491 PRECLINICAL PHARMACOLOGY MODELING OF HX009, A CLINICAL STAGE FIRST-IN-CLASS PD-1XCD47 BSAB, FOR ANTI-LYMPHOMA APPLICATIONS

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Background The important immune checkpoint inhibitors (ICIs), e.g. PD1/PD-L1 and CD47/SIRPα blockers, have yet to be successful for the majority of non-Hodgkin's lymphoma (NHL), albeit efficacious in NK/T-cell and Hodgkin's lymphoma, as well as in many solid tumors. CD47 targeting in the clinic, predominantly for lymphoma and AML remains challenging due to reported toxicities (*e.g.* anemia/thrombocytopenia) as well as insufficient efficacy. Many important lymphomas, *e.g.* T-cell lymphoma, relapsed/refractory DLBCL etc., remain to be unmet medical needs, warranting new treatment options, particularly immunotherapies. We hypothesized that the dual targeting both innate (CD47) and adoptive (PD-1) immune check points with a bi-specific antibody (BsAb) can significantly enhance efficacy, and that the hematological toxicity can be minimized through specific engineering.

Methods HX009, a 2x2 symmetric BsAb molecule targeting PD1/CD47, was designed and constructed by grafting a low affinity $SIRP_{\alpha}$ to the 3' of Fc HX008 (anti-PD1 IgG1-Mab) frame with weakened CD47 binding. A series of *in vitro* characterizations on the target binding and functional blocking were performed, followed by *in vivo* pharmacology modeling using several preclinical lymphoma models (10mg/kg, twice weekly, i.p.), including subcutaneous xenograft (Karpas-299-T/Raji-B lymphoma), patient-derived lymphoma xenografts (PDXs), and humanized mouse syngeneic B-cell lymphoma A20 (HuGEMM^{TM} PD1Xcd47) . Tumor growth inhibition (TGI) was calculated by measuring tumor volume biweekly.

Results HX009 target binding, ligand blocking and biological effects were confirmed *in vitro*, with little binding to RBCs along as little hematological toxicity in the NHP studies due to the confirmed reduced affinity to CD47. All tested xenograft modeling using T-/B- cell lymphoma CDXs and PDXs revealed strong anti-lymphoma activity by HX009, which was solely attributed to the CD47 targeting due to the lack of T-cell immunity in the xenografts. The humanized syngeneic mouse B-lymphoma A20 model with the presence of competent autologous immune-system revealed that both single targeting, either PD1 (HX008) or CD47 (SIRPα), had anti-tumor activity, while the dual targeting of both by HX009 caused synergistic anti-tumor activity. Finally, a panel of fully annotated lymphoma PDXs were tested in order to discover potential predicative biomarkers.

Conclusions HX009 demonstrated strong preclinical anti-lymphoma activity of HX009, confirming the contributions from both targeting MOAs (CD47/PD1), as well the superior activity of dual targeting as designed, validating our hypothesis. A Phase I/II study for this first-in-class BsAb is ongoing in patients with relapsed/refractory lymphoma, including both B and T cell subtypes (ClinicalTrials.gov Identifier: NCT05189093).

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