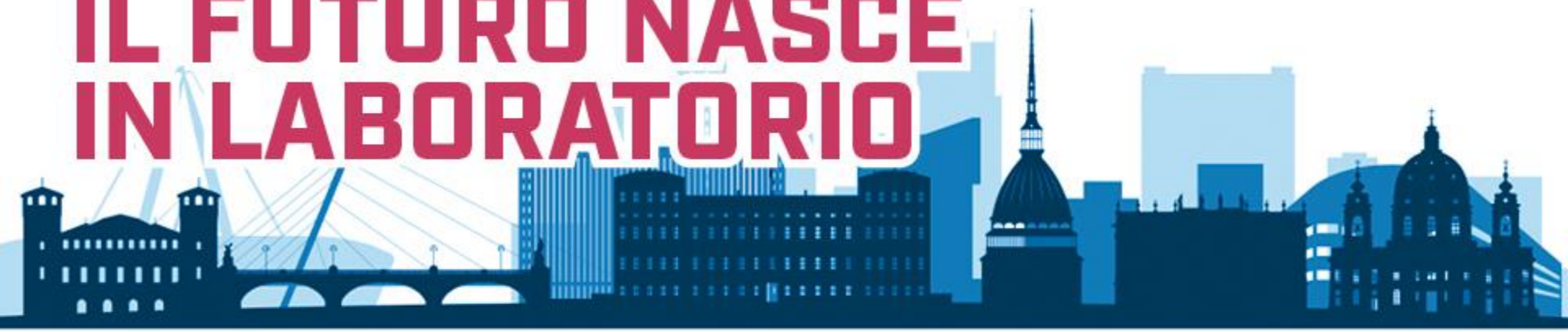
REGIONALE SIES – Delegazione Piemonte

YOUNG SCIENCE FORUM: IL FUTURO NASCE IN LABORATORIO



Protein degraders: dalla preclinica alla clinica

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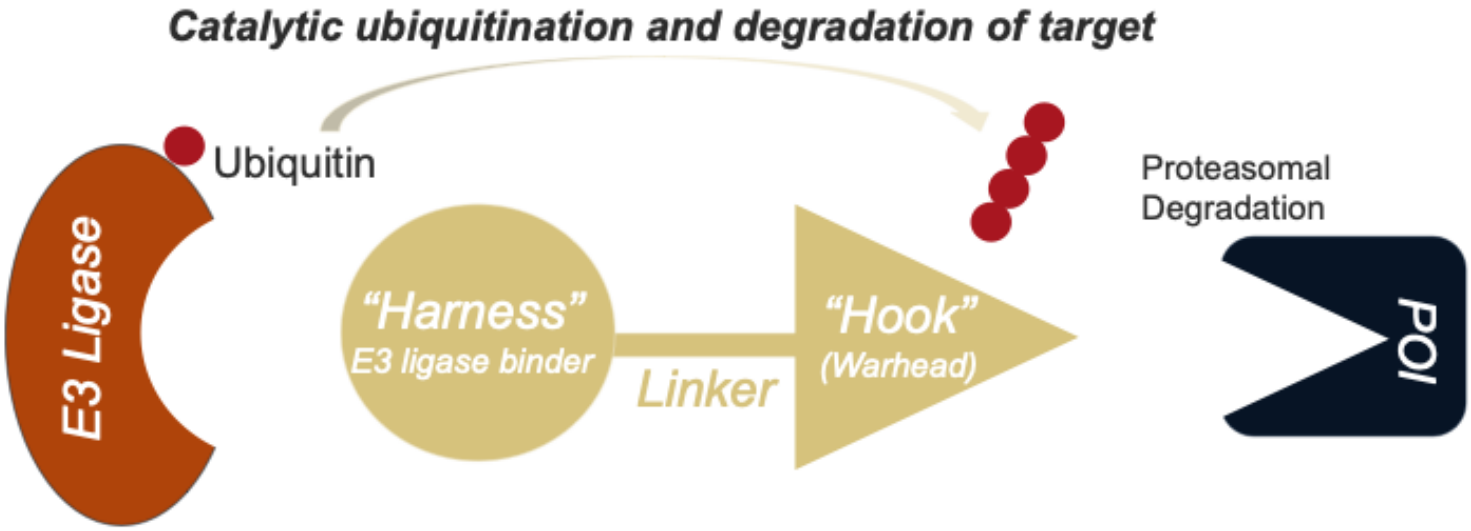
TORINO, ACCADEMIA DI MEDICINA | 4-5 GIUGNO 2026

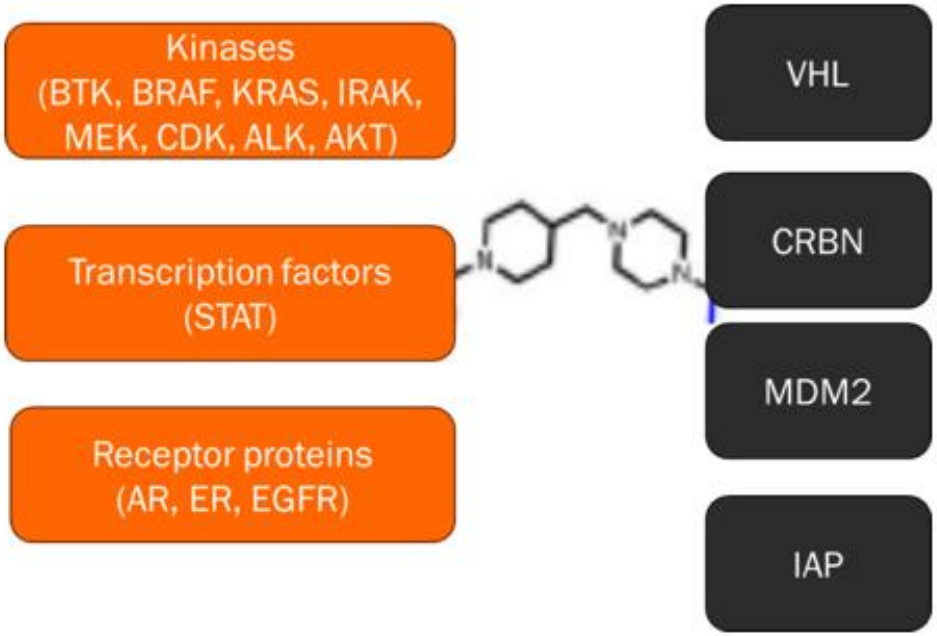
Disclosures of Riccardo Moia

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

What are degraders

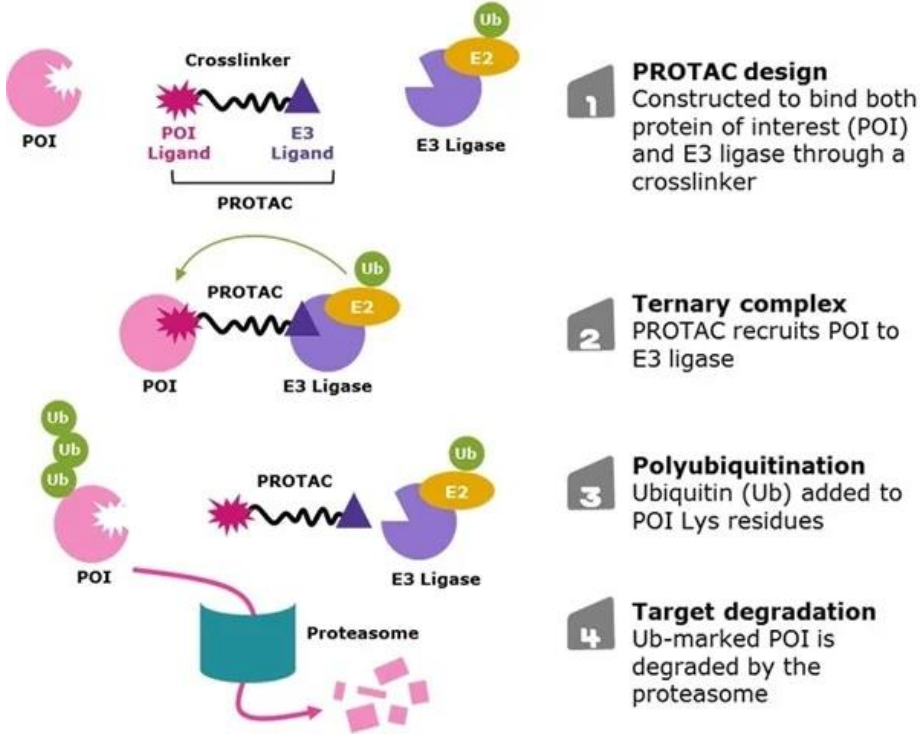


Hooks and Harnesses



Huynh T *et al.*, *Mol Cancer Ther*. 2024

Degraders mode of action



- Degraders can target any type of protein (i.e. not only proteins with kinase activity but also transcription factors and other)
- Can POI fragment be used as neoantigen to activate immune-systems?

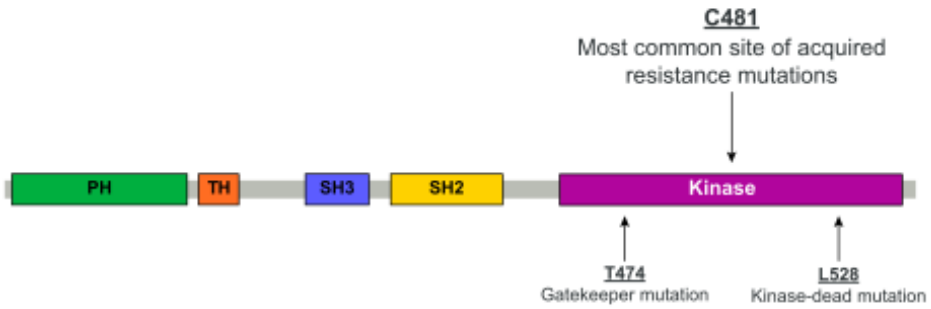
PROTAC: PROteolysis TArgeting Chimera

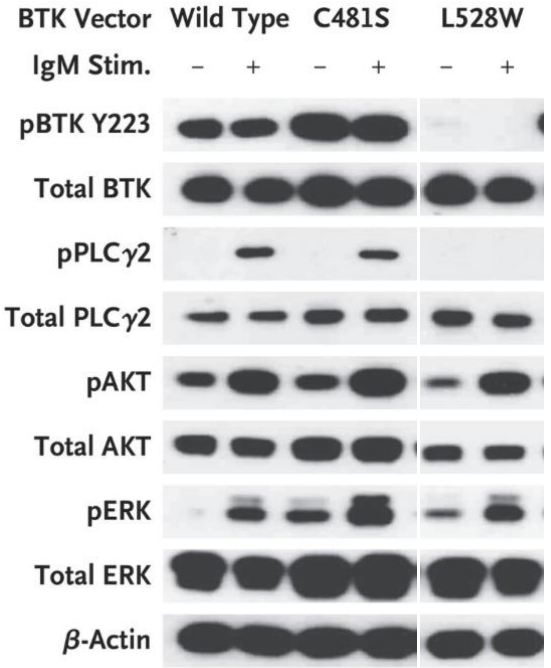
BTK degraders

In CLL and lymphoma, PROTACs targeting ALK, BRD4/BET, BCL2, and BCL2-XL are under pre-clinical development, whereas BTK degraders are the most advanced and have reached clinical development.

Agent	Target	Company	Phase
Bexobrutideg/NX-5948	BTK	Nurix Therapeutics	Phase 1 → Phase 2 and 3
NX-2127	BTK + IKFZ1/3	Nurix Therapeutics	Phase 1
BGB-16673	BTK	BeiGene	Phase 1/2 → Phase 3
AC676	BTK	Accutar Biotech	Phase 1
ABBV-101	BTK	AbbVie	Phase 1

Different types of BTK mutations

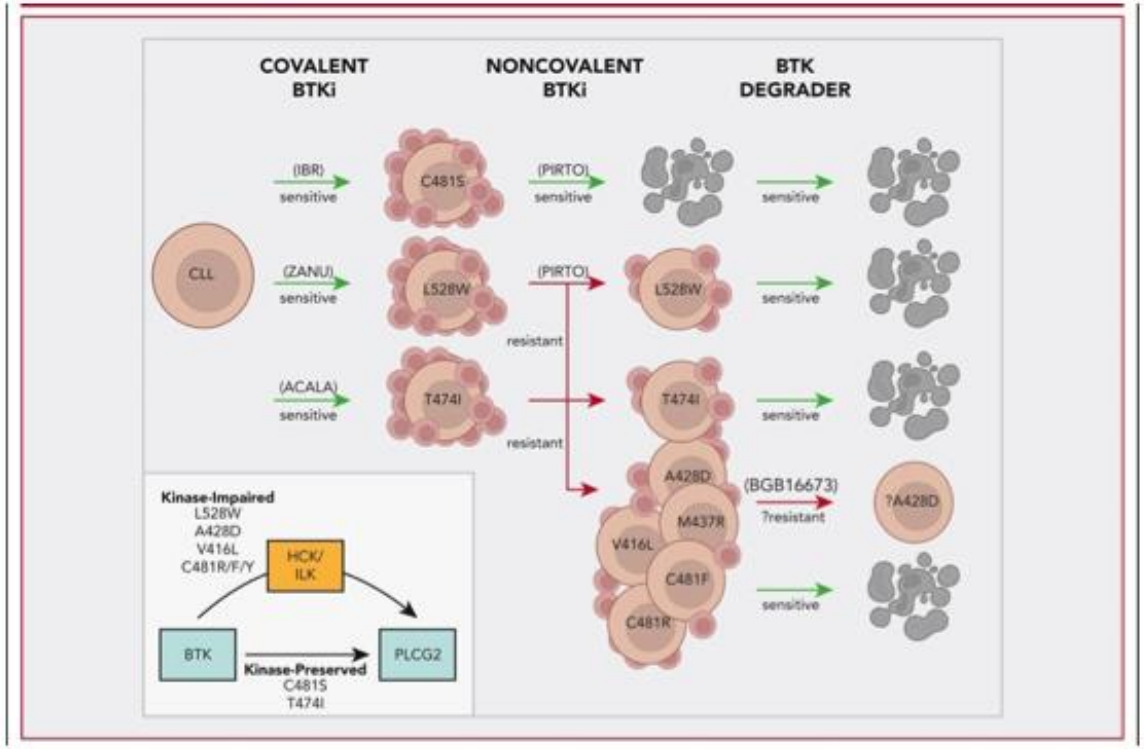




By degradation, instead of covalent/non-covalent inhibition, PROTACS do impair not only the kinase activity of target molecules (i.e. BTK), but also compensatory feedback activation or scaffolding function

Wang *et al., NEJM*. 2022

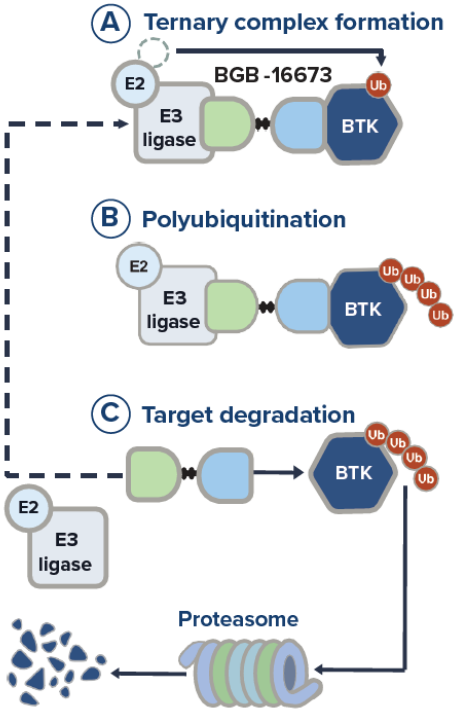
Degraders activity beyond BTK mutations



Tam *et al., Blood*. 2025

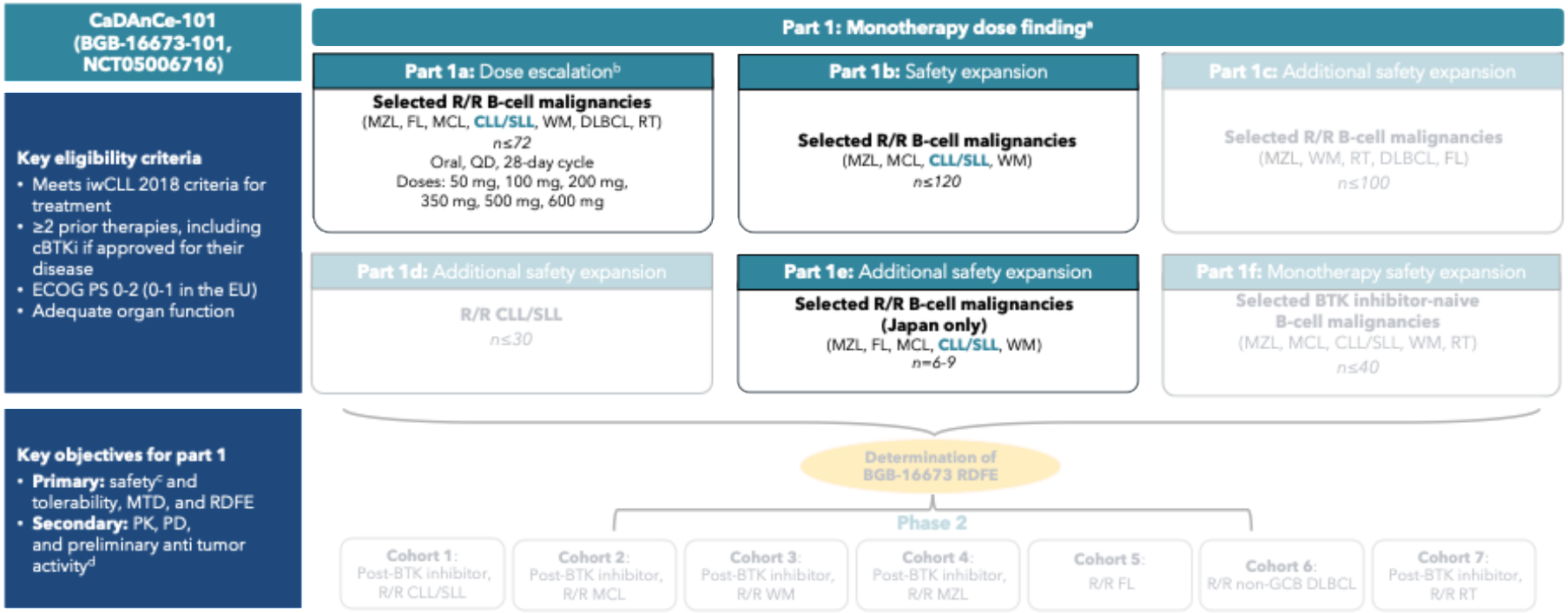
The BGB-16673 BTK degrader

- BGB-16673 is a highly selective, orally available BTK protein degrader that:
  - Blocks BCR signaling by mediating BTK degradation through the proteasome pathway
  - Disrupts both the catalytic activity of BTK and its protein scaffolding functions
  - Does not require sustained target binding; a single BGB-16673 molecule can degrade multiple BTK proteins
  - Shows CNS penetration in preclinical models



Ahn et al., ASH 2025

CaDAnCe-101 trial



Ahn et al., ASH 2025

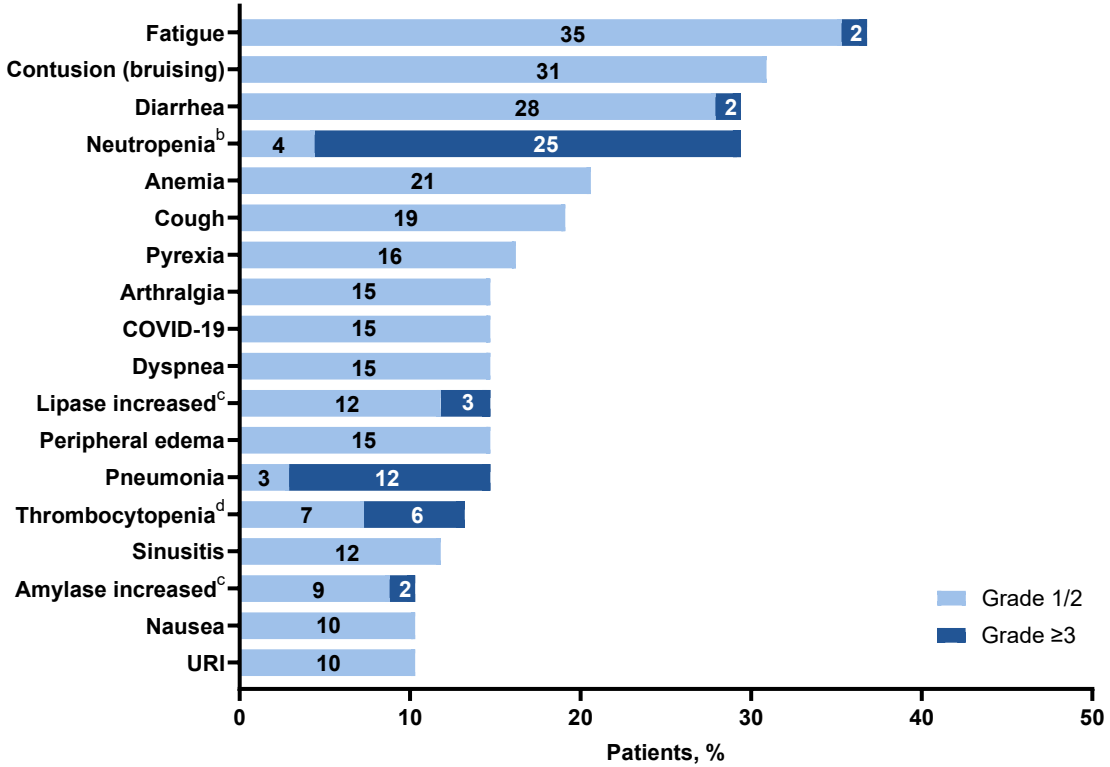
Patient characteristics

	Total (N=68)
Age, median (range), years	70 (47-91)
Male, n (%)	47 (69.1)
ECOG PS, n (%)	
0	38 (55.9)
1	29 (42.6)
2	1 (1.5)
CLL/SLL risk characteristics at study entry, n/N with known status (%)	
Binet stage C	29/64 (45.3)
Unmutated IGHV	38/49 (77.6)
del(17p) and/or *TP53* mutation	46/68 (67.6)
Complex karyotype (≥3 abnormalities)	22/44 (50.0)

	Total (N=68)
Mutation status, n/N (%)	
BTK mutation present	26/66 (39.4)
PLCG2 mutation present	10/66 (15.2)
BTK and *PLCG2* mutation present	5/66 (7.6)
No. of prior lines of therapy, median (range)	4 (2-10)
Prior therapy, n (%)	
Chemotherapy	49 (72.1)
cBTK inhibitor	64 (94.1)
ncBTK inhibitor	14 (20.6)
BCL2 inhibitor	56 (82.4)
cBTK + BCL2 inhibitors	44 (64.7)
cBTK + ncBTK + BCL2 inhibitors	12 (17.6)
Discontinued prior BTK inhibitor due to PD, n/N (%)[a]	57/64 (89.1)

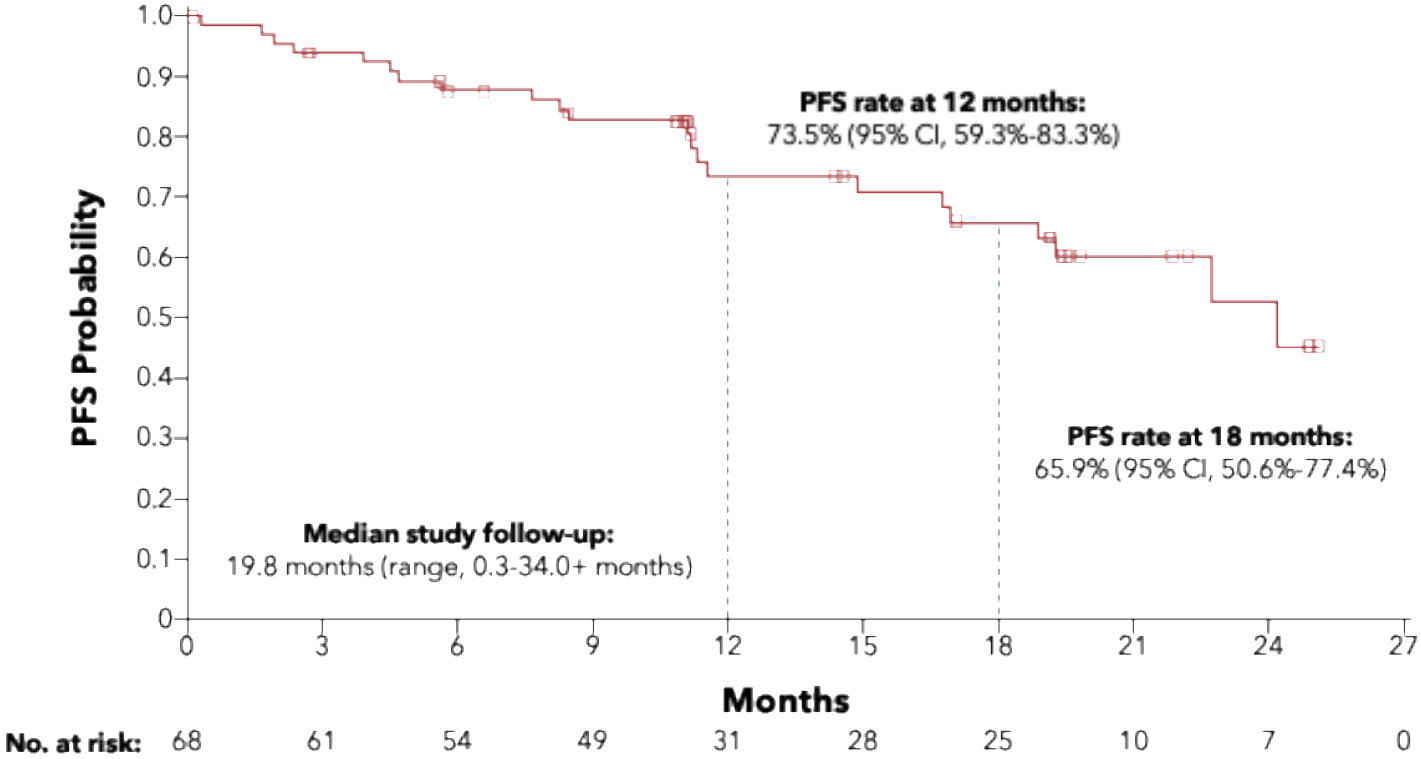
Ahn et al., ASH 2025

Safety profile of BGB-16673



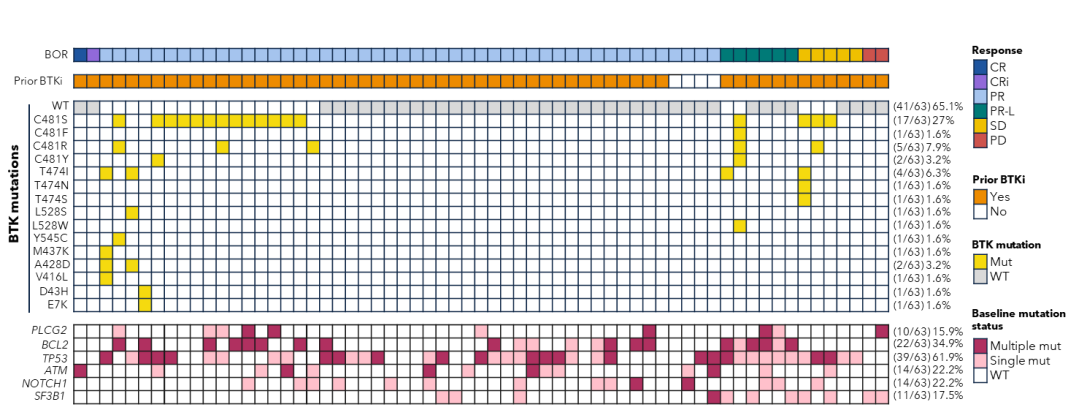
Ahn et al., ASH 2025

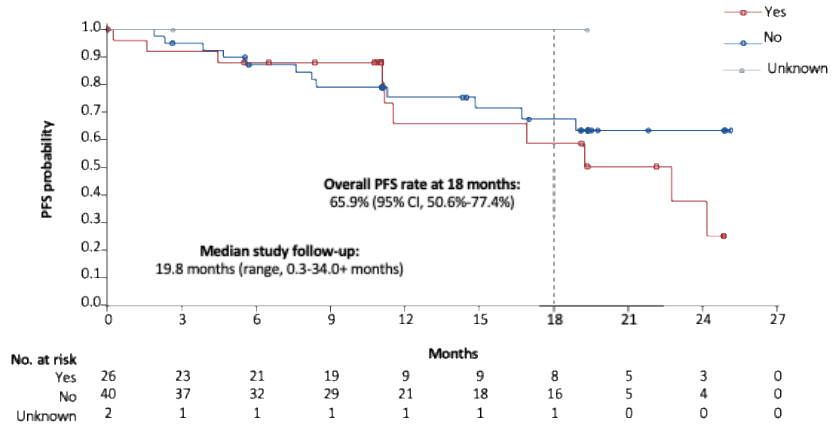
PFS estimates of BGB-16673



Ahn et al., ASH 2025

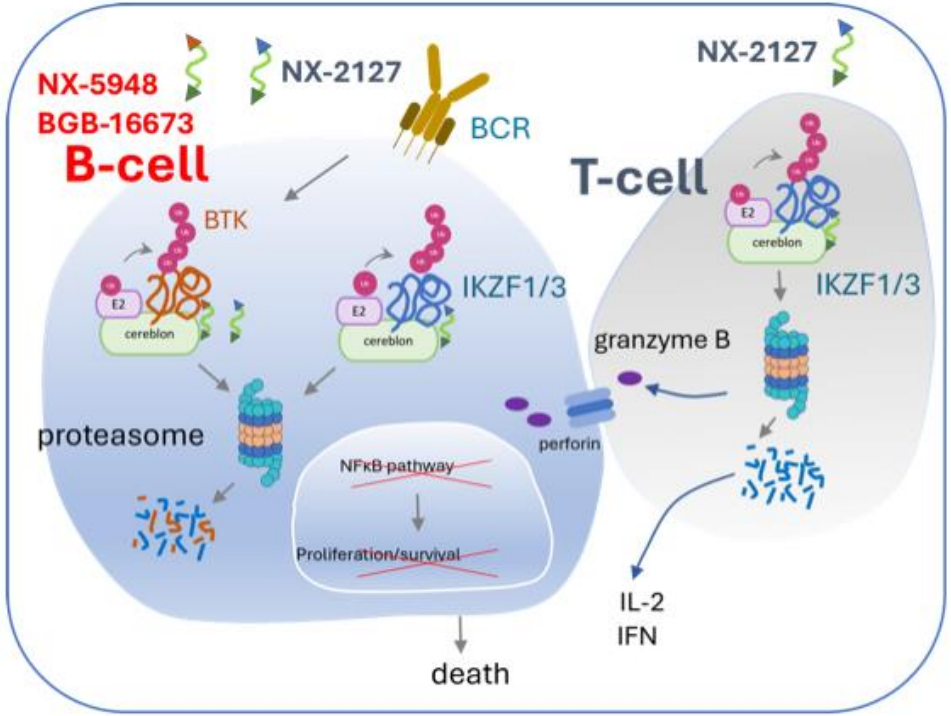
Responses occurred regardless of specific mutations



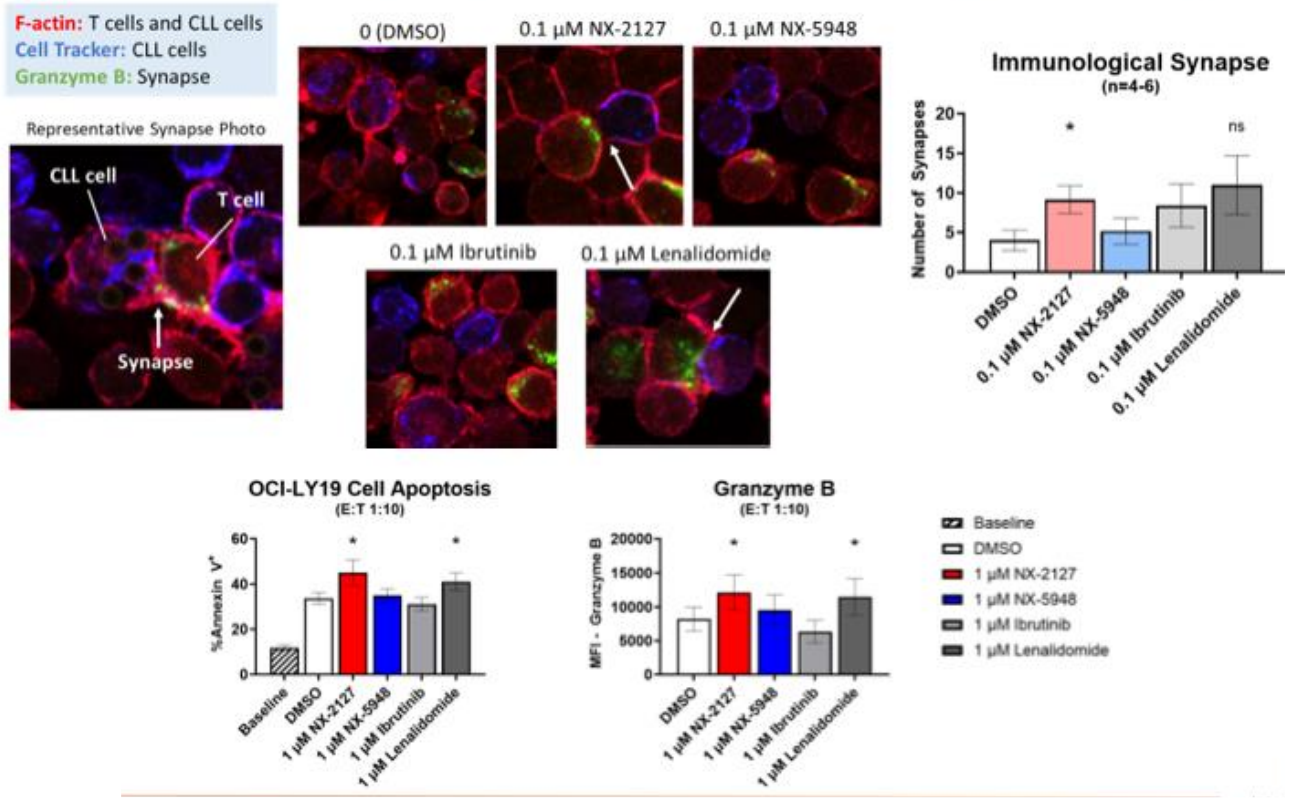


Ahn et al., ASH 2025

NX-5948 (bexobrutideg) and NX-2127 BTK degraders



NX-2127 promotes synapse formation and cytotoxicity



Huynh *et al.*, *ASH*. 2024

NX-5948(bexobrutideg)-301 trial

Baseline Disease Characteristics in Phase 1a/b and 1a

Multiple prior lines of therapy and a high prevalence of baseline mutations

Characteristics	Phase 1a/b – all patients (n=126)	Phase 1a (n=48)
ECOG PS, n (%)		
0	45 (35.7)	19 (39.6)
1	81 (64.3)	29 (60.4)
CNS involvement, n (%)	5 (4.0)	5 (10.4)
Median prior lines of therapy, n (range)	3.0 (1–17)	4.0 (2–12)
Previous treatments,[a] n (%)		
BTKi	108 (85.7)	47 (97.9)
cBTKi	106 (84.1)	47 (97.9)
ncBTKi	34 (27.0)	13 (27.1)
BCL2i	78 (61.9)	40 (83.3)
BTKi and BCL2i	75 (59.5)	39 (81.3)
CAR-T therapy	9 (7.1)	3 (6.3)
Bispecific antibody	5 (4.0)	1 (2.1)
PI3Ki	26 (20.6)	14 (29.2)
Chemo/chemo-immunotherapies	84 (66.7)	35 (72.9)
Mutation status,[b] n (%)	(n=111)	(n=47)
BTK	44 (39.6)	18 (38.3)
TP53	44 (39.6)	21 (44.7)
PLCG2	9 (8.1)	7 (14.9)
BCL2	8 (7.2)	6 (12.8)

[a]*Patients could have received multiple prior treatments;* [b]*Mutations presented here were centrally sequenced*

Data cutoff: 19 Sep 2025

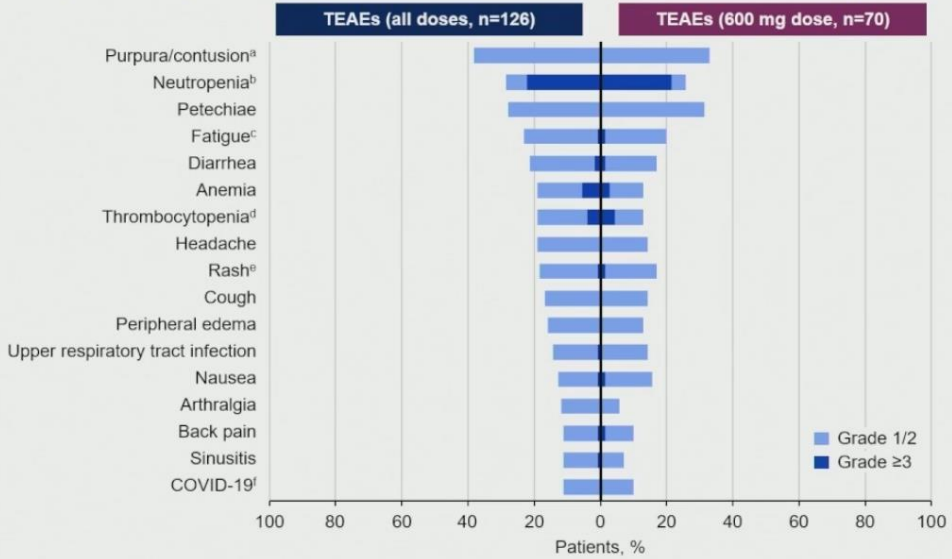
***BCL2**, B-cell lymphoma 2; **BCL2i**, BCL2 inhibitor; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CAR-T**, chimeric antigen receptor T cell; **CNS**, central nervous system; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ncBTKi**, non-covalent BTKi; **PI3Ki**, phosphoinositide 3-kinase inhibitor; **PLCG2**, phospholipase C gamma 2*

Omer *et al.*, *ASH*. 2025

Safety profile of Bexobrutideg

TEAEs in ≥10% in Phase 1a/b 600 mg Group vs All Patients

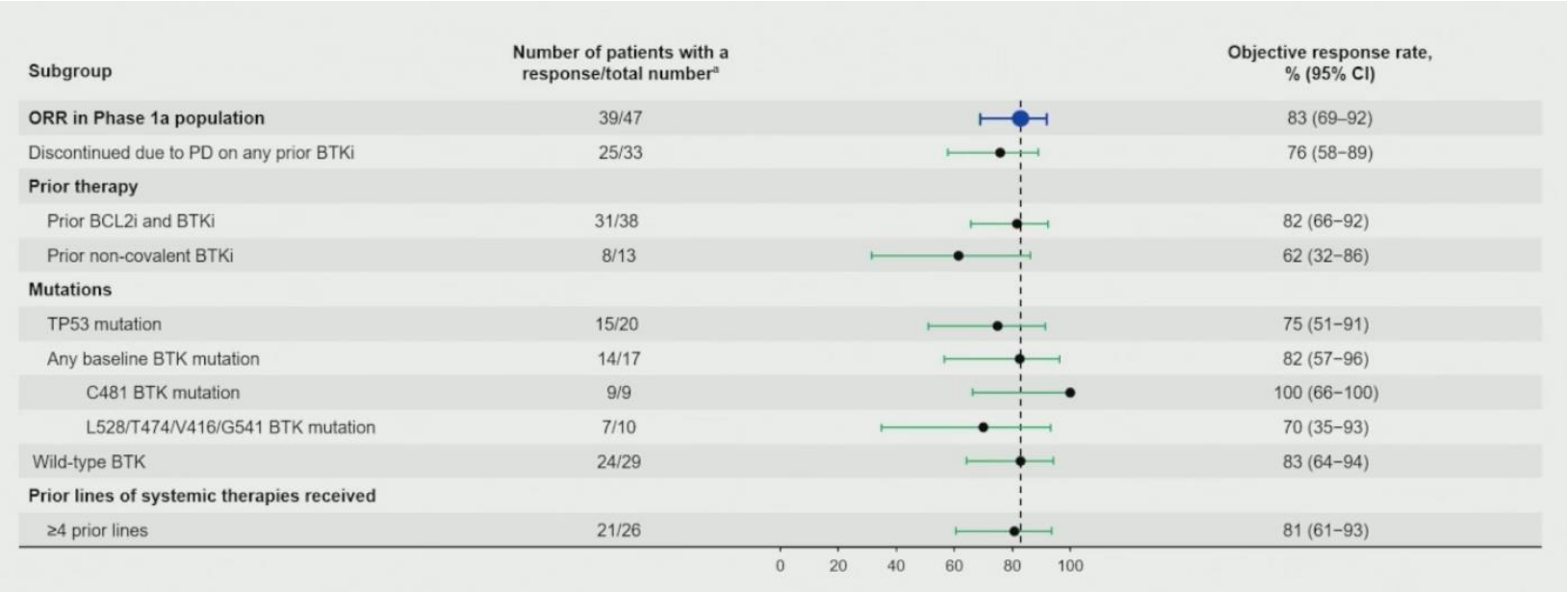
Comparable AE profile for patients at the RP2D 600mg dose and overall population



- Tolerable safety profile consistent with prior disclosures
- No dose-limiting toxicities
- No systemic fungal infections or Grade 4 infections of any kind reported
- Single event of new onset atrial fibrillation consistent with the rate in the age-matched general population
- 3 Grade 5 AEs (death not otherwise specified; pulmonary embolism; pneumonia; all deemed not related to bexobrutideg)

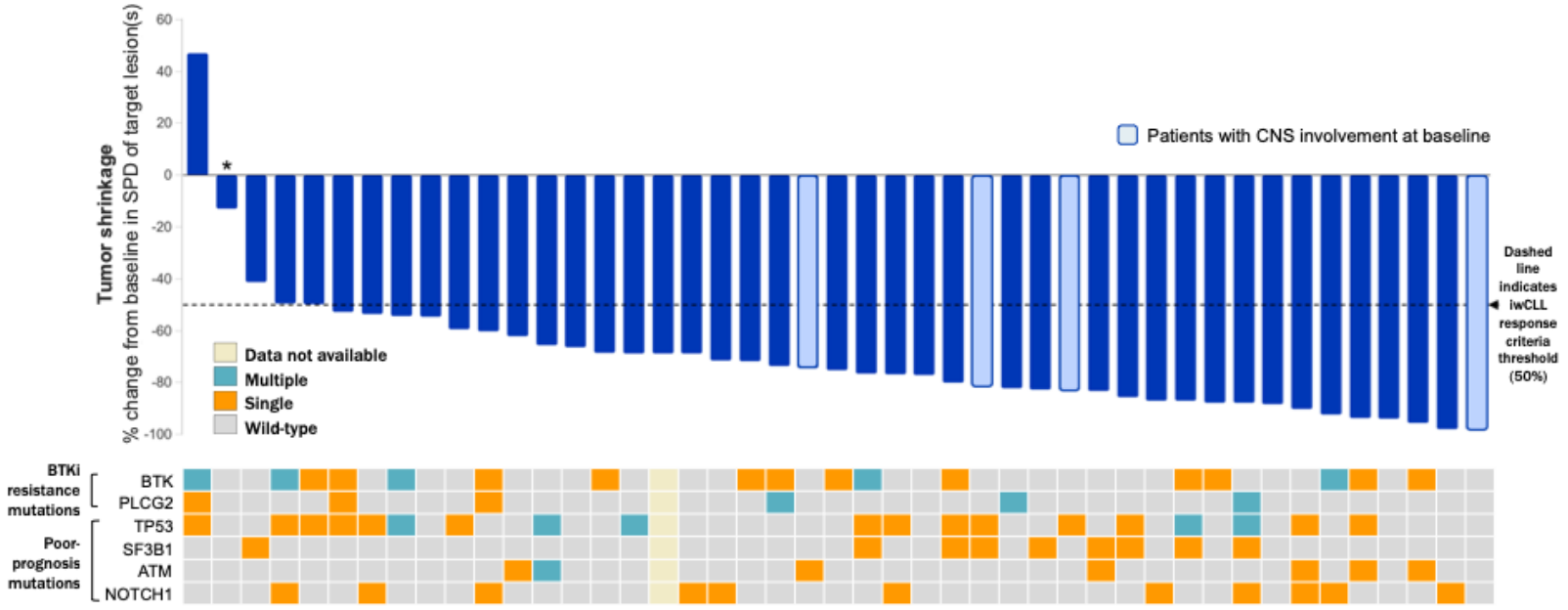
Omer *et al.*, *ASH*. 2025

Responses observed across different subgroups



Omer *et al.*, *ASH*. 2025

Bexobrutideg activity regardless of mutations



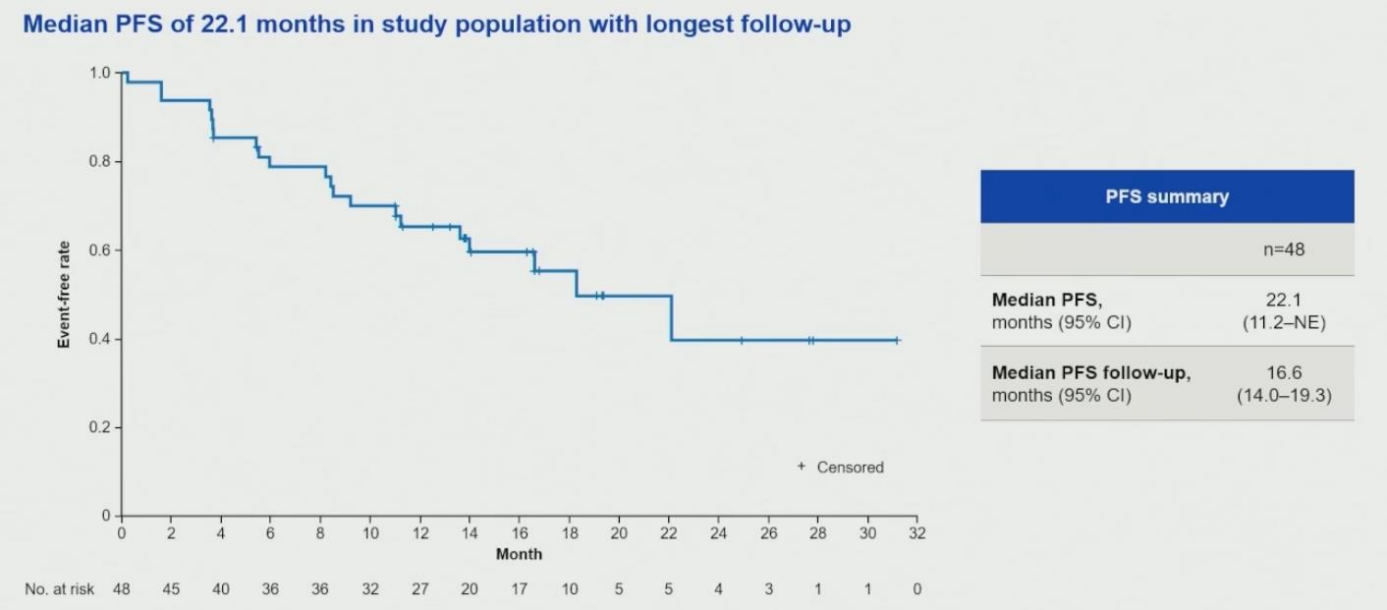
*Patient with Richter's transformation to Hodgkin's on biopsy

Note: patients without identified target lesion(s) at baseline are evaluated as disease-evaluable per iwCLL criteria, although they may not be represented in the waterfall plot

ATM, Ataxia-telangiectasia mutated; **BTK**, Bruton's tyrosine kinase; **BTKi**, BTK inhibitor; **CLL**, chronic lymphocytic leukemia; **CNS**, central nervous system; **iwCLL**, International Workshop on CLL; **NOTCH1**, neurologic locus notch homolog protein 1; **PLCG2**, phospholipase C gamma 2; **SPD**, sum of products diameters

Danilov *et al., ICML*. 2025

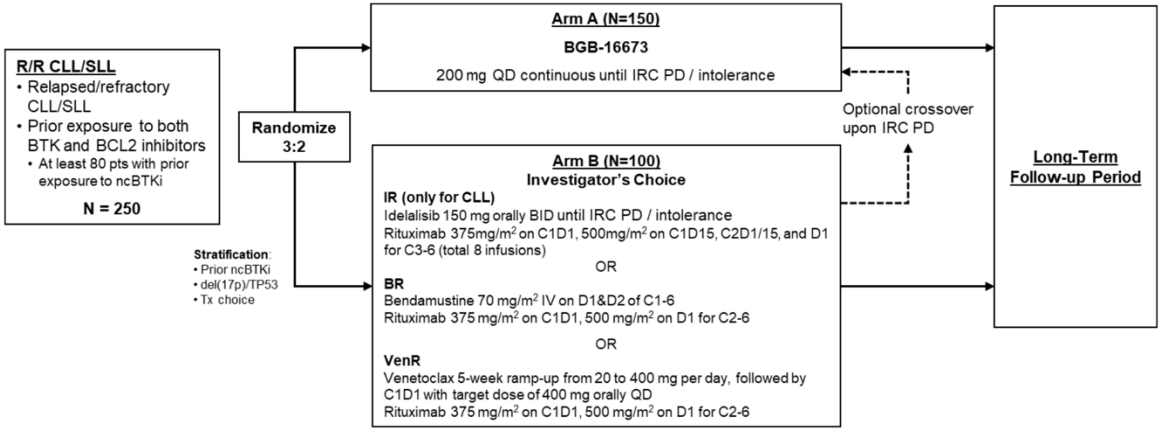
PFS estimates of Bexobrutideg



PFS summary	
	n=48
Median PFS, months (95% CI)	22.1 (11.2–NE)
Median PFS follow-up, months (95% CI)	16.6 (14.0–19.3)

Omer *et al.*, *ASH*. 2025

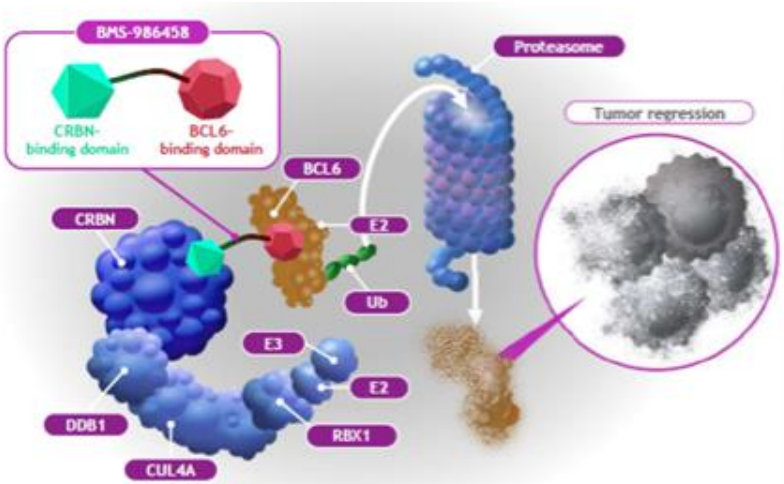
BGB-16673-302 trial active in Novara



1st patient: 8th line, PLT 60.000/ul, Spleen 26cm → after 1-year normal complete blood count, spleen 17cm

2nd patient: 11th line, bulky lymph nodes (10cm axillary) → 2-3cm after 1-month

BMS-986458 – a first-in-class oral selective BCL6 degrader



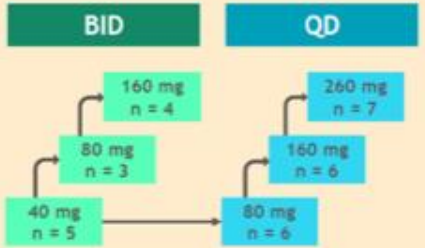
BCL6 degradation

- Tumor B-cell anti-proliferation/apoptosis
- Immune modulation in the TME

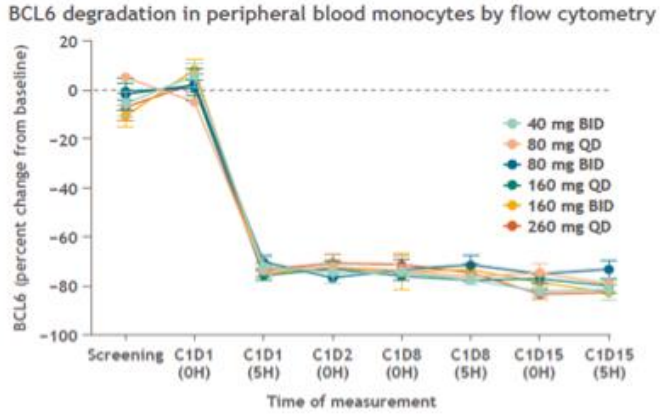
Key inclusion criteria

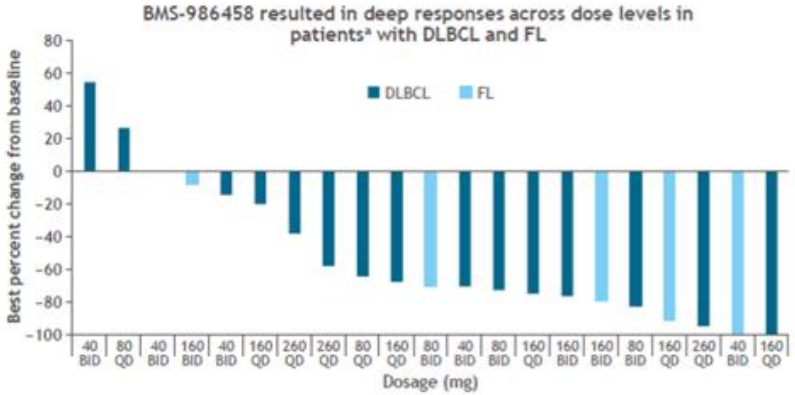
- Patients with R/R DLBCL with ≥ 2 prior regimens
  - Patients who exhausted or were ineligible for available therapy (including CAR T cell therapy and bispecific monoclonal antibodies) or were unwilling to receive them
- Patients with R/R FL (including FL 3B) with ≥ 2 prior regimens
- Measurable disease, as defined by the Lugano classification of NHL[2]

Single agent escalation (N = 31)



BMS-986458 induces BCL6 degradation and antitumor activity in Relapsed/Refractory DLBCL and FL after median 4 prior LOT





ORR 81%
CR 23.8%

Morschhauser et al., *ICML.* 2025

Potential mechanisms of resistance to degraders

Related to target (Protein of interest)	Related to E3 ligase	Activation of alternative pro-survival pathways
Target mutations BTK^{A428D} (Wong RL et al, 2024)	Mutations in CRBN	C-MYC TRAF2
Target downregulation	Downregulation of CRBN/promoter methylation	CDK6

Conclusions

- Degraders represent a novel approach for targeting oncogenic proteins
- BTK degraders are the most advanced compounds and have demonstrated in early-stage clinical trials meaningful efficacy with a manageable safety profile
- BTK degraders with IMID function also exhibit T-cell immunomodulatory effects in preclinical settings
- Degraders targeting other proteins are currently under development
- Mechanisms of resistance remain hypothetical and are currently under investigation

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