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

[1]Nirav N. Shah, [2]Dima El-Sharkawi, [3]David Lewis, [4]Astrid Pulles, [5]Zulfa Omer, [6]Talha Munir, [7]Graham P. Collins, [8]Kim Linton, [9]Alvaro Alencar, [10,11]Mary Gleeson, [12]Pam McKay, [13]Scott Huntington, [14]Sarah Injac

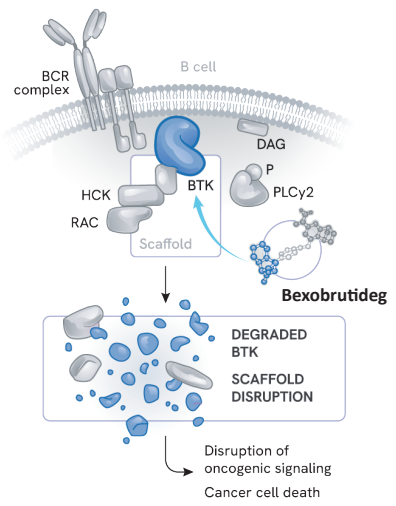
[1]Medical College of Wisconsin, Milwaukee, WI, USA; [2]Royal Marsden NHS Foundation Trust, Sutton, UK; [3]Derriford Hospital, Plymouth, UK; [4]UMC Utrecht Cancer Center, University Medical Center Utrecht, The Netherlands, on behalf of the Lunenburg Lymphoma Phase I/II Consortium – HOVON /LLPC; [5]University of Cincinnati, Cincinnati, OH, USA; [6]St. James's Hospital, Leeds, UK; [7]Oxford Cancer and Haematology Centre, Churchill Hospital, Oxford, UK; [8]University of Manchester, Manchester, UK; [9]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, USA; [10]Guy's and St Thomas' NHS Foundation Trust, London, UK; [11]Sarah Cannon Research Institute, London, UK; [12]Beatson West of Scotland Cancer Centre, Glasgow, Scotland; [13]Yale School of Medicine, New Haven, CT, USA; [14]Nurix Therapeutics, Inc., San Francisco, CA, USA

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.

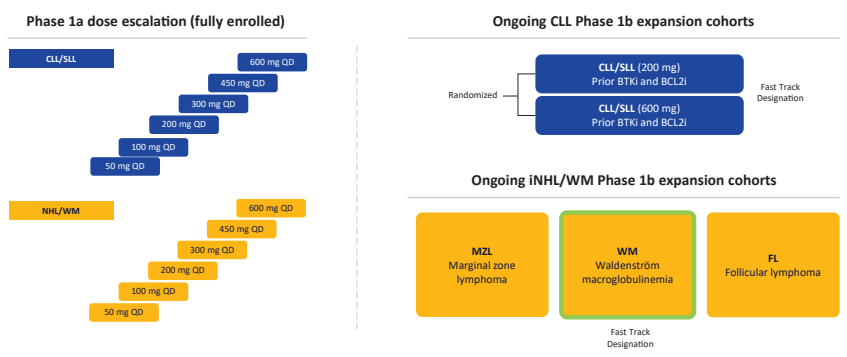
Figure 1. Bexobrutideg Mechanism of Action



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 in patients with an ECOG PS of 0-2.
- 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. NX-5948-301 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	4 (18.2)
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

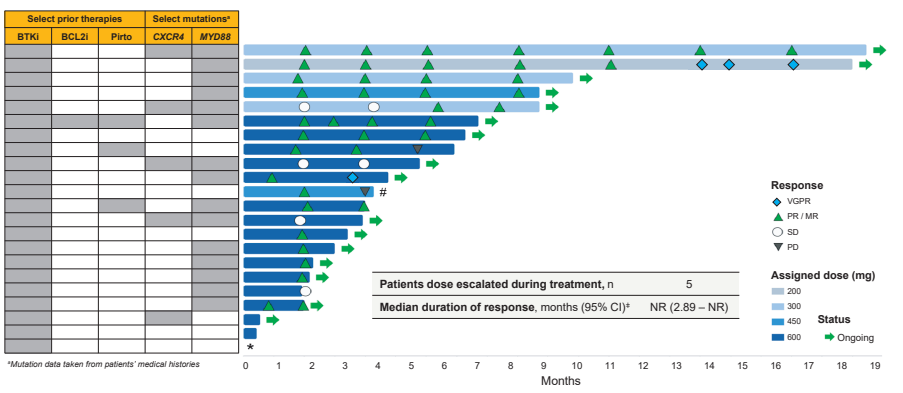
- As of 12 March 2025, 187 patients were enrolled in the overall study, including 22 with WM who were treated at four daily dose levels: 200 mg (n=1), 300 mg (n=3), 450 mg (n=2), 600 mg (n=16).
- The WM population comprised mainly elderly patients who had received multiple prior lines of targeted therapies (**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 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)



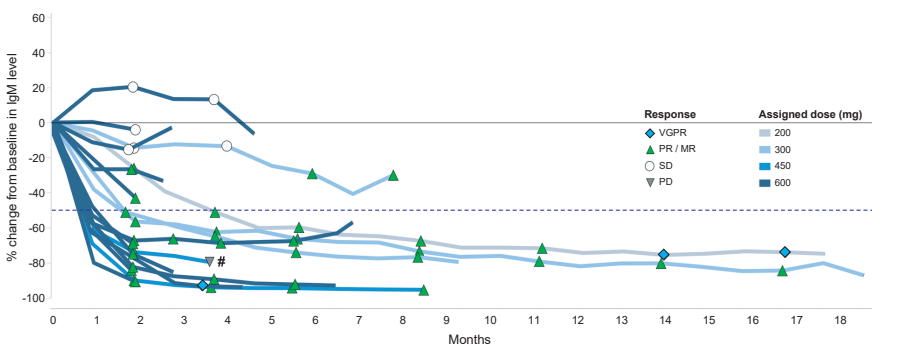
Ineligible, identified post 1st dose; #Transformed to DLBCL; ‡Based on Kaplan-Meier estimate Data cutoff: 12 Mar 2025

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
Previous treatments[a], 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

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



#Transformed to DLBCL

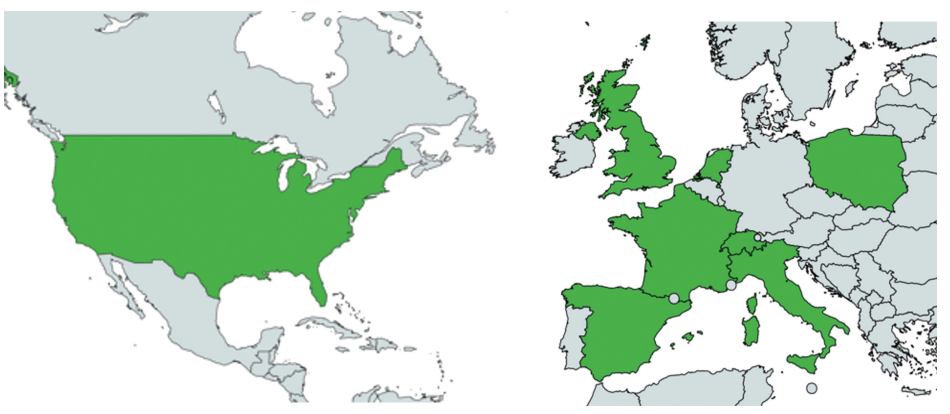
Conclusions

- 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.

Acknowledgements

- The authors are grateful to the patients and their families who enrolled in this trial.
- The authors would also like to thank:
  - All NX-5948-301 investigators and study sites in France, Italy, the United States, the United Kingdom, the Netherlands, Poland, Spain, and Switzerland for participating in this clinical research.
  - Nurix employees working on developing bexobrutideg and supporting the clinical trial.
- The NX-5948-301 study is sponsored by Nurix Therapeutics, Inc.

NX-5948-301 Active Study Sites



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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; **iNHL**, indolent 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

Presented at the Society of Hematologic Oncology (SOHO) 2025 Annual Meeting, Houston, Texas, USA, 3–6 September 2025