Bexobrutideg (NX-5948), a Novel Bruton's Tyrosine Kinase Degrader, Shows High Clinical Activity and Tolerable Safety in an Ongoing Phase 1a/b Study in Patients with Waldenström Macroglobulinemia

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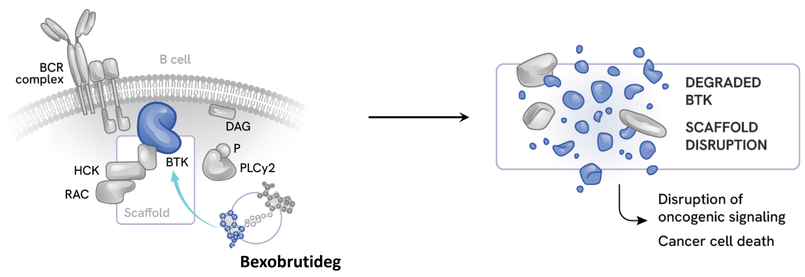
For information about this clinical trial please scan the QR code

Background

- The BCR signaling pathway mediated by BTK is a key driver in oncogenesis and a validated therapeutic target in patients with WM.
- BTK degraders:
  - can overcome treatment-emergent BTK inhibitor resistance mutations.[1,2]
  - address BTK scaffolding function – the transduction of BCR signal downstream from BTK in the absence of BTK enzymatic activity.[3]
  - demonstrated emerging activity in various B-cell malignancies including WM.[4,5]
- Bexobrutideg is a novel, orally administered, small molecule degrader that induces specific degradation of wild-type and mutant forms of BTK by ubiquitination via the cereblon E3 ligase complex and subsequent proteasomal degradation (**Figure 1**).
- Here we report updated findings from a Phase 1a/b trial of bexobrutideg in patients with WM.

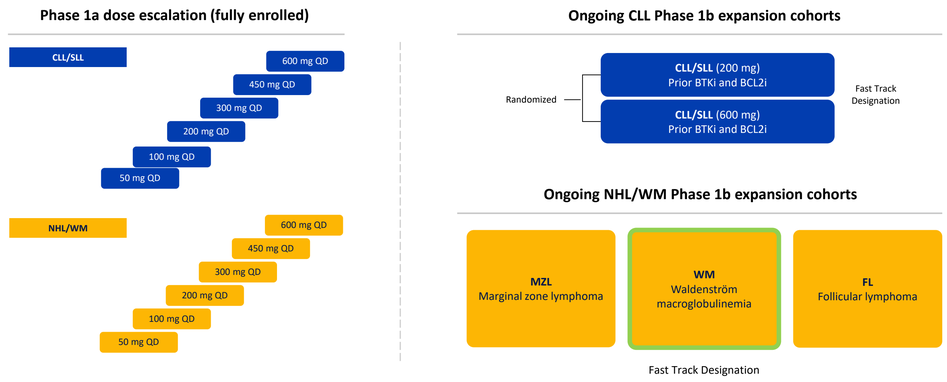
Figure 1. Bexobrutideg Mechanism of Action



Methods

- NX-5948-301 is a Phase 1 clinical trial evaluating safety/tolerability and activity of bexobrutideg in patients with relapsed/refractory B-cell malignancies, including WM, in parallel 3+3 dose-escalation then dose-expansion cohorts (**Figure 2**).
- Key eligibility criteria include prior treatment with a BTK inhibitor and ECOG PS 0–1. CNS involvement was allowed.
- Objectives:
  - Primary: safety/tolerability, establishment of maximum tolerated dose and identification of a recommended Phase 2 dose.
  - Secondary: characterization of the pharmacokinetic/pharmacodynamic profile and assessment of preliminary efficacy according to IWWM-6 criteria.

Figure 2. Trial design



Results

Table 1. Patient Demographics and Baseline Disease Characteristics – Patients with WM

Characteristics	Patients with WM (n=22)
Median age, years (range)	72.5 (58–86)
Male, n (%)	18 (81.8)
ECOG PS, n (%)	
0	8 (36.4)
1	14 (63.6)
CNS involvement, n (%)	2 (9.1)
Median prior lines of therapy (range)	3 (2–5)
Previous treatments[a], n (%)	
BTKi	22 (100.0)
ncBTKi	3 (13.6)
BCL2i	1 (4.5)
BTKi and BCL2i	1 (4.5)
Chemo/chemo-immunotherapies	21 (95.5)
Mutation status[b], n (%)	
MYD88	15 (68.2)
CXCR4	5 (22.7)

[a]Patients could have received multiple prior treatments; [b]Mutation status was gathered from historic patient records

Data cutoff: 12 Mar 2025

- As of 12 March 2025, 187 patients have been enrolled in the overall study, including 22 with WM who were treated at four daily dose levels: 200 mg (n=1), 300 mg (n=3), 450 mg (n=2), 600 mg (n=16).
- The WM population comprised mainly elderly patients who had received multiple prior lines of targeted therapies (**Table 1**).
- In the 19 response-evaluable patients with WM, bexobrutideg demonstrated a high ORR of 84.2% (2 VGPR, 11 PR, 3 MR, 3 SD, 0 PD) (**Table 2**).
- Clinical activity was observed in patients with baseline mutations and multiple prior lines of therapy (**Figure 3**).
- Responses were rapid and durable, with two patients reaching more than 1 year of follow-up (**Figure 3**).
- A steady decrease in IgM levels from baseline was observed in patients with WM treated with bexobrutideg (**Figure 4**).
- Bexobrutideg was well tolerated (**Table 3**), with safety profile consistent between WM, overall population, and previous reports.[6]
- AEs were mostly Grade 1–2; most common AEs were petechiae, diarrhea, purpura/contusion, neutropenia, and thrombocytopenia.
- No DLTs; two TEAEs resulting in drug discontinuation; two related SAEs but no Grade 5 AEs.

Table 2. Bexobrutideg Overall Response Assessment in Patients with WM: Phase 1a/1b

WM response-evaluable patients	Primary response analysis[b] ≥1 response assessment(s) at 8 weeks (n=19)
Objective response rate (ORR),[a] %	84.2
Best response, n (%)	
CR	0 (0.0)
VGPR	2 (10.5)
PR	11 (57.9)
MR	3 (15.8)
SD	3 (15.8)
PD	0 (0.0)
Median follow-up, months[c] (range)[d]	3.7 (1.9–18.9)

[a]Objective response rate includes CR + PR + MR; [b]Patients who progressed prior to their first response assessment and patients who discontinued for any reason after their first response assessment are included in the denominators; [c]Kaplan-Meier estimate; [d]Observed values

Data cutoff: 12 Mar 2025

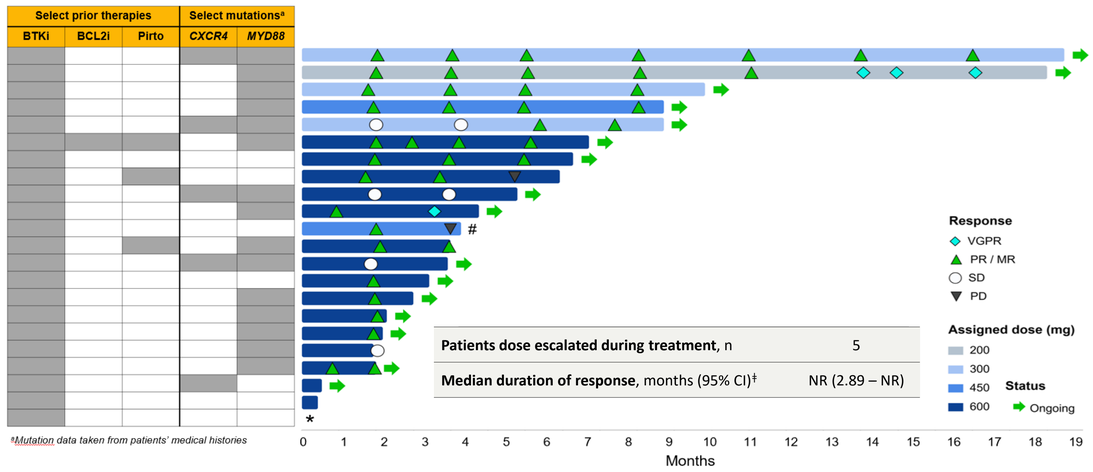
Table 3. TEAEs in ≥10% of Overall Population or Grade ≥3 TEAEs in ≥1 Patient or any SAEs

TEAEs, n (%)	Patients with WM (n=22)		
	Any grade	Grade ≥3	SAEs
Petechiae	6 (27.3)	–	–
Diarrhea	5 (22.7)	–	–
Purpura/contusion[a]	4 (18.2)	–	–
Neutropenia[b]	4 (18.2)	1 (4.5)	–
Thrombocytopenia[c]	4 (18.2)	1 (4.5)	–
Upper respiratory tract infection	4 (18.2)	–	–
Anemia	3 (13.6)	2 (9.1)	–
Headache	3 (13.6)	–	–
Rash[d]	3 (13.6)	–	–
COVID-19[e]	3 (13.6)	–	–
Fall	3 (13.6)	1 (4.5)	1 (4.5)
Lower respiratory tract infection	2 (9.1)	1 (4.5)	–
Arthralgia	2 (9.1)	–	–
Cough	2 (9.1)	–	–
Peripheral edema	2 (9.1)	–	–
Pneumonia[f]	2 (9.1)	–	–
Influenza	1 (4.5)	1 (4.5)	1 (4.5)
Influenzal pneumonia	1 (4.5)	1 (4.5)	1 (4.5)
Sepsis	1 (4.5)	1 (4.5)	1 (4.5)
Hypertension	1 (4.5)	1 (4.5)	–
Subdural hematoma[g]	1 (4.5)	–	1 (4.5)
Fatigue[h]	1 (4.5)	–	–

[a]Purpura/contusion includes episodes of contusion or purpura; [b]Aggregate of 'neutrophil count decreased' or 'neutropenia'; [c]Aggregate of 'thrombocytopenia' and 'platelet count decreased'; [d]Aggregate of 'rash' and 'rash maculopapular' and 'rash pustular'; [e]Aggregate of 'COVID-19' and 'COVID-19 pneumonia'; [f]Aggregate of 'pneumonia' and 'pneumonia klebsiella'; [g]Grade 1 AE in a patient on concurrent anti-coagulation; [h]Fatigue was transient

Data cutoff: 12 Mar 2025

Figure 3. Durable Responses Regardless of Prior Therapy or Mutation Status (n=22)

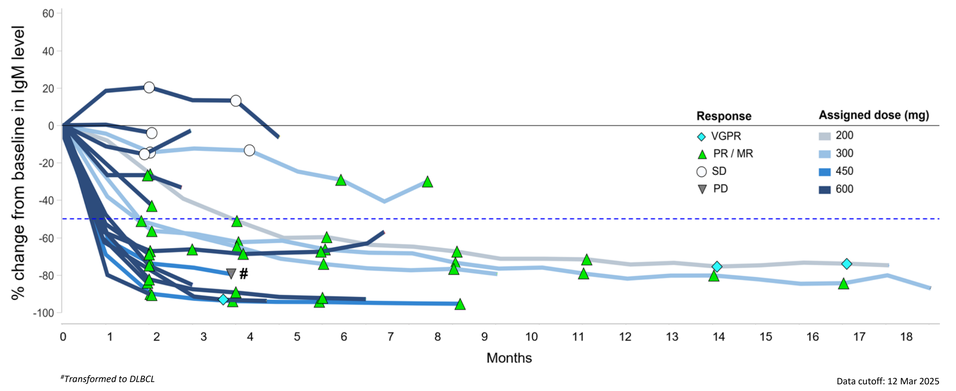


[a]Mutation data taken from patients' medical histories

**Ineligible, identified post 1st dose; #Transformed to DLBCL; ‡Based on Kaplan-Meier estimate*

Data cutoff: 12 Mar 2025

Figure 4. Percent Change in IgM Levels from Baseline in Patients with WM



#Transformed to DLBCL

Data cutoff: 12 Mar 2025

Conclusions

- Bexobrutideg is a novel small molecule BTK degrader that can overcome treatment-emergent BTKi resistance mutations and disrupt BTK scaffolding.
- In the ongoing WM portion of the Phase 1 NX-5948-301 study as of the 12 March 2025 datacut:
  - Median follow-up was 3.7 months, and most patients were still on treatment.
  - In 22 patients with WM, bexobrutideg was well tolerated, consistent with the overall study population and previous disclosures:
    - AEs were predominantly low grade; most common AEs were petechiae, diarrhea, purpura/contusion, neutropenia, and thrombocytopenia. No atrial fibrillation was observed.
    - No DLTs were noted; two TEAEs led to drug discontinuation. There were no Grade 5 AEs.
  - In 19 disease-evaluable patients with WM, durable and deepening responses were observed in a heavily pre-treated (3 median lines of treatment) population of patients, including those with CNS involvement and mutations in *MYD88* and *CXCR4:*
    - High ORR of 84.2% was observed, with 2 responses deepening to VGPR with longer duration on treatment.
    - Steady reduction in IgM levels occurred in most patients starting from the first IgM assessment (4 weeks), which continued to deepen at 8 weeks and beyond. Three patients had a 90%+ reduction in IgM levels.
    - Median duration of response was not reached.

Abbreviations

AE, adverse event; **BCL2i,** B-cell lymphoma 2 inhibitor; **BCR,** B-cell receptor; **BTK,** Bruton's tyrosine kinase; **BTKi,** Bruton's tyrosine kinase inhibitor; **CAR-T,** chimeric antigen receptor T-cell; **CIT,** chemo-immunotherapy; **CLL,** chronic lymphocytic leukemia; **CNS,** central nervous system; **CR**, complete response; **DLBCL,** diffuse large B-cell lymphoma; **DLT,** dose-limiting toxicity; **ECOG PS,** Eastern Cooperative Oncology Group performance status; **FL,** follicular lymphoma; **IgM,** immunoglobulin M; **IWWM,** International Workshop on WM; **MR,** minor response; **MZL,** marginal zone lymphoma; **ncBTKi**, non-covalent BTKi; **NHL,** non-Hodgkin's lymphoma; **ORR,** objective response rate; **PD,** progressive disease; **PI3Ki,** PI3 kinase inhibitor; **PR,** partial response; **QD**, once daily; **SAE,** serious adverse event; **SD,** stable disease; **SLL,** small lymphocytic lymphoma; **TEAE,** treatment emergent adverse event; **VGPR**, very good partial response; **WM,** Waldenström macroglobulinemia

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