NX-2127, a Degrader of BTK and IMiD Neosubstrates, for the Treatment of B-Cell Malignancies

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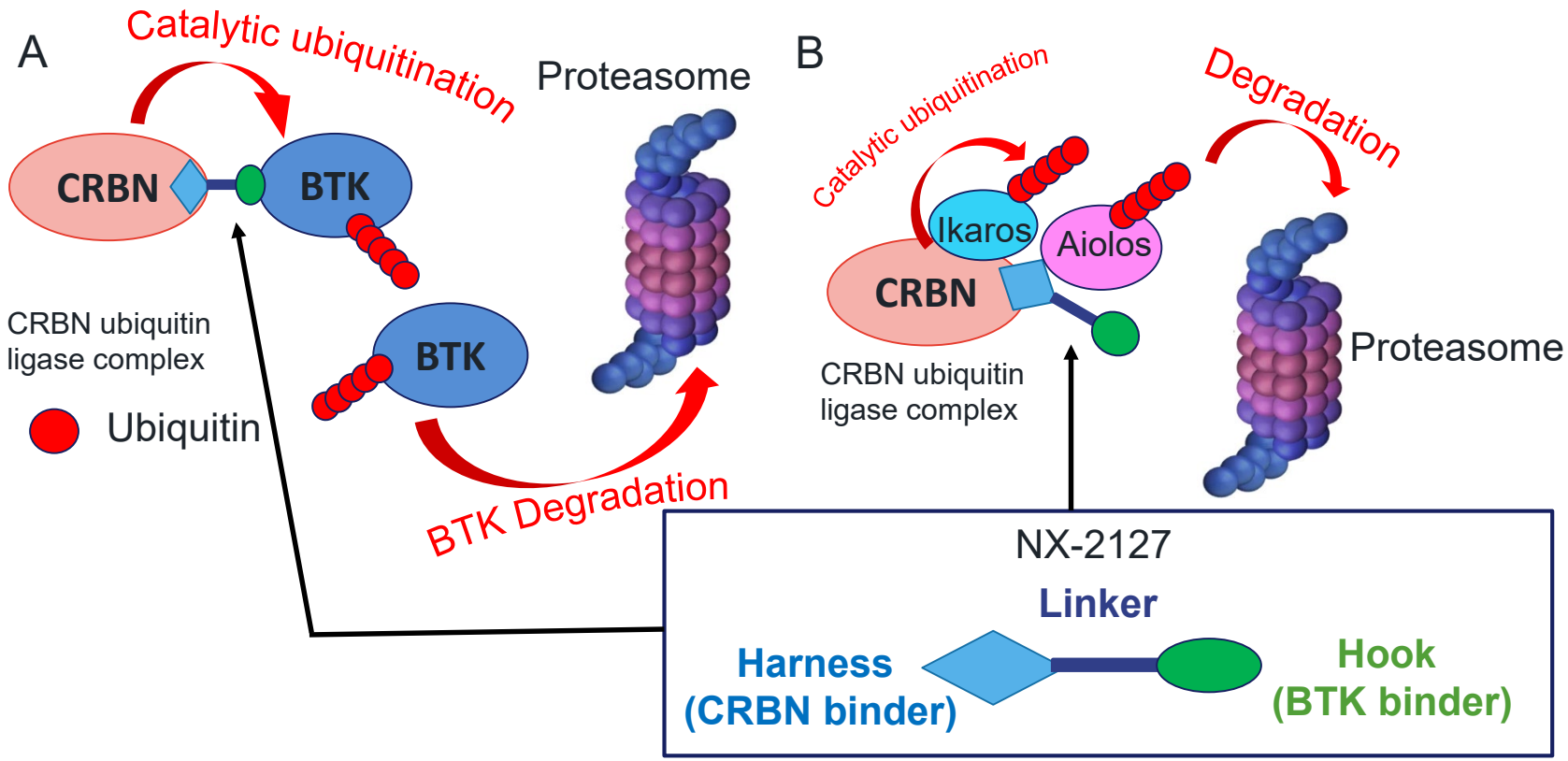
Disclosures

All authors of this presentation are current or former employees and shareholders of Nurix Therapeutics.

NX-2127 has a dual degradation mechanism of action for two clinically validated targets

- BTK is a tyrosine kinase involved in B cell development, differentiation and signaling
- BTK inhibitors are approved for treatment of B cell malignancies
- Mutations to BTK have conferred resistance to approved agents indicating an area of unmet medical need
- IMiD therapies have shown efficacy in some aggressive B-cell malignancies
- The dual action of BTK degradation and IMiD activity may provide a unique treatment strategy for relapsed/refractory B-cell malignancies

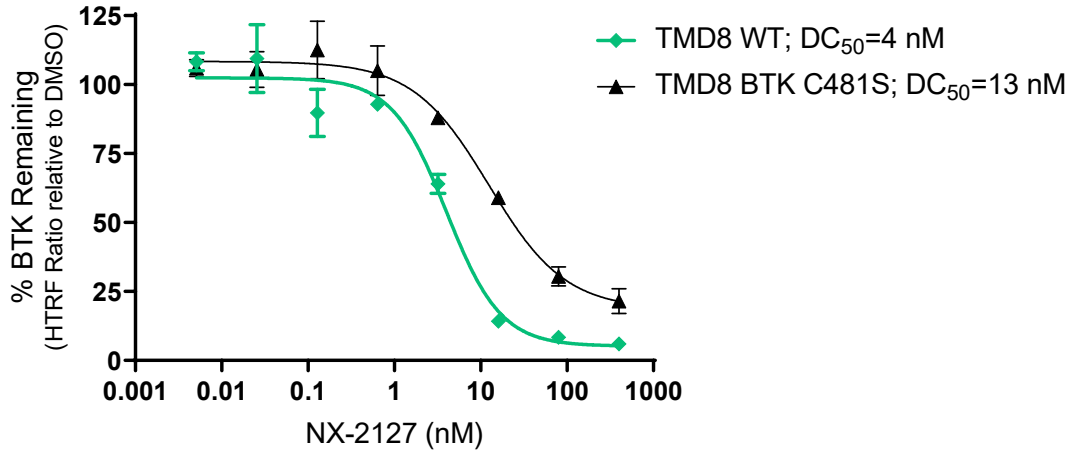


(A) NX-2127 is a novel, hetero-bifunctional, orally administered, Chimeric Targeting Molecule (CTM) that induces the degradation of Bruton's Tyrosine Kinase (BTK) in cells through recruitment of cereblon (CRBN), a component of the CRL4-CRBN ubiquitin ligase complex

(B) The engagement of NX-2127 also catalyzes neosubstrate degradation of Aiolos (IKZF3) and Ikaros (IKZF1), two transcription factors regulating T-cell function

NX-2127 catalyzes BTK degradation and anti-proliferative activity in cancer cell lines

A



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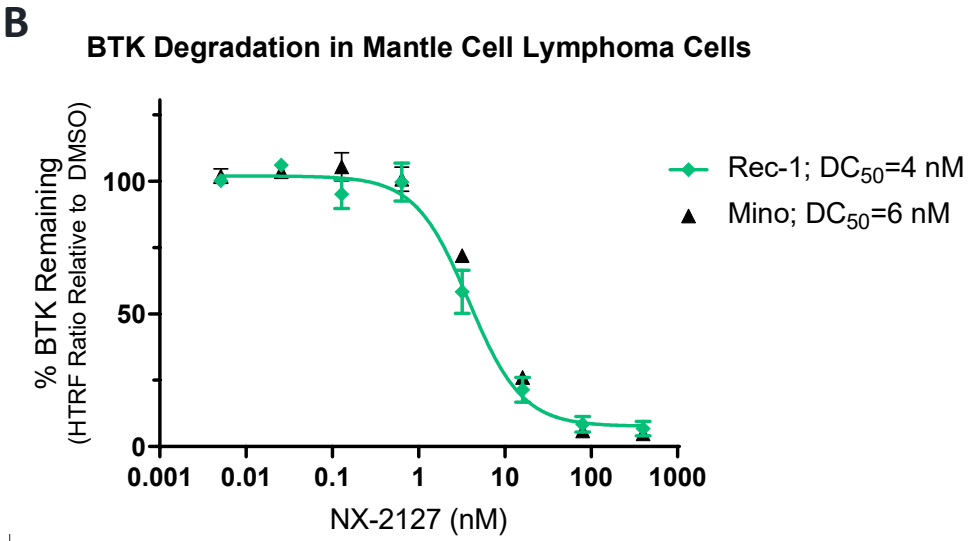

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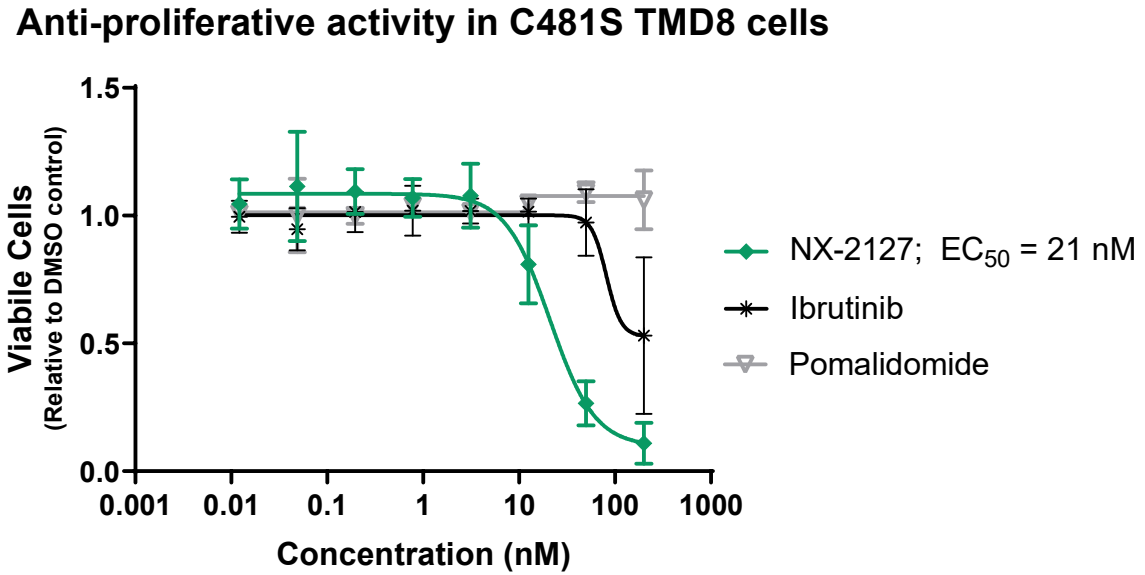


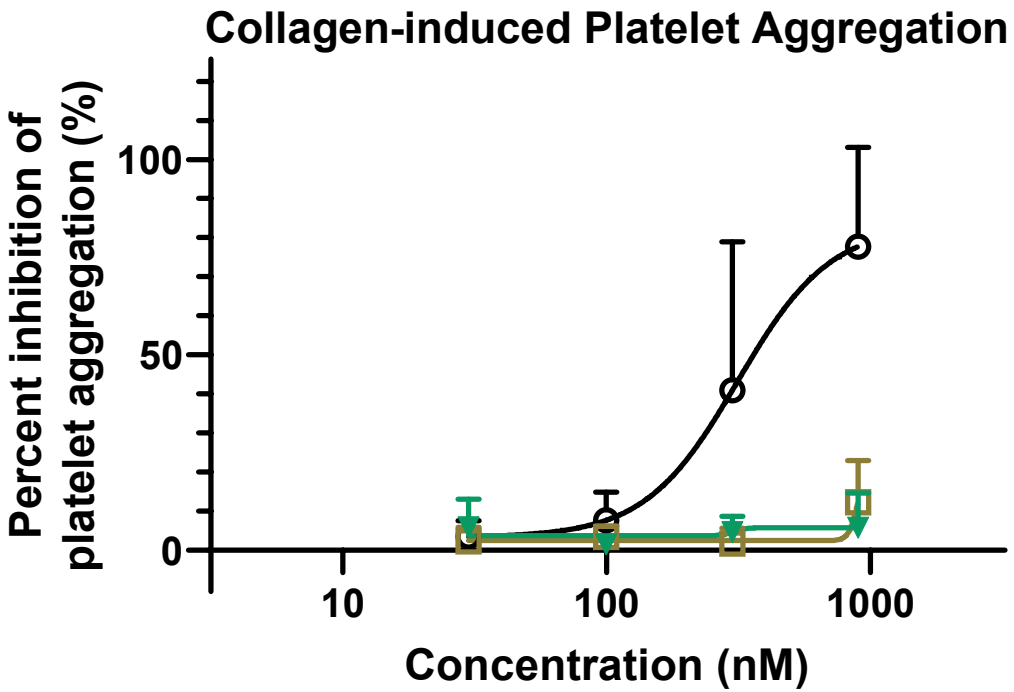
(A) NX-2127 catalyzes potent degradation of BTK in DLBCL cell lines (TMD8), including cells with the ibrutinib-resistance mutation BTK^{C481S}

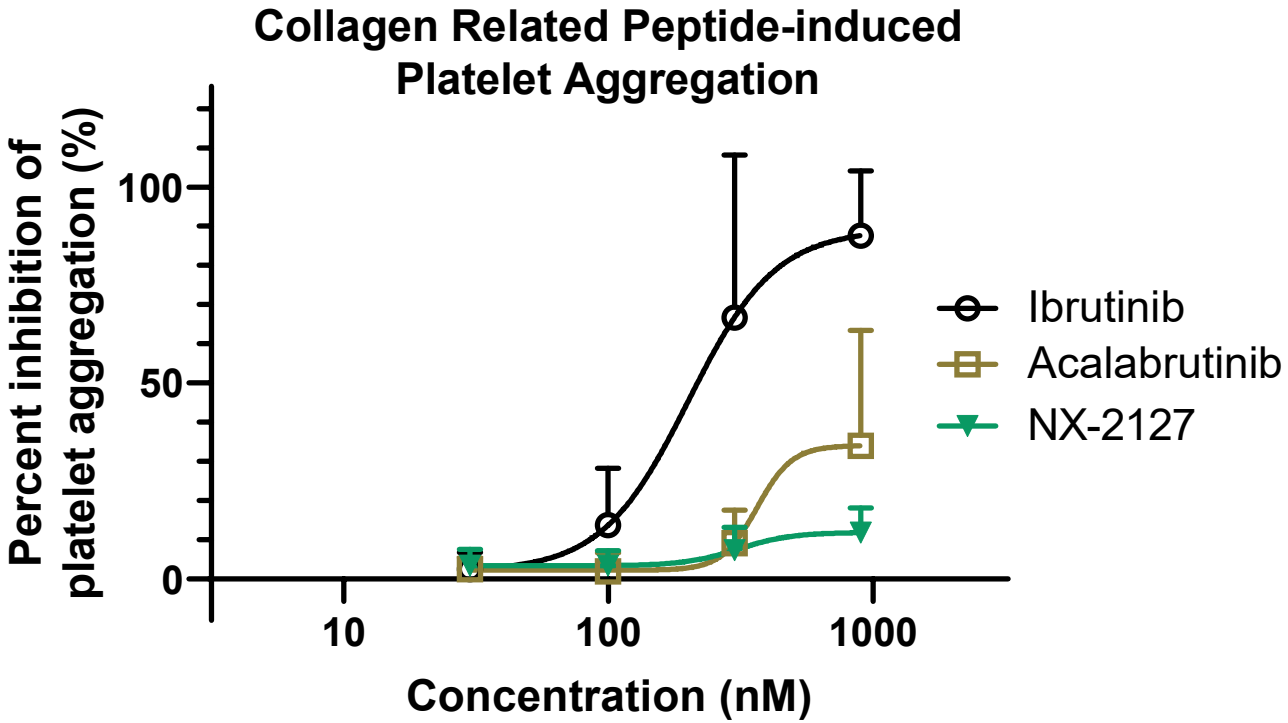
(B) NX-2127 catalyzes BTK degradation in Rec-1 and Mino mantle cell lymphoma cell lines

(C) NX-2127 potently blocks cell proliferation of BTK^{C481S} TMD8 cells relative to ibrutinib

DC_{50} = half maximal degradation concentration
HTRF = Homogeneous Time Resolved Fluorescence

NX-2127 has minimal *in vitro* effects on platelet aggregation





- NX-2127 does not show significant inhibition of platelet aggregation in an *in vitro* platelet aggregation assay

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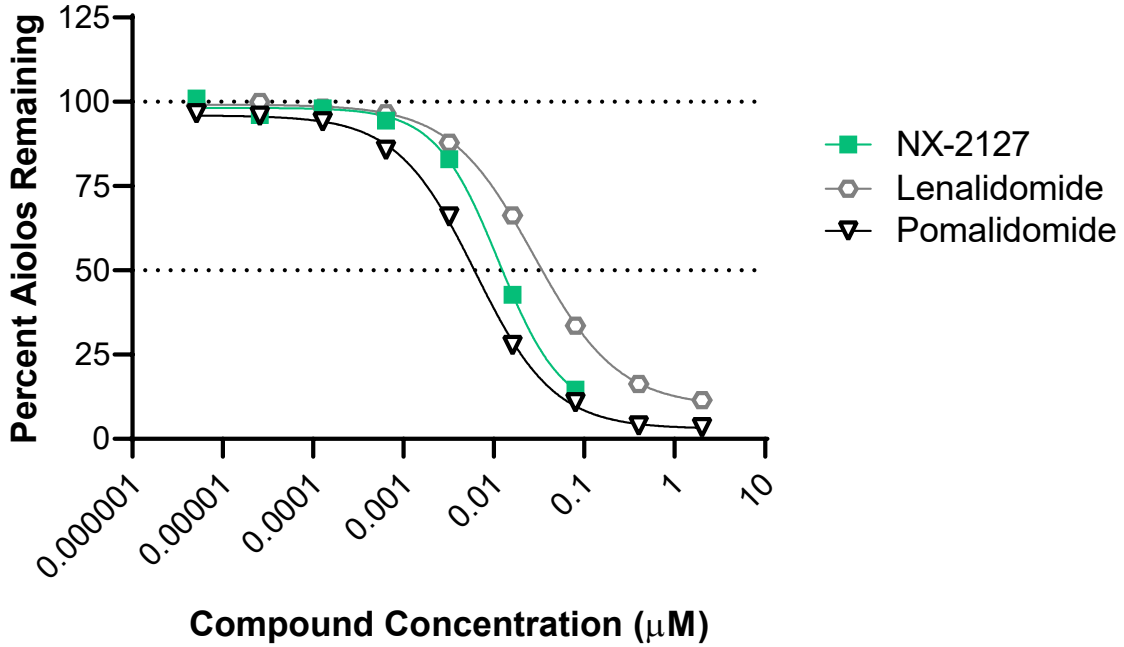
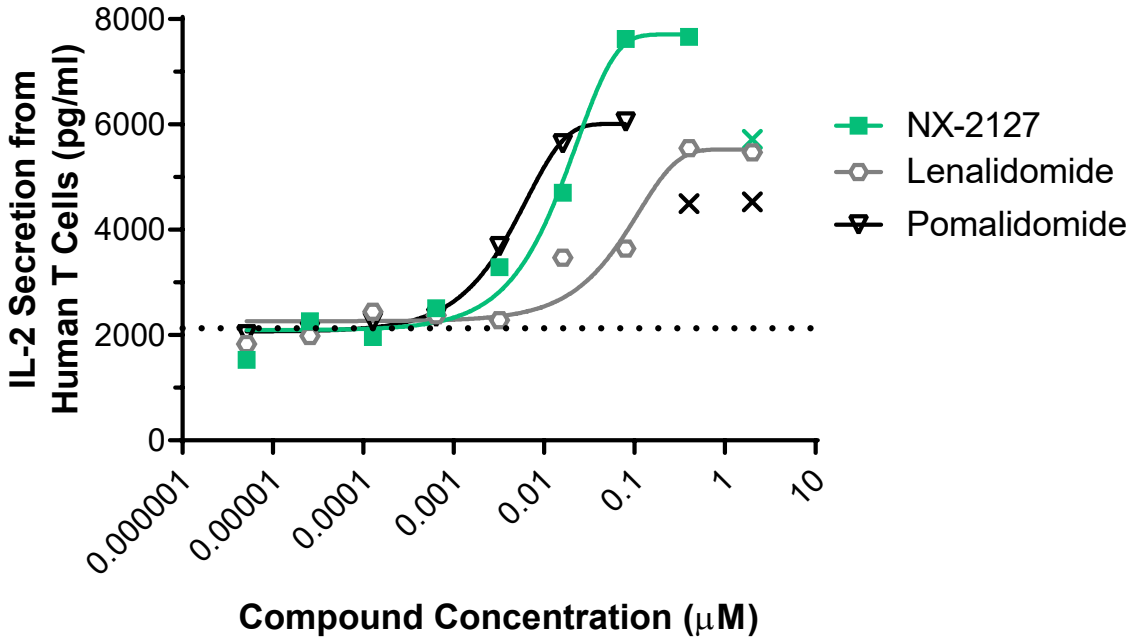
NX-2127 catalyzes Aiolos degradation and IL-2 production similar to IMiD drugs

IMiD Activity: Aiolos Degradation in Naïve Human T Cells



- NX-2127 degrades Aiolos with similar potency to that of pomalidomide and lenalidomide

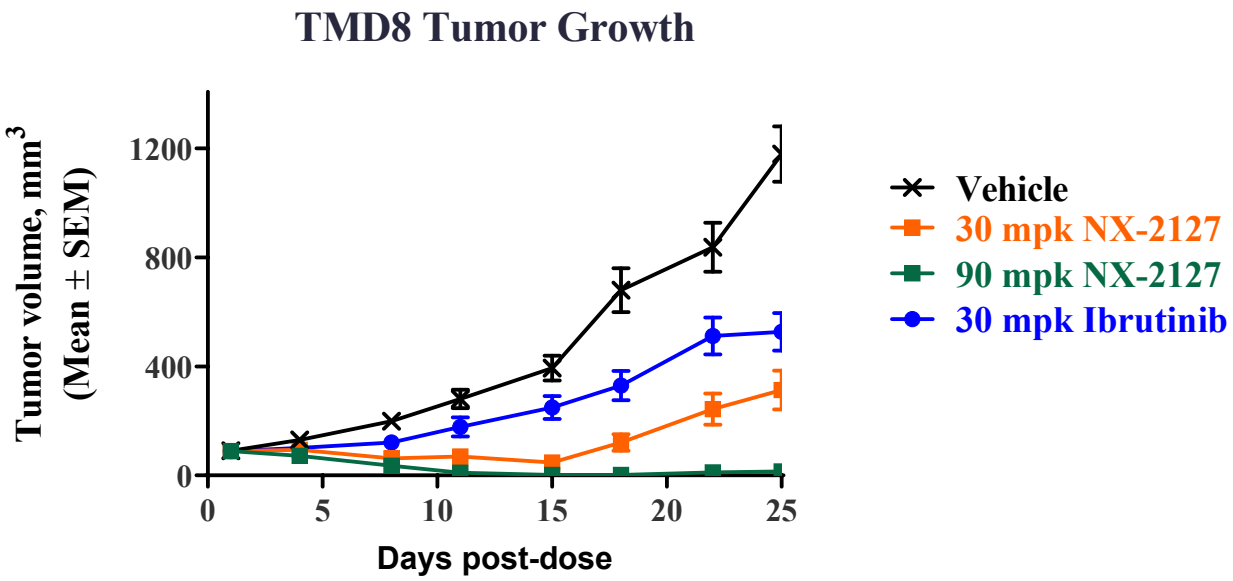
IMiD Activity: T Cell Activation and IL-2 Secretion



- NX-2127 exhibits IMiD-like activity by activation and IL-2 production following CD3/CD28 stimulation

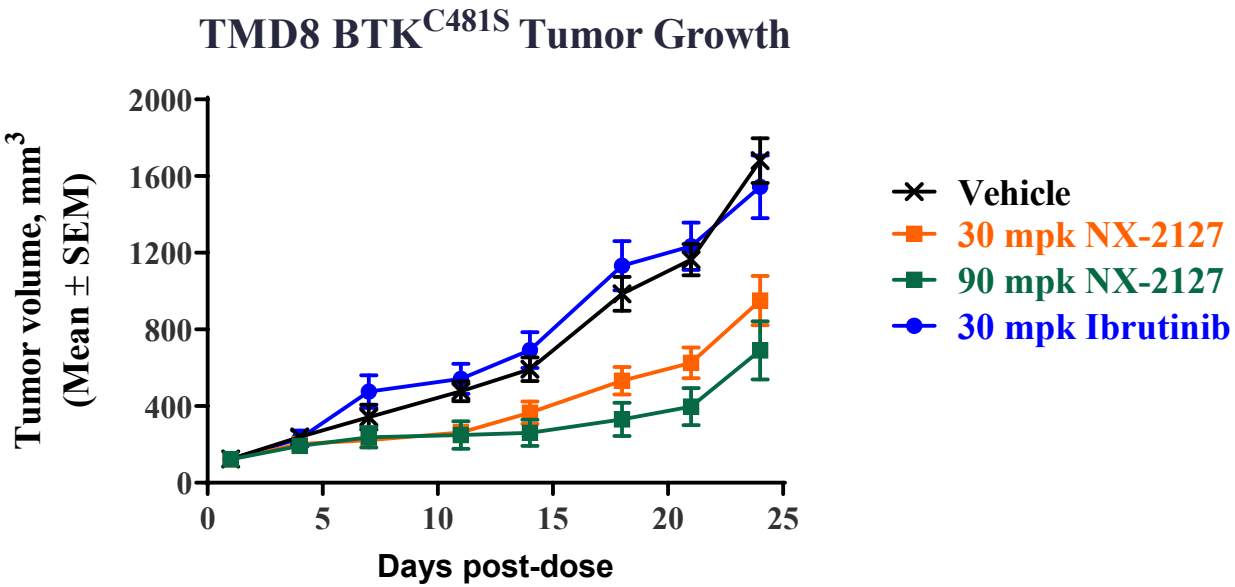
Oral Administration of NX-2127 Demonstrates Cancer Growth Inhibition in Mouse Xenograft Tumor Model

Tumor Growth Inhibition in Xenograft Model of Wild Type Lymphoma



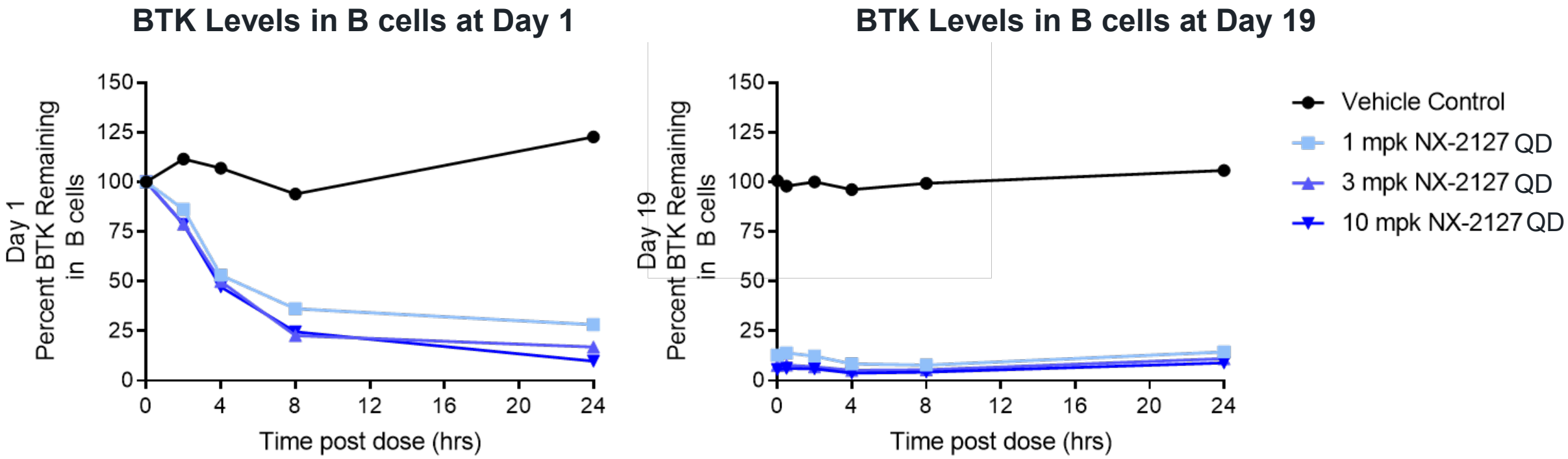
- NX-2127 demonstrates comparable tumor growth inhibition to ibrutinib in a xenograft mouse model containing tumors with a wild type BTK

Tumor Growth Inhibition in Xenograft Model of Mutant Ibrutinib-Resistant Lymphoma



- NX-2127 shows more potent tumor growth inhibition compared to ibrutinib in a xenograft mouse model containing tumors with the most common human resistance mutation (C481S) in BTK target protein

Oral Dosing of NX-2127 Degrades BTK in Cynomolgus Monkey



- NX-2127 induces significant degradation of BTK in 4 hours and more than 90% degradation through 24 hours post dose
- Once daily, oral dosing of NX-2127 maintains suppression of BTK protein levels throughout the 19-day duration of the study (NX-2127 PK $t_{1/2}$ = 5.4 h)

Summary and Conclusions

- NX-2127 catalyzes potent BTK degradation *in vitro* and results in anti-proliferative effects in human lymphoma cell lines
- The IMiD activity of NX-2127 is similar to that of IMiD drugs pomalidomide and lenalidomide and results in T-cell activation
- NX-2127 demonstrates potent BTK degradation *in vivo* upon oral dosing in cynomolgus monkey and displays anti-tumor effects in both wild-type and C481S mutant mouse xenograft tumor models
- NX-2127 combines BTK degradation with IMiD activity to provide an attractive therapeutic strategy in the setting of resistance mutations and an expanded set of B-cell malignancies

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