First-in-Class CBL-B Inhibitor NX-1607: Phase 1a Data in Patients with Advanced Solid Tumors

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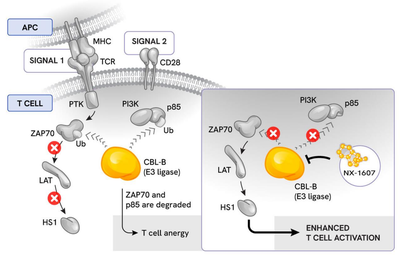
For information about this clinical trial please scan the QR code

Background

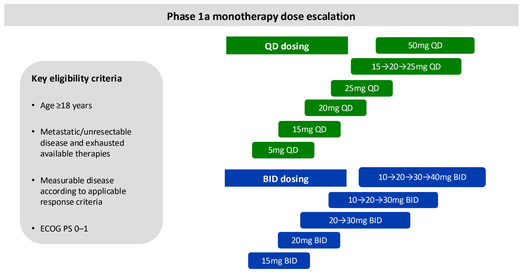
- CBL-B is a cytoplasmic E3 ubiquitin ligase that negatively regulates T cell activation, making it an attractive target for immuno-oncology.
- Inhibition of CBL-B in preclinical studies reverses T-cell exhaustion, alleviates tumor-induced immunosuppression, and may also exert direct anti-tumor effects.
- NX-1607 is a first-in-class oral inhibitor of CBL-B, offering a novel therapeutic approach to treat solid tumors by targeting a previously unaddressed pathway in oncology.
- NX-1607-101 (NCT05107674) is a first-in-human, multicenter, open-label Phase 1a/1b study evaluating the safety, pharmacokinetics, pharmacodynamics, and preliminary anti-tumor activity of NX-1607 in patients with relapsed/refractory solid tumors.
- Results from the NX-1607-101 study monotherapy dose escalation as of 26 July 2025 are reported herein.

Figure 1. NX-1607 Acts as an Intramolecular Glue to Inhibit CBL-B Activity and Enhance T Cell Activation



Methods

Figure 2. NX-1607-101 Study Design – Phase 1a/b Trial in Adults with Advanced Solid Tumors



Disposition and Demographics

Figure 3. Patient Disposition

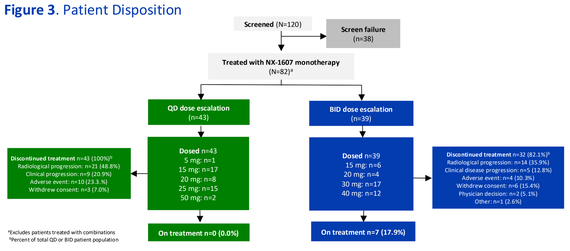


Table 1. Patient Demographics and Baseline Disease Characteristics

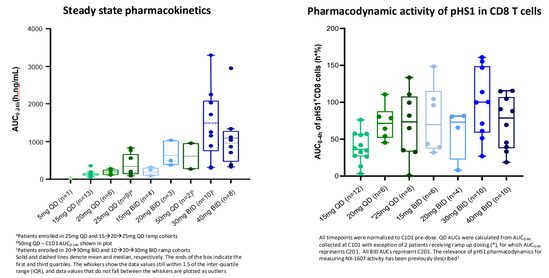
Characteristics	QD dosing (n=43)	BID dosing (n= 39)	Overall (N=82)
Median age, years (range)	62 (23–83)	64 (35–83)	62 (23–83)
Male, n (%)	26 (60.5)	23 (59.0)	49 (59.8)
Baseline ECOG PS, n (%)			
0	21 (48.8)	17 (43.6)	38 (46.3)
1	22 (51.2)	22 (56.4)	44 (53.7)
Ethnicity, n (%)			
Hispanic or Latino	0	3 (7.7)	3 (3.7)
Not Hispanic or Latino	28 (65.1)	35 (89.7)	63 (76.8)
Not reported	8 (18.6)	0 (0.0)	8 (9.8)
Unknown	7 (16.3)	1 (2.6)	8 (9.8)
Median prior lines of therapy, n (range)	3.0 (1–9)	4.0 (2–9)	3.5 (1–9)
Immunotherapies	1.0 (1–3)	1.0 (1–3)	1.0 (1–3)
Anti-cancer	3.0 (1–9)	4.0 (2–8)	3.0 (1–9)
Anti-cancer + immunotherapies	1.0 (1–1)	1.5 (1–2)	1.0 (1–2)
Tumor histology, n (%)			
Platinum-resistant epithelial ovarian	1 (2.3)	2 (5.1)	3 (3.7)
Gastroesophageal junction	1 (2.3)	1 (2.6)	2 (2.4)
Head and neck squamous cell	1 (2.3)	0 (0.0)	1 (1.2)
Metastatic melanoma	7 (16.3)	1 (2.6)	8 (9.8)
Non-small cell lung	2 (4.7)	2 (5.1)	4 (4.9)
Castration-resistant prostate	9 (20.9)	14 (35.9)	23 (28.0)
Malignant pleural mesothelioma	1 (2.3)	3 (7.7)	4 (4.9)
Triple-negative breast	0 (0.0)	1 (2.6)	1 (1.2)
Urothelial	1 (2.3)	0 (0.0)	1 (1.2)
Cervical	3 (7.0)	4 (10.3)	7 (8.5)
Microsatellite stable colorectal	17 (39.5)	11 (28.2)	28 (34.1)

- This was an elderly population with advanced cancer enrolled after multiple lines of prior treatment, including prior immuno-oncology therapies.

Results

Pharmacokinetics and Pharmacodynamics

Figure 4. Dose-Dependent Pharmacokinetics with Associated Increases in Pharmacodynamics of the CBL-B Proximal Biomarker pHS1

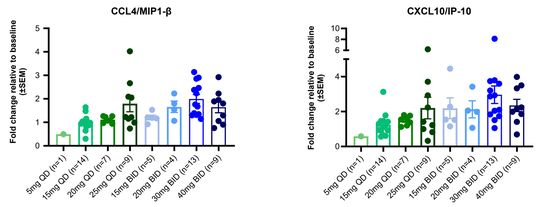


*Patients enrolled in 25mg QD and 15→20→25mg QD ramp cohorts
†50mg QD – C1D1 AUC_{0-24h} shown in plot
‡Patients enrolled in 20→30mg BID and 10→20→30mg BID ramp cohorts
Solid and dashed lines denote mean and median, respectively. The ends of the box indicate the first and third quartiles. The whiskers show the data values still within 1.5 of the inter-quartile range (IQR), and data values that do not fall between the whiskers are plotted as outliers

All timepoints were normalized to C1D1 pre-dose. QD AUCs were calculated from AUC_{0-24h} collected at C1D1 with exception of 2 patients receiving ramp up dosing (*), for which AUC_{0-4h} represents C2D1. All BID AUCs represent C2D1. The relevance of pHS1 pharmacodynamics for measuring NX-1607 activity has been previously described[1]

- NX-1607 demonstrates dose-dependent pharmacokinetics.
- NX-1607 increases the percentage of pHS1-positive CD8-T cells from baseline across dose cohorts.

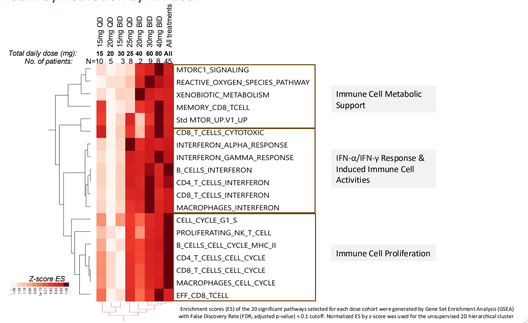
Figure 5. NX-1607 Demonstrates Dose-Responsive Peripheral Immune Activation via Increases in Distal Biomarkers: Chemokines CXCL10 and CCL4



- Chemoattractant for dendritic cell recruitment
- IFN-γ inducible chemokine recruiting effector T cells and NK cells

- NX-1607 led to an increase in the peripheral chemokines, CXCL10 and CCL4, at Cycle 2 Day 15, suggesting the upregulation of pro-inflammatory signaling and corresponding immune cell recruitment.

Figure 6. Gene Expression in PBMCs Demonstrates Dose-Responsive Modulation of Immune Pathway Activation by NX-1607



Enrichment scores (ES) of the 20 significant pathways selected for each dose cohort were generated by Gene Set Enrichment Analysis (GSEA) with False Discovery Rate (FDR, adjusted p-value) <0.1 cutoff. Normalized ES by z-score was used for the unsupervised 2D hierarchical cluster

- Transcriptomic profiling demonstrated dose-responsive enrichment of key immune signaling pathways.
- Pathways included enhanced immune cell metabolic support, progressive induction of IFN-α/IFN-γ response and downstream immune cell activities, and upregulation of inflamed immune cell proliferation programs.
- These data support a mechanistic relationship between dose and coordinated anti-tumor immune pathway engagement.

Safety

Table 2. Safety Overview

Adverse event	Doses ≥30 mg BID[a] (n=24)	Overall (N=82)
Dose-limiting toxicities[b,c]	0 (0%)	9 (11.0%)
TRAEs all grades	23 (95.8%)	70 (85.4%)
TRAEs ≥Grade 3	4 (16.7%)	20 (24.4%)
Treatment-related SAEs	0 (0%)	7 (8.5%)
Discontinuations due to TRAEs	1 (4.2%)	12 (14.6%)
Immune-related AEs[d]	2 (8.3%)	6 (7.3%)
Nausea TRAEs all grades	13 (54.2%)	39 (47.6%)
Vomiting TRAEs all grades	6 (25.0%)	26 (31.7%)
Nausea TRAEs ≥Grade 3	0 (0%)	2 (2.4%)
Vomiting TRAEs ≥Grade 3	0 (0%)	2 (2.4%)

[a]≥30mg BID includes 10→20→30mg BID and 10→20→30→40mg BID dose regimens, 20-30mg BID are not included
[b]DLTs observed at lower dose levels were managed by changing the dose regimens and adding anti-emetics, leading to improved tolerability of higher doses
[c]DLTs were as follows: acute kidney injury/increased creatine (n=2), hypotension (n=2), decreased albumin (n=1), syncope (n=1), vomiting (n=1), headache (n=1), dehydration (n=1)
[d]Immune-related adverse events were as follows: acute kidney injury/increased creatine (n=2); hypothyroidism (n=1); increased alkaline phosphatase/ALT (n=1); fatigue (n=1); arthralgia (n=1); rash (n=2)

- NX-1607 has a safety profile comparable to approved immuno-oncology agents[2,3] in early development.
- Most adverse events were ≤Grade 2 in severity.
- Active doses of ≥30mg BID are tolerable.

Clinical Activity

Figure 7. Duration of Treatment and Response by Tumor Type in Patients Receiving Doses ≥30mg BID

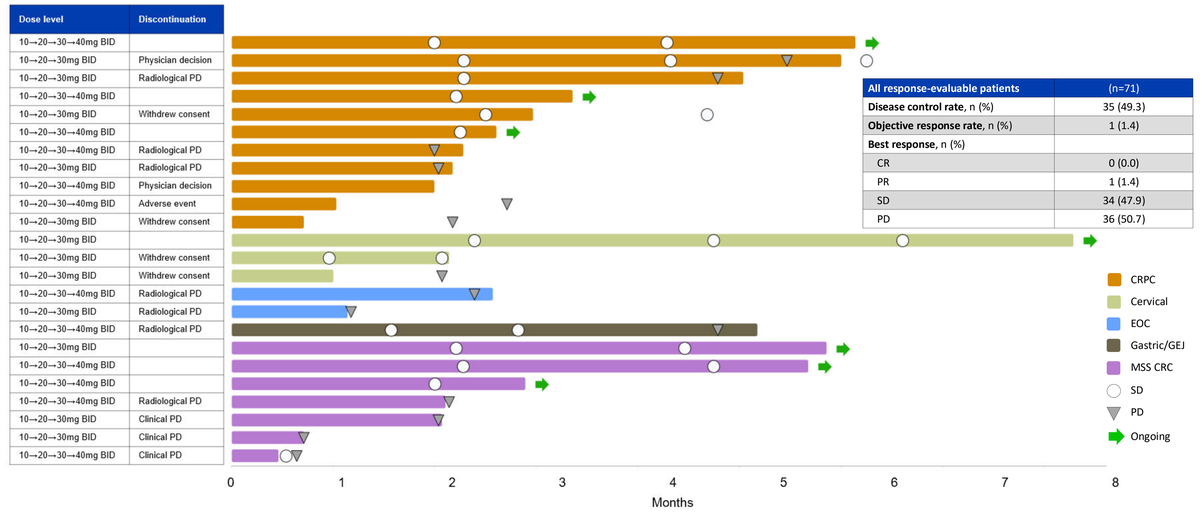


Table 3. NX-1607 Treatment Demonstrates Preliminary Signals of Clinical Benefit

Tumor type	Dose/schedule	Duration of treatment (months)[a]	Response (tumor volume change)	Biomarker reduction
MSS CRC	15mg QD	1.7	SD (–3.7%)	NA
MSS CRC	25mg QD	27.1	**PR (–37.5%)**	NA
MSS CRC	15mg BID	3.3	SD (–23.6%)	NA
MSS CRC[b]	10→20→30→40mg BID	5.3	SD (–23.9%)	CEA reduction of 26%
CRPC	5mg QD	8.5	SD (–10.5%)	PSA reduction of 30%
CRPC	15→20→25mg QD	3.1	SD (–11.1%)	NA
CRPC	20→30mg BID	6.6	SD[c]	PSA reduction of 90%; CTC from 12→0
CRPC	10→20→30mg BID	2.0	PD[c]	PSA reduction of 71%
CRPC	10→20→30mg BID	4.7	SD (–14.3%)	PSA reduction of 65%
CRPC	10→20→30mg BID	0.7	PD (+40.9%)	PSA reduction of 73%
Melanoma	15mg QD	0.9	SD (–10.9%)	NA
Melanoma	20mg QD	4.2	SD (–27.1%)	NA
NSCLC	15mg QD	9.8	SD (–4.8%)	NA
NSCLC	15mg BID	24.3	SD (–13.1%)	NA
Cervical[b]	10→20→30mg BID	8.2	SD (–5.7%)	NA
Gastroesophageal	10→20→30→40mg BID	4.8	SD (–18.5%)	NA

[a]Days (months) of clinical benefit calculated from C1D1 until clinical/radiological progression, adverse event or withdrew consent
[b]Patients are ongoing as of the data cut
[c]Bone-only disease and thus no corresponding tumor volume change information

- NX-1607 provided a high disease control rate (CR+PR+SD) of 49.3% overall and demonstrated meaningful clinical activity (tumor volume/biomarker reductions) across a broad range of indications.
- 7 patients achieved disease control (SD or PR) for ≥5 months on treatment; 1 patient reached 27 months on treatment with a best overall response of PR (CRC, **bolded**).

Case study 1. Patient with MSS CRC

Patient profile
- 59-year-old male with CRC
- 7 prior lines of therapy: FOLFOX, 5-FU+panitumumab +irinotecan, capecitabine, tipiracil/trifluridine (x2), 5-FU+irinotecan, nivolumab
- 8th line of therapy NX-1607, dosed at 25mg QD

Pharmacodynamic profile
- Proximal biomarker: the maximum %pHS1+CD8+ increased to ~80% from baseline
- Distal biomarkers: the maximum CXCL10 and CCL4 increased 2- and 6-fold over baseline

Anti-tumor profile
- PR at Week 27, confirmed at week 39
- Target lesion 28 x 24mm decreased to 28 x15mm (reduction of 37.5%)
- Patient developed PD at Week 87 but continued post progression to derive clinical benefit until Week 123

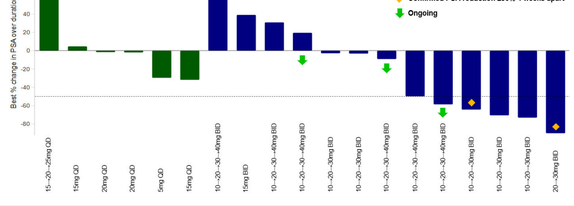
Case study 2. Patient with CRPC

Patient profile
- 72-year-old male with CRPC
- 2 prior lines of therapy: docetaxel and cabazitaxel
- 3rd line of therapy NX-1607, dosed with a ramp-up regimen at 20–30mg BID
- Bone-only disease

Pharmacodynamic profile
- Proximal biomarker: the maximum %pHS1+CD8+ increased to 62.6% from baseline
- Distal biomarker: the max CCL4 increased 3-fold over baseline. No data available for CXCL10

Anti-tumor profile
- Baseline PSA 592µg/L reduced by 56.3% at Week 9 to 259µg/L, by 83.9% at Week 27 to 95.1µg/L, and by 90.3% at Week 51 to 57.4µg/L.
- Baseline CTC 12/7.5mL reduced to 0 at Week 9 and confirmed at Week 27
- No new bone lesions

Figure 8. Clinical Activity in Patients with CRPC: ≥50% Reduction of PSA



- BID dosing shows promising and meaningful reductions in PSA in patients with CRPC.

Conclusions

- NX-1607 is a first-in-class oral CBL-B inhibitor demonstrating a novel immune checkpoint mechanism distinct from PD-1/PD-L1.
- NX-1607 is tolerable at pharmacologically active doses.
- Oral dosing of NX-1607 demonstrated dose-dependent exposure, increases in proximal and distal biomarkers, evidence of peripheral immune activation and reductions in tumor volume and cancer biomarkers, which together provide clinical proof that CBL-B inhibition can confer anti-tumor activity.
- NX-1607 monotherapy showed a high disease control rate of 49.3% with encouraging signals of clinical activity observed across multiple tumor types in heavily pretreated patients as with other successful immuno-oncology agents during early development, such as anti-PD1[2] and anti-CTLA4[3].
- Data support the continued development of NX-1607 as monotherapy or in combination with other agents for the treatment of advanced solid tumors.

NX-1607 monotherapy demonstrates the characteristics of an active immuno-oncology agent

Abbreviations

AE, adverse event; **AUC**, area under the curve; **BID**, twice daily; **C**, cycle; **CBL-B**, Casitas B-lineage lymphoma proto-oncogene B; **CEA**, carcinoembryonic antigen; **CR**, complete response; **CRC**, colorectal cancer; **CRPC**, castrate-resistant prostate cancer; **CTC**, circulating tumor cells; **D**, day; **ECOG PS**, Eastern Cooperative Oncology Group Performance Scale; **EOC**, epithelial ovarian cancer; **GEJ**, gastroesophageal junction; **IFN**, interferon; **MSS**, micro-satellite stable; **NA**, not available; **NSCLC**, non-small-cell lung cancer; **PD**, progressive disease; **pHS1**, phosphorylated HS1; **PR**, partial response; **PSA**, prostate-specific antigen; **QD**, once daily; **SAEs**, serious adverse events; **SD**, stable disease; **SEM**, standard error of the mean; **TRAEs**, treatment-related adverse events

Acknowledgments and Disclosures

- The authors are grateful to the patients and their families who enrolled in this trial. The authors would also like to thank:
  - All NX-1607-101 investigators and study sites for participating in this clinical research.
  - Nurix employees working on developing NX-1607 and supporting the clinical trial.
- The NX-1607-101 study is sponsored/funded by Nurix Therapeutics, Inc.
- Contact details and financial disclosures for the presenting author (Dr Anja Williams):
  - Contact email: anja.williams@hcahealthcare.co.uk
  - Financial disclosure: scientific adviser for Ellipses Pharma UK

References

1. Murthy P. SITC 2022.
2. Patnak A. Clin Cancer Res 2015;21:4286–93.
3. Weber J. J Clin Oncol 2008;26:5950–6.

Data cutoff: 26 July 2025

Presented at the ESMO 2025 Congress, Berlin, Germany, 17–21 October 2025