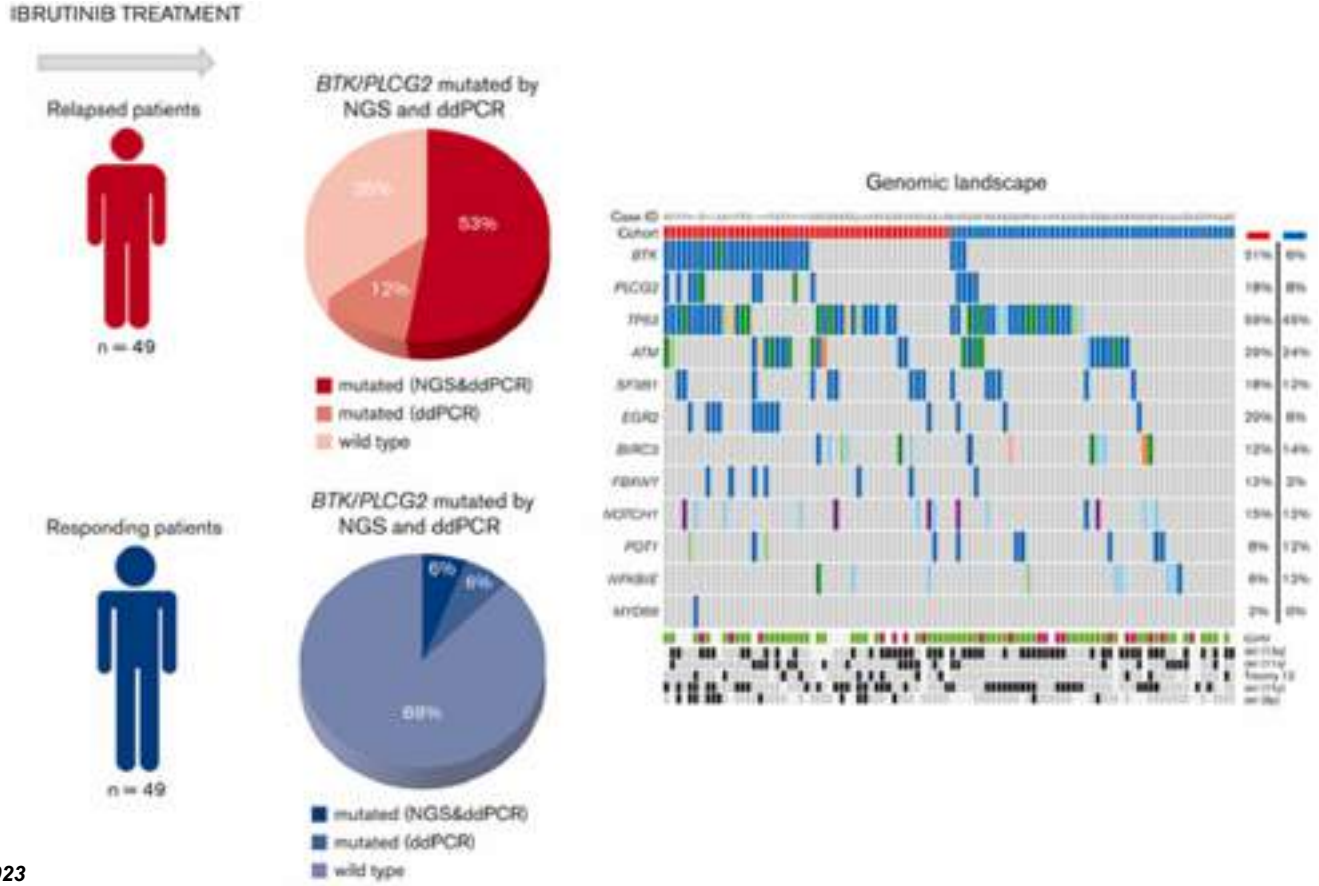
Mechanisms of BTK Inhibition and Resistance





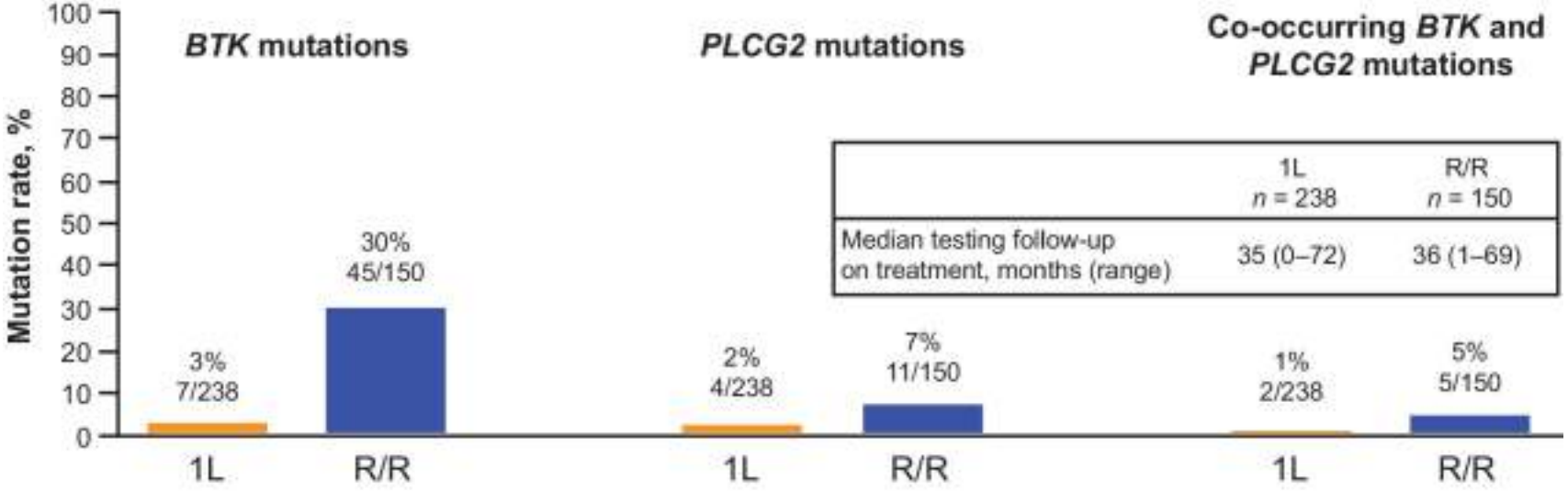
Wiestner A. Haematologica. 2021; Woyach J, et al. N Engl J Med. 2014

BTK mutations in pts with CLL relapsing on ibrutinib



Bonfiglio S et al. Blood Adv 2023

BTK mutations are rare in TN pts with CLL

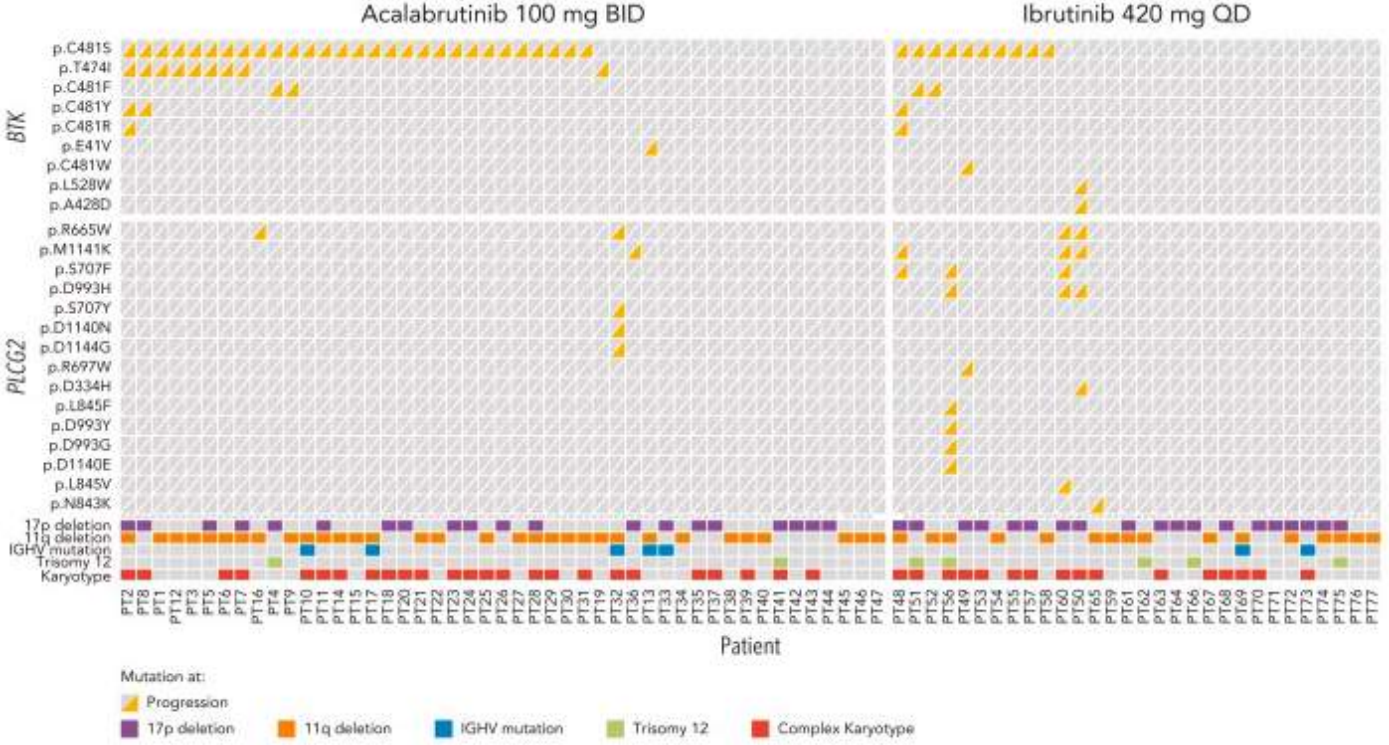


	1L *n* = 238	R/R *n* = 150
Median testing follow-up on treatment, months (range)	35 (0–72)	36 (1–69)

Median time to mutation detection: 1L NR, RR 61 months
3y mutation-free estimates: 1L 100%, RR 80%

Woyach JA et al, Clin Cancer Res. 2023

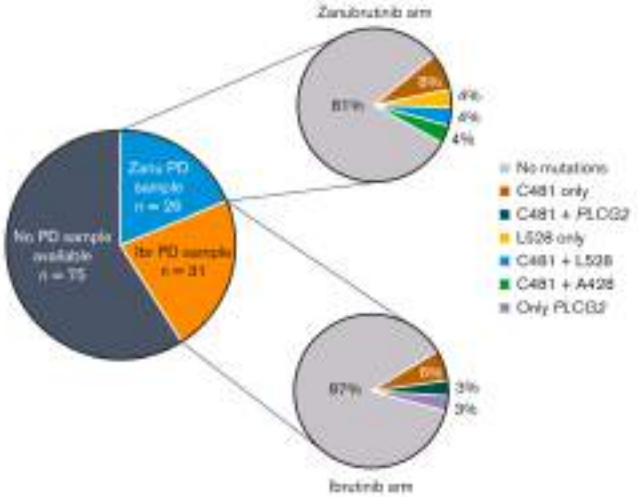
BTK mutations in pts with CLL relapsing on acalabrutinib



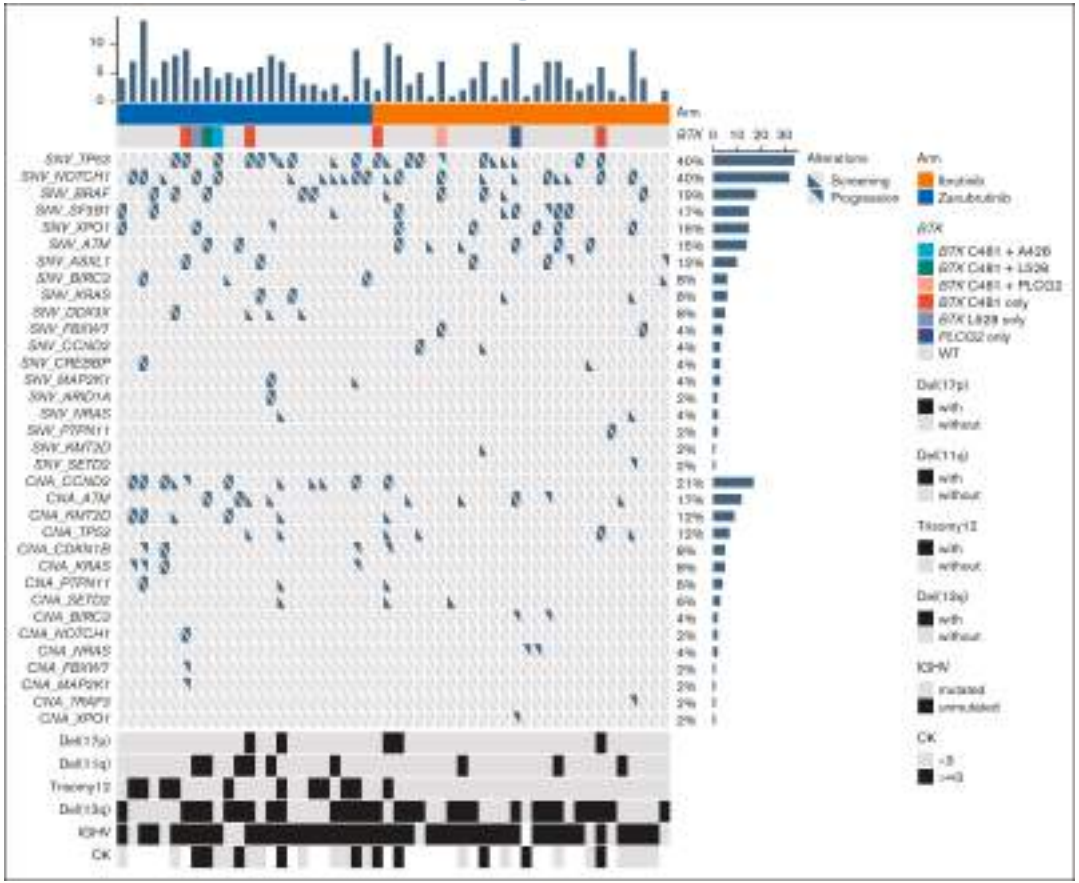
Emergent BTK mutations observed in 31/47 (66%) acalabrutinib- and 11/30 (37%) ibrutinib-treated patients

Woyach JA et al. Blood 2024

BTK mutations in pts with CLL relapsing on zanubrutinib



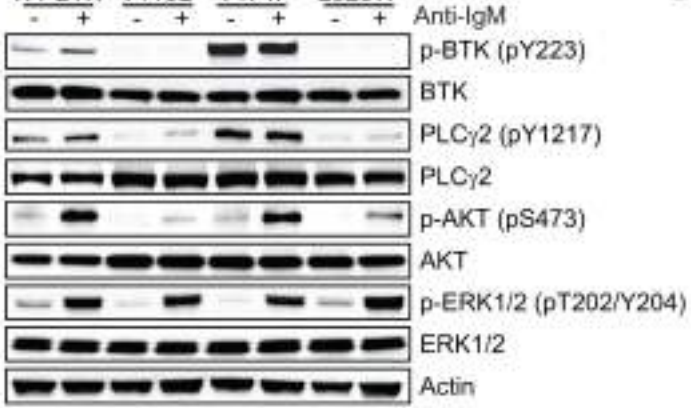
5/24 on zanubrutinib
3/28 on ibrutinib
Developed *BTK* mutations at PD



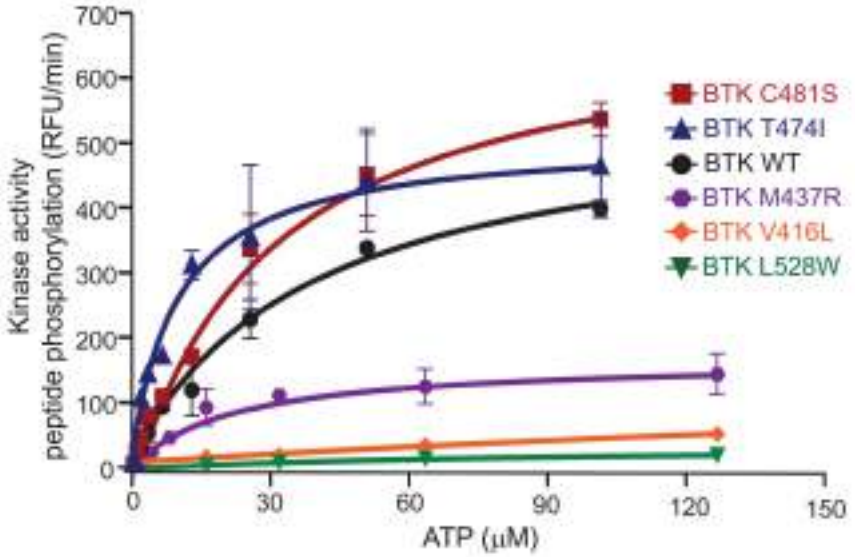
Brown JR et al. Blood Adv 2025

Kinase proficient vs impaired *BTK* mutations

A



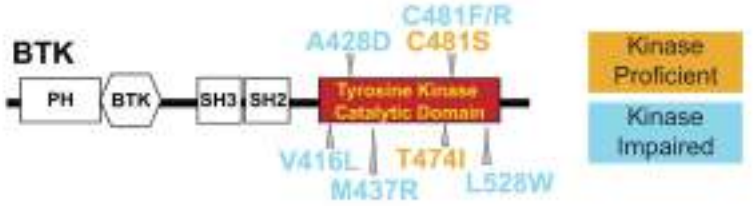
B



C

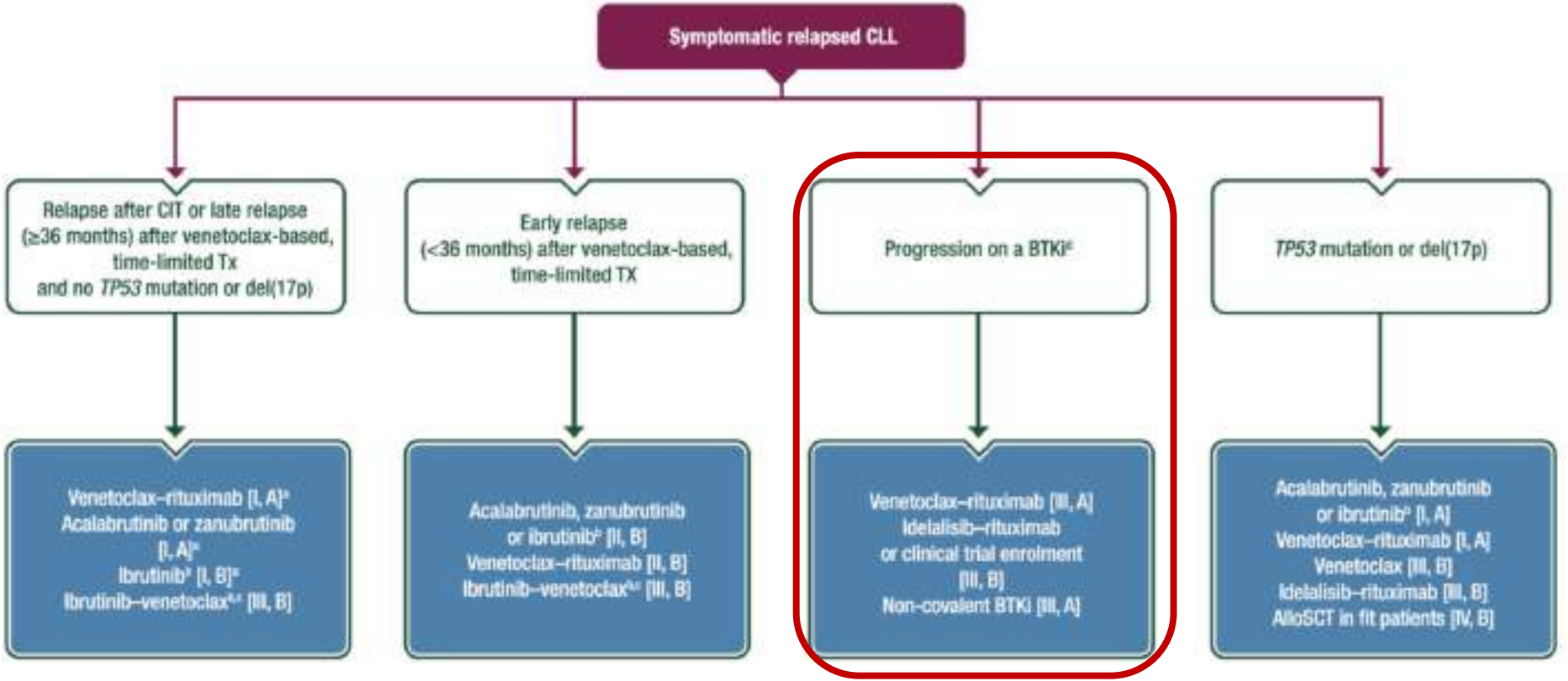
BTK Protein	Apparent $K_{m,ATP}$ (μM)	Relative Catalytic Efficiency (apparent $k_{cat}/K_{m,ATP}$) to WT
WT	45 ± 11	1
C481S	27 ± 8	2
T474I	10 ± 1	18
M437R	17 ± 4	0.11
V416L	243 ± 44	<0.01
L528W	103 ± 37	<0.01

D



Montoya S et al, Science 2024

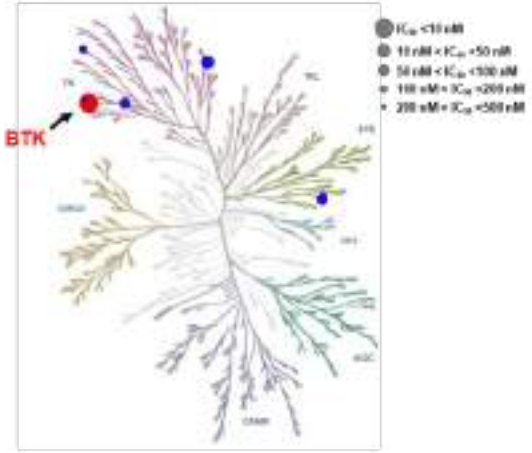
How to deal with PD on covalent BTKi



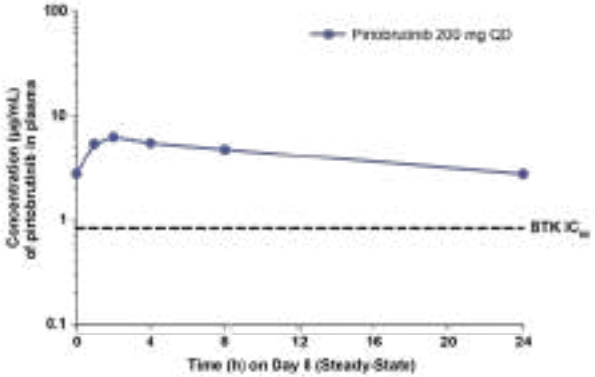
Eichhorst B, Ghia P et al. Ann Oncology 2024

Non-covalent BTKi: new kids on the block

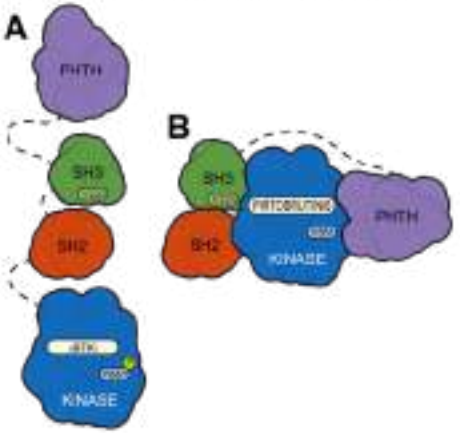
Highly selective for BTK[5,6]



Plasma exposures exceeded BTK IC_{90} throughout dosing interval



Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[7]



- Inhibits both WT and C481-mutant BTK with equal low nM potency[7]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[7]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[7]

Mato et al, Lancet 2021; Brandhuber et al. Clin Lymphoma Myeloma Leuk 2018; Gomez et al. Blood.2023

Pirtobrutinib Phase 1/2 BRUIN Trial

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median age, years (range)	69 (36-88)	69 (36-87)	68 (41-88)
Male, n (%)	192 (68)	106 (69)	86 (67)
Rai staging, n (%)			
0-II	147 (52)	94 (61)	53 (41)
III-IV	120 (43)	58 (38)	62 (48)
Missing	15 (5)	2 (1)	13 (10)
Bulky Lymphadenopathy ≥5 cm, n (%)	88 (31)	42 (27)	46 (36)
ECOG PS, n (%)			
0	144 (51)	89 (58)	55 (43)
1	118 (42)	56 (36)	62 (48)
2	20 (7)	9 (6)	11 (9)
Median number of prior lines of systemic therapy, (range)	4 (1-11)	3 (1-9)	5 (1-11)
Prior therapy, n (%)			
BTK inhibitor	282 (100)	154 (100)	128 (100)
Anti-CD20 antibody	251 (89)	127 (83)	124 (97)
Chemotherapy	228 (81)	114 (74)	114 (89)
BCL2 inhibitor	128 (45)	0 (0)	128 (100)
PI3K inhibitor	71 (25)	17 (11)	54 (42)
CAR-T	17 (6)	2 (1)	15 (12)
Allogeneic stem cell transplant	7 (3)	1 (1)	6 (5)

Characteristics	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Median time from diagnosis to first dose, years (IQR)	11 (8-15)	11 (7-15)	12 (8-15)
Reason for any prior BTKi discontinuation[a], n (%)			
Progressive disease	217 (77)	110 (71)	107 (84)
Toxicity/Other	64 (23)	43 (28)	21 (16)

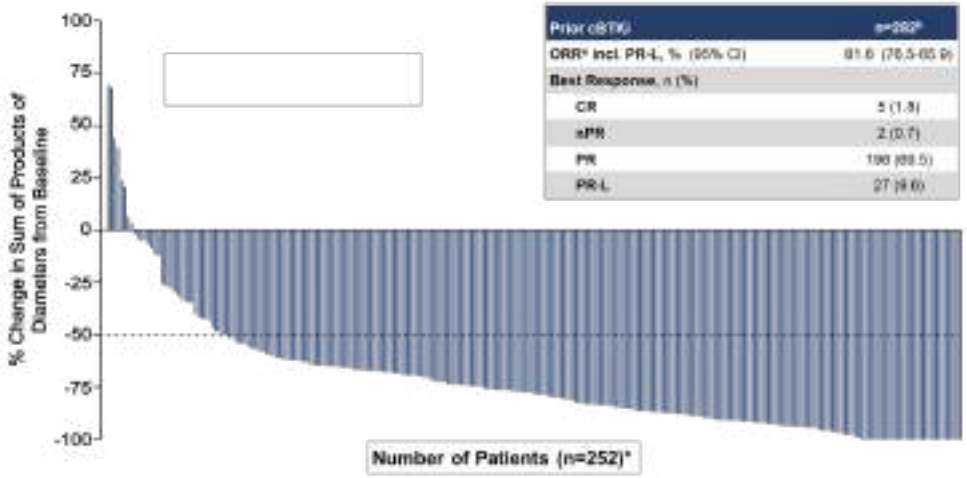
Baseline Molecular Characteristics[b]	Prior cBTKi (n=282)	BCL2i-N (n=154)	BCL2i-E (n=128)
Mutation status, n/n available (%)			
BCL2 mutated	19/246 (8)	0/133 (0)	19/113 (17)
BTK C481-mutant	96/245 (39)	57/138 (41)	39/107 (36)
PLCG2-mutant	18/245 (7)	10/138 (7)	8/107 (8)
High Risk Molecular Features, n/n available (%)			
17p deletion and/or TP53 mutation	104/217 (48)	57/123 (46)	47/94 (50)
IGHV unmutated	193/225 (86)	100/125 (80)	93/100 (93)
Complex Karyotype	33/73 (45)	17/41 (42)	16/32 (50)
11q deletion	47/202 (23)	28/115 (24)	19/87 (22)

[a]In the event more than one reason was noted for discontinuation, disease progression took priority. [b]Molecular characteristics were determined centrally and are presented based on data availability, in those patients with sufficient sample to pass assay quality control.

Woyach JA, Oral presentation ASH 2023

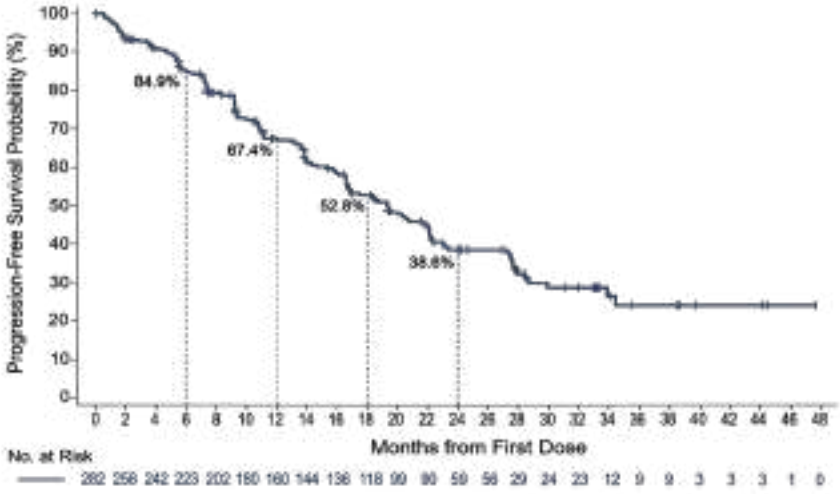
Pirtobrutinib clinical efficacy in heavily pretreated pts

Median follow-up of 30 months



Prior cBTKi	n=252*
ORR* incl. PR-L, % (95% CI)	81.6 (76.5-85.9)
Best Response, n (%)	
CR	5 (1.8)
aPR	2 (0.7)
PR	190 (69.5)
PR-L	27 (9.6)

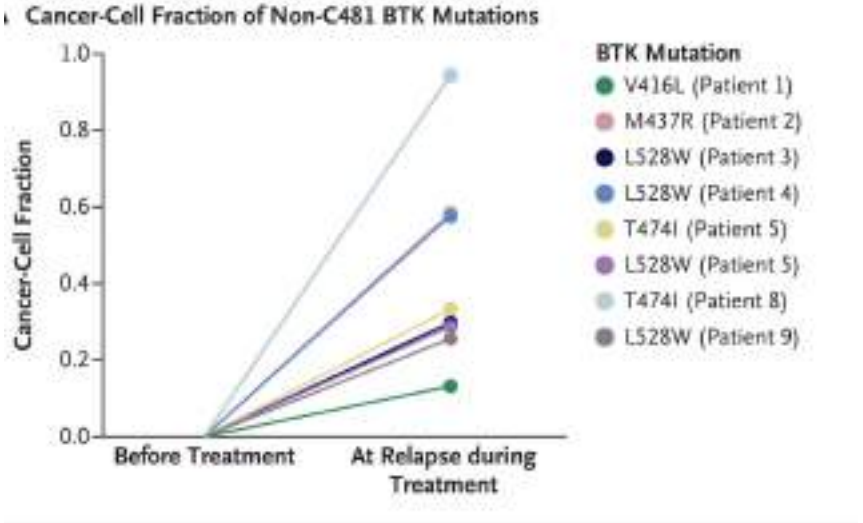
Progression-free survival

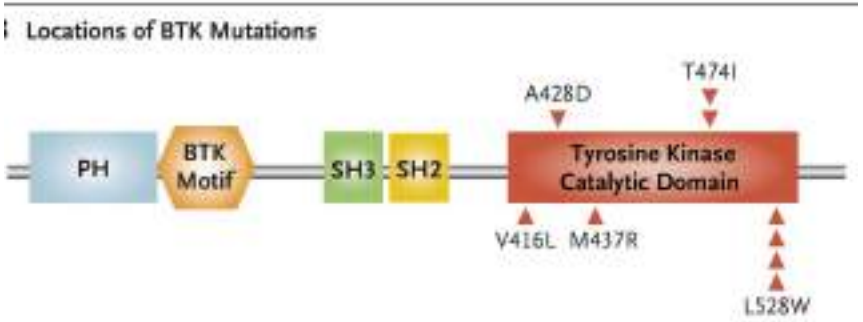


ORR (including PR-L) **~80%** regardless of prior BCL2i
Median PFS: **19.4** months **overall**, **23.0** months for **BCL2i-N** patients and **15.9** months for **BCL2i-E** patients

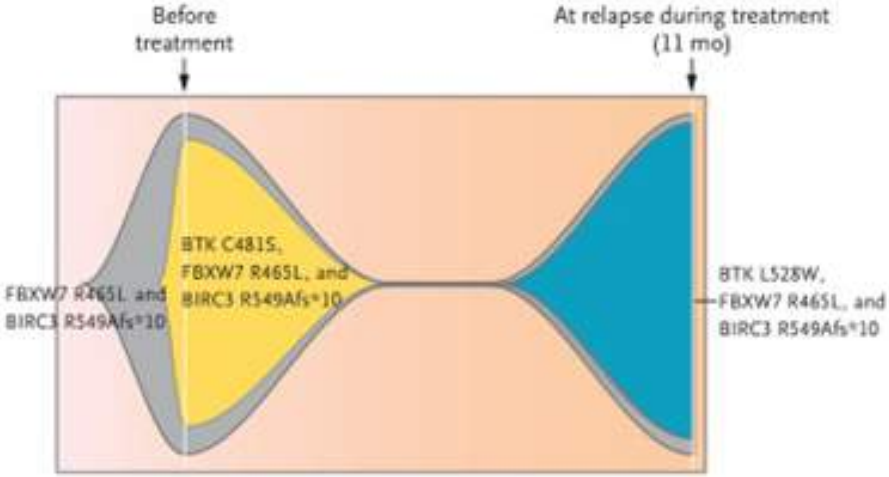
Woyach JA, Oral presentation ASH 2023

BTK mutations in pts with CLL relapsing on pirtobrutinib



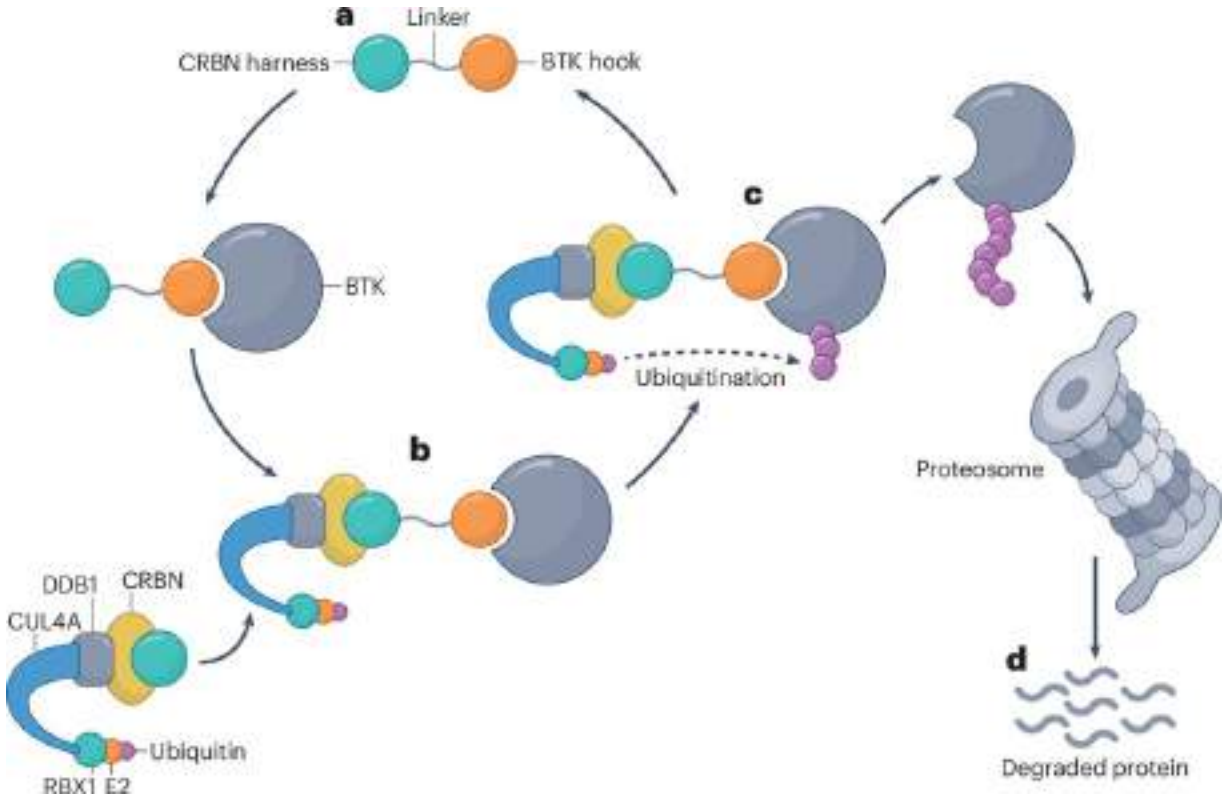


Clonal dynamics on pirtobrutinib



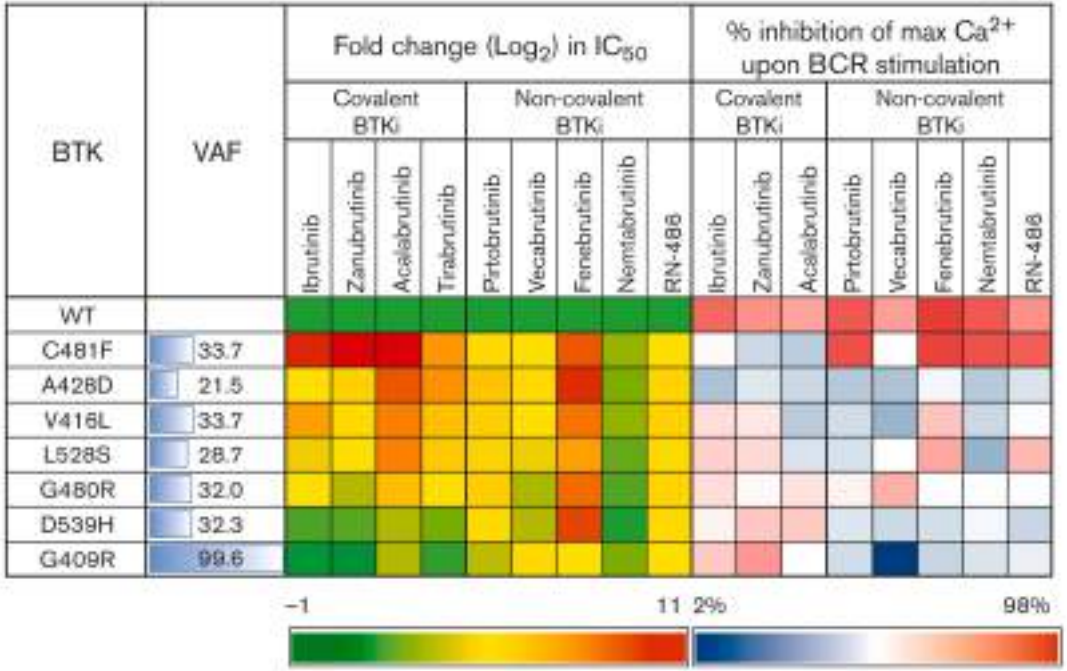
Wang E et al, NEJM 2022

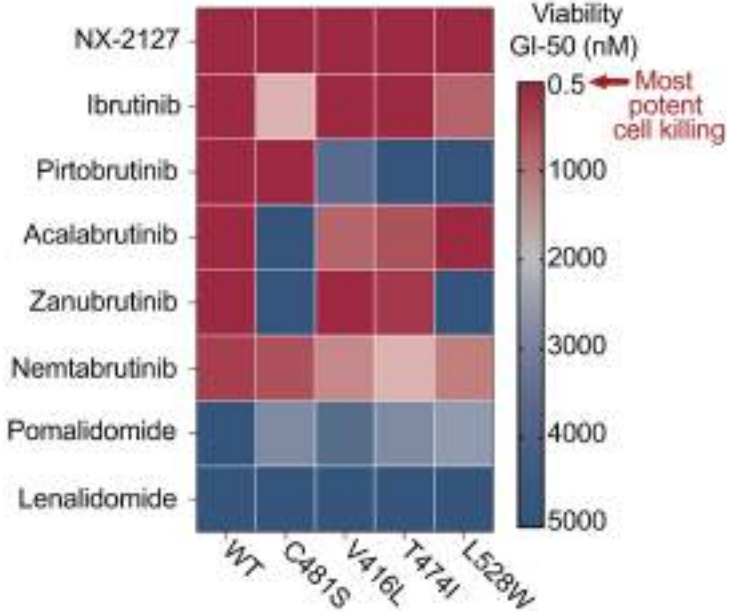
BTK degraders: are they ready for the prime time?



Stanchina MD et al, Nat Rev Clin Oncol. 2024

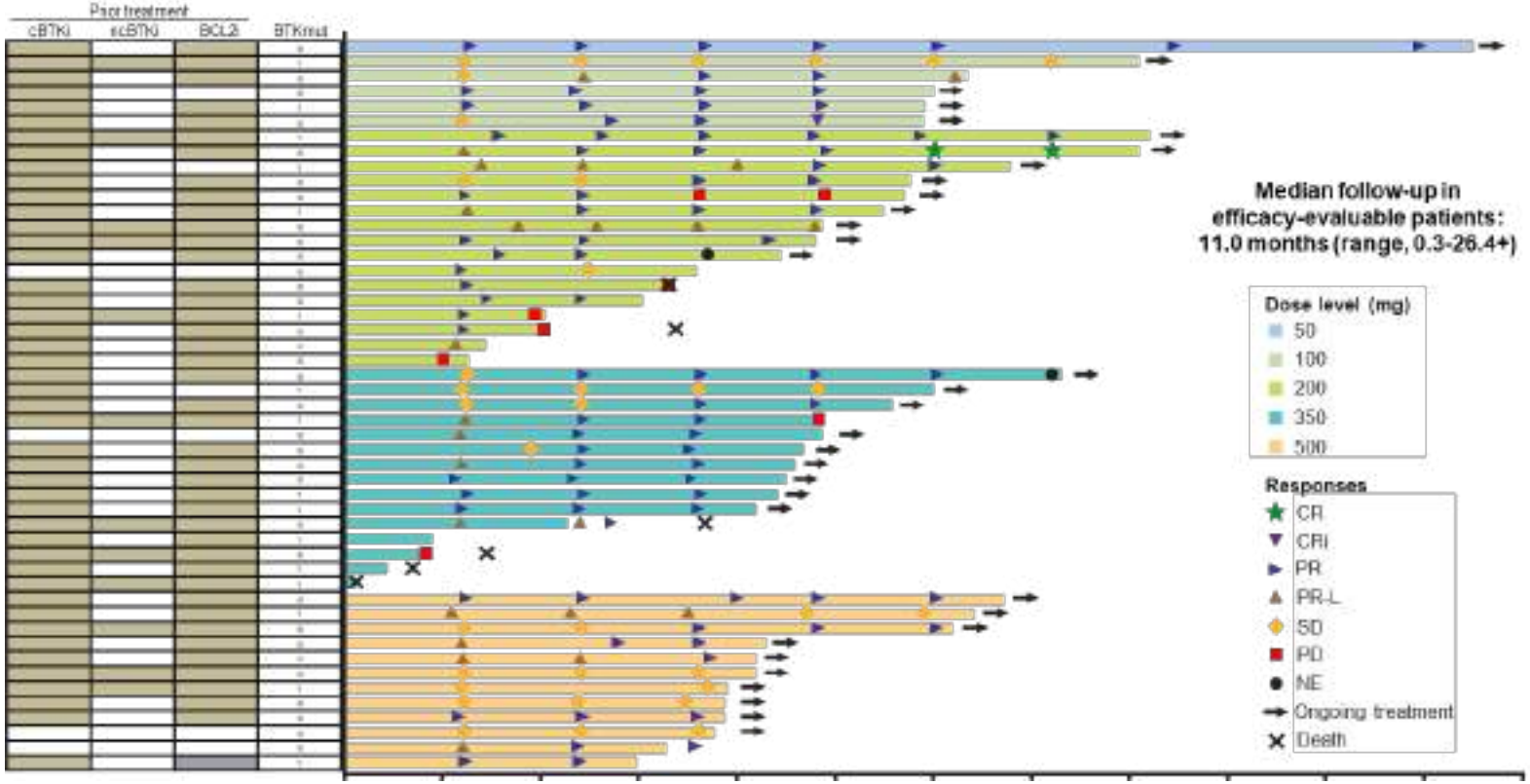
In vitro response of *BTK* mutants BTK-targeting agents





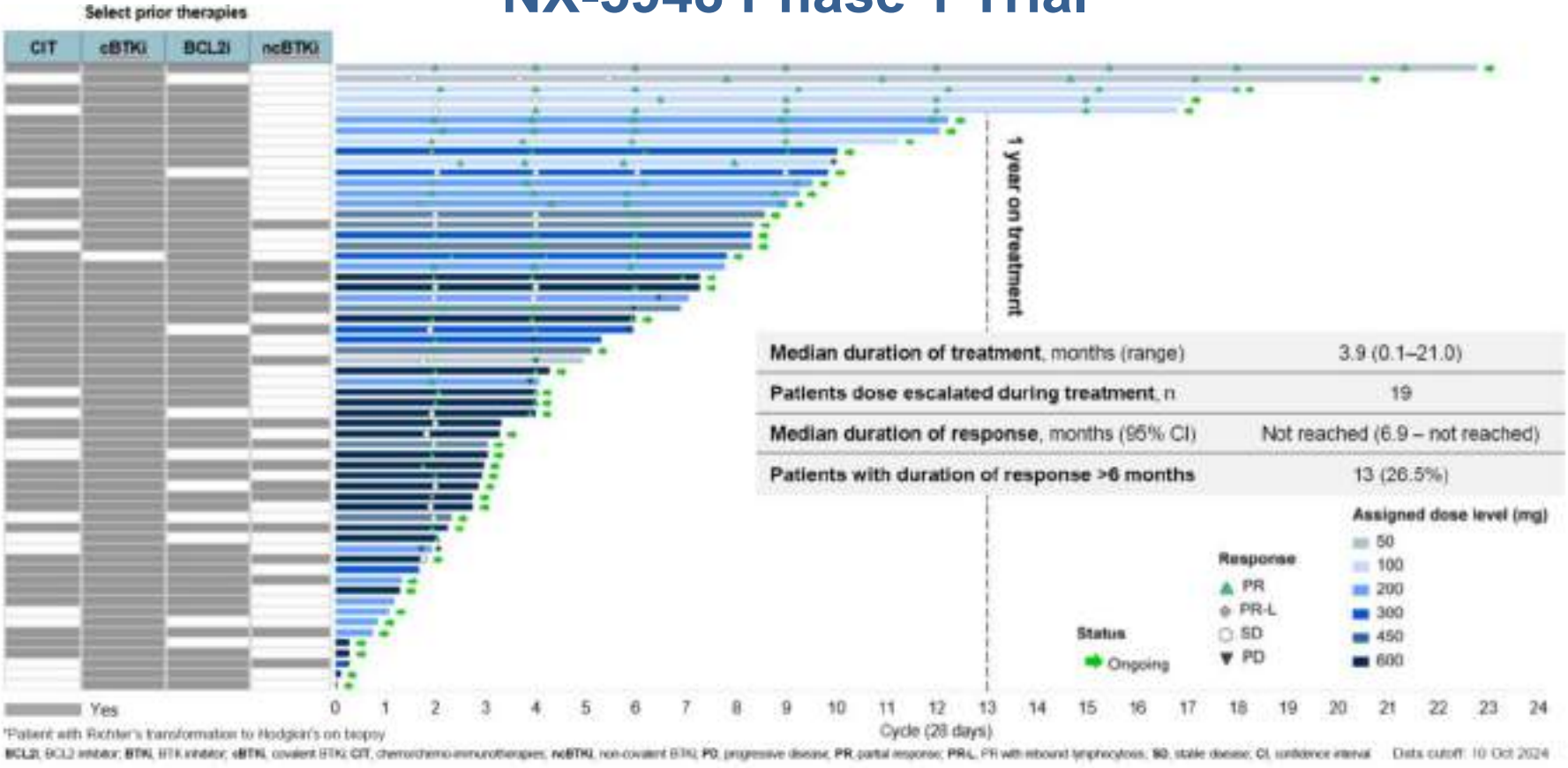
QI J et al, Blood Adv 2023; Montoya S et al, Science 2024

BGB-16673 Phase 1 Trial



Thompson M, Oral presentation ASH 2024

NX-5948 Phase 1 Trial



Shah NV, Oral presentation ASH 2024

Thank you

Prof Paolo Ghia

Strategic Research Program on CLL
Elisa Albi, Francesca Martini, Emanuela Sant'Antonio, Fabrizio Mavilia, Antonella Capasso, Maria Colia, Catalina Combi, Virginia Sgarlato, Eloise Scarano

Laboratory of B Cell Neoplasia
Silvia Heltai, Michela Frenquelli, Pamela Ranghetti, Eleonora Perotta, Francesca Gandini, Jessica Bordini, Athanasios Pseftogkas, Chiara Lenzi, Daniela Belloni, Alessandro Campanella, Silvia Bonfiglio

Malignant B cells biology and 3D modelling Unit
Cristina Scielzo, Federica Barbaglio

Laboratory of Lymphocyte Activation
Ilenia Sana, Elena Mantioni, Marta Muzio

CERTH and Papanicolau Hospital, Thessaloniki
Anastasia Hadzidimitrious, Andreas Agathangelidis, Anna Vardi, Thomas Chatzikonstantinou, Niki Stavroyianni, Kostas Stamatopoulos

Karolinska Institutet, Stockholm
Viktor Ljungstrom, Richard Rosenquist