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 SIRPα 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™ 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).