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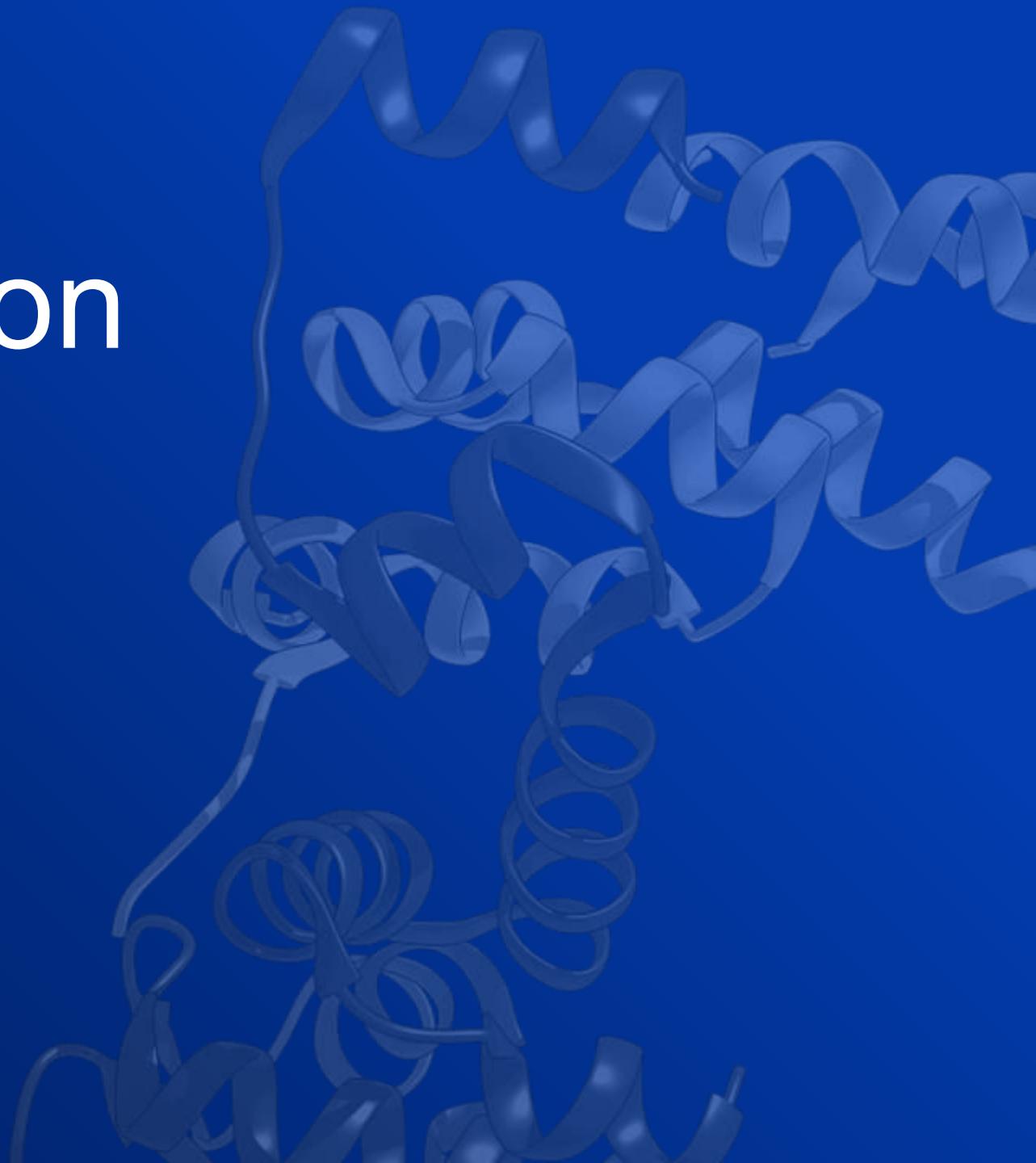
Clinical Update on Bexobrutideg: The First ‘-Deg



Gwenn Hansen, Ph.D.

8th Annual TPD & Induced Proximity Summit
October 28, 2025
Boston, MA

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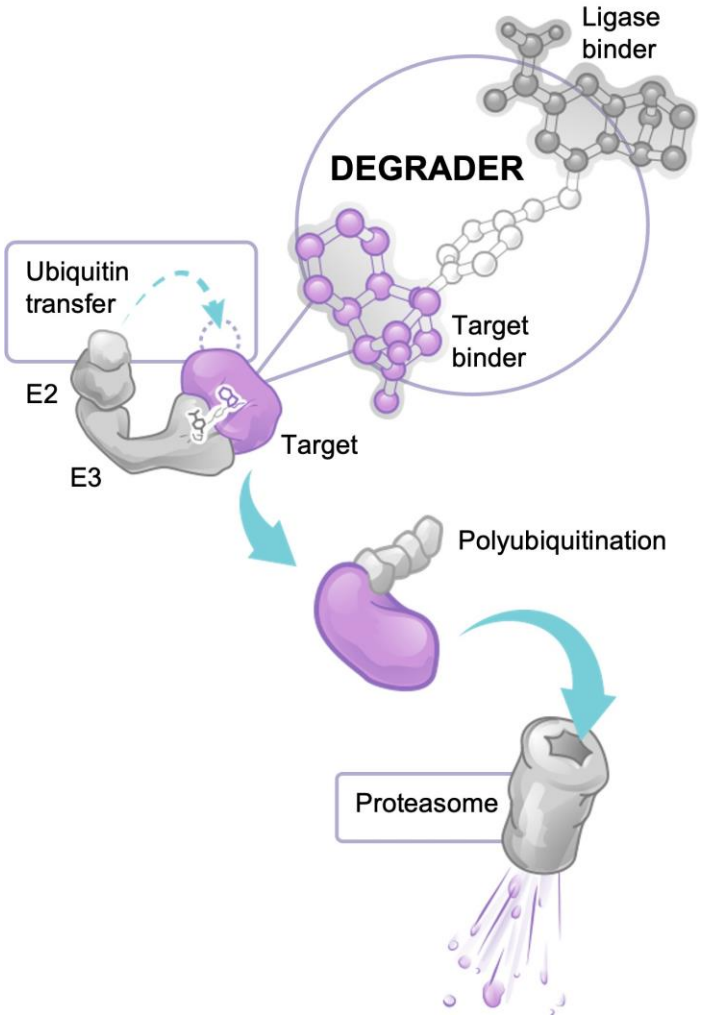
Establishing Degrader-Based Medicines at the Forefront of Patient Care

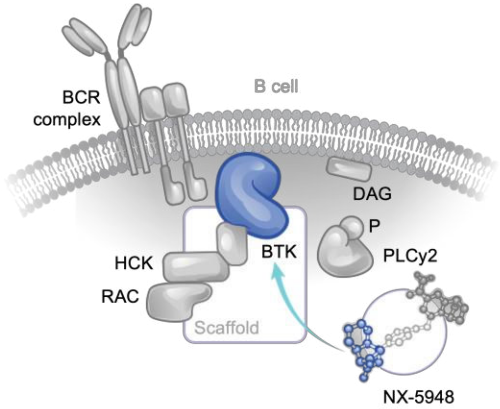
- Degraders act as molecular matchmakers, bringing together two key players:
  - An E3 ligase (a key part of a cell's protein degradation machinery)
  - A disease-causing target protein
- This process, called induced proximity, enables the E3 ligase to tag the target protein with ubiquitin to mark it for disposal by the proteasome – the cell's protein recycling center
- Given their ability to eliminate target proteins, degraders can achieve effects similar to genetic therapies that silence disease-causing genes



Degrader Therapies Are Not Just Relevant for ‘Undruggable’ Targets

Meeting the needs of patients with breakthrough therapies

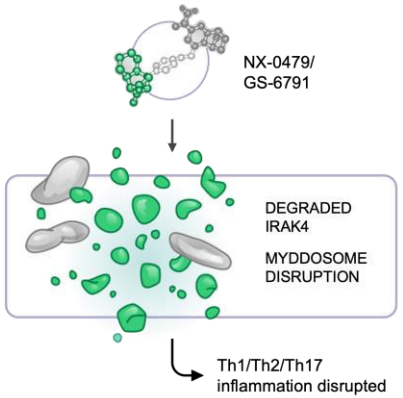
Clinically validated targets where inhibitors fail to address resistance and scaffolding



Kinase targets in cancer

BTK – B-cell malignancies and I&I

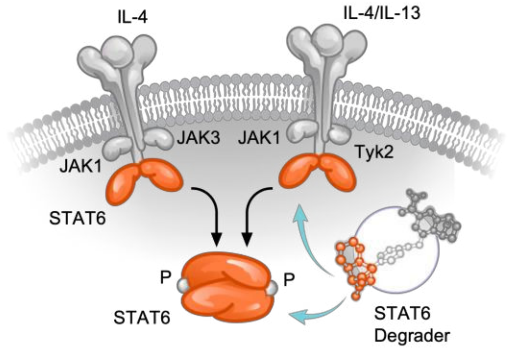
Unmet medical need where inhibitors are not sufficient to drive efficacy



Signaling proteins with scaffolding function

IRAK4 – Chronic Inflammation

"Undruggable" targets



Transcriptions factors; fusion proteins; E3 ligases

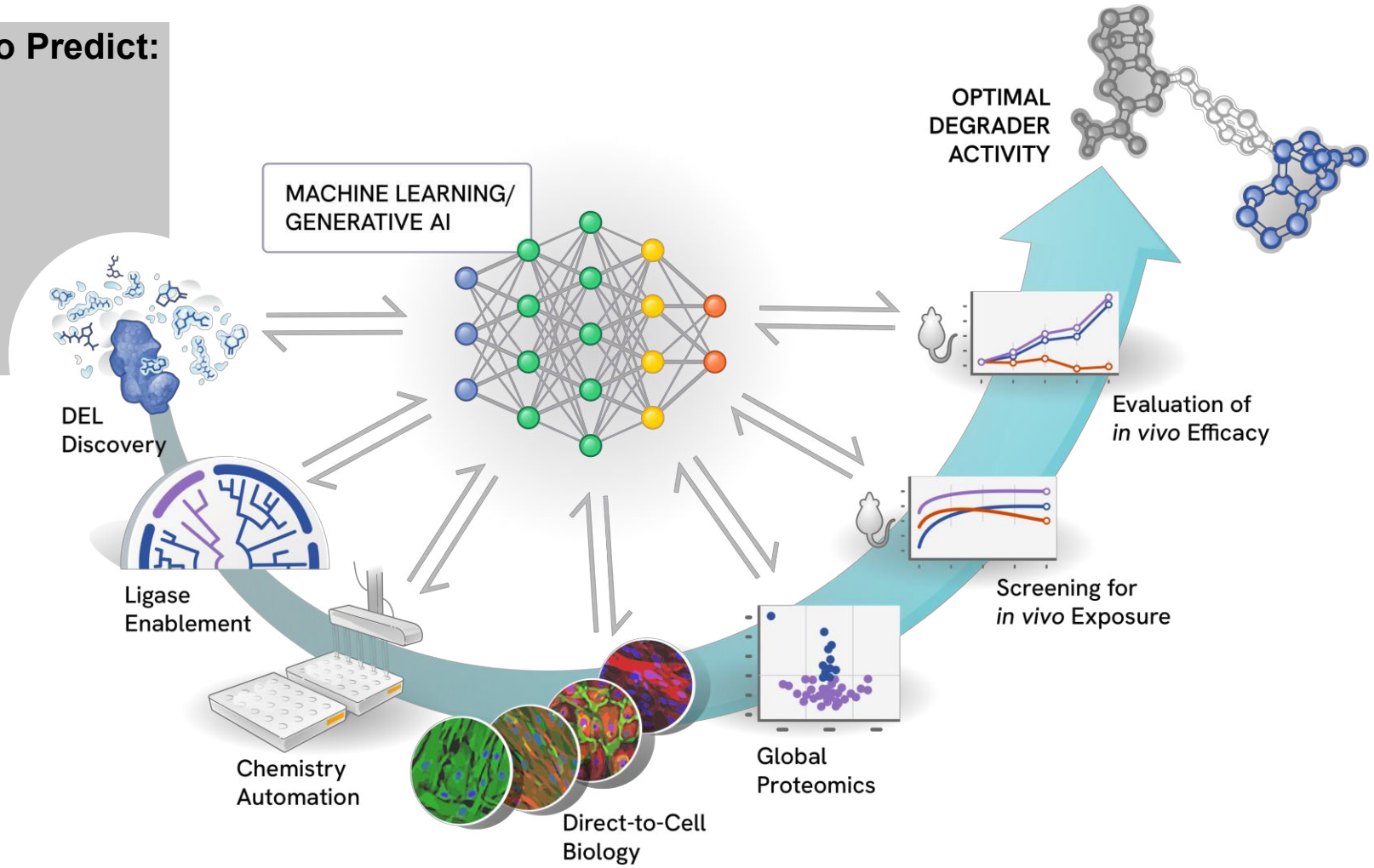
STAT6 – T2 inflammatory diseases

***BTK**, Bruton’s tyrosine kinase; **I&I**, inflammation and immunology; **IRAK4**, interleukin-1 receptor-associated kinase 4; **STAT6**, signal transducer and activator of transcription 6*

Writing the Rule Book of Degrader Design By Combining Empiricism With Machine Learning

Degrader Properties Are Difficult to Predict:

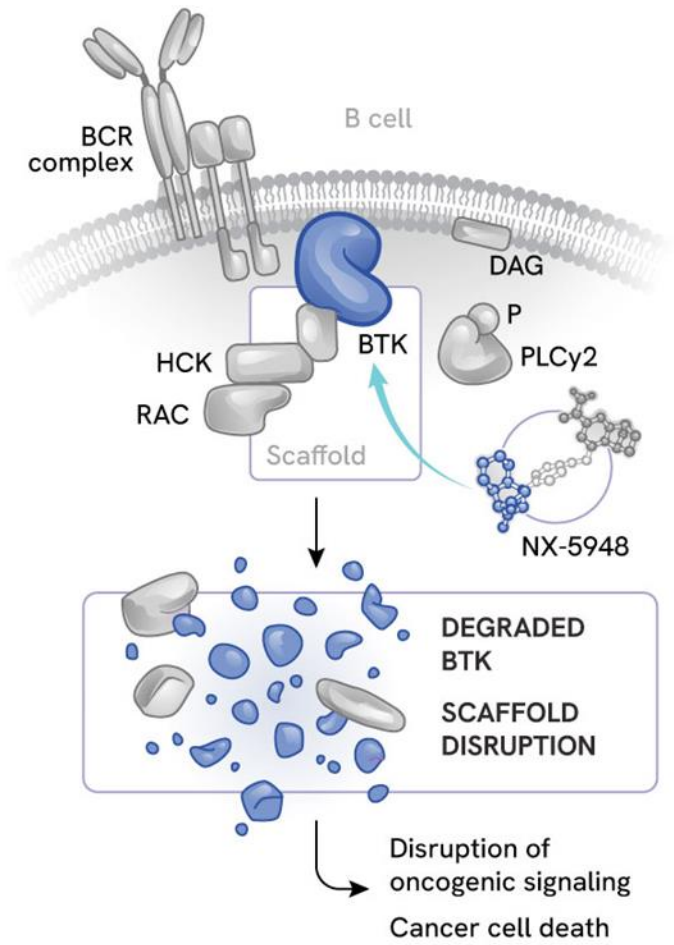
- Solubility
- Permeability
- Selectivity
- Exposure
- Oral Bioavailability
- CNS Penetration



TPD, targeted protein degradation; **DAC**, degrader antibody conjugate; **DEL**, DNA encoded library

Bexobrutideg – The First “deg” with a Potential Best-in-Class Profile

Novel MOA Against a Clinically and Commercially Proven Target



- ✓ Active against wildtype BTK and demonstrated ability to overcome treatment-emergent resistance mutations
- ✓ Addresses BTK scaffolding function unlike current BTK inhibitors
- ✓ Acts catalytically driving degradation at low free-plasma concentrations
- ✓ Crosses the blood brain barrier and demonstrated clinical activity in the CNS
- ✓ Demonstrated robust clinical activity in difficult to treat B-cell malignancies
- ✓ Wide therapeutic index drug with no evidence of QTc prolongation

***BTK**, Bruton's tyrosine kinase; **CNS**, central nervous system; **MOA**, mechanism of action.*

Bexobrutideg 600 mg Once Daily Oral Dose Cleared by Global Regulators for Pivotal Monotherapy Trials in Relapsed/Refractory CLL

- **Highest dose tested in Phase 1 cleared by global regulators for pivotal monotherapy studies in r/r CLL**
  - U.S. Food and Drug Administration (FDA), in accordance with Project Optimus
  - U.K Medicines and Healthcare products Regulatory Authority (MHRA)
  - European Medicines Agency (EMA)
- **Global designations in CLL support regulatory interactions**
  - Fast Track Designation with FDA
  - PRIME designation with EMA
- **Pivotal Phase 2 trial underway**
  - First site activated in October 2025
- **Confirmatory Phase 3 trial initiation planned for H1 2026**
  - Key study start up activities underway

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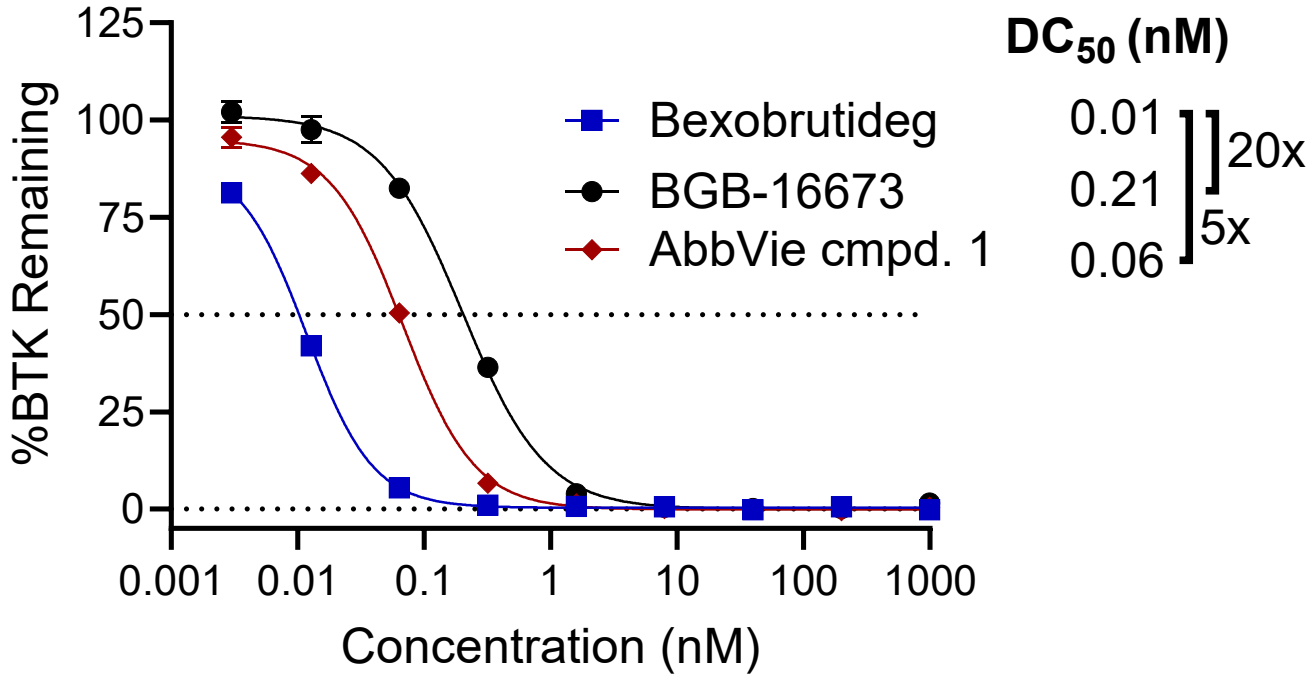
Bexobrutideg Displays Best-in-Class BTK Degradation Potency

BTK Degradation in Human B Cells



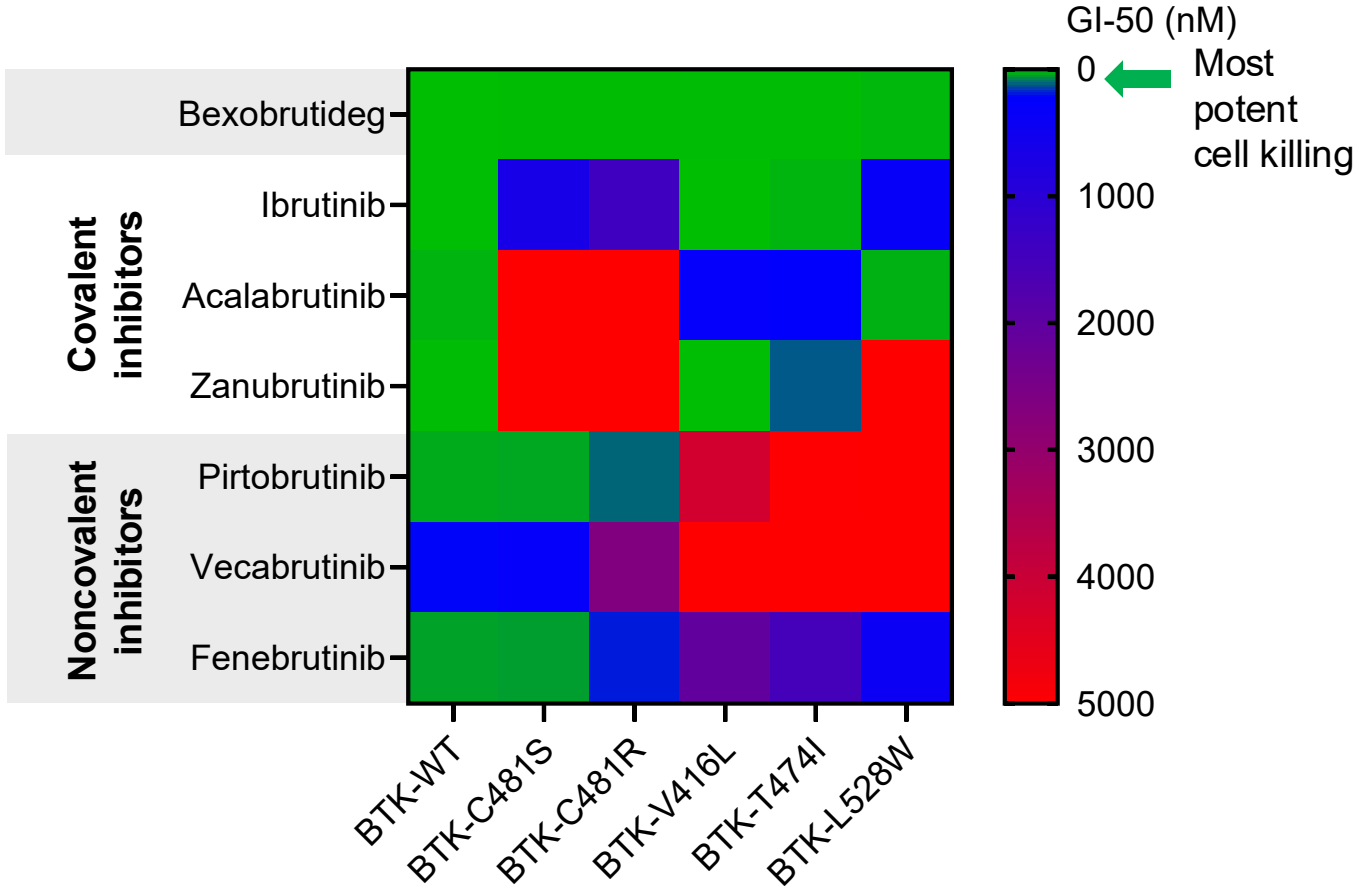
Bexobrutideg is **20x** more potent than BGB-16673 and **5x** more potent than AbbVie cmpd. 1

Degradation assessed at 24 hours by flow cytometry in human peripheral blood mononuclear cells, gated on CD20+ B cells
AbbVie cmpd. 1 is example 1 from WO 2023/183811 A1

Bexobrutideg Degrades Wild-Type and Mutated BTK with Superior Coverage Compared to All BTK Inhibitors

- All inhibitors have resistance mutation liabilities
- Bexobrutideg displays potent cell killing in the context of key resistance mutations
- We have shown that BTK degradation translates into clinical responses across key mutation classes

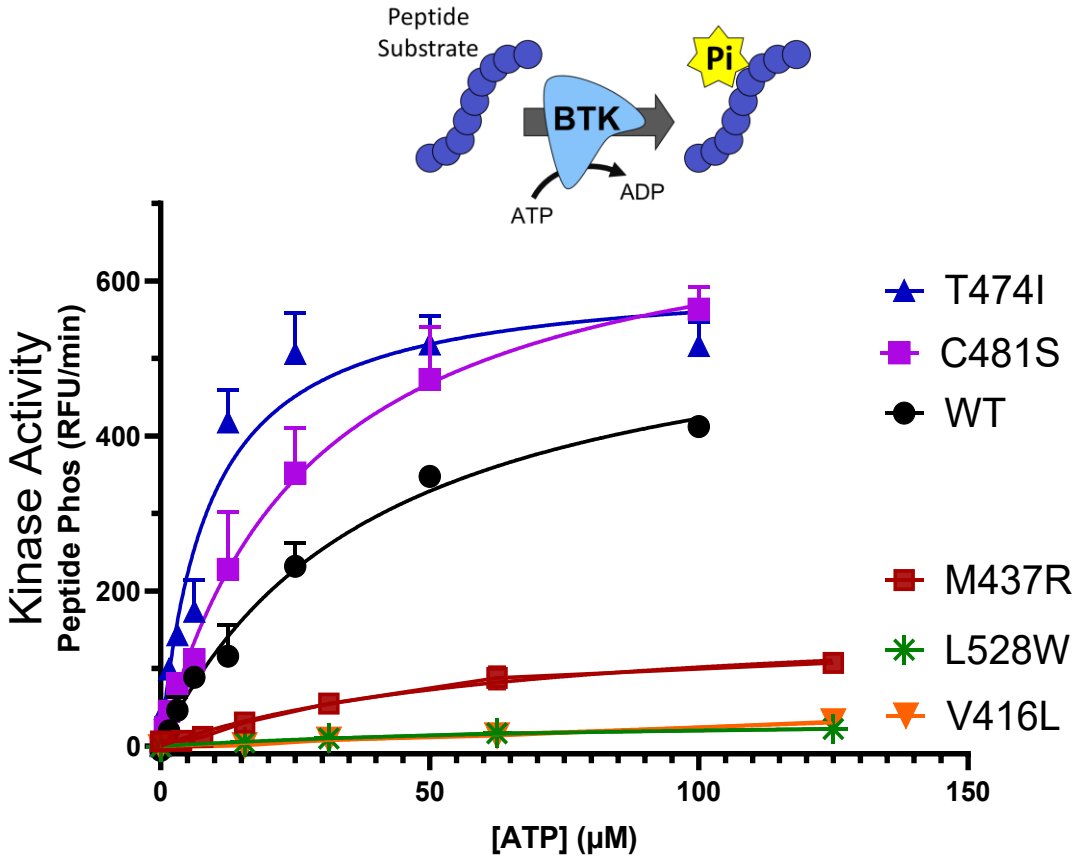
Bexobrutideg shows superior mutational coverage and cell killing compared to BTK inhibitors



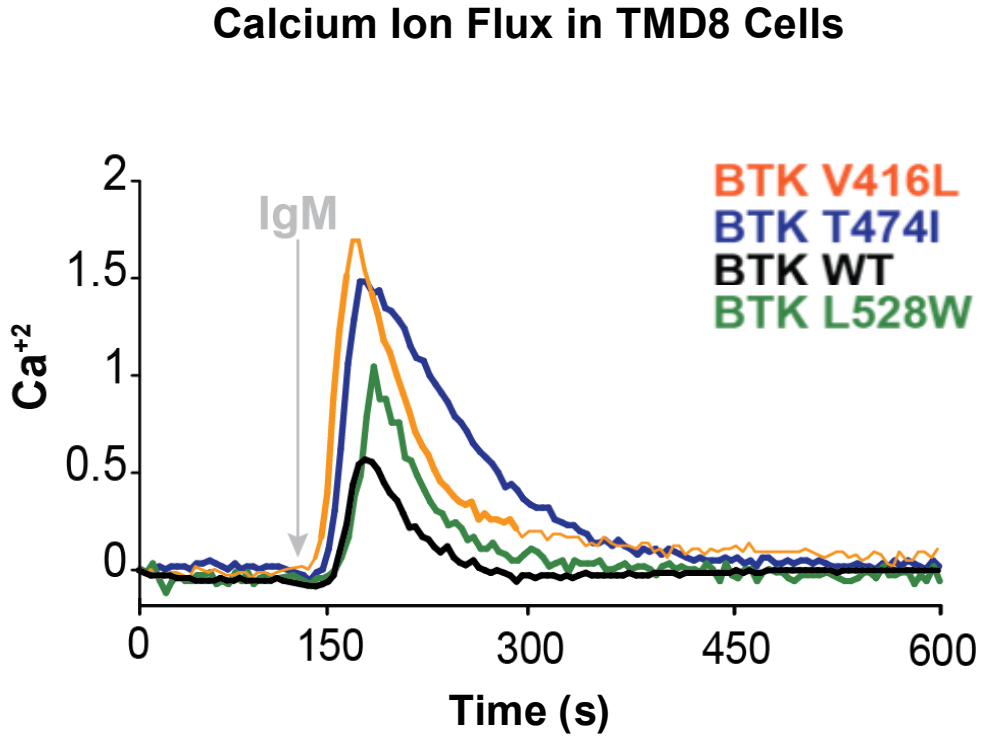
***BTK**, Bruton's tyrosine kinase; **GI-50** growth inhibition 50%; **WT** wildtype*

Clinically Emergent BTK Mutations Lack Kinase Activity Yet Propagate Signaling

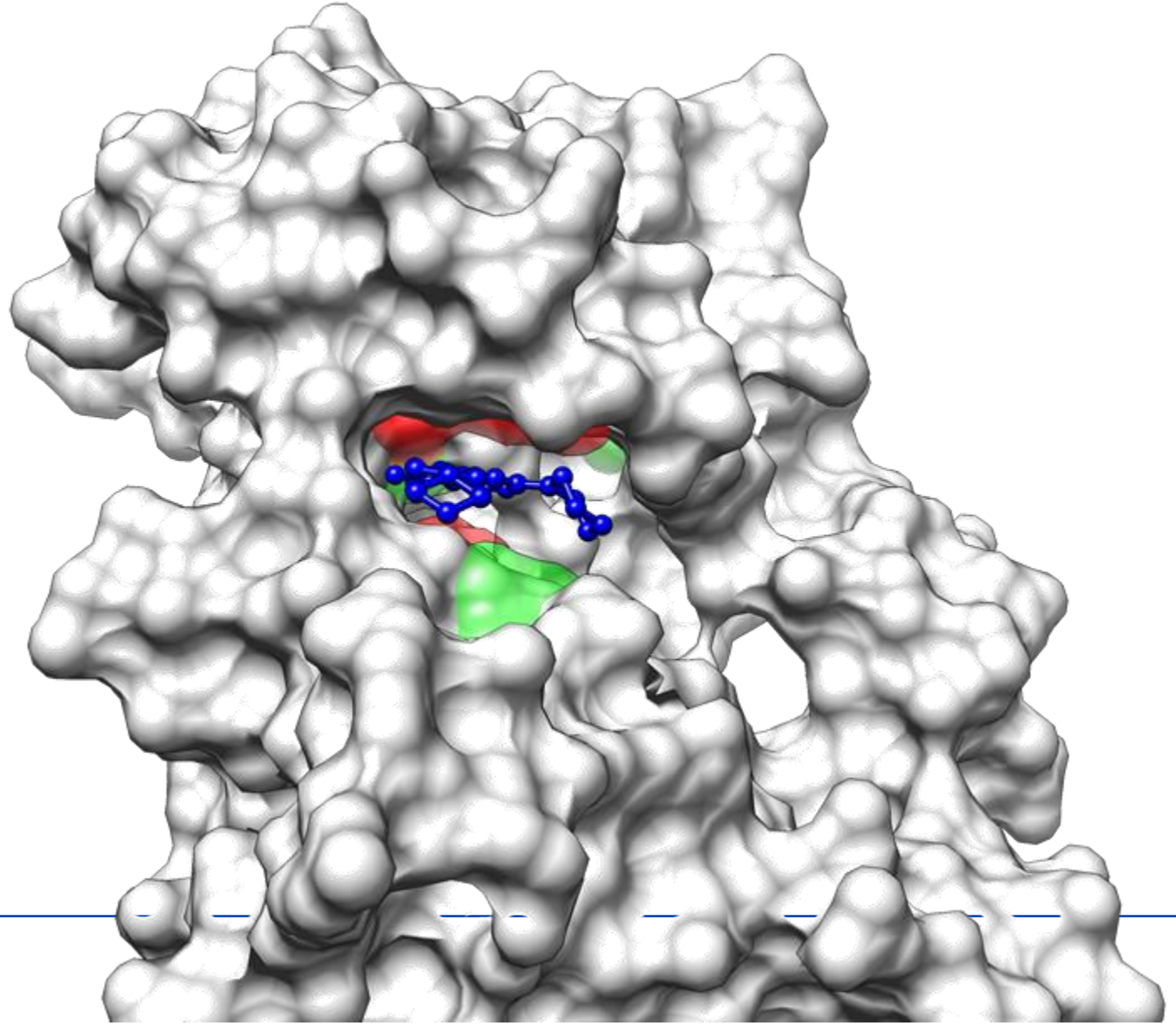
BTKi-resistant mutations V416L and L528W lack kinase activity



BTK kinase-dead mutations V416L and L528W propagate BCR signaling



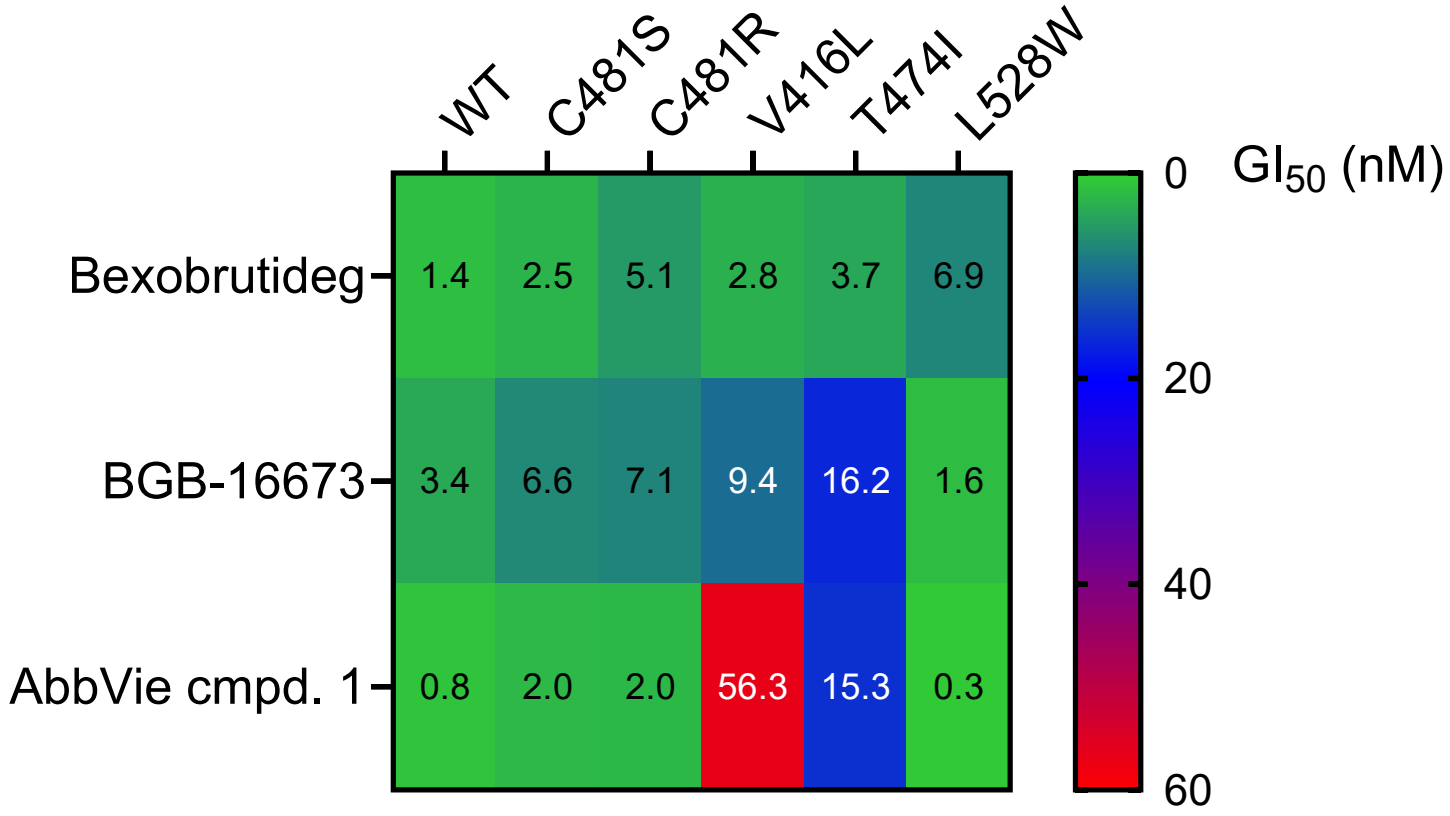
Bexobrutideg Binds in ATP Pocket Avoiding Interactions With Common Mutations



Bexobrutideg Displays the Most Potent Coverage Across BTK Mutations Compared to Other BTK Degraders

Bexobrutideg demonstrates GI_{50} values of <10 nM across relevant mutations, while BGB-16673 and AbbVie cmpd. 1 display potential liabilities

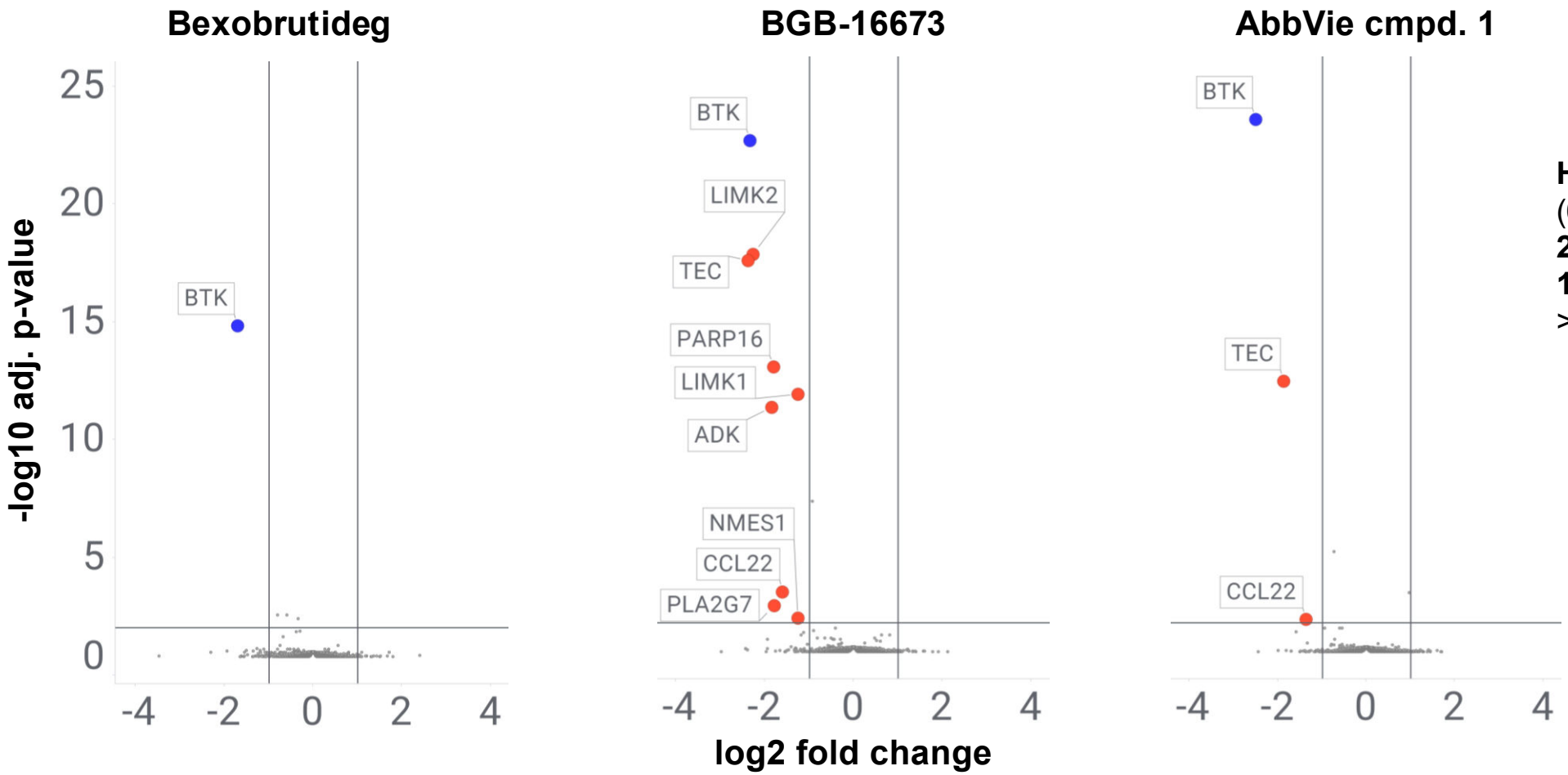
Cell Killing Activity Across Clinically Relevant Mutations



Viability assessed at 72 hours in TMD8 cells harboring CRISPR knock-ins of each BTK mutant. AbbVie cmpd. 1 is example 1 from WO 2023/183811 A1

Bexobrutideg Is an Exquisitely Selective BTK Degrader

Global Proteomics in human PBMCs at clinically relevant exposures



Human PBMCs
(6 healthy donors)
24-hour treatment
10xDC90
>8700 proteins detected

AbbVie cmpd. 1 is example 1 from WO 2023/183811 A1

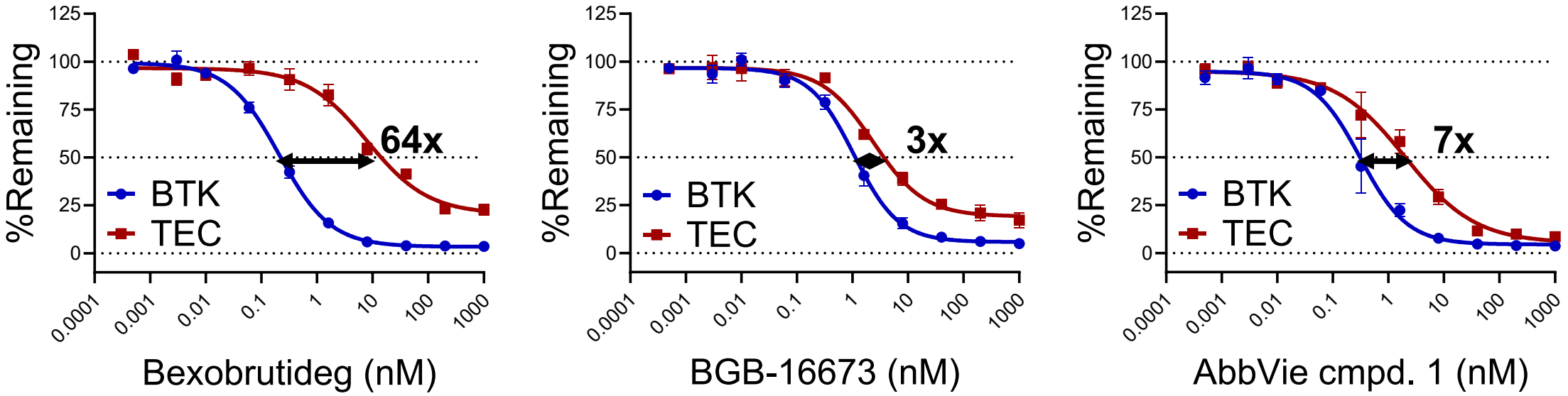
***PBMC**, peripheral blood mononuclear cell*

Bexobrutideg Has Best-In-Class Selectivity of BTK Over TEC

Selectivity of BTK over TEC is anticipated to provide safety advantage from lower cardiovascular side effects[a]

	Bexdeg	BGB-16673	AbbVie cmpd. 1[b]	Acala.	Zanu.	Ibrutinib
BTK/TEC Selectivity[c,d]	64x	3x	7x	25x	7x	7x

AbbVie and BeOne BTK degraders potently degrade TEC in K562 cells



a. Chen et al. 2024. Heart, Lung and Circulation 33: S481. *b. AbbVie cmpd. 1 is example 1 from WO 2023/183811 A1*
c. Degradation selectivity assessed in K562 cells at 24 hours; Mean ± SEM from n = 3 independent experiments is displayed
d. Inhibitor selectivity is the ratio of BTK and TEC IC_{50} values from O'Brien et al. 2021. Front Oncol 11: 720704.

Bexobrutideg Has Best-In-Class Selectivity

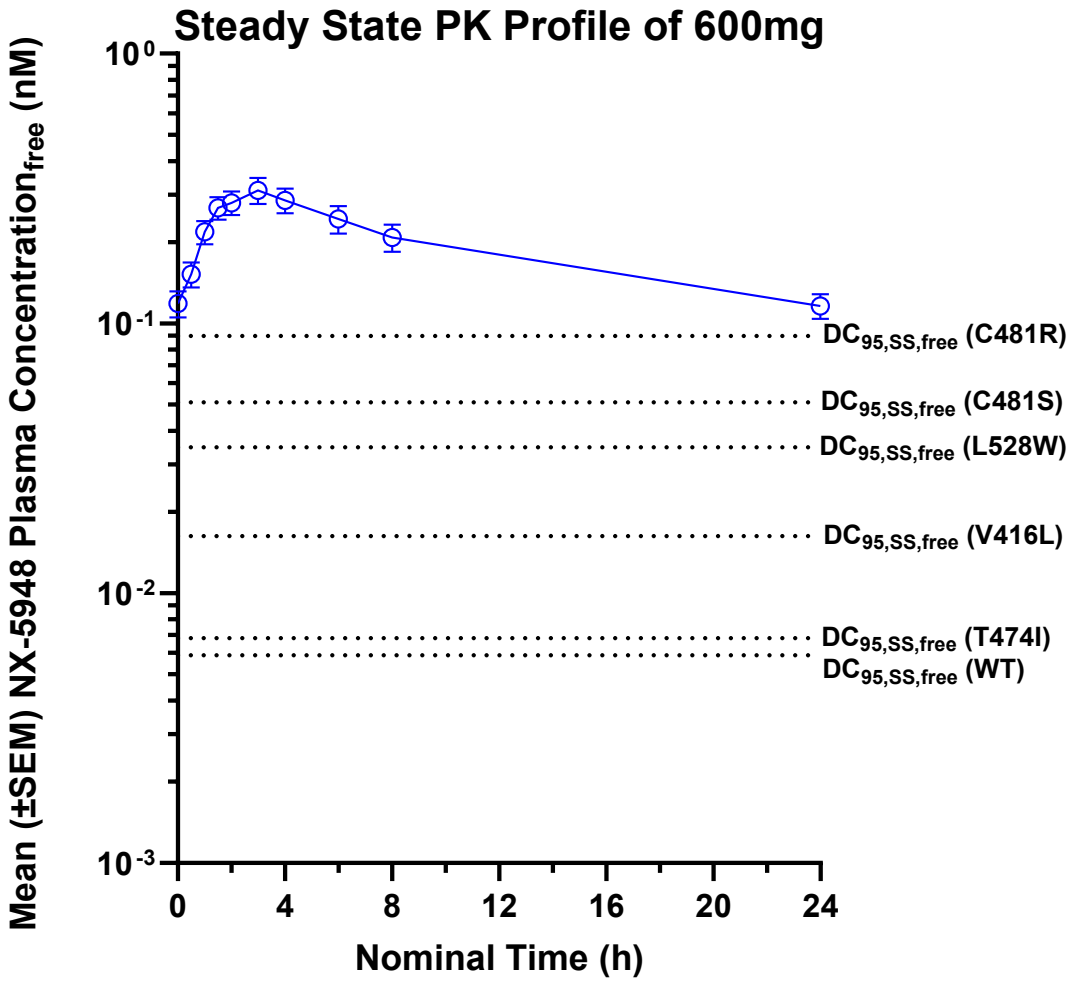
In vitro dose-dependent degradation assays used to confirm off target liabilities predicted by global proteomics

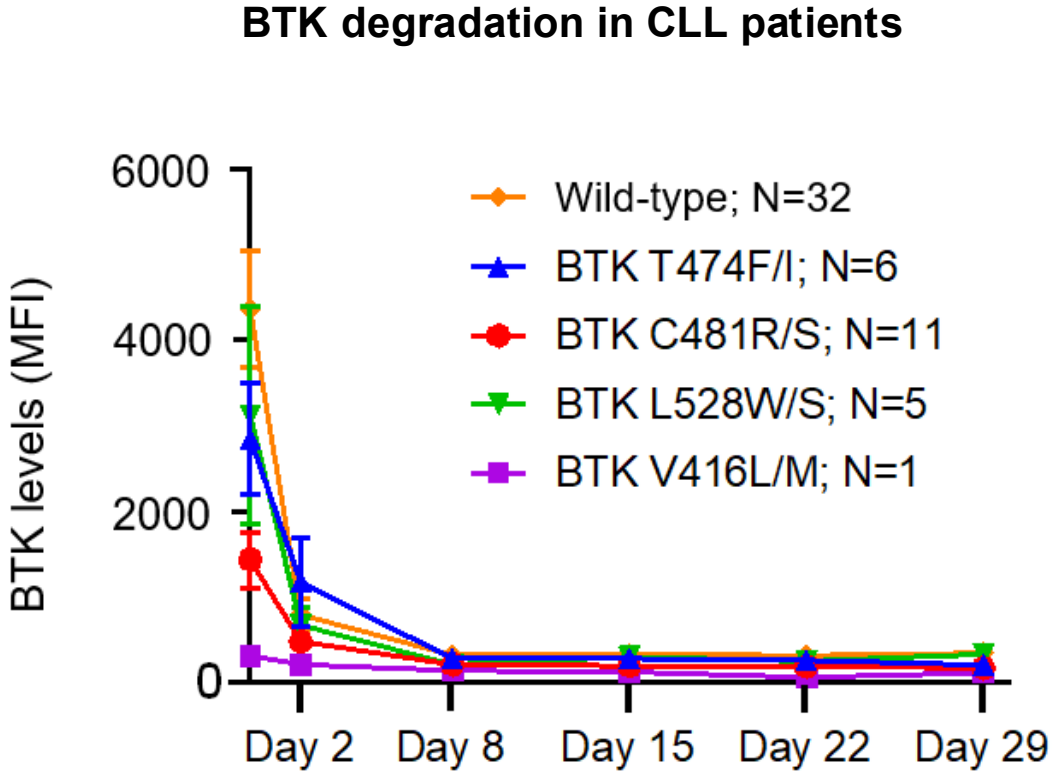
Target		Parameter	Bexobrutideg	BGB-16673	AbbVie cmpd. 1
BTK	Bruton's tyrosine kinase	DC_{50}	0.010 nM	0.206 nM	0.063 nM
LCK	Lymphocyte-specific kinase	Fold Selectivity (ratio of DC_{50} at 24h)	2,300x	49x	>10,000x
CSK	C-terminal Src kinase		4,200x	39x	6,000x
ADK	Adenosine kinase		>10,000x	60x	>10,000x
TEC	Tyrosine kinase expressed in hepatocellular carcinoma		64x	3x	7x

- **LCK** humans with loss of LCK have combined immune deficiency syndrome with severely defective T cell signaling and suffer from opportunistic infections[1]
- **CSK** human genetics shows low expression is associated with hypertension; knockdown in animal models causes hypertension[2]
- **ADK** is an important metabolic enzyme. ADK deficiency in humans has been shown to cause abnormal liver function, hypermethionemia and encephalopathy.[3] ADK-deficient mice are not viable and have abnormal liver function.[4]
- **TEC** is a tyrosine kinase related to BTK. Combined loss of BTK and TEC leads to cardiac hypertrophy and ventricular fibrosis in mice.[5]

BTK degradation assessed by flow cytometry in human PBMCs (hPBMCs), gated on CD20+ B cells. LCK/CSK/ADK DC_{50} values are compared to BTK DC_{50} in primary B cells, TEC DC_{50} values are compared to BTK DC_{50} in K562 cells. LCK degradation by bexobrutideg assessed by Jess SimpleWestern in bulk hPBMCs. CSK degradation by bexobrutideg assessed by flow cytometry in hPBMCs, gated on CD4+ T cells. LCK and CSK degradation by BGB-16673 and AbbVie cmpd. 1 assessed by flow cytometry in hPBMCs, gated on CD3+ CD8- (LCK) and CD3+ (CSK) T cells. Bexobrutideg did not significantly degrade ADK in global proteomics in hPBMCs (top conc. = 1000 nM). ADK degradation by BGB-16673 and AbbVie cmpd.1 assessed by Jess SimpleWestern in HepG2 cells. TEC degradation assessed by Jess SimpleWestern in K562 cells. AbbVie cmpd. 1 is example 1 from WO 2023/183811 A1 [1] Keller et al. 2024. J Clin Immunol. **44**(4). [2] Hyon-Ju Lee et al. 2016. PLOS One **11**(1): e0146841. [3] Bjursell et al. 2011. Am J Hum Gen **89**(4): 507–515. [4] Boison et al. 2002. Proc Nat Acad Sci **99**(10): 6985-6990. [5] Chen et al. 2024. Heart, Lung and Circulation **33**: S481.

Once a Day 600 mg Oral Dose of Bexobrutideg Achieves Optimal Coverage of Wild Type and Mutant BTK in CLL

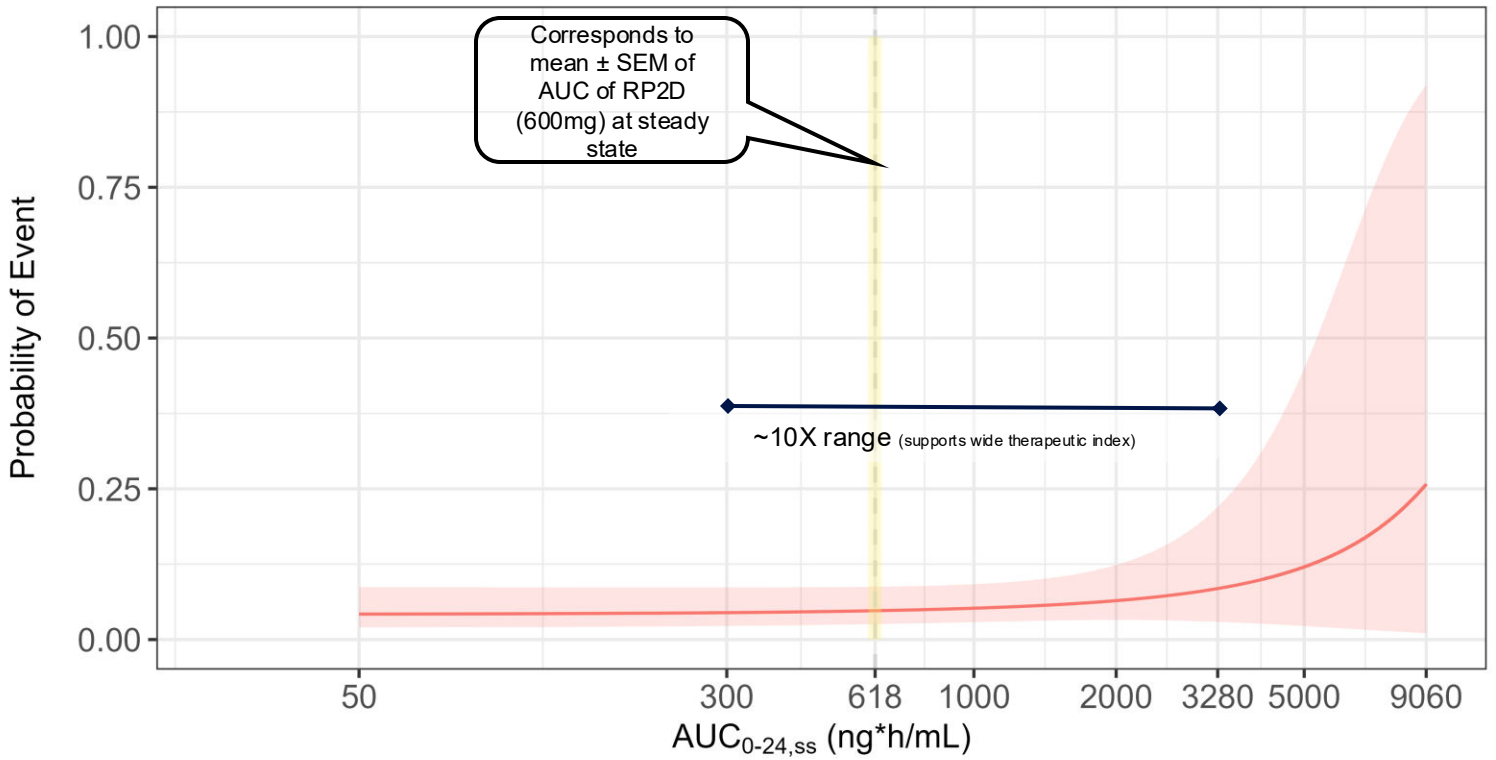




Note: Some patients have multiple BTK mutations

Arithmetic Mean (SEM) of n=90 are plotted for PK concentrations; PK Datacut: 27 May 2025
Avg = average; BTK = Bruton's tyrosine kinase; DC95 = concentration resulting in 95% degradation of target; SS = steady state; WT = wild type;
Horizontal dashed lines represent the free DC95 potency values at SS for WT BTK and mutants of interest (C481R, C481S, L528W, V416L, and T474I), as well as the avg value across these mutants of interest. Potency parameter (DC) was adjusted for rate of resynthesis using methodology published by Haid et.al, Clinical Pharmacology & Therapeutics, Vol 116 (3), September 2024.
PD Datacut: 10 Oct 2024

Interim Exposure-Response Analysis Suggests Bexobrutideg is a Wide Therapeutic Index Drug



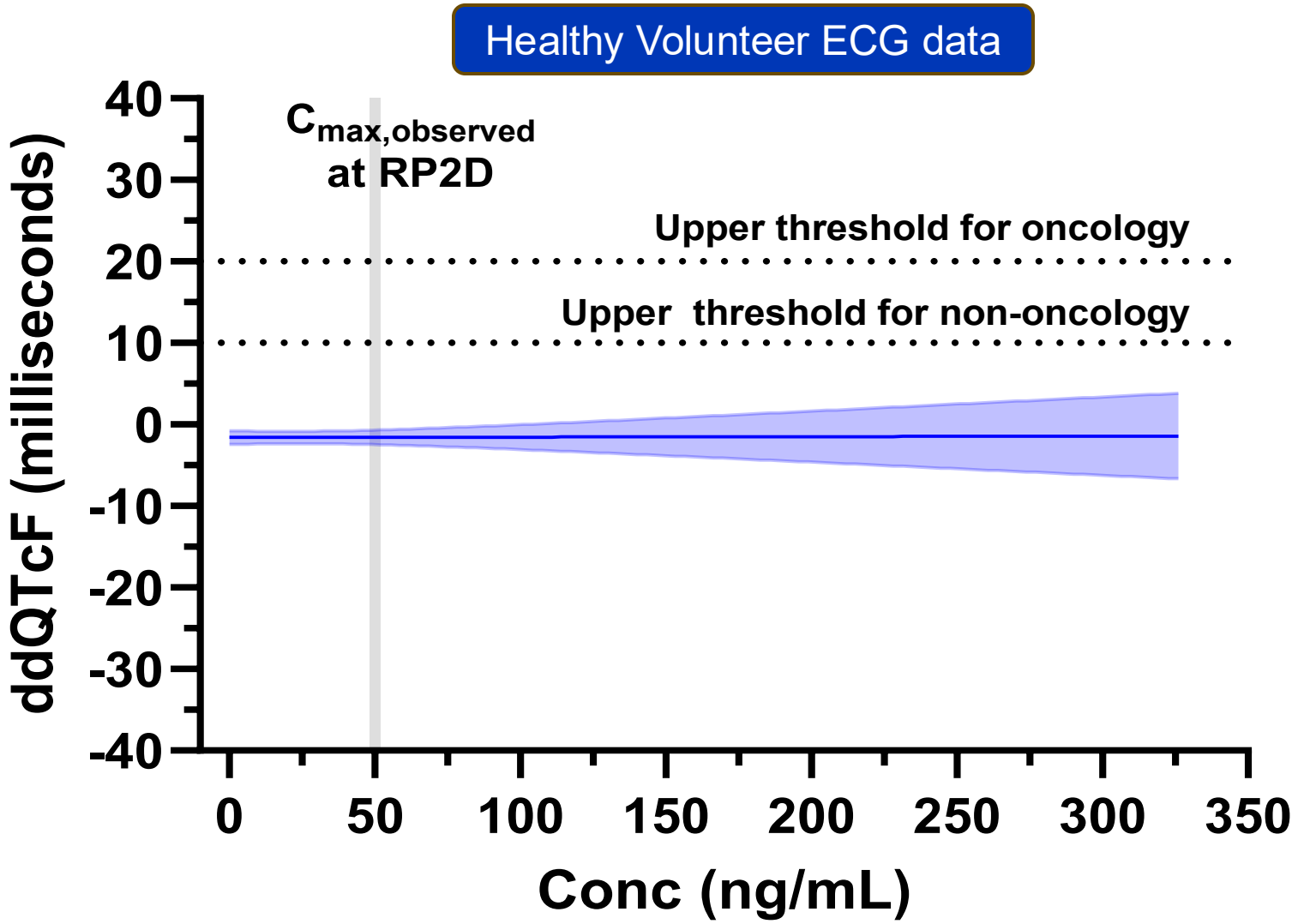
Grade 3 or greater Related SAEs

Line and shaded regions represent mean and 90% confidence intervals of the safety/efficacy endpoints

PK Datacut 27May2025

- A flat safety profile was observed across the exposure range (300-3300 ng*h/mL), extending beyond the RP2D
- A >10-fold therapeutic window suggests NX-5948 is a wide therapeutic index drug
- The selective profile observed using hPBMC global proteomics aligns with clinical exposure response analysis for safety.

Preliminary Concentration-QT Analysis Shows Lack of QTc Prolongation at Therapeutic & Supra-Therapeutic Steady State Exposures (600mg)



- Interim data for Bexobrutideg shows no prolongation of QTc interval in healthy volunteers
- Similar observations in patient population
- No cardiosafety signals were observed preclinically in either the in vitro (hERG) or in vivo (cyno telemetry) studies

ddQTcF, QT interval double corrected (dd) for heart rate using Fridericia's formula and placebo; RP2D, Recommended Phase 2 Dose
Solid blue line denotes regression line; blue shaded region denotes 90% confidence interval
Grey shaded vertical bar denotes geometric mean of Cmax at RP2D (600mg, qd)

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Bexobrutideg Safety Profile: Well Tolerated in Patients with Relapsed/Refractory CLL

TEAEs, n (%)	Patients with CLL/SLL (n=48)		
	Any grade	Grade ≥3	SAEs
Purpura/contusion[a]	22 (45.8)	–	–
Diarrhea	15 (31.3)	2 (4.2)	–
Fatigue[b]	15 (31.3)	–	–
Neutropenia[c]	14 (29.2)	11 (22.9)	–
Rash[d]	13 (27.1)	1 (2.1)	1 (2.1)
Petechiae	12 (25.0)	–	–
Headache	12 (25.0)	–	–
Thrombocytopenia[e]	11 (22.9)	1 (2.1)	–
Anemia	9 (18.8)	2 (4.2)	–
COVID-19[f]	9 (18.8)	–	–
Peripheral edema	9 (18.8)	–	–
Cough	8 (16.7)	–	–
Lower respiratory tract infection	7 (14.6)	1 (2.1)	1 (2.1)
Nausea	7 (14.6)	–	–
Pneumonia[g]	6 (12.5)	2 (4.2)	2 (4.2)
Arthralgia	6 (12.5)	–	–
Upper respiratory tract infection	5 (10.4)	–	–
Vomiting	5 (10.4)	1 (2.1)	–
Respiratory syncytial virus infection	2 (4.2)	1 (2.1)	2 (4.2)

- No dose-limiting toxicities
- No new atrial fibrillation
- No new ventricular arrhythmias
- No systemic fungal infections

[a]Purpura/contusion includes episodes of purpura or contusion; [b]Fatigue was transient; [c]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [d]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [e]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [f]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'; [g]Aggregate of 'pneumonia' and 'pneumonia klebsiella'

***CLL**, chronic lymphocytic leukemia; **SAE**, serious adverse event; **SLL**, small lymphocytic lymphoma; **TEAE**, treatment-emergent AE*

Data cutoff: 12 Mar 2025

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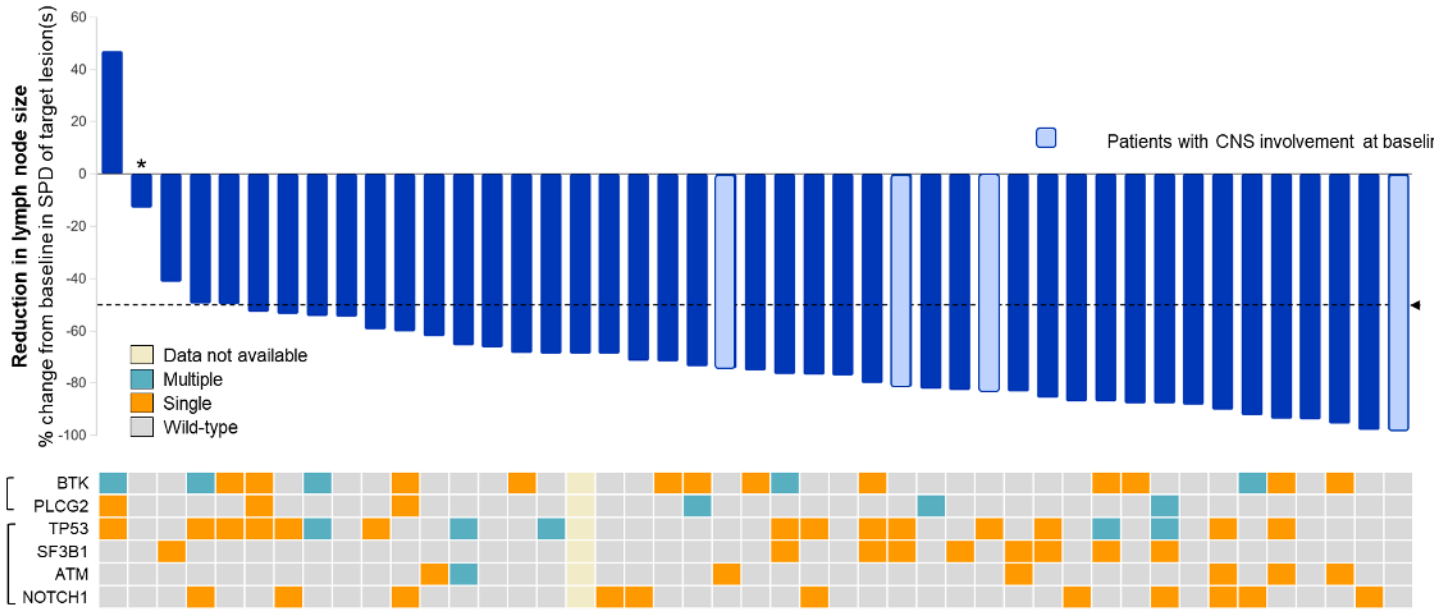
Bexobrutideg Has Consistently Demonstrated Strong Clinical Activity

Efficacy Data Across All Patients

CLL response-evaluable patients[a]	Response analysis (n=47)
Objective response rate (ORR),[b] % (95% CI)	80.9 (66.7–90.9)
Best response, n (%)	
Complete response (CR)	1 (2.1)
Partial response (PR)	37 (78.7)
PR with rebound lymphocytosis (PR-L)	0 (0.0)
Stable disease (SD)	7 (14.9)
Progressive disease (PD)	2 (4.3)
Median follow-up, months[c] (range)[d]	9.0 (1.6–26.1)

Efficacy Data Per Patient Regardless of Mutations or High Risk Cytogenetic Features



[a]Patients who were treated with bexobrutideg having ≥1 post-baseline disease assessment or documented clinical PD. [b]Objective response rate was evaluated using iwCLL criteria and included CR + PR + PR-L. [c]Kaplan-Meier estimate; [d]Observed values

***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*

Data cutoff: 12 Mar 2025

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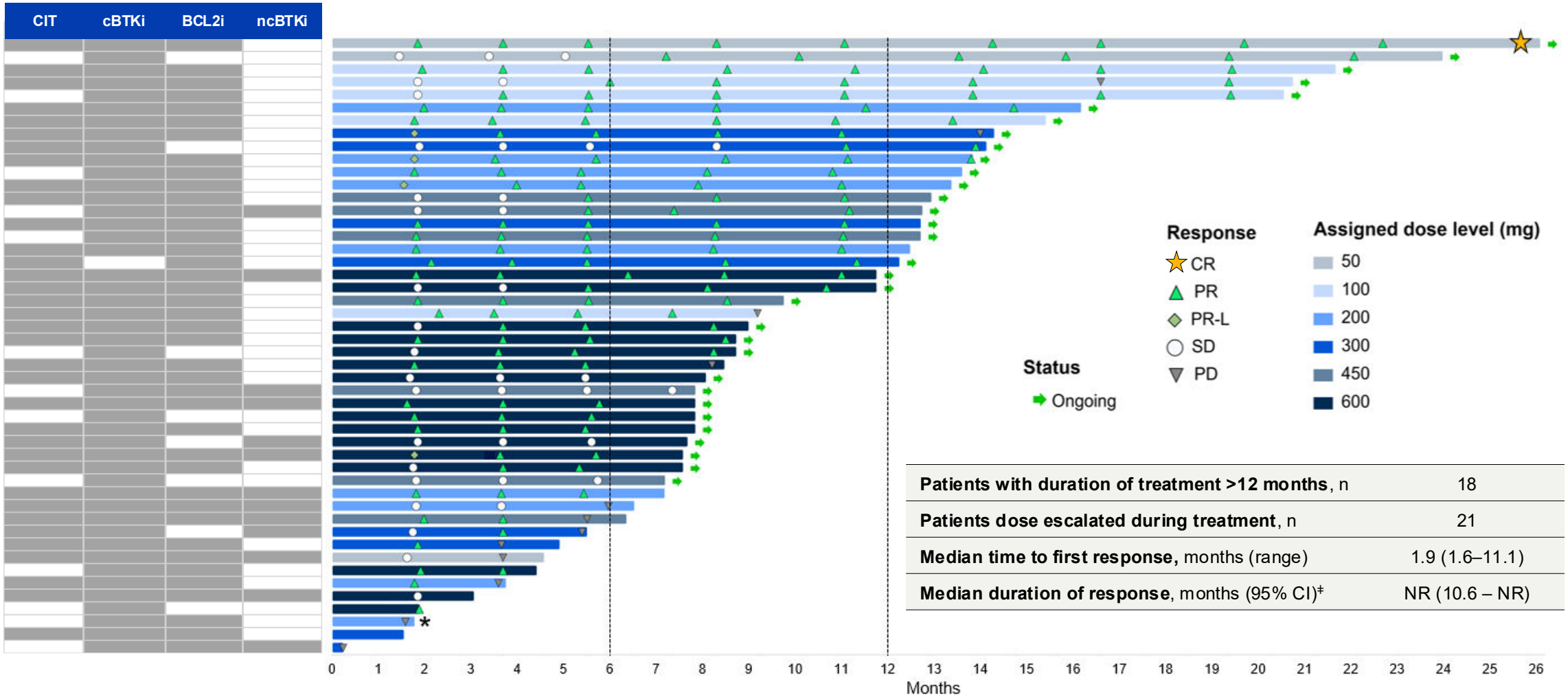
Bexobrutideg Demonstrates Durable Responses in Patients with Relapsed/Refractory CLL (n=48)



Patients with duration of treatment >12 months, n	18
Patients dose escalated during treatment, n	21
Median time to first response, months (range)	1.9 (1.6–11.1)
Median duration of response, months (95% CI)‡	NR (10.6 – NR)

**Patient with Richter's transformation to Hodgkin's on biopsy;* ‡Kaplan-Meier estimate

Data cutoff: 12 Mar 2025

***BCL2i**, BCL2 inhibitor; **BTKi**, BTK inhibitor; **cBTKi**, covalent BTKi; **CI**, confidence interval; **CIT**, chemo/chemo-immunotherapies; **CR**, complete response; **ncBTKi**, non-covalent BTKi; **NE**, not evaluable; **NR**, not reached; **PD**, progressive disease; **PR**, partial response; **PR-L**, PR with rebound lymphocytosis; **SD**, stable disease*

Deepening Response Leading to a Complete Response

Case report: patient with CR after 26 months on treatment

Patient demographics and disease characteristics

- 71-year-old Female with CLL
- Initial CLL diagnosis: 2014
- BTK mutation status: no BTK mutations

Prior treatments

1. Bendamustine + Rituximab (Benda-R)
2. Ibrutinib + Venetoclax (Ibr + Ven)

Bexobrutideg treatment

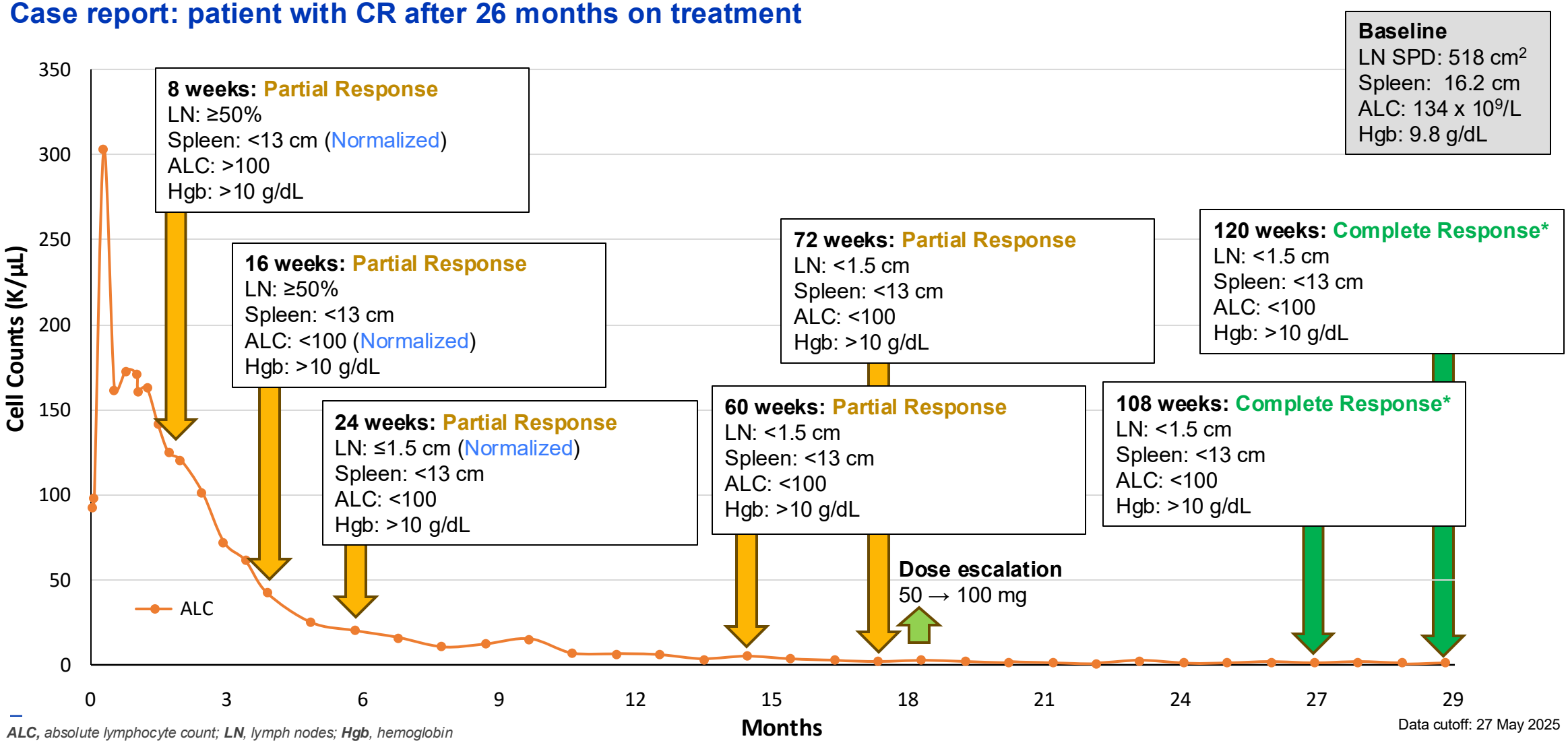
- Starting dose: 50 mg -> 100mg at month 17
- C1D1: 10 Jan 2023
- Current cycle (at May 27 2025 DCO): 32
- All related TEAEs were Grade 1
- Current status: ongoing, Complete Response*

*as assessed by investigator per iwCLL criteria including bone marrow assessment

Data cutoff: 27 May 2025

Deepening Response Leading to a Complete Response

Case report: patient with CR after 26 months on treatment



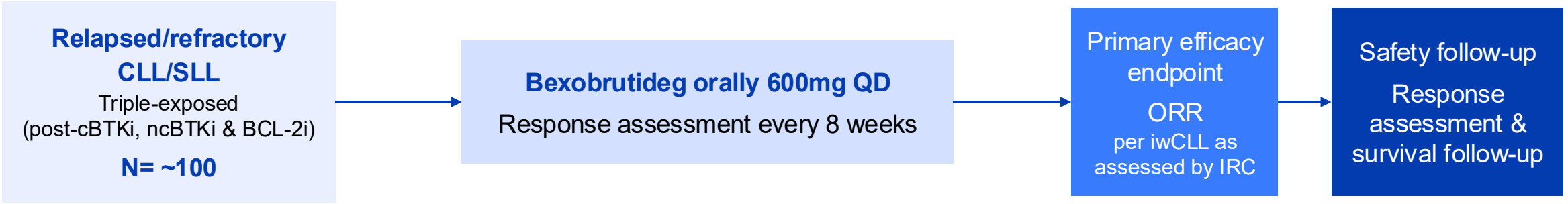
*ALC, absolute lymphocyte count; **LN**, lymph nodes; **Hgb**, hemoglobin*
**as assessed by investigator per iwCLL criteria including bone marrow assessment*

Data cutoff: 27 May 2025

Registrational Pathway for Bexobrutideg in R/R CLL

Phase 2 Single-Arm Study for Potential Accelerated Approval

Triple-exposed CLL patients who progressed on or did not respond to prior therapy

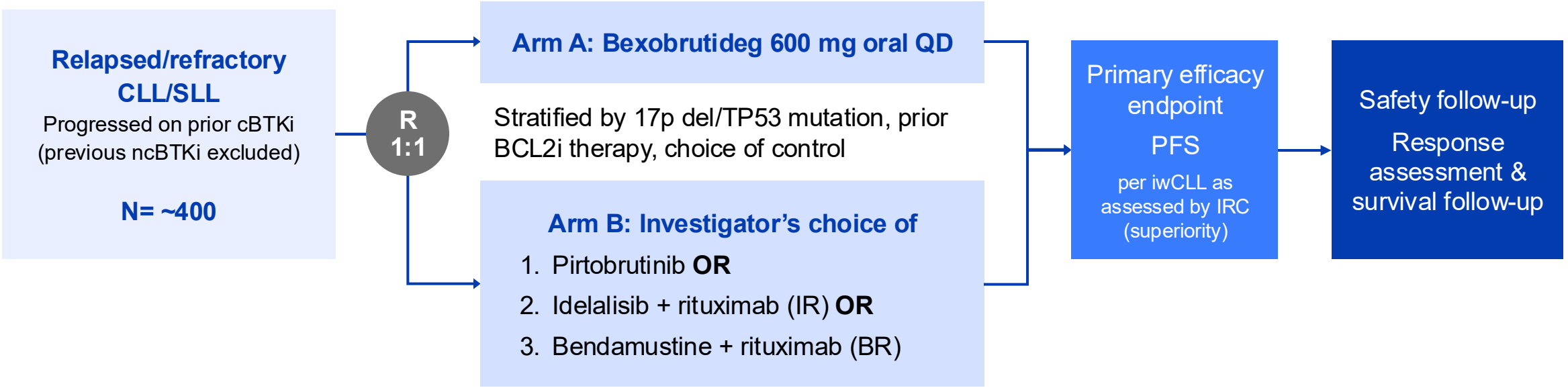


- Accelerated approval strategy depends on:
  - FDA's determination of unmet need at time of regulatory review
  - Adequate enrollment in confirmatory Phase 3 trial
- Trial designed to support potential accelerated approval in a high unmet need treatment setting
  - Post-cBTKi, post-ncBTKi, and post-BCL-2i (triple exposed)
- First site activated October 2025
  - 600 mg cleared for initiation of pivotal studies

***CLL**, chronic lymphocytic leukemia; **ORR,** objective response rate; **iwCLL,** International Workshop on CLL; **IRC,** Independent Review Committee; **QD,** once daily; **SLL,** small lymphocytic lymphoma; **cBTKi,** covalent BTK inhibitor; **ncBTKi,** non-covalent BTK inhibitor; **BCL-2i,** BCL-2 inhibitor*

Confirmatory Phase 3 Trial for Full Approval

2L+ CLL patients who progressed on prior covalent BTK inhibitor

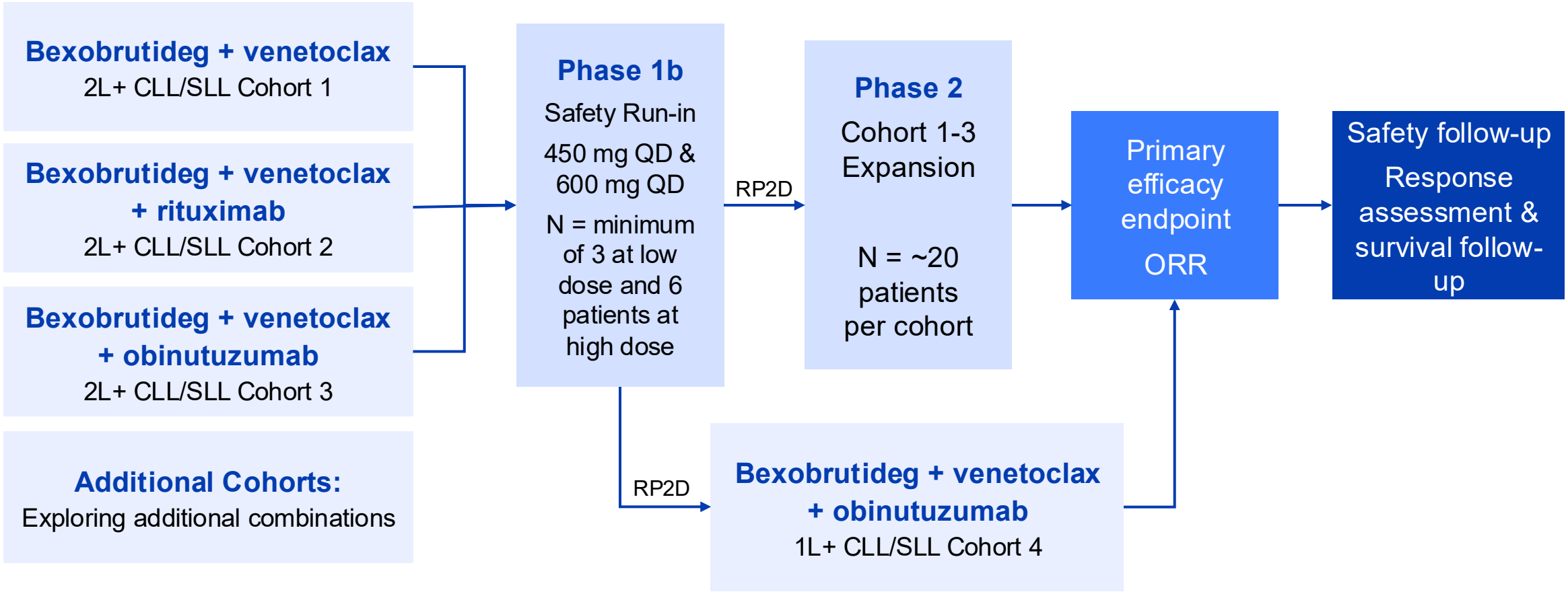


- Single trial strategy to support global approval
- Investigator's choice control arm:
  - Provides clinical relevance across geographies
  - Addresses current and emerging standards of care
  - Maximizes enrollment opportunities
  - Provides option for cross over to bexobrutideg upon documented progression

__CLL__, chronic lymphocytic leukemia; __PFS__, progression-free survival; __iwCLL__, International Workshop on CLL; __IRC__, Independent Review Committee; __QD__, once daily; __SLL__, small lymphocytic lymphoma; __ncBTKi__, non-covalent BTK inhibitor

Phase 1b/2 Combination Study to Address Emerging Treatment Standards in CLL

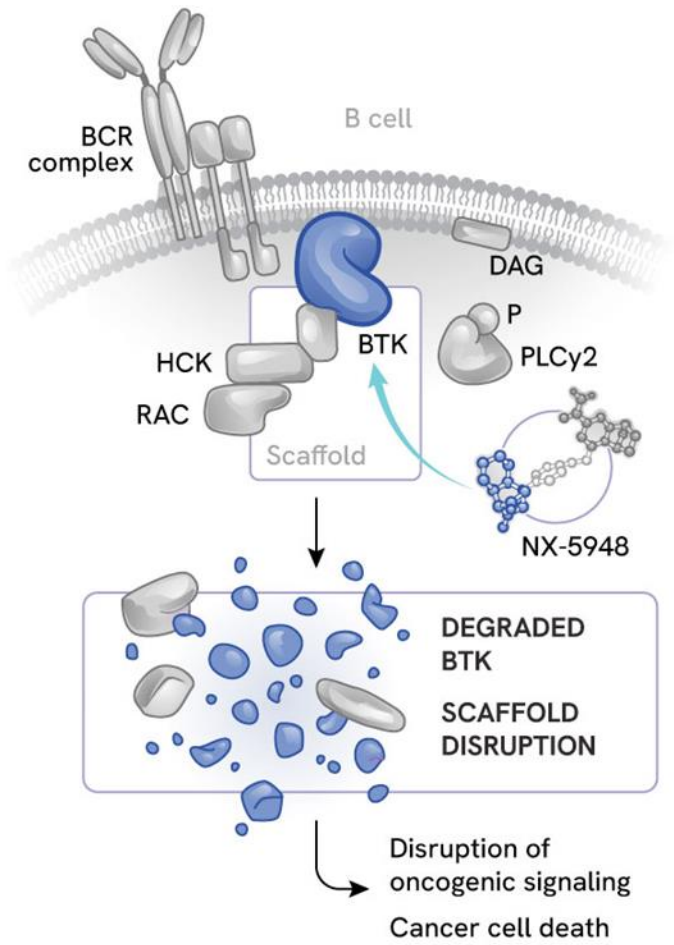
Combination regimen of bexobrutideg + BCL-2i maximizes 2L market share opportunity and provides potential path to 1L CLL



***CLL**, chronic lymphocytic leukemia; **SLL**, small lymphocytic lymphoma; **ORR**, objective response rate; **QD**, once daily; **RP2D**, recommended Phase 2 dose*

Bexobrutideg – The First “deg” with a Potential Best-in-Class Profile

Novel MOA Against a Clinically and Commercially Proven Target



- ✓ Active against wildtype BTK and demonstrated ability to overcome treatment-emergent resistance mutations
- ✓ Addresses BTK scaffolding function unlike current BTK inhibitors
- ✓ Acts catalytically driving degradation at low free-plasma concentrations
- ✓ Crosses the blood brain barrier and demonstrated clinical activity in the CNS
- ✓ Demonstrated robust clinical activity in difficult to treat B-cell malignancies
- ✓ Wide therapeutic index drug with no evidence of QTc prolongation

***BTK**, Bruton's tyrosine kinase; **CNS**, central nervous system; **MOA**, mechanism of action.*

Thank you