7114 Therapeutic Potential of BTK-targeted Degrader in B-Cell Malignancies Harboring Ibrutinib-Resistant Mutation

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Abstract

The long-term efficacy of Ibrutinib is limited by the emergence of resistance mutations (e.g., C481S, L528W). These mutations preclude formation of a covalent bond with BTK, leading to diminished drug efficacy and disease progression[1]. Therefore, novel therapeutic strategy is urgently needed for patients who have acquired resistant mutations of Ibrutinib. Targeted protein degradation represents a potential and powerful means to overcome Ibrutinib resistance.

Methods

To evaluate BTK degradation as a strategy to overcome ibrutinib resistance, we characterized Bexobrutideg (NX-5948), a novel Cereblon E3 ligase-engaging small molecule that induces BTK protein degradation[2]. *In vitro*, NX-5948 exhibited potent antiproliferative effects against Ibrutinib-sensitive and -resistant B-cell malignancy models (including BTK-C481S and BTK-L528W mutants). *In vivo*, NX-5948 achieved significant tumor growth inhibition in CDX models harboring these resistance mutations as well as in Ibrutinib-induced resistant DLBCL PDX model, demonstrating its potential to overcome clinical resistance to Ibrutinib.

Results

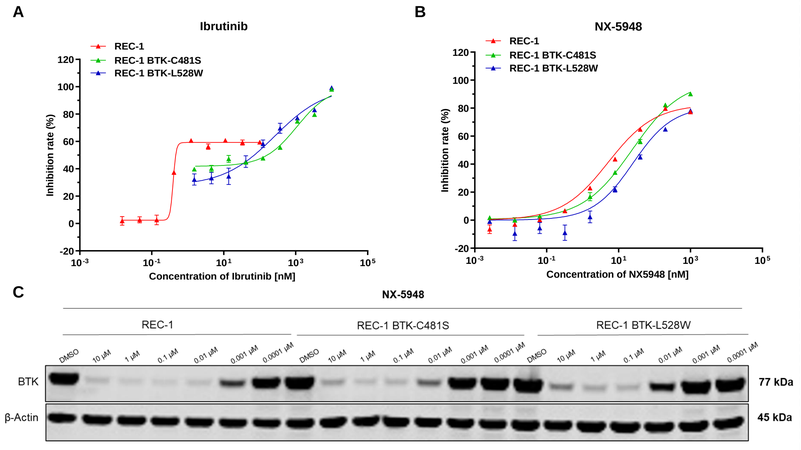

Figure 1. *In vitro* validation of NX-5948 in cell lines. (A, B) Inhibition rate curves of Ibrutinib (A) and NX5948 (B) in REC-1, REC-1 BTK-C481S and REC-1 BTK-L528W cell lines (C) BTK protein degradation in REC-1, REC-1 BTK-C481S and REC-1 BTK-L528W cell lines by western blot.

Results

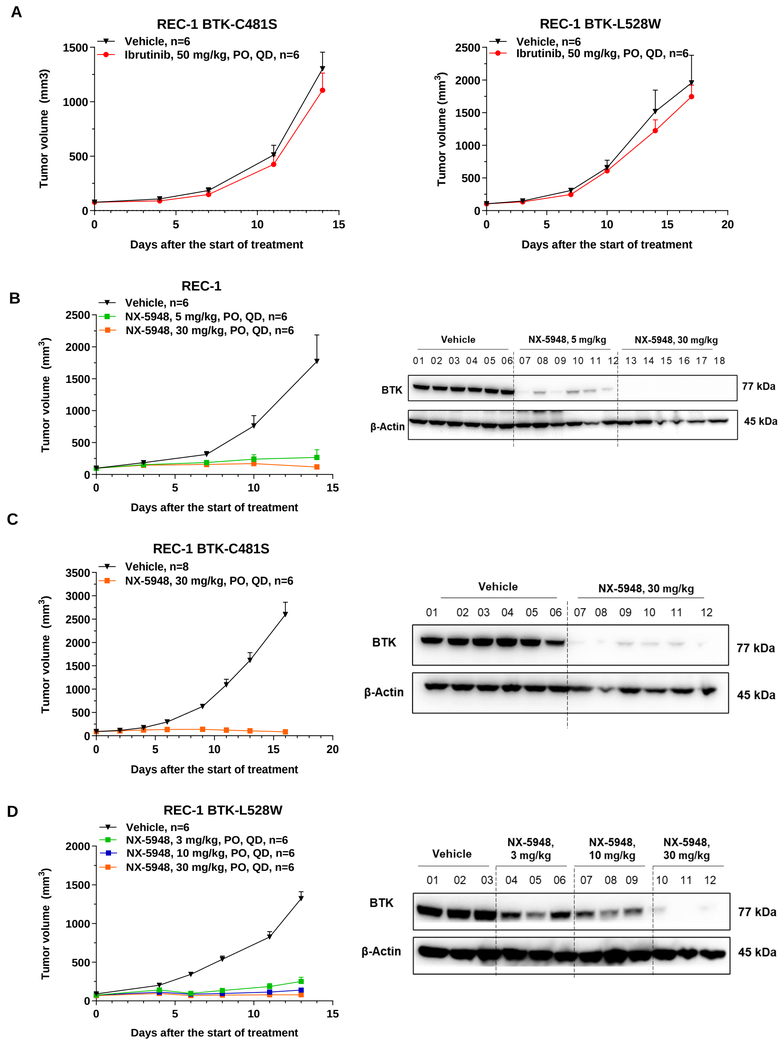

Figure 2. Therapeutic efficacy of NX-5948 in lymphoma CDX models. (A) Tumor growth curves of CDX models treated with Ibrutinib. (B, C, D) Tumor growth curves of CDX models treated with NX-5948, along with BTK protein expression in CDX tumor samples by western blot.

Results

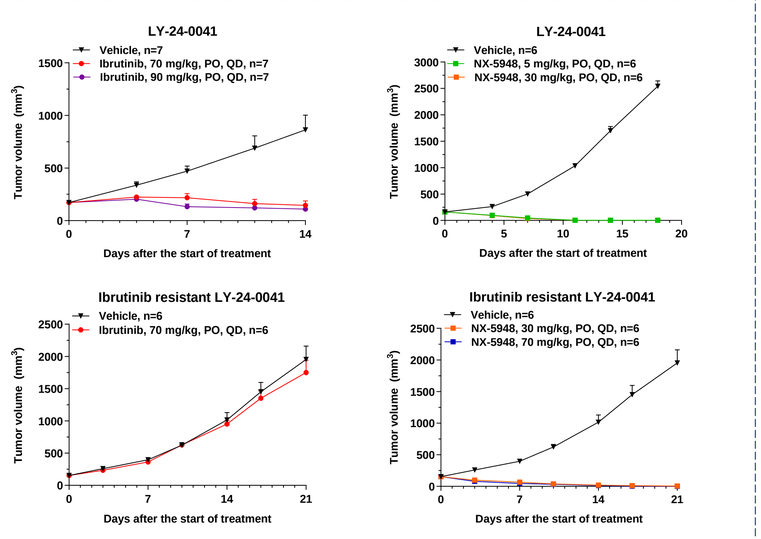

Figure 3. Therapeutic efficacy of NX-5948 in DLBCL PDX models. (A, B) Tumor growth curves of Ibrutinib sensitive LY-24-0041 model (A) and Ibrutinib-induced resistant model Ibrutinib-R-LY-24-0041 (B) treated with Ibrutinib and NX-5948.

Conclusions

In summary, we have successfully established two Ibrutinib-resistant CDX models (REC-1 BTK-C481S and REC-1 BTK-L528W) and one Ibrutinib-resistant DLBCL PDX model (Ibrutinib-R-LY-24-0041) and validated the anti-tumor activity of BTK-targeted degrader NX-5948 in these Ibrutinib-resistant models. These findings support that BTK degrader could be a promising strategy to cure patients with B-cell malignancies and even bypass resistance by previous generation of BTK targeting strategies.

References

1. Montoya S, Bourcier J et al. “Kinase-impaired BTK mutations are susceptible to clinical-stage BTK and IKZF1/3 degrader NX-2127” **Science**. 2024 Feb 2;383(6682):eadi5798. doi: 10.1126/science.adi5798.
2. Searle E , Forconi F , Linton K ,et al. “Initial Findings from a First-in-Human Phase 1a/b Trial of NX-5948, a Selective Bruton's Tyrosine Kinase (BTK) Degrader, in Patients with Relapsed/Refractory B Cell Malignancies” [J].**Blood**, 2023, 142(Sup1):3.DOI:10.1182/blood-2023-179508.

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