Targeting BTK: Inhibitors vs Degraders

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

Targeting BTK: Inhibitors vs Degraders

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Disclosures

- Research Support: AstraZeneca, BeiGene
- Consulting: AstraZeneca, BMS
- Speakers Bureau: BeiGene

Talk Outline

- Inhibitors vs. Degraders
- B-cell receptor signalling
- FDA approved BTK inhibitors
  - Covalent and non-covalent BTKi
- BTK resistance and how this informs targeting mechanism
- BTK degraders
  - NX2127
  - BGB-16673

Inhibitors vs. Degraders

Inhibitors – Under Selective "Pressure"

Pros:

-Wealth of data on mechanism

-Proven clinical efficacy

-Resistance mechanisms established

Cons:

-Requires binding pocket

-Occupancy-driven pharmacology

-Continued exposure and high local concentrations required

Degraders:

Pros:

-Eradication of target using UPS

-UPS can target "undruggable" targets

Cons:

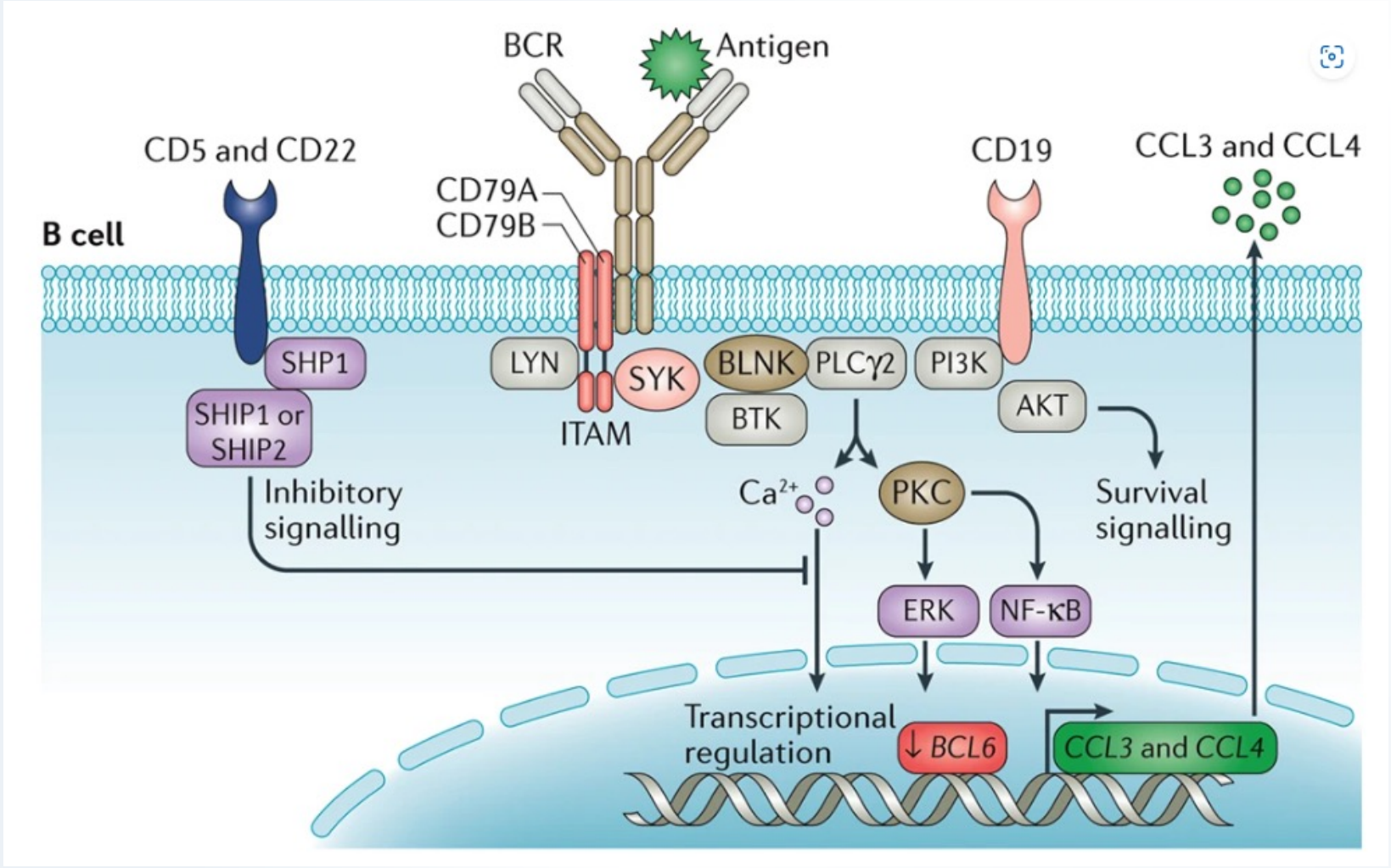
-Off-target effects unknown/ Toxicity?

-Clinical efficacy unknown

-Resistance Mechanisms?

Casan and Seymour, Blood, 2024

BCR Signaling



Burger and Weistner, Nature Reviews Cancer, 2018

Targeting BTK – Molecule Landscape

- FDA Approved BTK inhibitors:

  1st Generation:

  - Ibrutinib – cBTKi – Approved for CLL, WM, and GVHD

  2nd Generation:

  – Acalabrutinib – cBTKi – CLL and MCL

  – Zanubrutinib – cBTKi – CLL, WM, MCL, MZ, and FL

  3rd Generation:

  – Pirtobrutinib – ncBTKi – MCL and CLL

- In the Pipeline BTK inhibitors:

  -Nemtabrutinib – ncBTKi

  -LP168 – nc/cBTKi

- In the Pipeline BTK Degraders

  – NX-2127

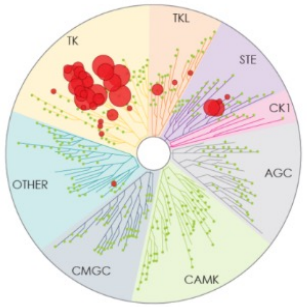
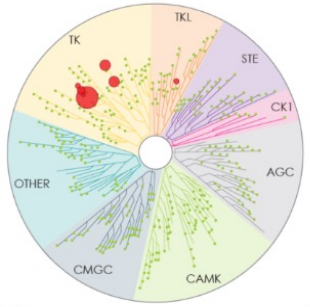
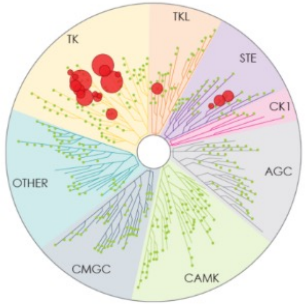
  – NX-5968

  – BGB-11673

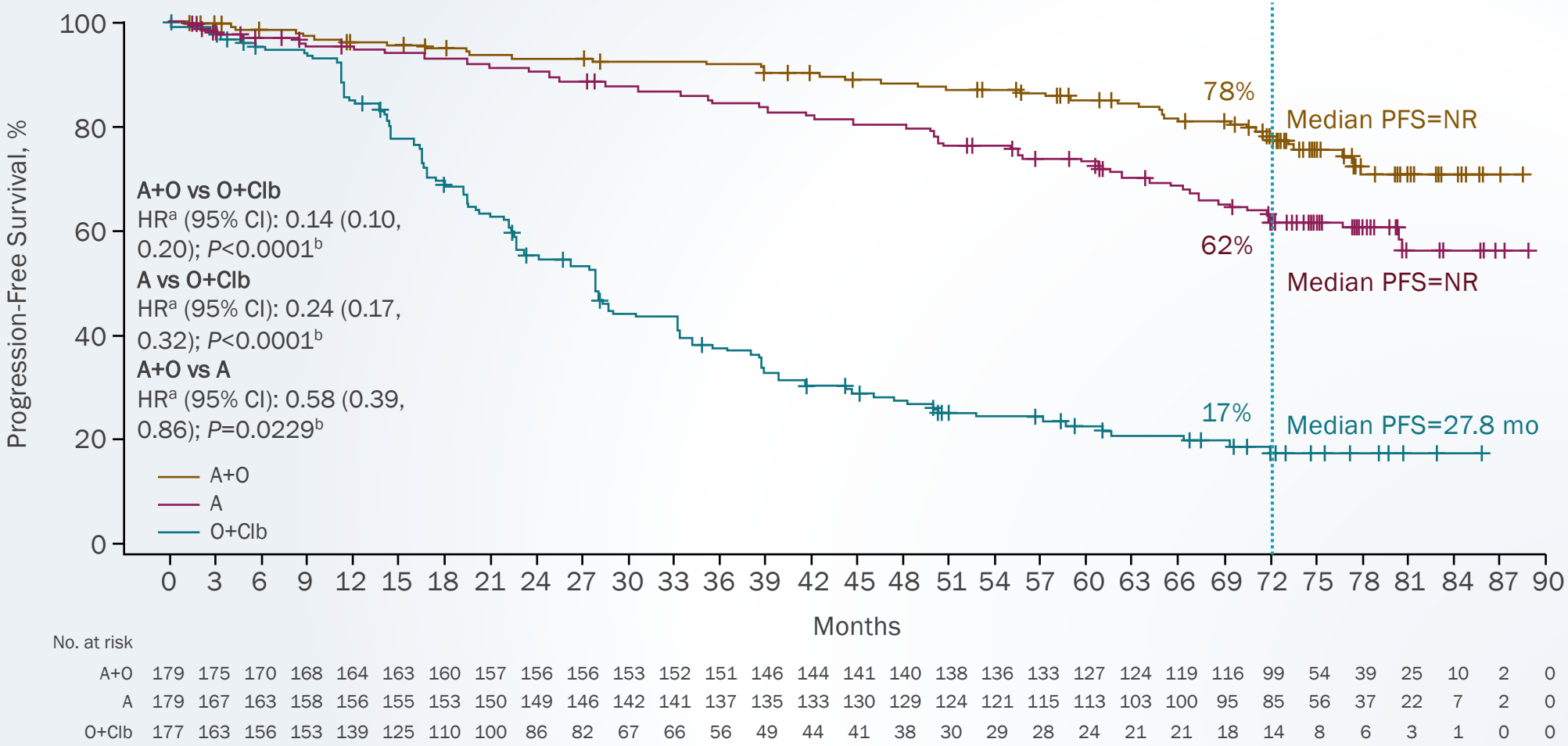
  – AC0676

  – ABBC-101

Covalent BTK inhibitors - Comparison

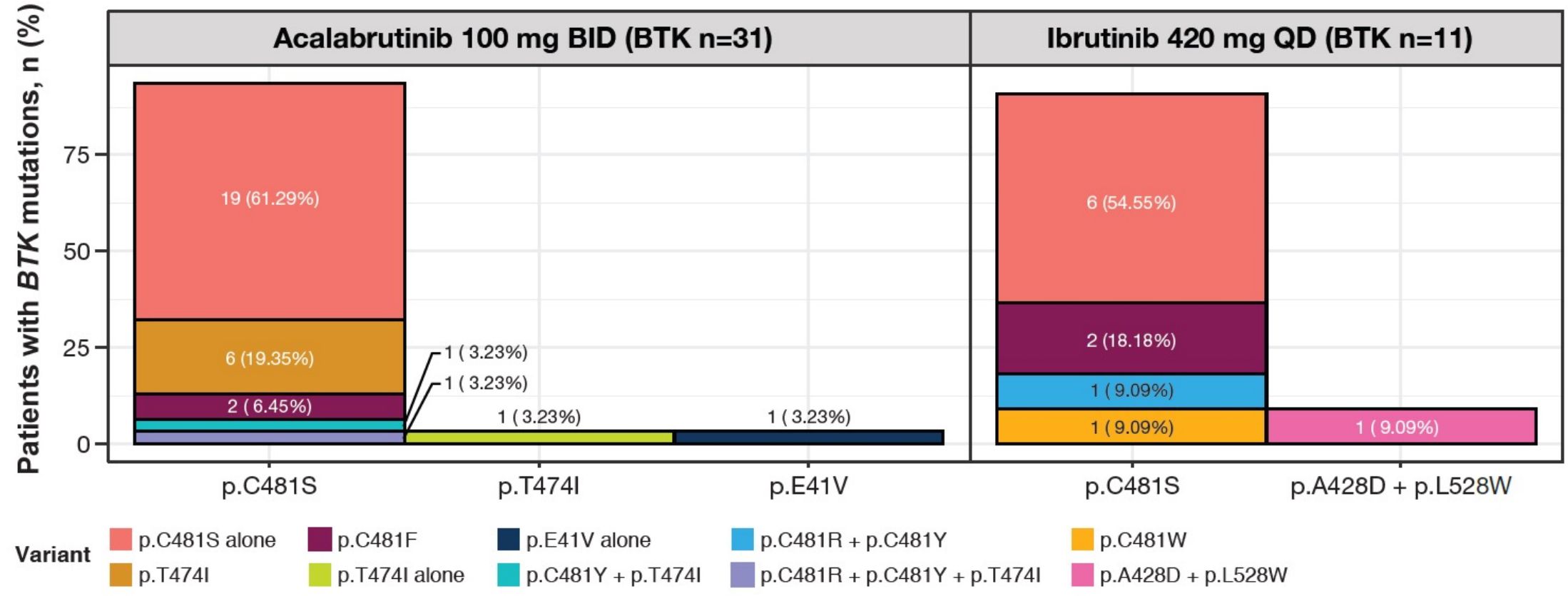
	Ibrutinib	Acalabrutinib	Zanubrutinib
FDA Approvals	**CLL**, WM	**CLL**, MCL	**CLL**, MCL, WM, MZL, FL
Dosing	420mg PO daily	100mg PO BID	160mg PO BID or 320mg PO daily
Approved Combinations	Obinutuzumab, Rituximab (Venetoclax – EMA approval)	Obinutuzumab	None
Selectivity			

Long term results of ELEVATE-TN – Frontline Acalabrutinib for CLL



Sharman et al, ASH 2023

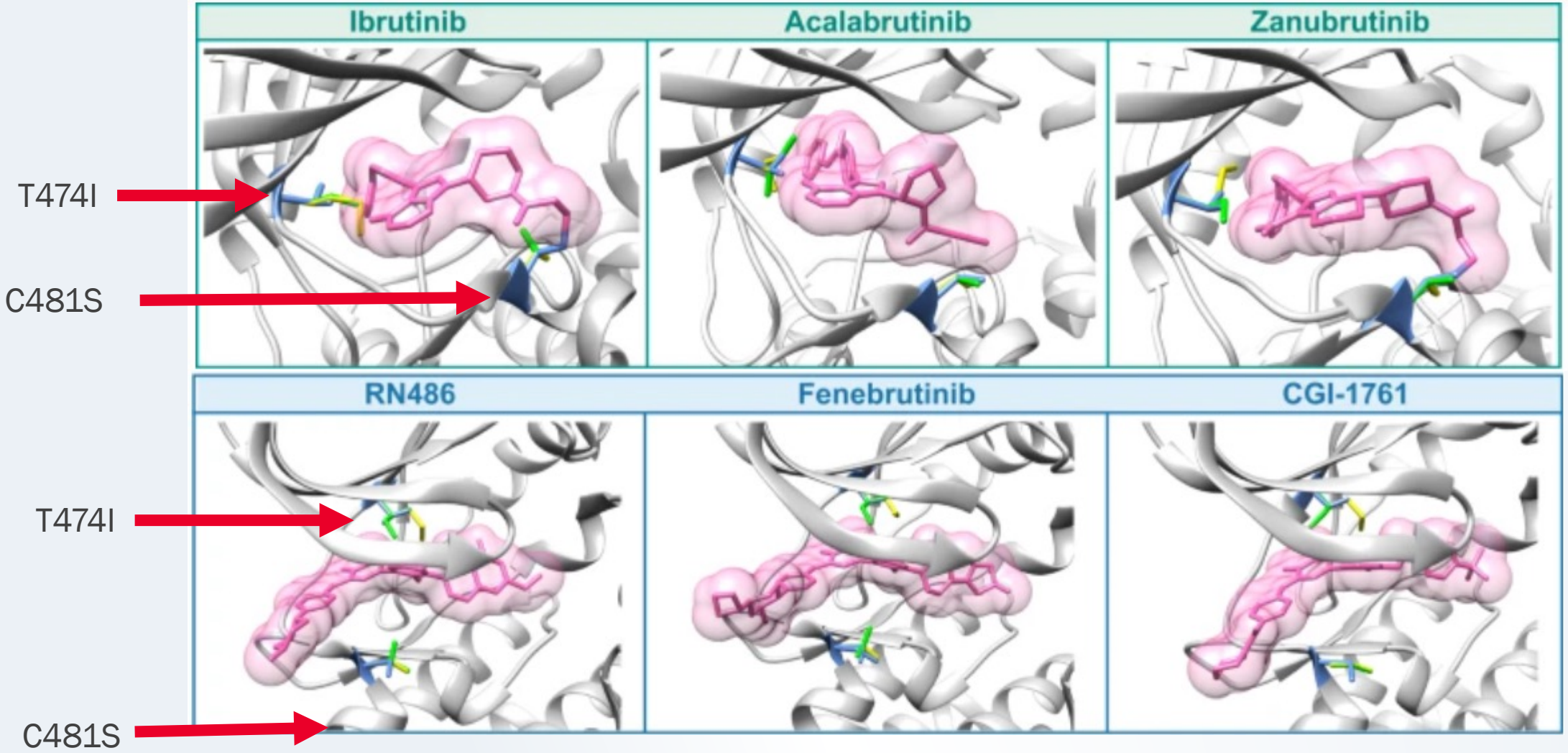
Despite clinical efficacy – Resistance mutations occur



-48 and 36 patients treated with acalabrutinib and ibrutinib on ELEVATE-RR had paired samples at baseline and progression analyzed for resistance mutations

Woyach et al, ASH 2023

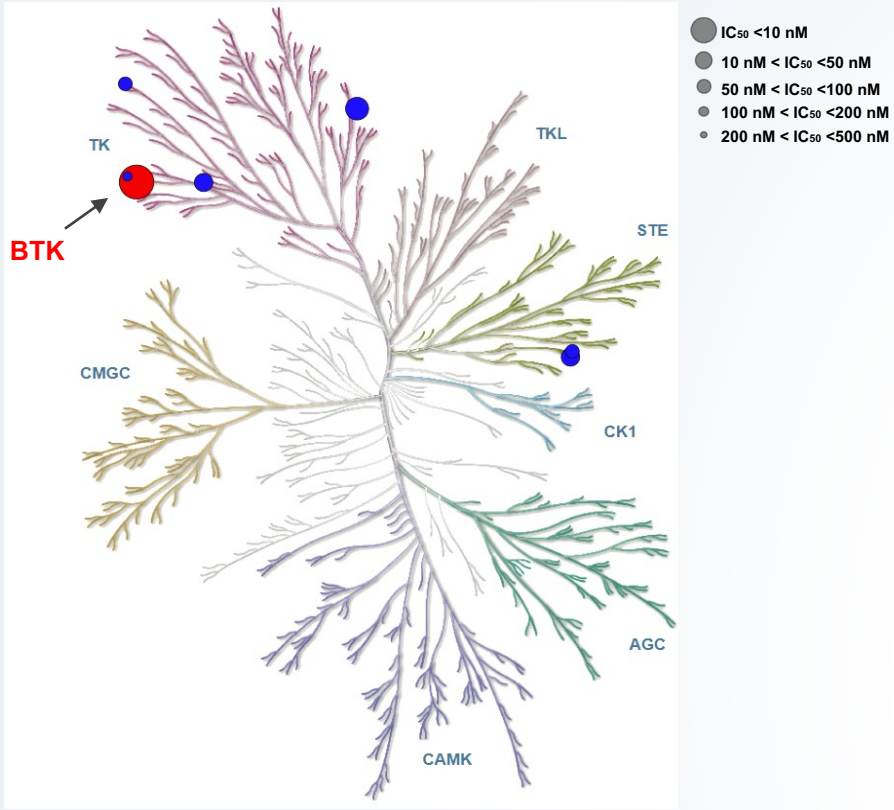
ncBTKi can overcome mutations that inhibit binding



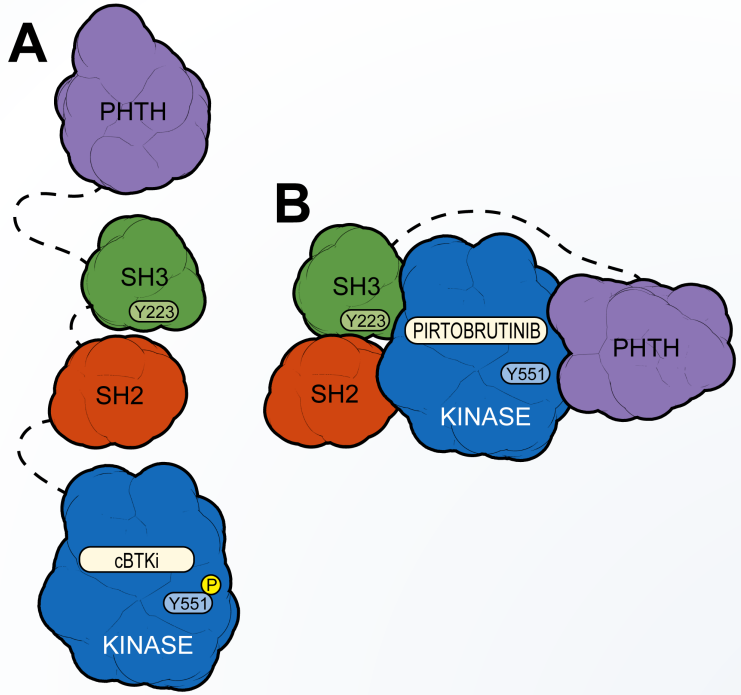
Estupinan et al Leukemia, 2021

Non-covalent BTKi - Pirtobrutinib

Highly selective for BTK



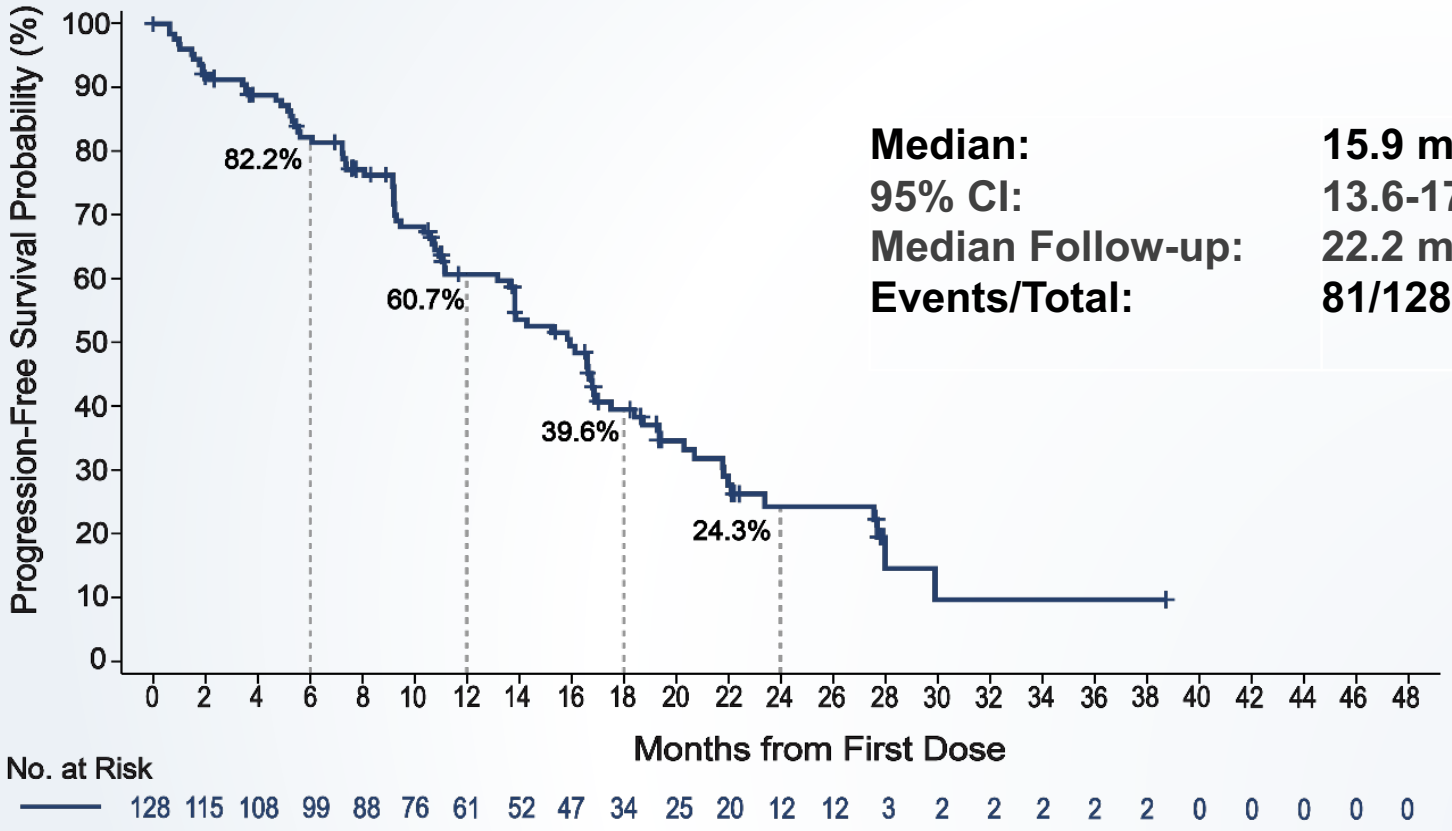
Pirtobrutinib may stabilize/maintain BTK in a closed inactive conformation[7]



Woyach et al ASH, 2023

ncBTK – Pirtobrutinib – Results of the BRUIN Study

BTKi and BCL2i Treated Patients



Median:	**15.9 months**
95% CI:	**13.6-17.5**
Median Follow-up:	**22.2 months**
Events/Total:	**81/128**

Woyach et al ASH, 2023

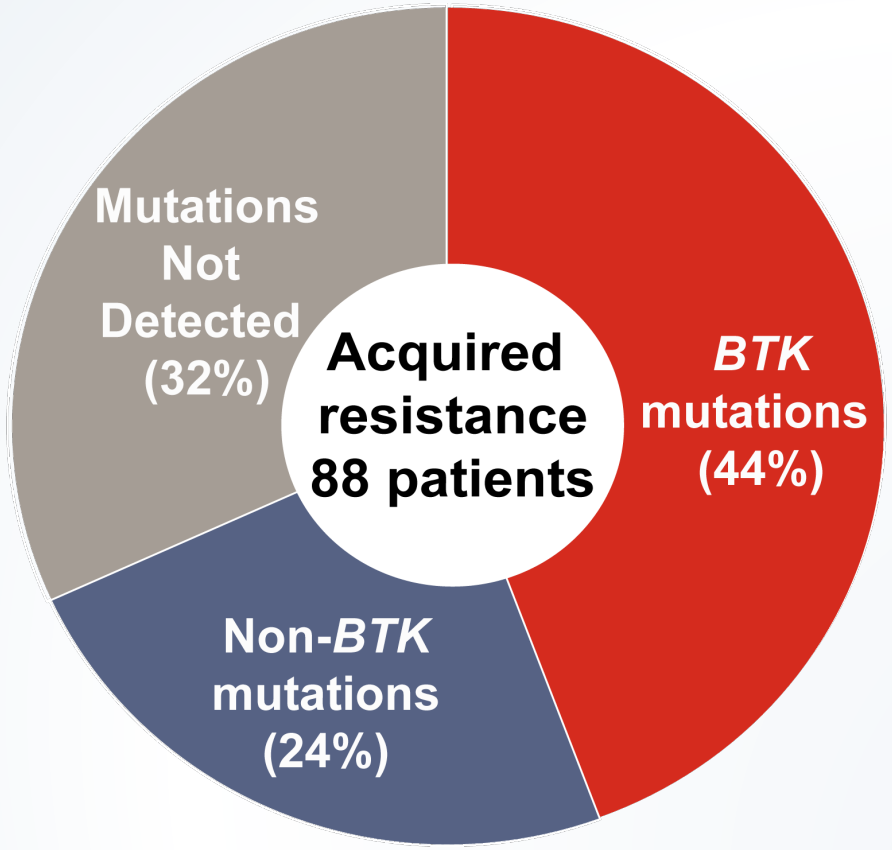
Pirtobrutinib is very well tolerated

	Treatment-Emergent AEs in Patients with CLL/SLL (n=282)			
	All Cause AEs, (≥20%), %		Treatment-Related AEs, %	
AEs of Interest[a]	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Infections	74.1	30.9	12.8	4.3
Bruising	30.1	0.0	19.1	0.0
Rash	24.5	1.1	5.7	0.4
Arthralgia	22.7	1.4	4.3	0.0
Hemorrhage	13.5	2.1	4.6	1.1
Hypertension	14.2	4.3	3.5	0.4
Atrial Fibrillation/Flutter	4.6	1.8	1.4	0.7

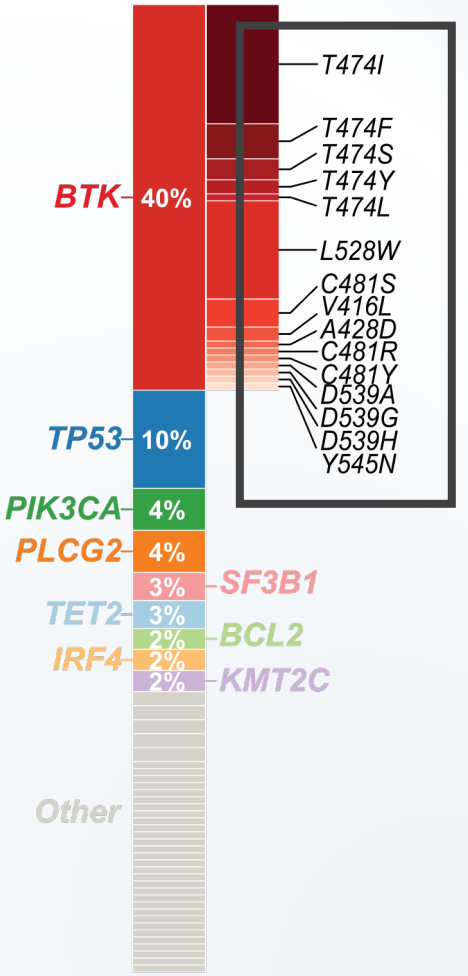
Woyach et al ASH, 2023

Resistance continues to occur on ncBTKi

- 68% (60/88) acquired mutations at PD
  - 44% (39/88) had at least one acquired *BTK* mutation at PD
    - 64% (25/39) who acquired a *BTK* mutation had a *BTK* mutation at baseline
- 56% (49/88) did not acquire a *BTK* mutation
  - The most frequently acquired non-*BTK* mutation was *TP53*
- 32% (28/88) had no acquired mutations detected at PD

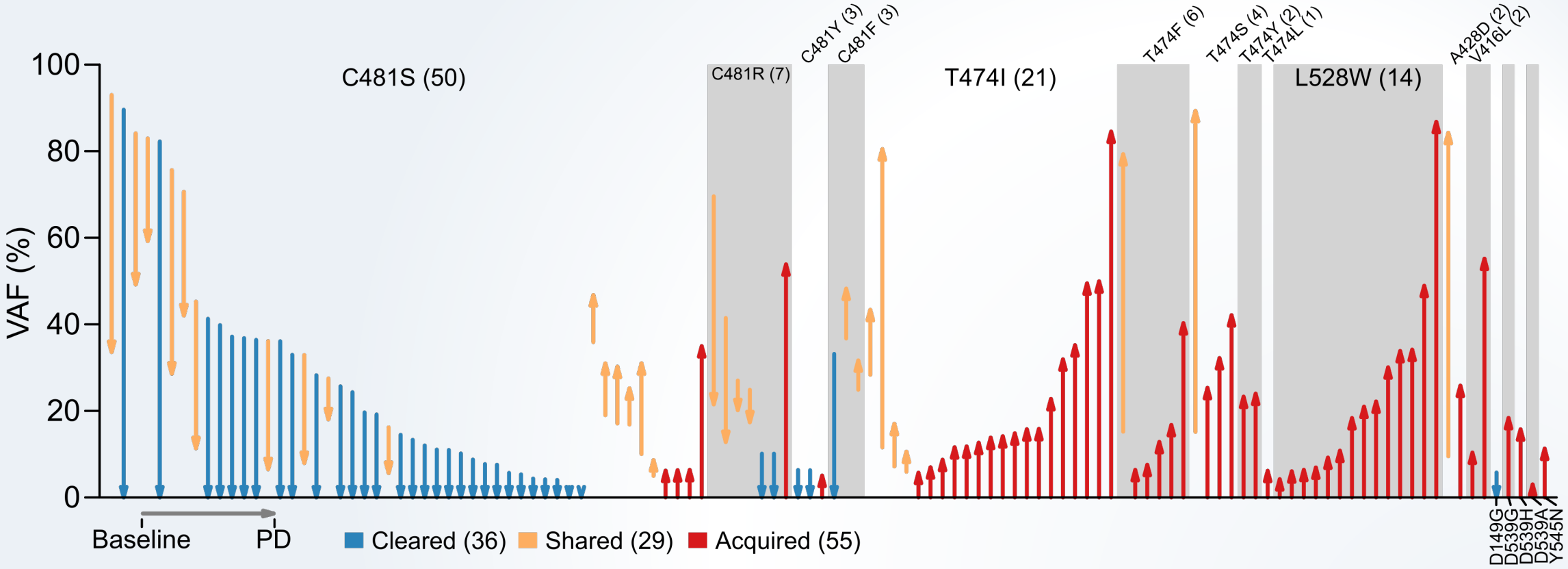


138 acquired mutations



Brown et al ASH, 2023

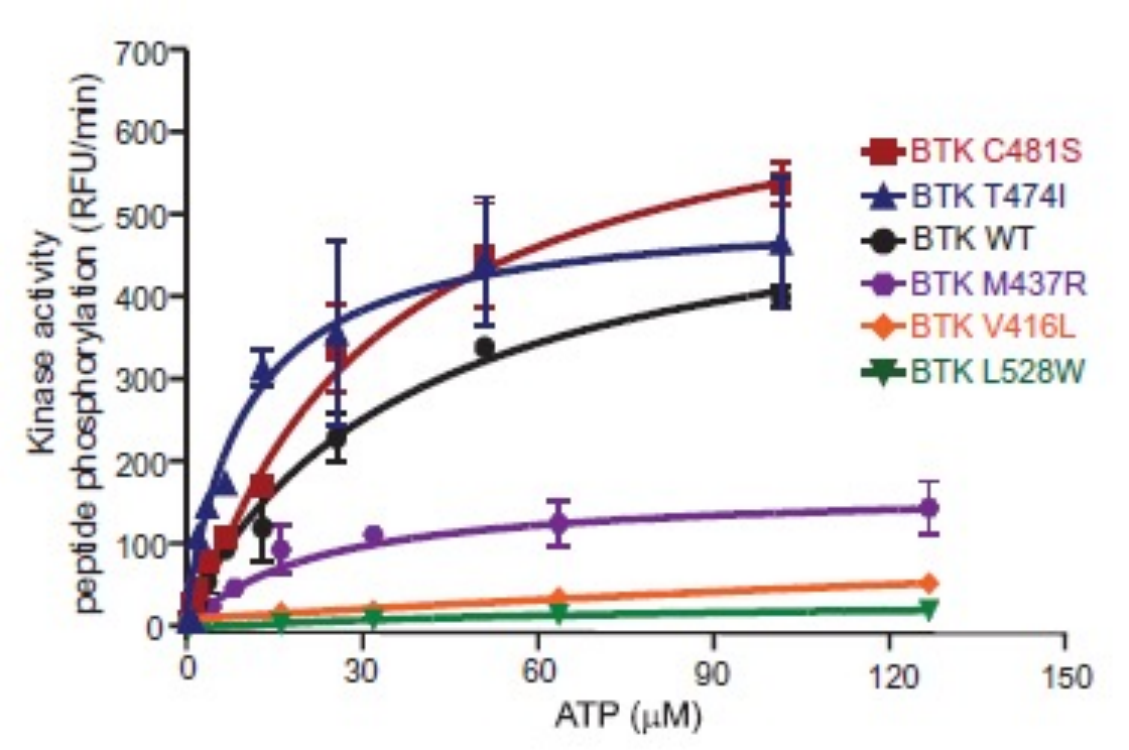
T474i and L528w mutations increased in VAF at progression

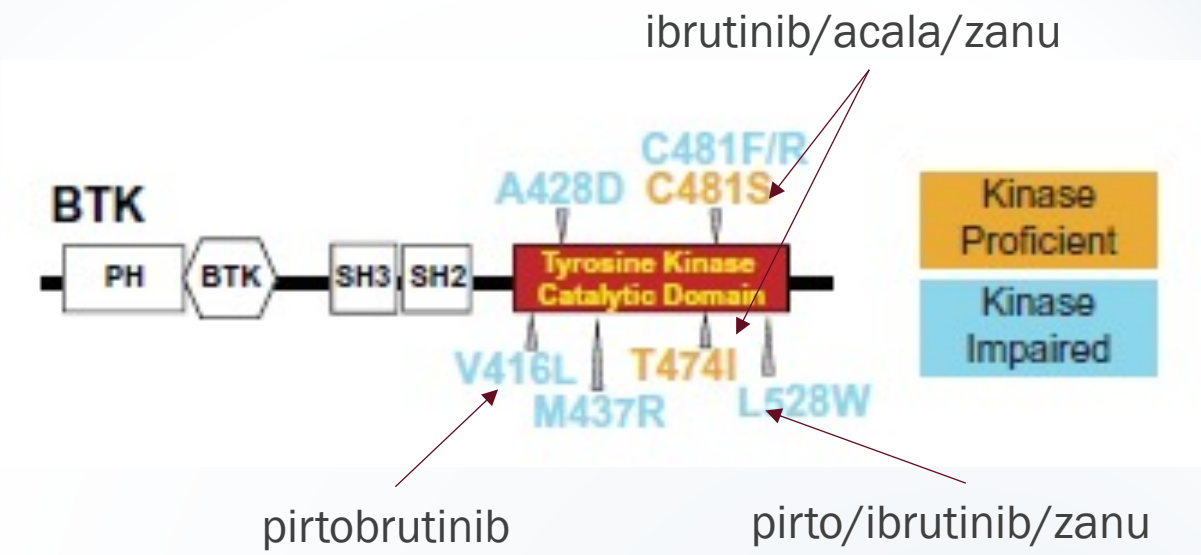


- Change in VAF of 120 BTK mutations detected at baseline and/or at progression
  - 36 cleared, 29 shared, and 55 acquired

Brown et al ASH, 2023

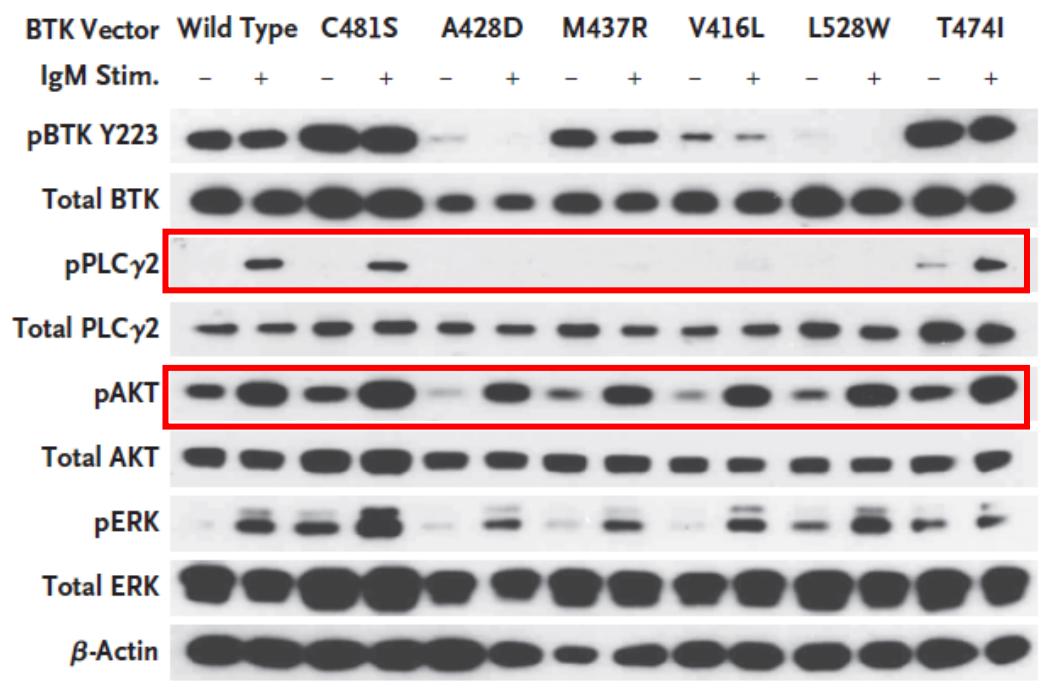
Kinase proficient vs. Kinases impaired mutations

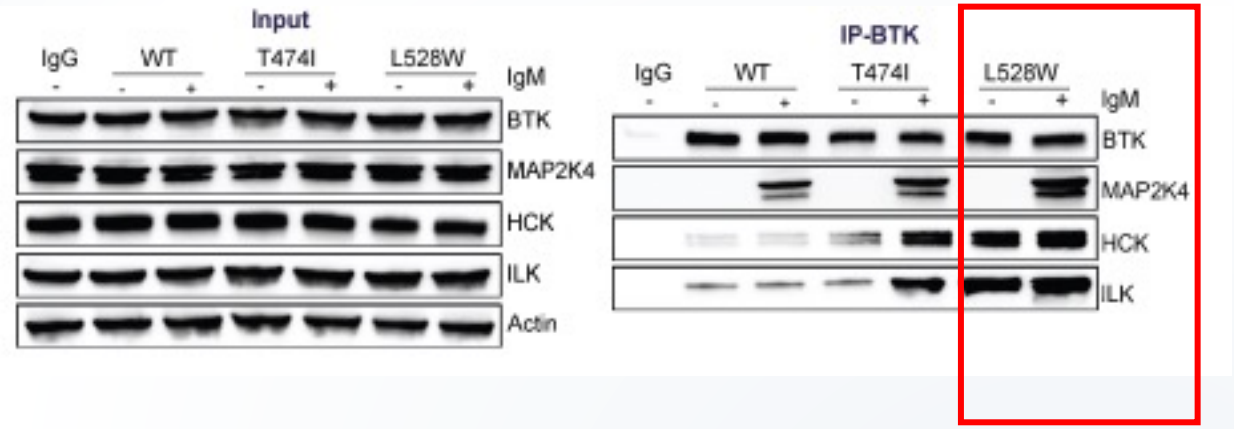




Montoya et al Science, 2024

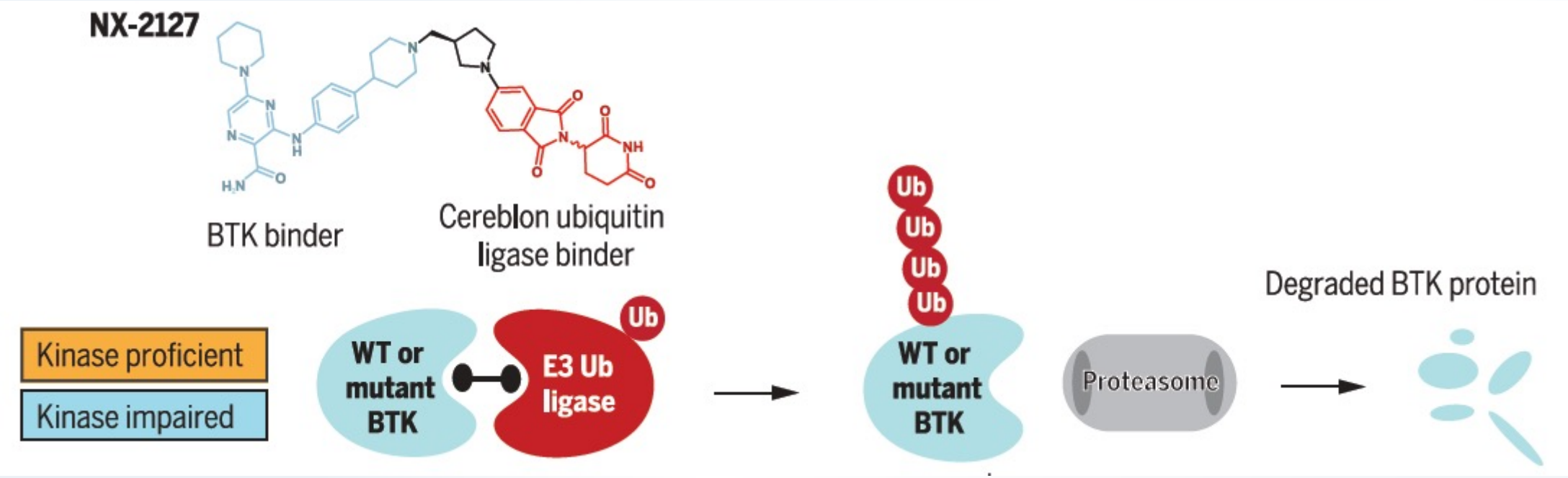
Kinase impairs scaffold effect allows for downstream signaling





Wang et al NEJM 2022, Montoya et al Science 2024

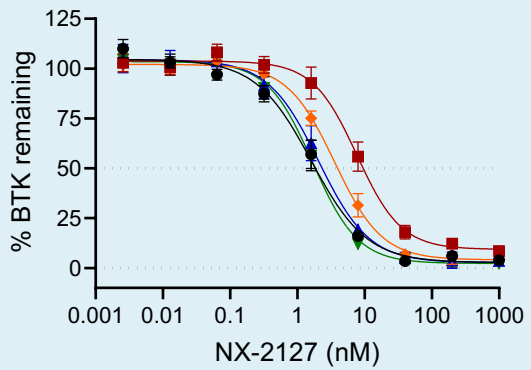
NX-2127 – Example of BTK degrader



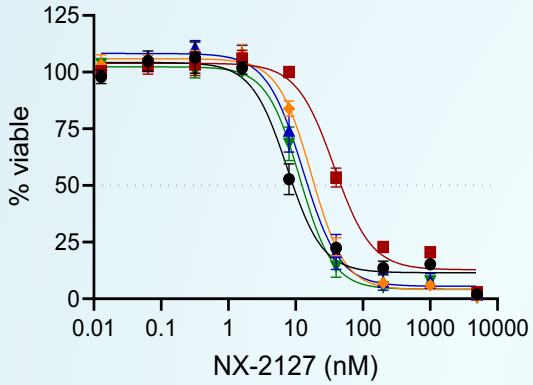
Montoya et al Science 2024

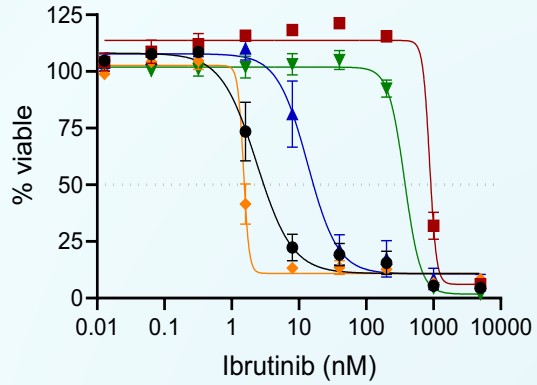
NX-2127 Pre-clinical data

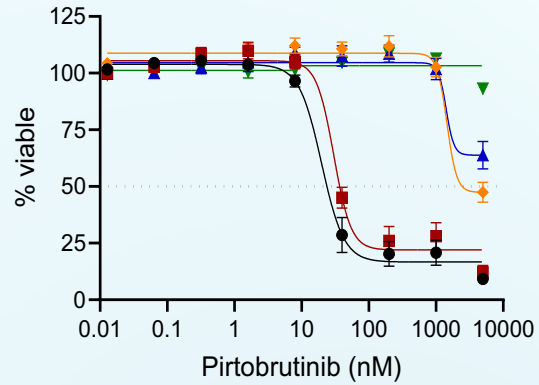
BTK degradation



Cell viability







- BTK-WT
- BTK-C481S
- BTK-V416L
- BTK-T474I
- BTK-L528W

Noviski M et al, AACR 2023 (abstract #2850)

NX-2127 in CLL: patient characteristics

Characteristics	CLL (n=23)	Overall population (N=36)
Median age, years (range)	75 (61–90)	75 (50–92)
Female, n (%)	9 (39.1)	13 (36.1)
Male, n (%)	14 (60.9)	23 (63.9)
Lines of prior therapy, median (range)	5 (2–11)	4 (2–11)
BTKi, n (%)	23 (100)	31 (86.1)
Pirtobrutinib, n (%)	8 (34.8)	11 (30.6)
BTKi and BCL2i, n (%)	18 (78.3)	19 (52.8)
cBTKi, ncBTKi, and BCL2i, n (%)	7 (30.4)	7 (19.4)
***BTK* mutation present**[a], n (%)	10 (48)	11 (35)
C481	5 (24)	5 (16)
L528W	4 (19)	4 (13)
T474	3 (14)	4 (13)
V416L	1 (5)	1 (3)
***BCL2* mutation present**[a], n (%)	4 (19)	4 (13)
***PLCG2* mutation present**[a], n (%)	0 (0)	1 (3.2)

Mato et al ASH 2022

NX-2127 in CLL/NHL: Adverse events

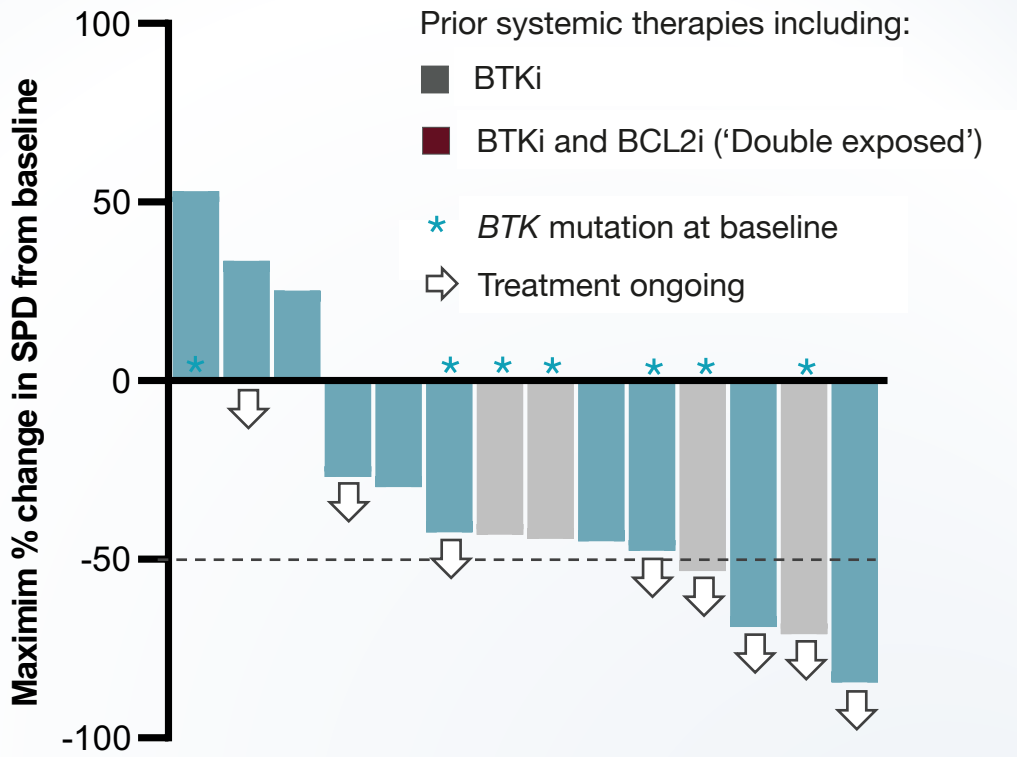
- The most common TEAEs were fatigue (51.4%), neutropenia (45.9%), and hypertension (32.4%).

Treatment-emergent AEs occurring in >15% of total population, n (%)	Any grade (N=37)	Grade 3+ (N=37)
Fatigue	19 (51.4)	–
Neutropenia[a]	17 (45.9)	16 (43.2)
Hypertension	12 (32.4)	3 (8.1)
Constipation	9 (24.3)	–
Contusion[b]	9 (24.3)	–
Dyspnea	9 (24.3)	1 (2.7)
Thrombocytopenia[c]	9 (24.3)	3 (8.1)
Anemia	7 (18.9)	5 (13.5)
Diarrhea	7 (18.9)	–
Headache	7 (18.9)	–
Pruritis	7 (18.9)	–
Atrial fibrillation/Atrial flutter[d]	6 (16.2)	3 (8.1)
Confusional state	6 (16.2)	–
Nausea	6 (16.2)	–
Petechiae	6 (16.2)	–
Rash maculo-papular	6 (16.2)	–

Danilov et al ICML 2023

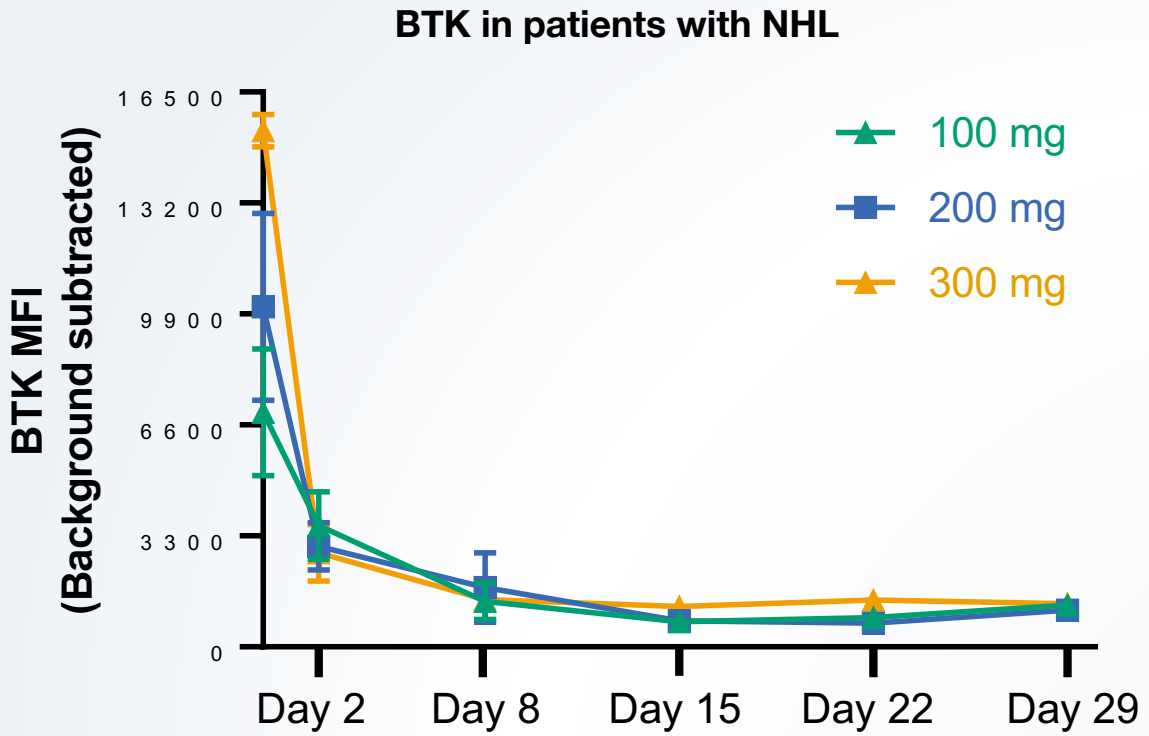
NX-2127 in CLL: responses

Disease-evaluable patients	n=15
Objective response rate,[a] % (95% CI)	33 (12–62)
Best response, n (%)	
CR	0 (0)
PR	5 (33.3)
SD	5 (33.3)
PD	2 (13.3)
NE[b]	3 (20)



Mato et al ASH 2022

NX-2127 in CLL/NHL: *in vivo* BTK degradation



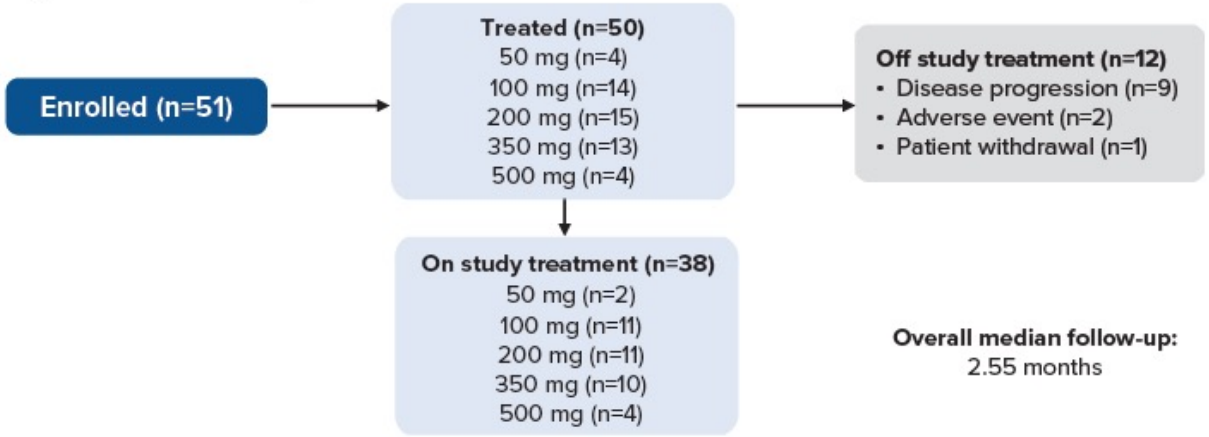
Dose (mg)	Day 2 (n)	Day 8 (n)	Day 15 (n)	Day 22 (n)	Day 29 (n)
100	4	3	2	3	3
200	6	5	6	3	3
300	2	2	2	1	1

BTK, Bruton's tyrosine kinase

Danilov et al ICML 2023

BGB-16673 – Another BTK Degrader

Figure 3. Patient Disposition[a]



Parameter	Total (N=50)
Age, median (range), years	70.5 (26-91)
Sex, n (%)	
Male	33 (66.0)
Female	17 (34.0)
ECOG PS, n (%)	
0-1	47 (94.0)
2	3 (6.0)
Disease type, n (%)	
CLL/SLL	24 (48.0)
MCL	7 (14.0)
MZL	3 (6.0)
WM	6 (12.0)
DLBCL	2 (4.0)
FL	6 (12.0)
RT	2 (4.0)
Number of prior lines of therapy, median (range)	4 (2-10)
Prior covalent BTK inhibitor	40 (80.0)
Prior noncovalent BTK inhibitor	7 (14.0)
Discontinued BTK inhibitor due to PD	28 (56.0)
BCL2 inhibitor	28 (56.0)
Mutation status, n/N (%)	
BTK mutation present	7/24 (29.2)
PLCG2 mutation present	2/24 (8.3)
BCL2 mutation present	12/27 (44.4)

Seymour et al ASH 2023

BGB-16673 – Responses by disease type

	CLL/SLL (n=10)	MCL/MZL/ WM/ FL (n=16)	DLBCL/RT (n=2)	All (n=28)
BOR, n (%)				
CR	0	1 (6.3)	0	1 (3.6)
PR	6 (60.0)	7 (43.8)	0	13 (46.4)
PR-L	1 (10.0)	N/A	0	1 (3.6)
MR	0	1 (6.3)	0	1 (3.6)
SD	2 (20.0)	3 (18.8)	0	5 (17.9)
PD	0	3 (18.8)	2 (100.0)	5 (17.9)
Discontinued prior to first assessment	1 (10.0)	1 (6.3)	0	2 (7.1)
ORR, n (%)[a]	**7 (70.0)**	**9 (56.3)**	**0**	**16 (57.1)**
Median time to first response, months[b]	2.83	2.33	N/A	2.76

Seymour et al ASH 2023

BGB-16673 Side Effects

	50 mg (n=4)		100 mg (n=14)		200 mg (n=15)		350 mg (n=13)		500 mg (n=4)		All (N=50)	
Patients, n (%)	All Gr	Gr ≥3	All Gr	Gr ≥3	All Gr	Gr ≥3	All Gr	Gr ≥3	All Gr	Gr ≥3	All Gr	Gr ≥3
Contusion	0	0	6 (42.9)	0	5 (33.3)	0	2 (15.4)	0	2 (50.0)	0	**15 (30.0)**	**0**
Diarrhea	2 (50.0)	0	2 (14.3)	0	2 (13.3)	0	4 (30.8)	0	2 (50.0)	0	**12 (24.0)**	**0**
Fatigue	0	0	3 (21.4)	0	4 (26.7)	0	1 (7.7)	0	2 (50.0)	0	**10 (20.0)**	**0**
Amylase increased[a]	1 (25.0)	0	3 (21.4)	0	2 (13.3)	0	2 (15.4)	0	0	0	**8 (16.0)**	**0**
Neutropenia/ neutrophil count decreased	1 (25.0)	1 (25.0)	3 (21.4)	2 (14.3)	2 (13.3)	1 (6.7)	1 (7.7)	1 (7.7)	1 (25.0)	1 (25.0)	**8 (16.0)**	**6 (12.0)**
Lipase increased[a]	1 (25.0)	0	2 (14.3)	1 (7.1)	2 (13.3)	0	2 (15.4)	1 (7.7)	0	0	**7 (14.0)**	**2 (4.0)**
Pyrexia	1 (25.0)	0	4 (28.6)	0	1 (6.7)	0	1 (7.7)	0	0	0	**7 (14.0)**	**0**
Cough	2 (50.0)	0	2 (14.3)	0	1 (6.7)	0	1 (7.7)	0	0	0	**6 (12.0)**	**0**
Pooled TEAEs of interest												
Any bleeding	2 (50.0)	1 (25.0)	7 (50.0)	0	6 (40.0)	0	4 (30.8)	1 (7.7)	2 (50.0)	0	**21 (42.0)**	**2 (4.0)[b]**
Any infection[c]	2 (50.0)	1 (25.0)	6 (42.9)	2 (14.3)	7 (46.7)	3 (20.0)	4 (30.8)	2 (15.4)	1 (25.0)	0	**20 (40.0)**	**8 (16.0)**
Atrial fibrillation/ flutter	0	0	0	0	0	0	0	0	0	0	**0**	**0**
Hypertension	0	0	0	0	0	0	0	0	0	0	**0**	**0**

Seymour et al ASH 2023

BTK degraders in clinical trials

Drug name	NCT#
NX-2127 NX-5948	NCT04830137 NCT05131022
BGB-16673	NCT05006716
AC0676	NCT05780034
ABBV-101	NCT05753501

What does the future hold?

- Front line trials of ncBTKi
- Phase 2 studies evaluating the efficacy of BTK degraders in R/R CLL
- Sequencing of BTK inhibitors and degraders
- Combination studies – BCL2i + ncBTKi +/- anti-CD20
  → Can we sub in BTK Degraders here?
- Are we living in a world where BTK will continuously be targeted?

CONCLUSION: BTKi vs. BTK Degrader

- Not enough data for BTK degraders to really call this a “versus” situation

- Questions remain about BTK degraders:
  - Should they have worked better?
  - What might be the resistance mechanism to the degrader?
  - Could this have unknown repercussions?

- Questions remain about BTK inhibitors:
  - Should we be using ncBTKi in earlier lines?
  - Can we sequence ncBTKi to cBTKi?

- My main conclusions – I am glad that we have so many options for patients with CLL since I began practice.

Thanks!