NX-1607: Translational Insights From a First-in-Human Study of an Oral CBL-B Inhibitor in Advanced Solid Tumors

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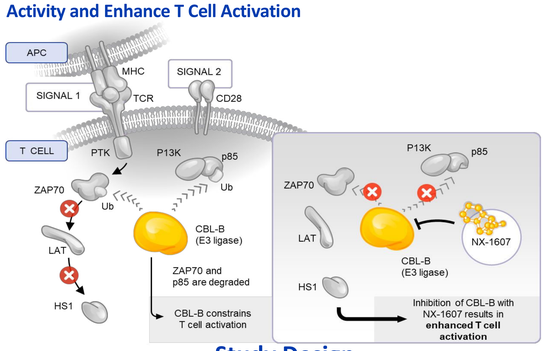
Introduction

- Casitas B-lineage lymphoma proto-oncogene B (CBL-B) is an E3 ubiquitin ligase that functions as a cytoplasmic immune checkpoint, constraining immune cell activation.
- NX-1607 is a first-in-class, orally bioavailable, small-molecule inhibitor of CBL-B with the potential to enhance antitumor immunity. In preclinical models, NX-1607 effectively inhibits tumor growth by reshaping the intra-tumoral innate and adaptive immune response [1,2].
- In the ongoing Phase 1 study NX-1607-101 (NCT05107674), NX-1607 showed a tolerable safety profile with a 49.3% disease control rate, demonstrating evidence of clinical activity in heavily pretreated patients [3].
- Here, we present pharmacodynamic effects and exploratory biomarkers associated with clinical benefit in peripheral blood, including intra-tumoral effects from a single case study.

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



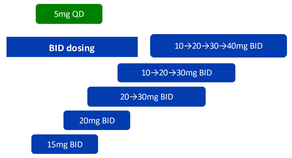
Study Design

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

Phase 1a monotherapy dose escalation

Key eligibility criteria

- Age ≥18 years
- Metastatic/unresectable disease and exhausted available therapies
- Measurable disease according to applicable response criteria
- ECOG PS 0–1

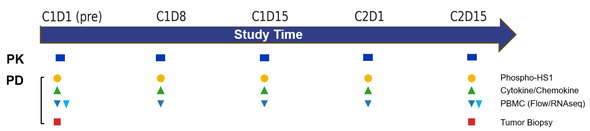


Translational Strategy & Methods

Figure 3A. Translational Strategy and Biomarker Plan

Whole blood / PBMCs	Plasma	Tumor Biopsy: FFPE
Proximal PD biomarker Phospho HS1 (pHS1)	PK	IHC of distal PD biomarkers (i.e. T cells, NK cells, activation)
T-cell Phenotype & Function (e.g. exhaustion/activation)	Circulating chemokines/cytokines	RNA Seq (agnostic evaluation of response in TME)
RNA Seq (agnostic evaluation of pharmacodynamic modulation in circulation)		

Figure 3B. PK/PD Sampling Schema and Schedule

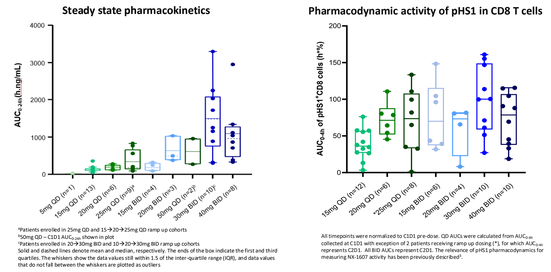


Methods:

- Proximal biomarker (pHS1) was evaluated in whole blood post ex vivo CD3/CD28 stimulation. All timepoints were normalized to C1D1 pre-dose. QD AUCs were calculated from AUC_{0-4h} collected at C1D1. All BID AUCs represent C2D1. The details of measuring pHS1 as readout for NX-1607 activity has been previously described [3].
- Chemokines/cytokines were evaluated in plasma from patients using the Human CytokineMAP v1.0 panel.
- Collected cryopreserved PBMC (cPBMC) were used for evaluation of T-cell phenotype and function by flow cytometry (IBN/ICS panels).
- Bulk RNAseq was used to assess GEP profiling in PBMCs and in FFPE biopsies.
- IHC of paired tumor biopsies from one patient with stable disease was evaluated using clinically validated markers.
- GSEA and Gene Signature Enrichment analyses were performed with publicly available GO database and published deconvolution gene signatures [4-8].

Results

Figure 4. NX-1607 Demonstrates Dose-dependent PK and PD Modulation of the Proximal Biomarker pHS1

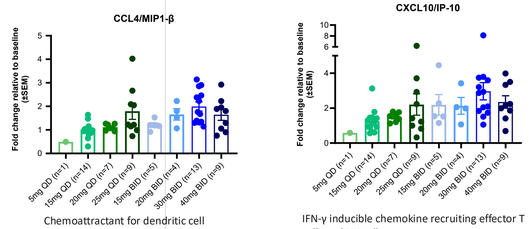


[a]Patients enrolled in 25mg QD and 15→20→25mg QD ramp up cohorts
[b]50mg QD – C1D1 AUC_{0-4h} shown in plot
[c]Patients enrolled in 20→30mg BID and 10→20→30mg BID ramp up cohorts
Solid and dashed lines denote mean and median, respectively. The ends of the box indicate the first and third quartiles. 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_{0-4h} collected at C1D1 with exception of 2 patients receiving ramp up dosing [a], 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[3].

- 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 the Distal Biomarkers: Chemokines CXCL10 and CCL4

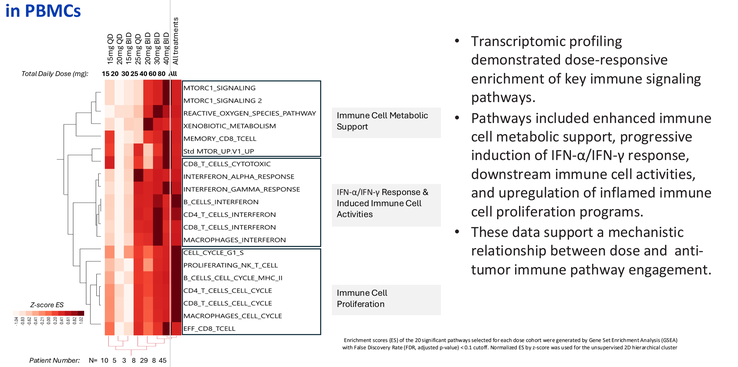


Chemoattractant for dendritic cell recruitment

IFN-γ inducible chemokine recruiting effector T cells and NK cells

- NX-1607 treatment led to an increase in the peripheral chemokines, CXCL10 and CCL4 at C2D15, suggesting the upregulation of pro-inflammatory signaling and corresponding immune cell recruitment.

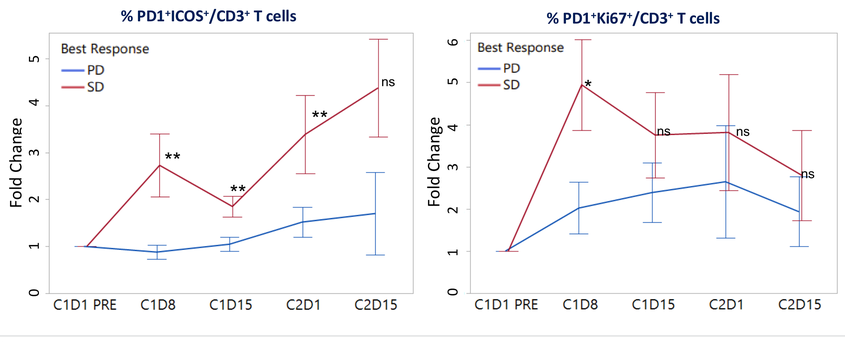
Figure 6. NX-1607 Induces Dose-responsive Activation of Immune Signaling Pathways in PBMCs



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, downstream immune cell activities, and upregulation of inflamed immune cell proliferation programs.
- These data support a mechanistic relationship between dose and anti-tumor immune pathway engagement.

Figure 7. NX-1607 Induces Peripheral T cell Activation and Proliferation in Patients with Stable Disease (SD)



Post-treatment phenotypic changes in T cells from peripheral blood were evaluated by flow cytometry and depicted as the fold change from baseline. In patients with SD, NX-1607 induced greater enrichment of circulating $PD1^+$ T cells expressing proliferation ($Ki67^+$) and activation/costimulatory markers ($ICOS^+$), reflecting active TCR engagement in response to treatment.

(Statistical significance of differences between SD (N=7-10) and PD (N=3-8) was evaluated for each time point using Mann-Whitney test. Statistical significance: not significant (ns) P > 0.05, * P ≤ 0.05, ** P ≤ 0.01.)

Conclusions

- Exposure to NX-1607 exhibits a dose-responsive PK profile in patients, leading to the activation of both innate and adaptive immunity.
- Enrichment and activation of peripheral $PD1^+$ T cells was observed in patients with stable disease and associated with clinical benefit, consistent with the hypothesized mechanism of action of NX-1607.
- A case study of a patient with stable disease provides evidence that NX-1607-induced peripheral immune activation trends reflect remodeling of the tumor microenvironment (TME); establishing a link between systemic immune activation and local tumor control.

Abbreviations

CTL: cytotoxic T lymphocyte. **Tcm: c**entral memory T-cell; **Tem**: effector memory T-cell; **Tscm**: T-stem cell memory; **NK:** natural killer cell; **PD:** progressive disease; **SD:** stable disease; **mCRPC**: metastatic castration-resistant prostate cancer; **IHC:** immunohistochemistry; **PBMC:** peripheral blood mononuclear cells; **Flow**: flow cytometry; **RNAseq:** RNA sequencing; **C1D1:** cycle1 day1; **C1D15**: cycle1 day15; **GSEA**: gene enrichment analysis; **TCR**: T-cell receptor; **TIL**: tumor-infiltrated T cells; **TME**: tumor microenvironment

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Figure 8. Case Study: NX-1607 Reshapes Intra-tumoral Innate and Adaptive Immune Responses in a mCRPC Patient with Stable Disease (SD)

A. *Patient profile and clinical course*

Clinical Presentation

METASTATIC CASTRATION RESISTANT PROSTATE CANCER
73-year-old male

5 prior lines of therapy:
Bicalutamide
Enzalutamide
Docetaxel
Enzalutamide
CCS1477+Darolutamide

6th line of therapy:
NX-1607, dosed with 30mg BID

Objective Response

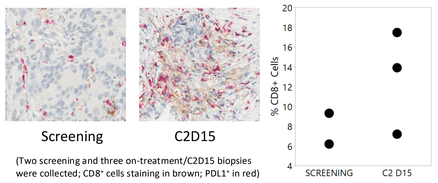
BEST RESPONSE, STABLE DISEASE

Assessment Schedule:
Week 9: Stable Disease
Week 18: Stable Disease
Week 27: Progressive disease with new skeletal lesions

PSA Response: No reduction in PSA observed throughout treatment.

Stable Disease Achieved for 27 Weeks

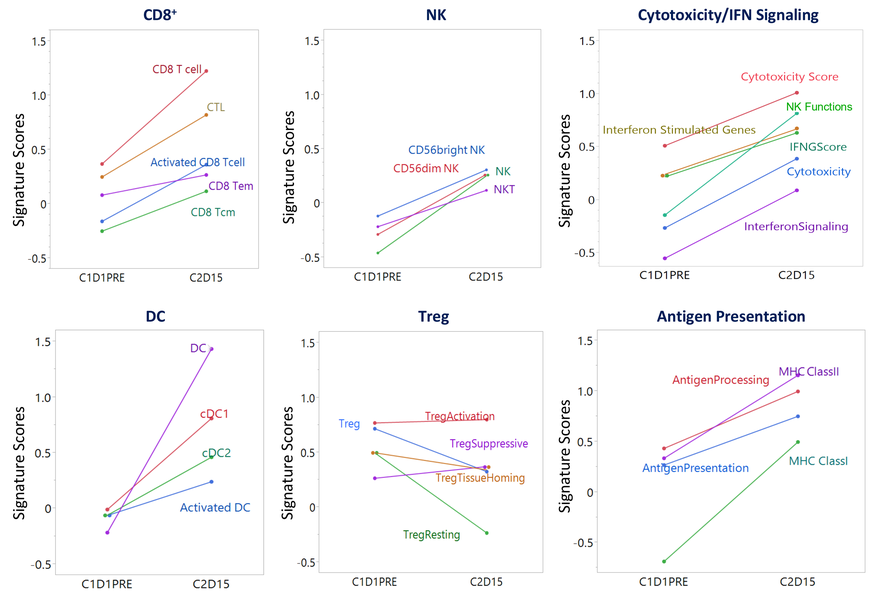
B. *NX-1607 increases the density of $CD8^+$ TIL*



(Two screening and three on-treatment/C2D15 biopsies were collected; $CD8^+$ cells staining in brown; $PDL1^+$ in red)

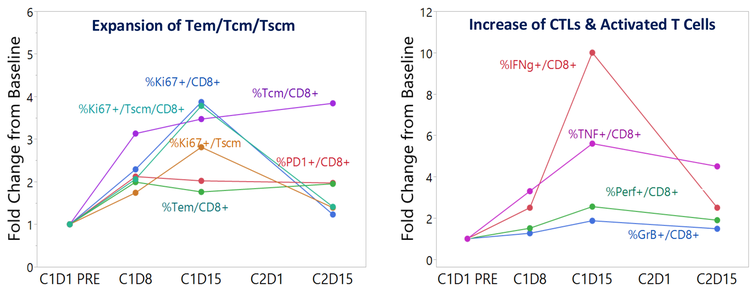
IHC analysis of paired metastatic lymph node tumor biopsies (screening vs. C2D15) from one patient with SD, showed an increase in the $\%CD8^+$ TILs post treatment, reflecting the pharmacodynamic promotion of "inflamed" TME.

C. *NX-1607 enhances gene signatures of immune responses within a tumor*



Gene signatures of immune subpopulations and corresponding function scores were used for the enrichment analysis of bulk tumor RNA of the patient with SD. NX-1607 enhanced effector cell ($CD8^+$ T and NK) and antigen-presenting cell (DC) activities in the TME, leading to elevated cytotoxic and interferon-driven immune responses. Treg signatures were downregulated, suggesting NX-1607 lowers the immune suppressive signatures in the TME.

D. *NX-1607 enhances expansion and activation of T cell subsets in the periphery*



Phenotypic analysis of peripheral blood T-cells by flow cytometry shows an expansion of CTL, Tem, Tcm, Tscm and $PD1^+$ (antigen-experienced) $CD8^+$ subsets at C1D8 persisting through C2D15, indicative of enhanced antitumor immunity and responsiveness.