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New Targeted Treatments in CLL

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Disclosures for Andrew D. Zelenetz, MD, PhD

Research Support/P.I.	Genentech/Roche, Gilead, MEI, BeiGene
Employee	None
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Major Stockholder	None
Speakers Bureau	None
Scientific Advisory Board	Lymphoma Research Foundation, Adaptive Biotechnologies
Stockholder	None (not including potential holding of a 401K mutual fund)

- I will discuss the following off label and/or investigational use in my presentation:
  - Investigational agents including mosunetuzumab; glofitamab; epcoritamab; odronexamab; IGM-2323
  - Off-label use: polatuzumab

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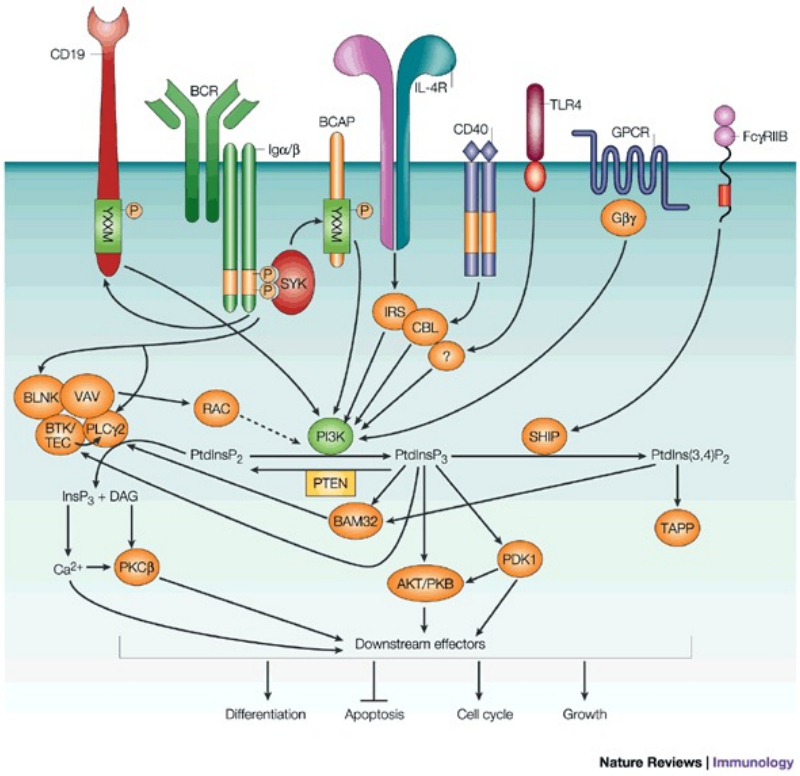
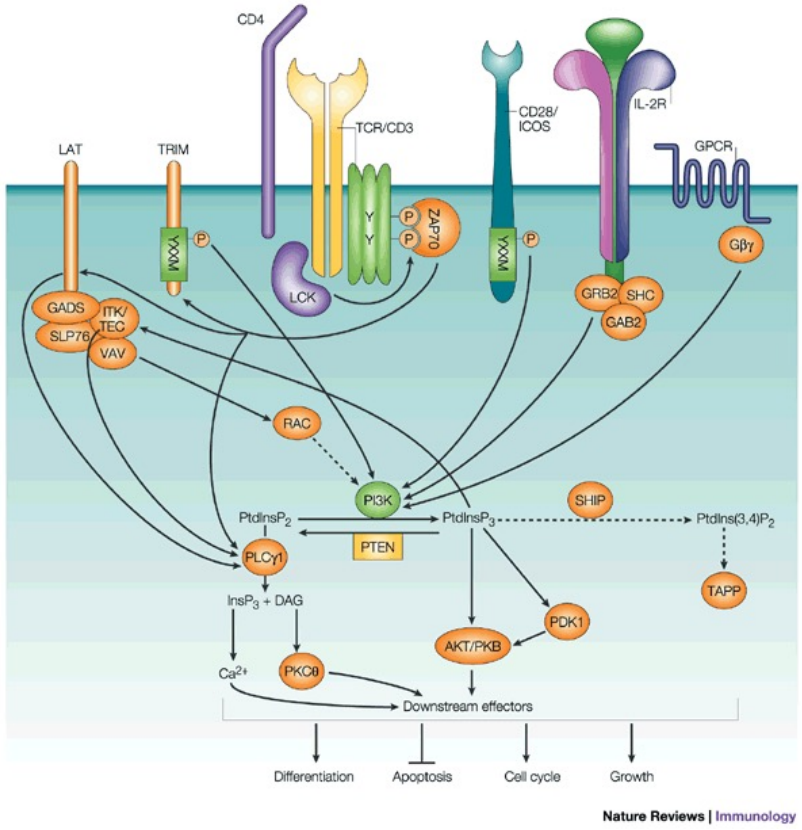
The Rise and Fall and Rise Again of PI3Kδ Inhibitors

PI3K activation and signaling

B cells



T cells



Validated target: **CLL, FL, MZL, WM**

PTCL

Okkenhaug & Vanhaesebroeck, Nature Rev Immunol (2003) 3:317–330

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PI3Kδ for FL: All approved drugs have been withdrawn

Initial Approval Information	Post-Approval Trials	Outcome
Idelalisib PI3Kδi		
2014: Regular approval CLL 2014: Accelerated approval R/R FL ORR 54% and SLL ORR 58%	2016: 3 RCTs halted in CLL or iNHL for increased deaths and toxicity CLL 1L BR ± Idela iNHL R/R Idela+R v Placebo+R iNHL R/R BR ± Idela Pooled analysis for deaths: Idela arms 7.4% vs 3.5% control; OS HR 2.29 (1.26-4.18)	Voluntary withdrawal of FL/SLL indications (02/2022)
Copanlisib PI3Kα/δi		
2017: Accelerated approval ≥3L FL, ORR 59%, DOR 12.2 months	CHRONOS-3 RCT COPA+R v Placebo+R PFS HR 0.53, OS HR 0,87 (0.57, 1.35)	Voluntary withdrawal of NDA based on CHRONOS-3
Duvelisib PI3Kγ/δi		
2018: Regular approval for CLL PFS HR 0.52 2018: Accelerated approval ≥3L FL ORR 42%	DUO mature OS HR 1.09 FL RCT not done	ODAC votes 8-4 that final OS did not support benefit-risk ratio in CLL Voluntary withdrawal of FL indication (12/2021)
Umbralisib PI3Kδi + CK1εi		
2021: Accelerated approval ≥3L FL ORR 43%, ≥1 anti-CD20 MZL, 49%	UNITY-CLL: Umbra + Ublitux v Obin-Chloram in 1L and R/R CLL PFS HR 0.55; OS HR 1.23	Voluntary withdrawal 04/2022

FDA Briefing Document PI3K Inhibitors in Hematologic Malignancies, 04/21/2022

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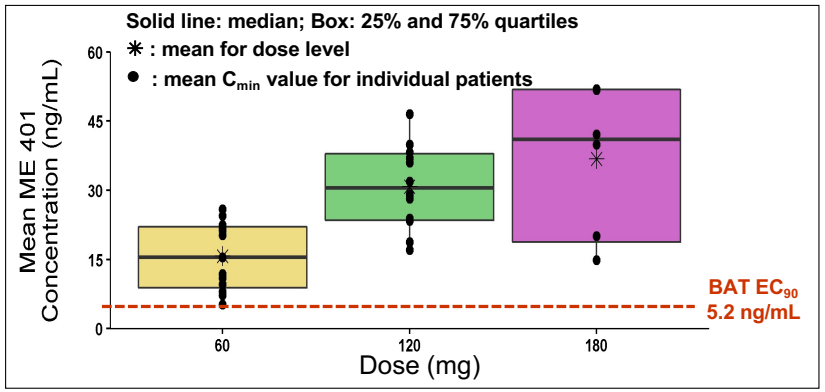
Zandelisib (ME-401): A Novel Potent PI3Kδ Inhibitor

- Oral, potent, selective, structurally differentiated PI3Kδ Inhibitor
- Inhibits PI3Kδ at nanomolar concentrations
  - Mean IC50 = 0.6 nM
- Highly selective to the δ isoform

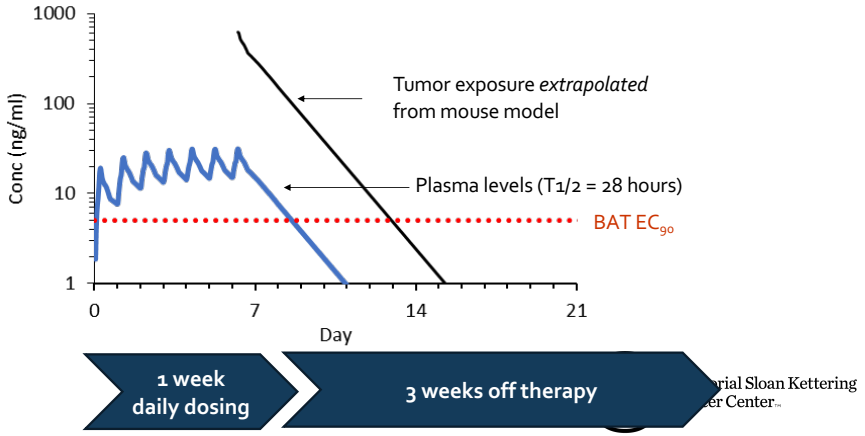
PI3K isoform	α	β	γ
IC_{50} fold increase	22,867	30	713

- Volume of distribution ~100x blood volume
  - Extensive distribution to tissues
- Readily permeates into cells
- Residence time on PI3Kδ protein ~5.5 hours
  - Prolonged target signal inhibition

Evaluation of the Optimal Biological Dose (Providing EC_{90} in BAT assay)



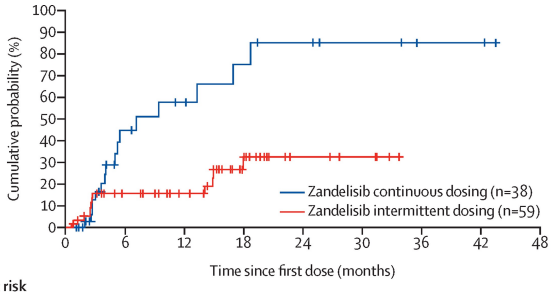
PK Supports Intermittent Dosing



Soumerai et al. ASCO 2018, Abstract 7519, Zelenetz et al. ICML 2019

Zandelisib: Safety and Efficacy

Intermittent Dosing Reduces Adverse Events of Special Interest

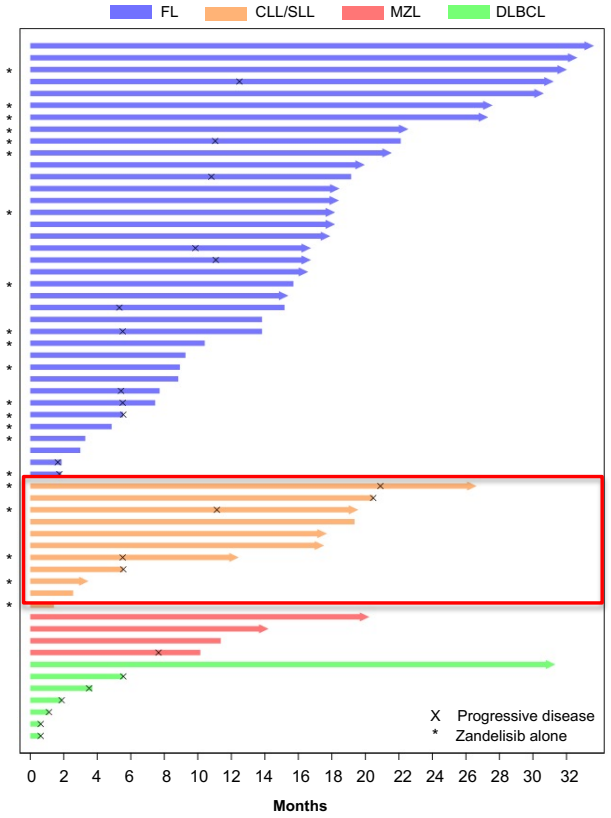


Number at risk (number censored)									
Zandelisib continuous dosing	38 (0)	17 (10)	13 (12)	10 (13)	8 (14)	6 (16)	3 (19)	3 (19)	0 (22)
Zandelisib intermittent dosing	59 (0)	38 (13)	31 (20)	15 (32)	6 (41)	4 (43)	0 (47)	0	0

	Continuous Dosing (n=38)			Intermittent Dosing (n=59)		
	Gr 1-2	Gr 3	Gr 4	Gr 1-2	Gr 3	Gr 4
Diarrhoea or colitis	24%	24%	0	37%	8%	0
Rash, all types	32%	5%	0	24%	5%	0
ALT/AST elevation	21%	5%	0	22%	5%	0
Pneumonia	3%	16%	0	3%	2%	0
Mucositis	16%	3%	0	2%	0	0
Pneumonitis	0	0	0	2%	2%	0

Efficacy

	n	ORR (%)	CR (%I)
FL			
Overall	62	51 (82%)	14 (23%)
Zandelisib mono	41	32 (78%)	9 (22%)
Zandelisib-R	21	19 (90%)	5 (24%)
Refractory to rituximab	8	7 (88%)	1 (13%)
Relapsed to rituximab	13	12 (92%)	4 (31%)
CD Zandelisib mono	25	19 (76%)	4 (16%)
ID	37	32 (86%)	10 (27%)
Zandelisib monotherapy	18	14 (78%)	5 (28%)
Zandelisib plus rituximab	19	18 (95%)	5 (26%)
CLL/SLL			
Overall	20	20 (100%)	5 (25%)
Zandelisib mono	13	13 (100%)	4 (31%)
Zandelisib-R	7	7 (100%)	1 (14%)
CD Zandelisib mono	10	10 (100%)	3 (30%)
ID	10	10 (100%)	2 (20%)
Zandelisib monotherapy	4	4 (100%)	1 (25%)
Zandelisib plus rituximab	6	6 (100%)	1 (17%)
MZL			
Zandelisib-R (ID)	4	4 (100%)	1 (25%)
DLBCL			
Zandelisib-R	9	1 (11%)	1 (11%)



Ongoing development has focused on FL and MZL, but activity in CLL is being evaluated following prior BTKi

Pagel et al. Lancet Oncol (2022) 23:1021-1030

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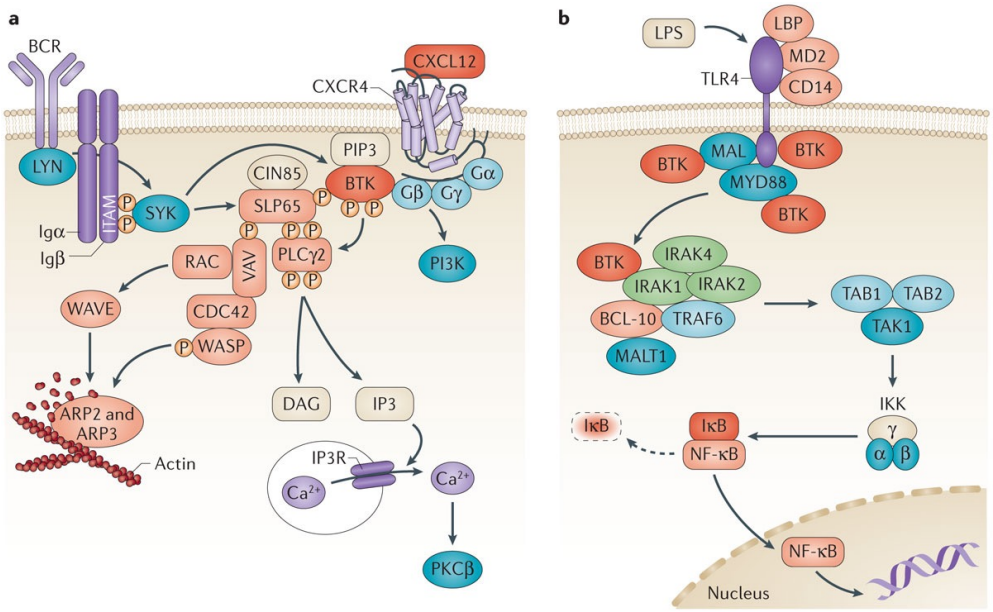
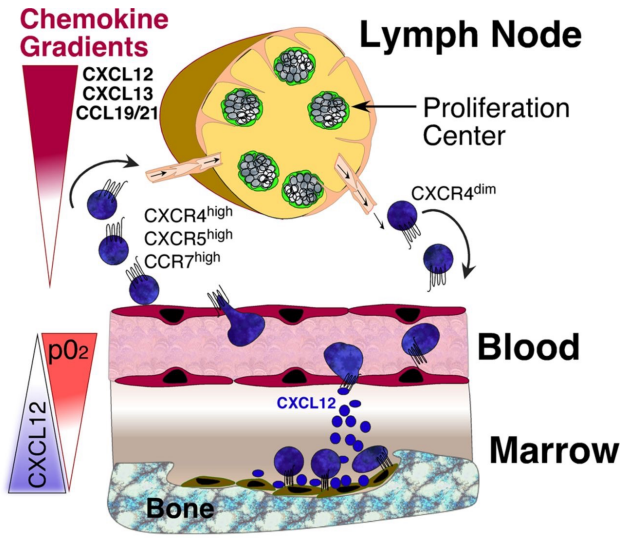
Beyond Covalent BTK Inibitors

BTK has a central role is B-cell signaling and migration

BTK is Central to BCR and TLR Signaling





CLL (and MCL) cells migrate to the extracellular microenvironment via chemokine gradients. Cell response is dependent on signaling via BTK. This accounts for the early lymphocytosis with BTKi

Hendriks et al. Nature Reviews Cancer 14, 219–232 (2014); Davids and Burger, Open Journal of Hematology, 2012, 3(S1)-3, Jan A. Burger, and Emili Montserrat Blood 2013;121:1501-1509

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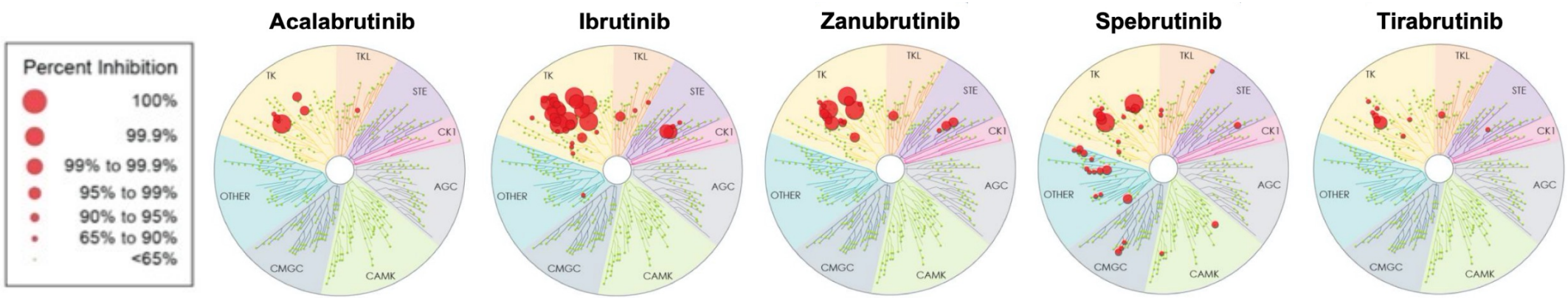
Covalent Bruton Tyrosine Kinase inhibitors

Act by covalent binding to C481, reactivation by new synthesis of BTK



FDA Approved	Yes	Yes	Yes	No	No
CLL/SLL	1L, R/R	1L, R/R		NA	NA
MCL	R/R	R/R	R/R	NA	NA
MZL		R/R	R/R	NA	NA
WM		R/R	R/R	NA	NA
Chronic GvHD		≥ 1 systemic therapy		NA	NA

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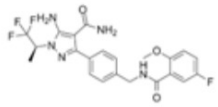
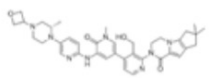
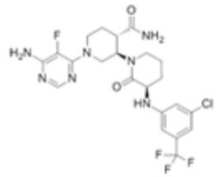
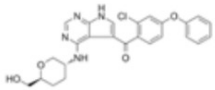
Kaptein et al. Amer Soc Hematol Meeting Expo (2018), Abstract 1871

Non-Covalent BTKis

Table 1. Summary of characteristics of non-covalent BTKi in clinical development.

Non-Covalent BTKi	Pirtobrutinib	Fenebrutinib	Vecabrutinib	Nemtabrutinib
Structure				
Other names	LOXO-305	GDC-0853	SNS-062	ARQ-531
Binding to BTK	Blocks ATP binding site of BTK	Hydrogen bonds with K430, M477, D539	Decreases surface expression of B-cell activation markers	Hydrogen bonds with E475, Y476
Other enzyme activity	Minimal	Minimal	Activity on ITK No activity on EGFR	Activity on SRC, ERK, AKT Inhibits signalling downstream of PCLG2
Side effects (%)	Fatigue (20%) Diarrhea (17%) Contusion (13%) Neutropenia (13%)	Fatigue (37.5%) Nausea (33%) Diarrhea (29%) Thrombocytopenia (25%) Headache (21%)	Anemia (37.5%) Headache (25%) Neutropenia (25%) Night sweats (25%)	Nausea (10%) Diarrhea (10%) Fatigue (8%) Neutropenia (8%) Dysgeusia (8%) Rash (8%)
Clinical development	Phase Ib/II ongoing in B-cell malignancies Phase III ongoing in MCL Phase III ongoing in CLL	Terminated in B-cell malignancies Ongoing in multiple sclerosis	Terminated in B-cell malignancies	Phase Ib ongoing in B-cell malignancies Phase II ongoing in B-cell malignancies

Lewis, J. Pers Med 2021, 11(8), 764

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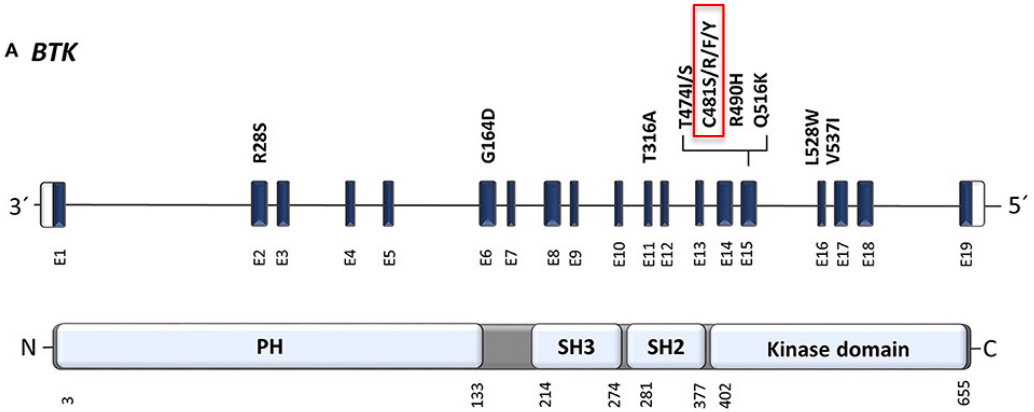
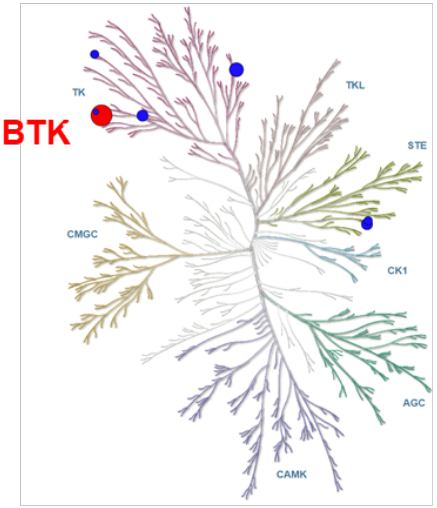
Non-covalent BTK inhibitors

Mutations Causing Resistance to Covalent BTKi

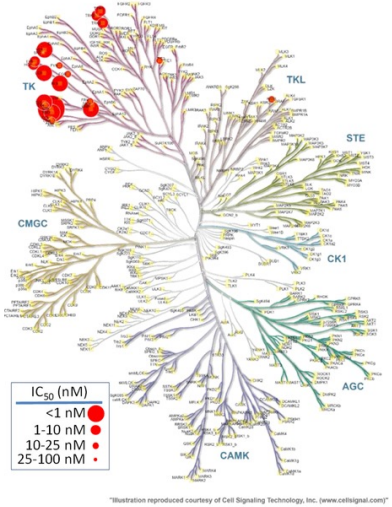


C841S is the dominant mutation seen clinically though multiple mutations result in resistance to covalent BTKis

Pirtobrutinib (Loxo-305)



Nemtabrutinib (MK-1026) (ARQ 531)



Compete for binding of ATP to the active site, but do not bind to C481

Reiff et al. Cancer Discov (2018) 8:1300-1325; Mato et al. ASH 2019

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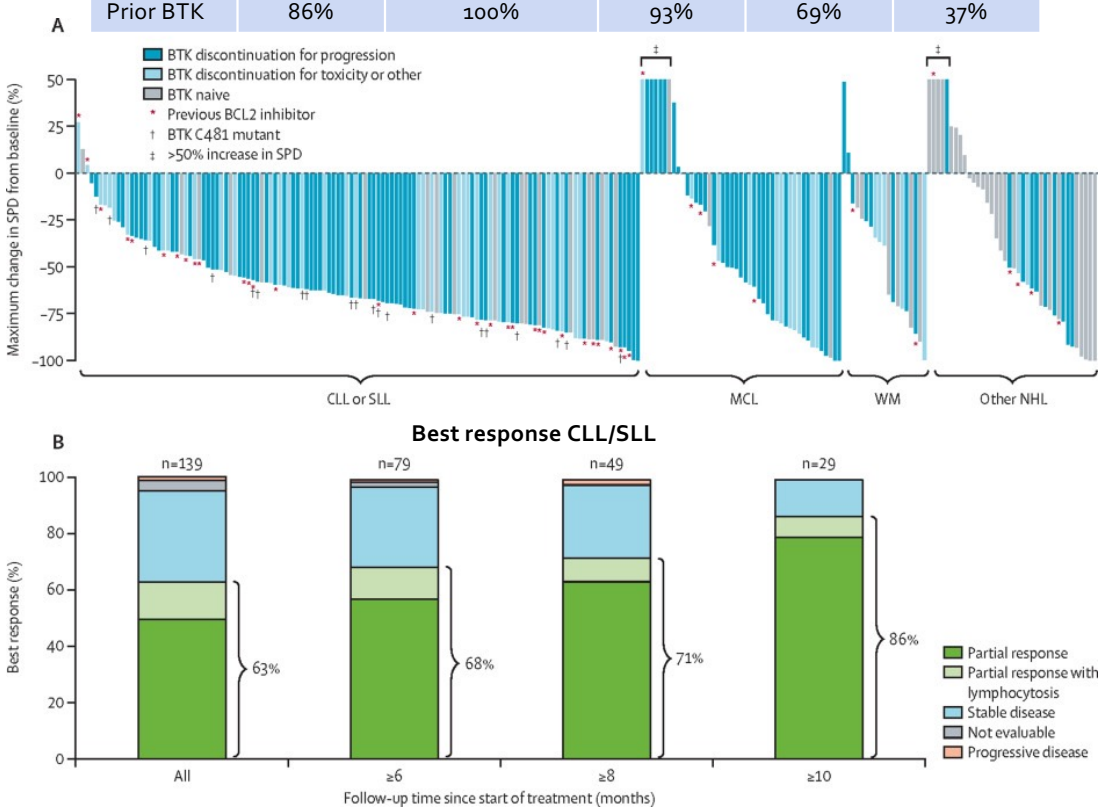
Pirtobrutinib for relapsed/refractory B-cell malignancies

	CLL/SLL	CLL/SLL C481s	MCL	WM	FL
ORR	63%	71%	52%	68%	50%
N	139	24	56	19	8
Prior BTK	86%	100%	93%	69%	37%

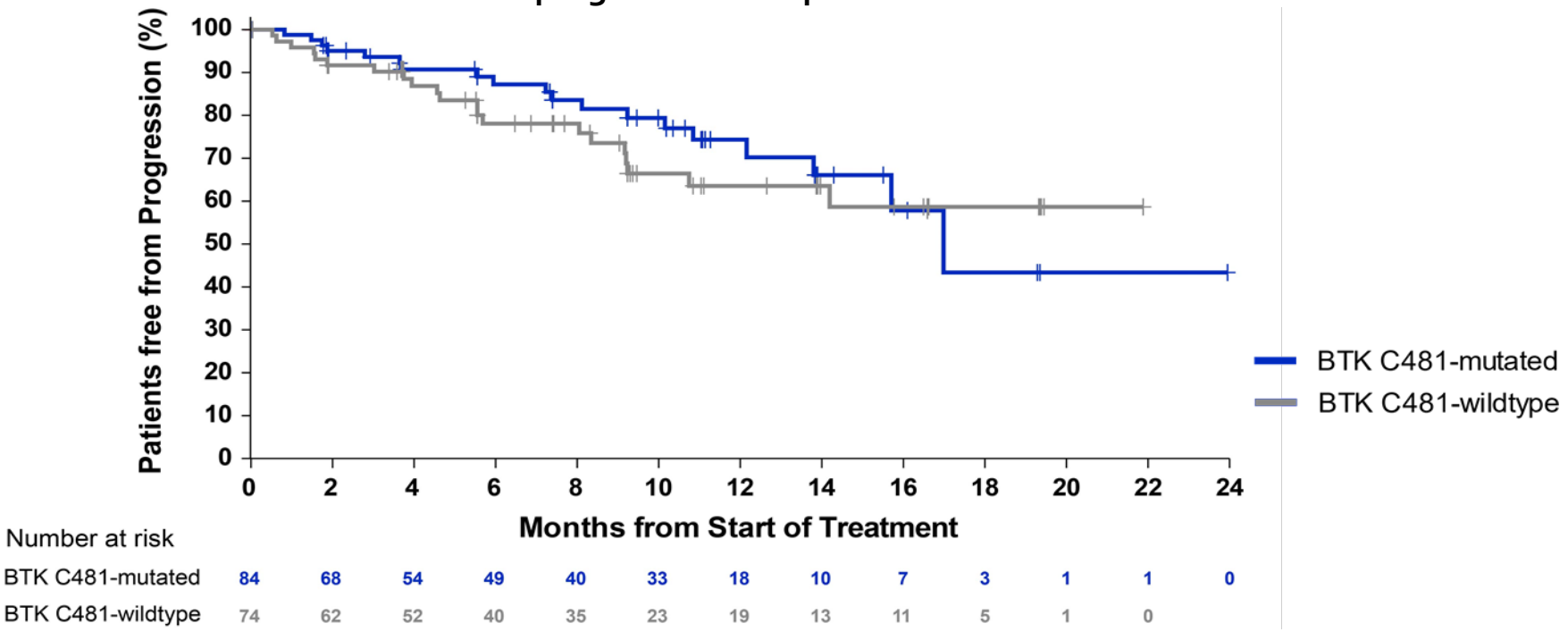


Mato et al. Lancet (2021) 397:892-901

	Adverse events, regardless of attribution					Treatment-related AEs	
	Grade 1	Grade 2	Grade 3	Grade 4	Any grade	Grades 3 or 4	Any grade
Adverse event							
Fatigue	40 (12%)	22 (7%)	3 (1%)	0	65 (20%)	2 (1%)	27 (8%)
Diarrhoea	45 (14%)	10 (3%)	0	0	55 (17%)	0	28 (9%)
Contusion	37 (12%)	5 (2%)	0	0	42 (13%)	0	29 (9%)
Neutropenia[a]	5 (2%)	4 (1%)	19 (6%)	13 (4%)	41 (13%)	17 (5%)	20 (6%)
Nausea	25 (8%)	5 (2%)	0	0	30 (9%)	0	10 (3%)
Cough	20 (6%)	9 (9%)	0	0	29 (9%)	0	2 (1%)
Headache	22 (7%)	5 (2%)	2 (1%)	0	29 (9%)	1 (<1%)	13 (4%)
Dyspnoea	16 (5%)	9 (3%)	1 (<1%)	0	26 (8%)	0	6 (2%)
Constipation	20 (6%)	4 (1%)	1 (<1%)	0	25 (8%)	0	6 (2%)
Anaemia	6 (2%)	6 (2%)	12 (4%)	0	24 (7%)	4 (1%)	10 (3%)
Pyrexia	19 (6%)	2 (1%)	1 (<1%)	0	23 (7%)	1 (<1%)	6 (2%)
URI	4 (1%)	19 (6%)	0	0	23 (7%)	0	3 (1%)
Back pain	14 (4%)	8 (3%)	0	0	22 (7%)	0	2 (1%)
Peripheral oedema	18 (6%)	4 (1%)	0	0	22 (7%)	0	2 (1%)
Rash maculopapular	18 (6%)	2 (1%)	0	0	20 (6%)	0	9 (3%)
Abdominal pain	10 (3%)	7 (2%)	1 (<1%)	0	18 (6%)	0	4 (1%)
Dizziness	16 (5%)	2 (1%)	0	0	18 (6%)	0	8 (3%)
Hyperuricaemia	17 (5%)	0	0	0	17 (5%)	0	9 (3%)
Arthralgia	13 (4%)	3 (1%)	0	0	16 (5%)	0	5 (2%)
Pruritus	13 (4%)	3 (1%)	0	0	16 (5%)	0	8 (3%)
Adverse event of special interest							
Bruising[b]	48 (15%)	5 (2%)	0	0	53 (16%)	0	37 (12%)
Rash[c]	30 (9%)	5 (2%)	0	0	35 (11%)	0	18 (6%)
Arthralgia	13 (4%)	3 (1%)	0	0	16 (5%)	0	5 (2%)
Haemorrhage[d]	10 (3%)	4 (1%)	1 (<1%)[e]	0	15 (5%)	0	5 (2%)
Hypertension	2 (<1%)	9 (3%)	4 (1%)	0	15 (5%)	0	4 (1%)
Afib/flutter	0	2 (1%)	0	0	2 (1%)	0	0

BTK C481 Mutation Status is not Predictive of Pirtobrutinib

Progression-free survival by BTK C481 mutation status[a] in CLL/SLL patients with progression on a prior BTK inhibitor



Data cutoff date of 16 July 2021. Response status per iwCLL 2018 according to investigator assessment. [a]BTK C481 mutation status was centrally determined and based on pre-treatment samples.

Mato et al. Lancet (2021) 397:892-901

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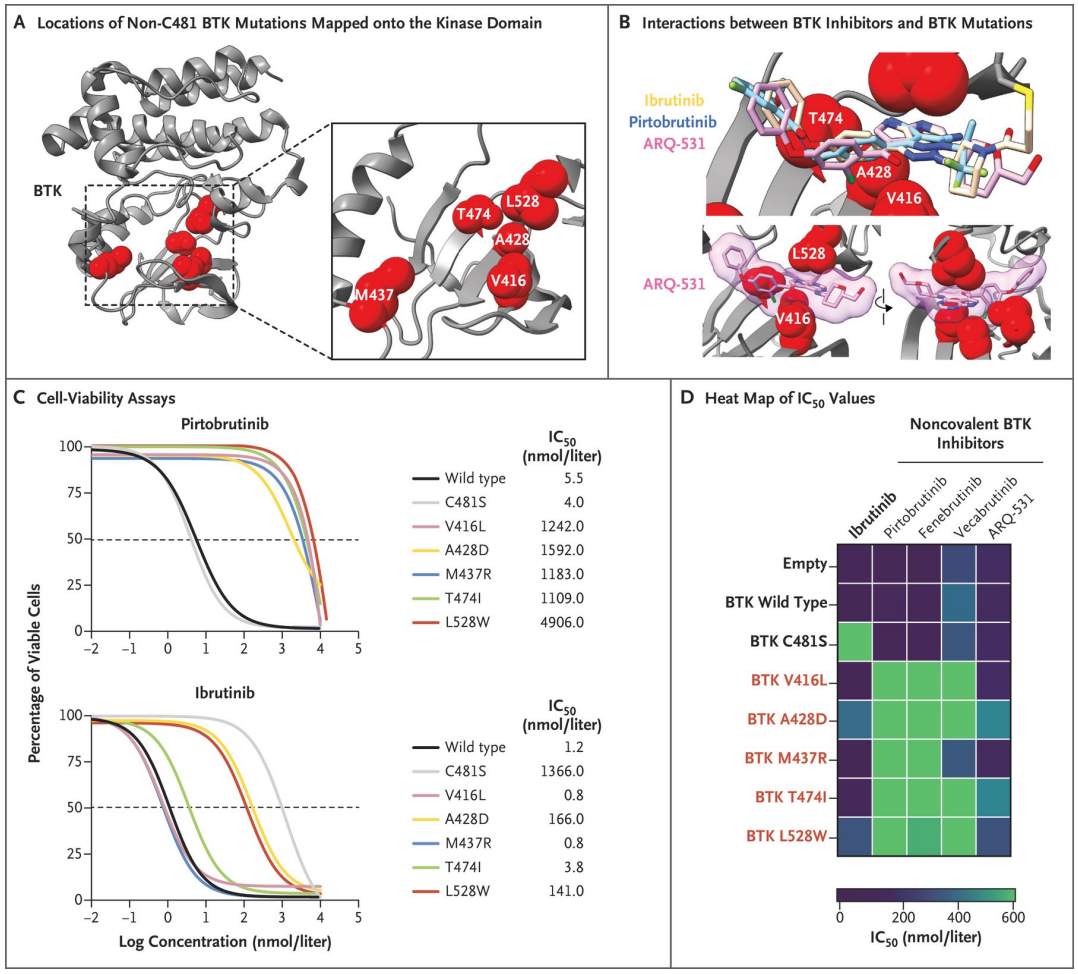
Mechanisms of BTK resistance to BTKi



Wang et al. N Engl J Med (2022) 386:735-743

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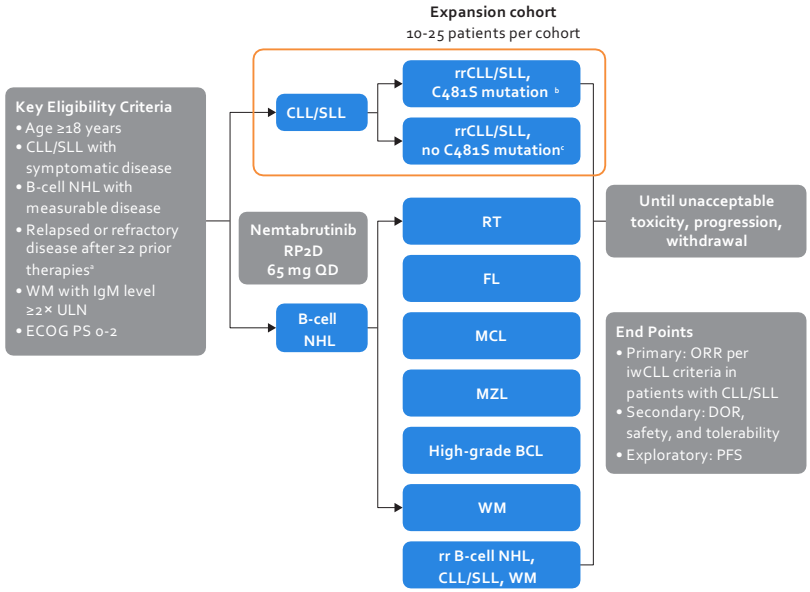
Nemtabrutinib: Non-covalent BTKi

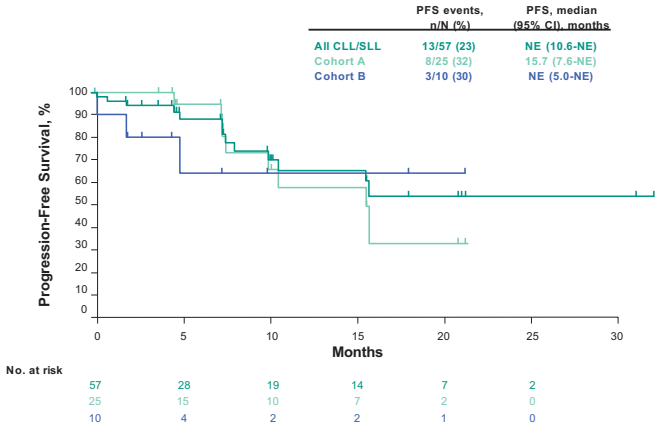
BELLWAVE-001 Schema



Efficacy

	CLL/SLL 65 mg QD n = 57	CLL/SLL Cohort A[a] n =25	CLL/SLL Cohort B[b] n =10
ORR	30 (53) [39-66]	15 (60) [39-79]	4 (40) [12-74]
CR	2 (4) [0.4-12]	0 (0) [0-14]	1 (10) [0.3-45]
PR	15 (26) [16-40]	5 (20) [7-41]	2 (20) [3-56]
PR-L	13 (23) [13-36]	10 (40) [21-61]	1 (10) [0.3-45]
SD	17 (30) [18-43]	8 (32) [15-54]	3 (30) [7-65]
PD	2 (4) [0.4-12]	0 (0) [0-14]	2 (20) [3-56]
No assessment	8 (14) [6-26]	2 (8) [1-26]	1 (10) [0.3-45]

[a]Cohort A comprises patients with rrCLL/SLL who received ≥2 prior therapies including covalent BTKi, and who have C481S mutation.
[b]Cohort B comprises patients with rrCLL/SLL who received ≥2 prior therapies, are intolerant to BTKi, and have no C481S mutation.



Safety

	CLL/SLL n=74	
All TEAEs, n (%)[a]	74 (100)	
Grade ≥3 TEAEs[b]	55 (74)	
Nemtabrutinib-related TEAE	51 (69)	
Grade ≥3 nemtabrutinib-related TEAEs[c]	22 (30)	
Nemtabrutinib-related TEAEs leading to discontinuation[d]	9 (12)	
TEAEs ≥20%, n (%)	**All**	**Grade ≥3**
Dysgeusia	27 (36)	0 (0)
Hypertension	26 (35)	10 (14)
Peripheral edema	25 (34)	1 (1)
Cough	24 (32)	0 (0)
Fatigue	24 (32)	2 (3)
Constipation	23 (31)	1 (1)
Neutrophil count decreased	23 (31)	20 (27)
Dizziness	22 (30)	0 (0)
Nausea	22 (30)	2 (3)
Pyrexia	22 (30)	3 (4)
Diarrhea	21 (28)	2 (3)
Dyspnea	21 (28)	5 (7)
Arthralgia	18 (24)	1 (1)
Platelet count decreased	18 (24)	10 (14)
Upper respiratory tract infection	17 (23)	1 (1)
Chills	16 (22)	0 (0)
Pneumonia	16 (22)	10 (14)
Anemia	15 (20)	9 (12)

Woyach et al. AACR 2022

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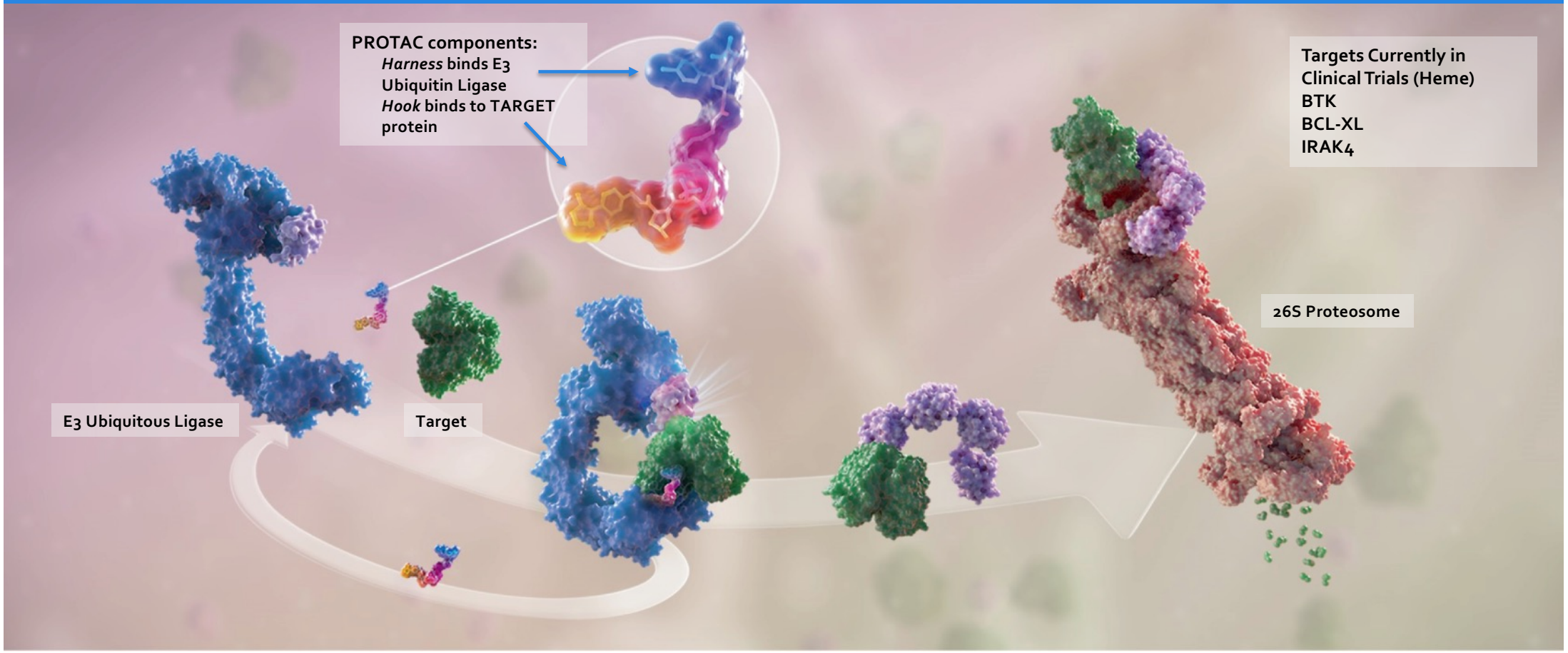
Proteolysis-targeted chimera (PROTAC)



Bekes et al. Nat Rev Drug Discov 2022, 21:181-200

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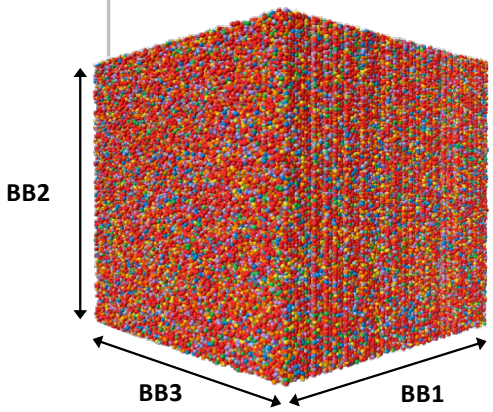
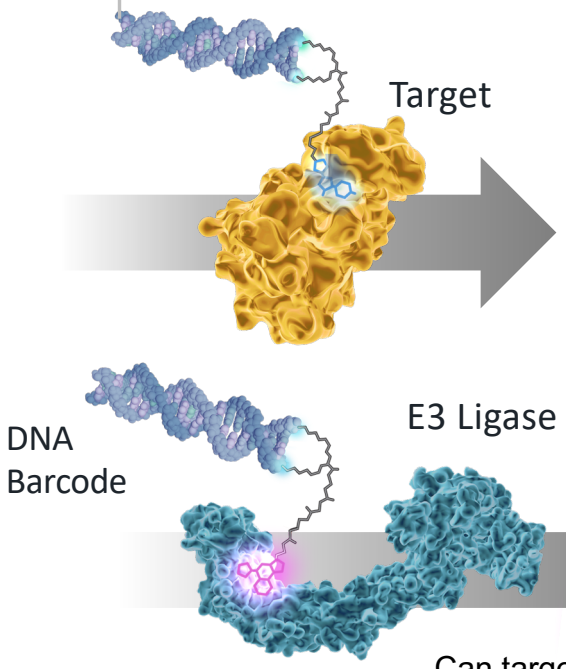
DNA-Encoded Library Screening Enables Efficient Chimeric Targeting Molecule Discovery and Design

1 Billions of proprietary DNA-Encoded Library (DEL) compounds



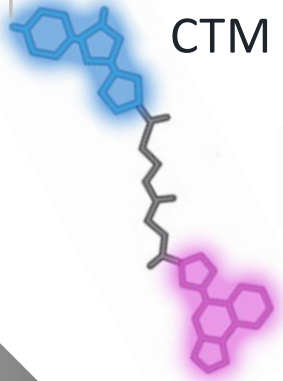
BB = Chemical Building Blocks

2 Target proteins and E3 ligases are screened using DEL

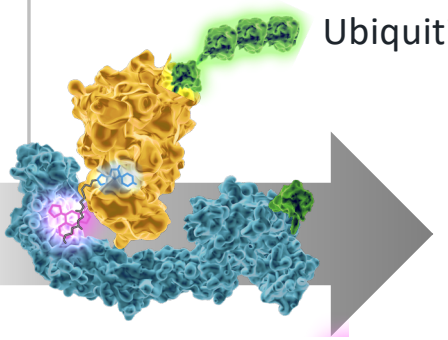


Can target E3 Ligases with or without IMID activity

3 Binders from DEL are joined via a linker to construct CTMs



4 CTM recruits E3 ligase to target protein, triggering ubiquitin transfer and degradation



Brown NURIX Therapeutics, 9th Whistler Hem Malig, 2022

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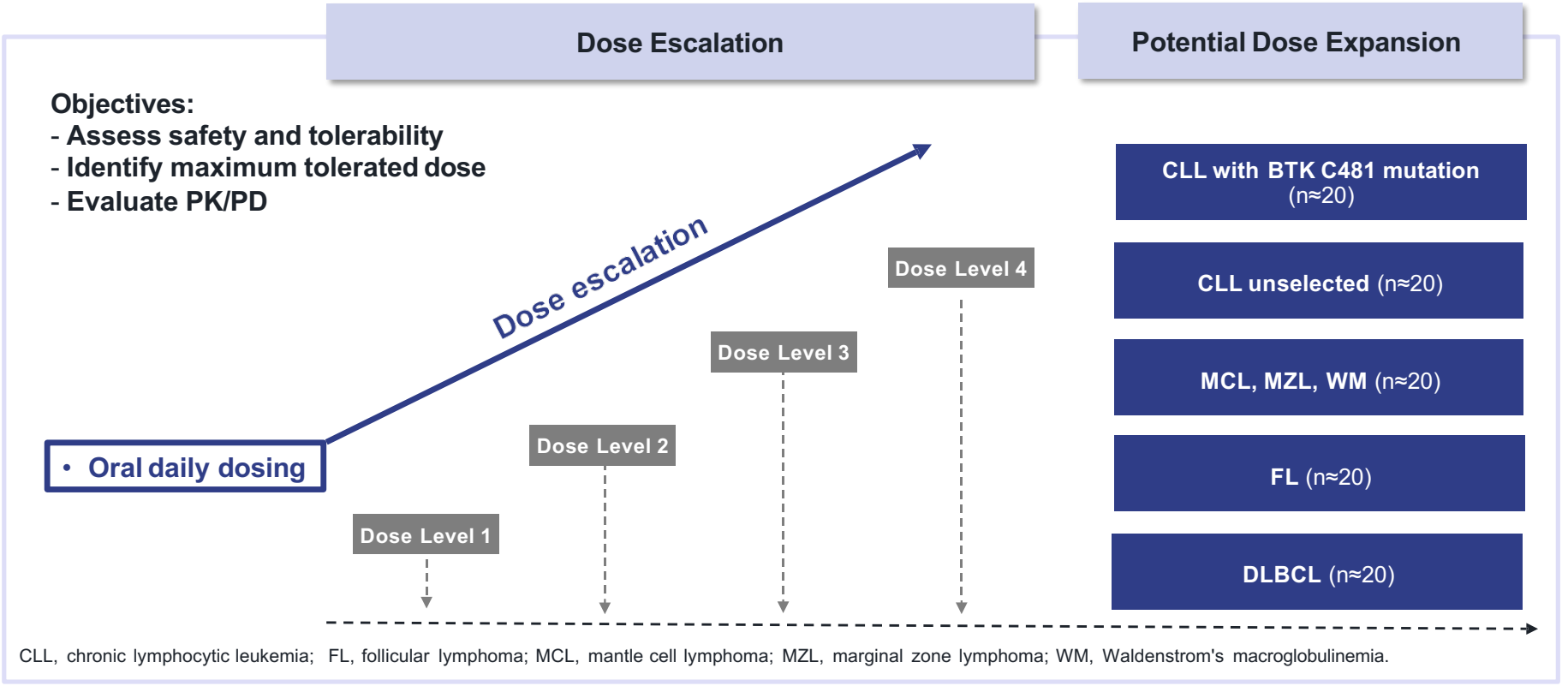
NX-2127-001 (MSK 21-207): Phase 1 First-in-Human Clinical Trial Design

Two-Part Phase 1 Monotherapy Trial of NX-2127 in Relapsed or Refractory B-Cell Malignancies



CLL, chronic lymphocytic leukemia; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; WM, Waldenstrom's macroglobulinemia.

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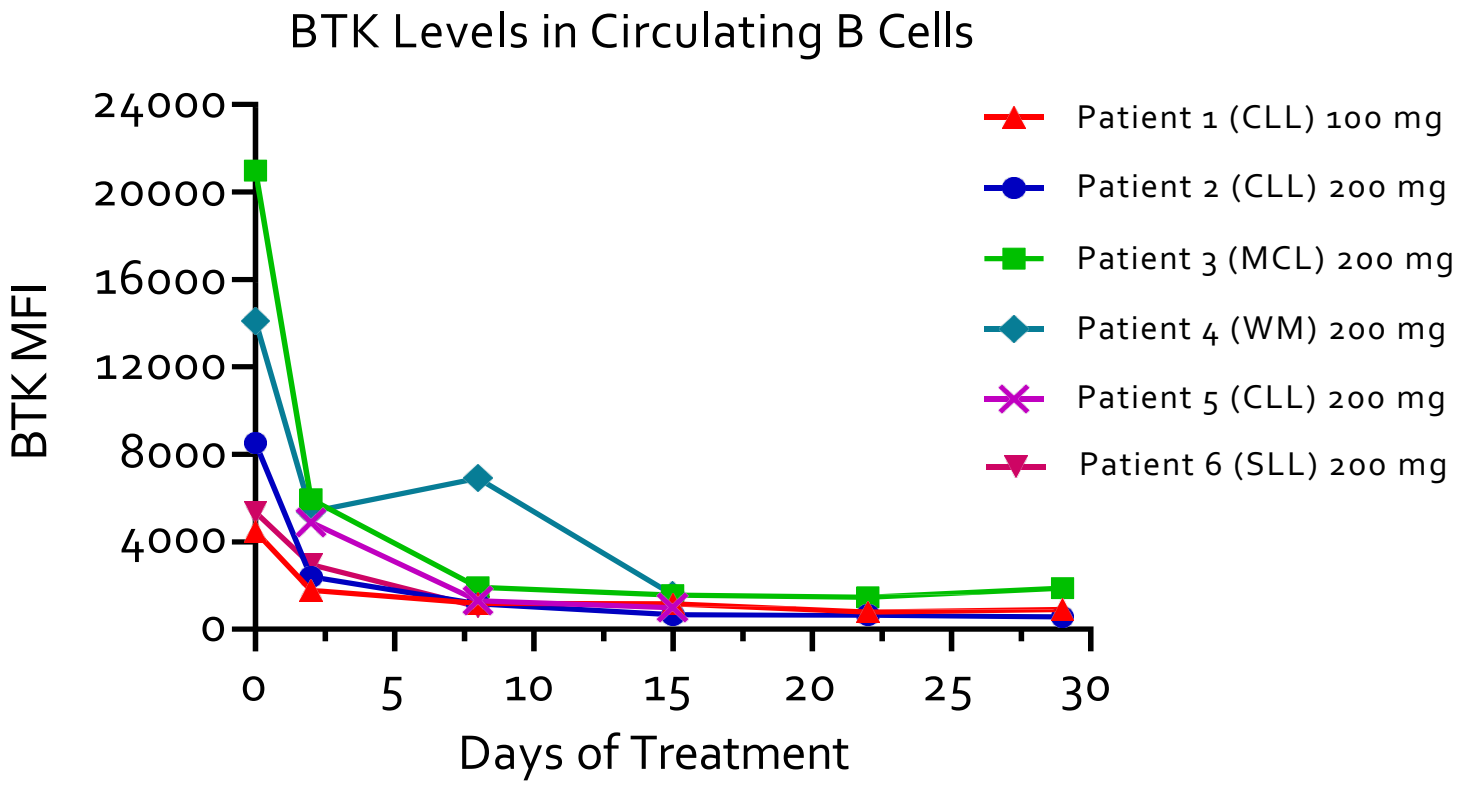
Robust BTK Degradation Observed in All Patients Dosed Regardless of Baseline BTK Protein Levels

- Oral daily treatment of NX-2127 induced a rapid and significant decrease in BTK levels that was sustained throughout dosing
- Patients have varying levels of BTK in B cells at the start of treatment



MFI: geometric mean fluorescence intensity in circulating CD19+ B cells.

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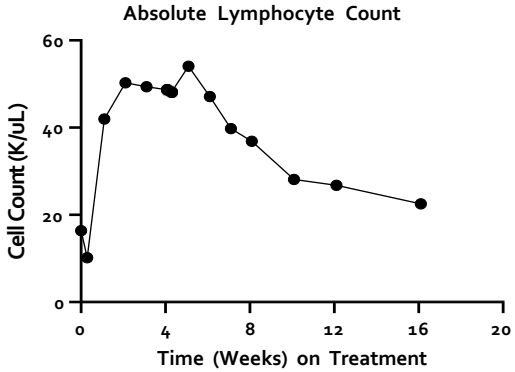
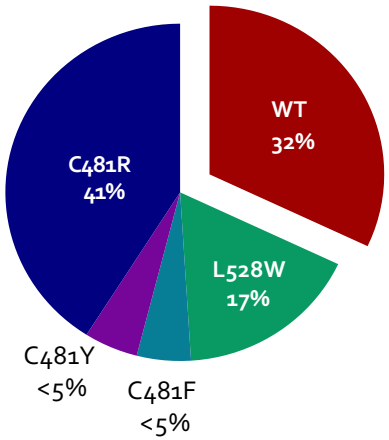
Clinical Response Observed in Patient 1

- **Patient history**
  - 78-year-old male with stage IV CLL
  - Rituximab, 2015
  - Ibrutinib, 2015-2021
- **Disease status at study entry**
  - Bone Marrow Involvement: 85.4%
  - Spleen: Enlarged (15.7 cm)
  - Nodal disease: up to 4.2 cm
  - Multiple resistance mutations

Safety	
Exposure	No dose interruptions or modifications
DLT's	None
SAE's	None
Grade 3 or > AE	Neutropenia (ANC = 860), resolved without intervention



Up to 68% of Leukemia Cells with BTK Mutations



Disease Assessment

Time Point	Hgb (g/dL)	Plt (K/uL)	ALC (K/uL)	Spleen (cm)	Spleen % change[a]	Lymph Node SPD (cm^2)	Nodal SPD % Change	Response[b]
Baseline	14.3	112	16.4	15.7	---	27.1	---	-----
Week 8	13.2	133	36.9	14.8	-33%	13.4	-51%	Stable Disease[c]
Week 16	14.1	114	22.5	14.2	-56%	10.8	-60%	Partial remission with lymphocytosis

[a] Spleen % change is the percent change to a reference "normal" of 13 cm.
[b] Response for this patient as per International working group on chronic lymphocytic leukemia (iw CLL)
[c] Listed as partial remission in database.
DLT: dose limiting toxicity; SAE: serious adverse event; AE: adverse event; ANC: absolute neutrophil count; Hgb: hemoglobin, Plt: platelet count, ALC: absolute lymphocyte count, SPD: sum of product diameters

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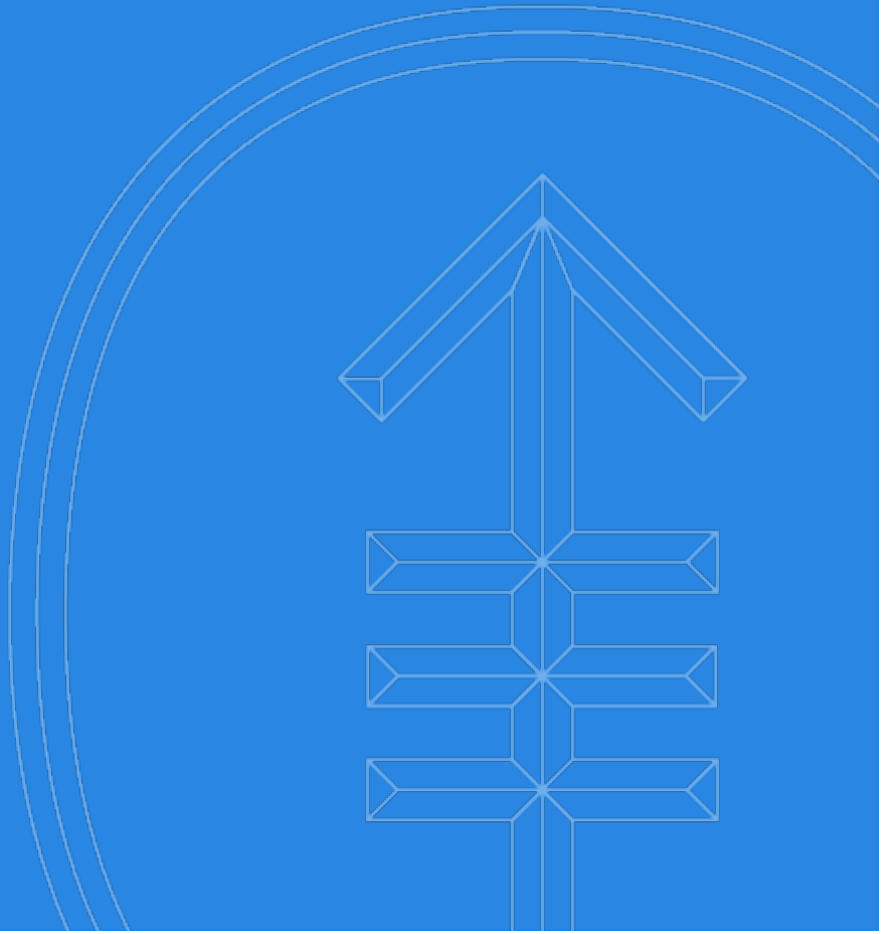
BH3 Mimetics

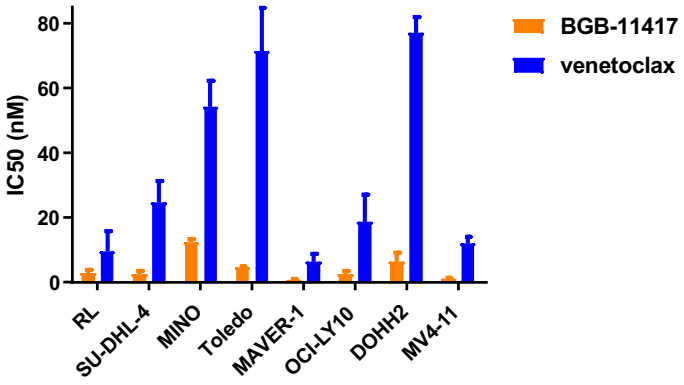


BGB-11417: Potent and highly selective inhibitor of BCL2

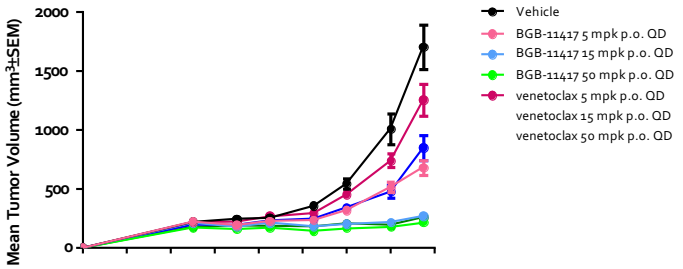
Potency and selectivity profile of BGB-11417

In vitro assays	BGB-11417	Venetoclax
SPR binding assay K_D (nM)		
Bcl-2 WT	0.035	1.3
Bcl-2 G101V	0.28	34
TR-FRET assay IC_{50} (nM)		
Bcl-2 WT	0.014	0.20
Bcl-X_L	28	65
Mcl-1	>10000	>10000
Bcl-w	1803	2730
Bcl2A1	>10000	>10000
Cell survival assay IC_{50} (nM)		
$RS_{4;11}$ cell line	0.42	3.4
$Molt_4$ cell line	2314	2790

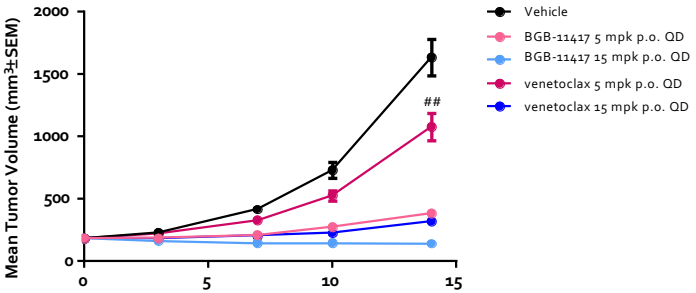
Cell-killing by BGB-11417 and Venetoclax in hematological cancer cell lines



DLBCL Xenograft (Toledo)



MCL Xenograft (MAVER-1)



Hu et al. Cancer Res (2020) 80(16_Supplement):3077

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Phase 1/1B study of BGB-11417: Schema

Monotherapy Cohorts

Part 1: DOSE ESCALATION (BGB-11417 Monotherapy)

Cohort	Population	Disease	Planned N
1A	R/R	NHL (FL, DLBCL, MZL,or transformed NHL)	15-30
1B	R/R (low TLS risk)	CLL/SLL	15-30
1C	R/R (high TLS risk[a])	CLL/SLL	3-6
1D	R/R	MCL	3-6
1E	R/R	WM	3-6

RP2D

RP2D per cohort will be decided based on SMC review of available safety and activity data

Part 2: EXPANSION (BGB-11417 Monotherapy)

Cohort	Population	Disease	Planned N
2A	R/R (food effect)	Indolent NHL (FL, MZL)	10
2B	R/R (food effect)	Aggressive NHL (DLBCL, transformed NHL)	10
2C	R/R (low TLS risk)	CLL/SLL	20
2D	R/R (high TLS risk*)	CLL/SLL	10
2E	R/R (prior ven)	CLL/SLL	10
2F	R/R	MCL	20
2G	R/R	WM	20

Combination Cohorts

Part 3: DOSE FINDING (BGB-11417 + Zanubrutinib Combination)

Cohort	Population	Disease	Planned N
3A	R/R	CLL/SLL	15-30
3B	R/R	MCL	3-6

RP2D

RP2D per cohort will be decided based on SMC review of available safety and activity data

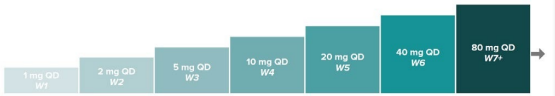
Part 4: EXPANSION (BGB-11417 + Zanubrutinib Combination)

Cohort	Population	Disease	Planned N
4A	R/R	CLL/SLL	30
4B	TN	CLL/SLL	20
4C	R/R	MCL	20

Ramp-Up Scheme Examples:

Cohort 1A: NHL – 3-day ramp-up

Cohort 1B: CLL – Weekly ramp-up



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Tam et al. Blood (2021) 138 (Supplement 1): 1419.

Phase 1/1B study of BGB-11417: Treatment-Emergent Adverse Events and Dose-Limiting Toxicities

Overall Treatment-Emergent Adverse Events

AEs, n (%)	BGB-11417 Monotherapy (N=25)	BGB-11417 + Zanubrutinib Combination (N=11)	All Patients (N=36)
Any AE	22 (88)	9 (82)	31 (86)
Grade ≥3 AEs	11 (44)	0	11 (30)
Serious AEs	9 (36)	0	9 (25)
Leading to death	2 (8)	0	2 (6)[a]
AEs leading to hold of BGB-11417	4 (16)	0	4 (11)[b]
AEs leading to dose reduction of BGB-11417	0	0	0
AEs leading to discontinuation of BGB-11417	1 (4)	0	1 (3)[c]

DLTs in Dose-Escalation Cohorts

Cohort	40 mg	80 mg	160 mg	320 mg	640 mg
Monotherapy					
NHL (1A)	0/3	0/4	1/4[d]	0/3	TBD
CLL (1B)	—	1/4[e]	TBD	TBD	TBD
Combination					
CLL (3A)	0/4	0/3	TBD	TBD	TBD

[a]Neither related to study drug; 1 death secondary to disease progression and 1 GI hemorrhage subsequent to bowel surgery. [b]ALT increased and GGT increased; neutropenia, pyrexia, and febrile neutropenia; GI hemorrhage and small intestinal obstruction; neutropenia. [c]GI hemorrhage subsequent to bowel surgery. [d]DLT of grade 3 febrile neutropenia. [e]DLT of grade 4 neutropenia. AE, adverse event; ALT, alanine aminotransferase; CLL, chronic lymphocytic leukemia; DLT, dose limiting toxicity; GGT, gamma-glutamyl transferase; GI, gastrointestinal; NHL, non-Hodgkin lymphoma.

Tam et al. Blood (2021) 138 (Supplement 1): 1419.

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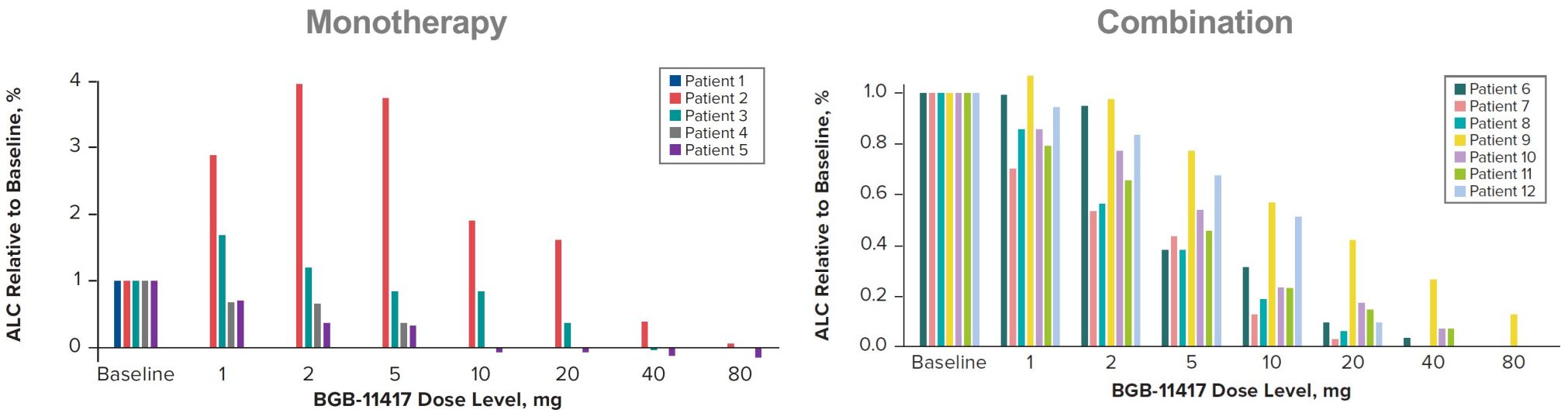
Phase 1/1B study of BGB-11417: Reduction in ALC during ramp-up in patients with CLL[a]



- Significant reduction in ALC was noted among all patients with CLL during ramp-up, with reduction in lymphocytes noted at dose levels as low as 1 mg

[a]Figures represent reduction in ALC above the ULN ($4x10^9$/L) compared to pre-BGB-11417 baseline before next dose escalation (or after 1 week at target dose) per dose. Patients receive each BGB-11417 dose level for 1 week before escalating to the next dose. Patients on combination therapy were also receiving zanubrutinib during BGB-11417 ramp-up, beginning 8-12 weeks before the first BGB-11417 dose (note: patient 1, with normal baseline ALC, was excluded from the monotherapy figure).

Tam et al. Blood (2021) 138 (Supplement 1): 1419.

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Summary: PI3K and BTK inhibitors

- PI3Kδ is a validated target with clinical efficacy in CLL/SLL, FL, MZL and WM
  - Clinical utility is limited by toxicity
  - Need to explore alterative dosing strategies including lower dosing and intermittent dosing
  - Novel trial designs should evaluate optimal biological doses and include prospective integrated safety databases

- BTK is a validated target with clinical efficacy in CLL/SLL, FL, MZL, WM and chronic GvDH
  - Pirtobrutinib, a non-covalent, BTK inhibitor may extend the efficacy of BTK inhibition
  - BTK can also be targeted with PROTACs promoting degradation of BTK which also may overcome resistance mutations