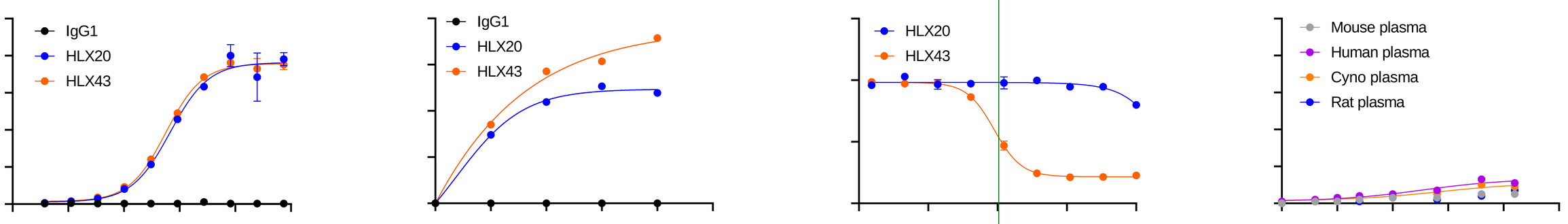
PD-1/PD-L1 monoclonal antibodies, as the most successful immune checkpoint inhibitors, have revolutionized the treatment of cancer. However, there are still many patients with positive PD-L1 expression who do not respond to or develop resistance to PD-1/PD-L1-targeted therapy. The favorable expression of PD-L1 in tumors makes it an attractive target for ADC development, which might alter the treatment for PD-1/PD-L1 inhibitor refractory/resistant (R/R) cancers.

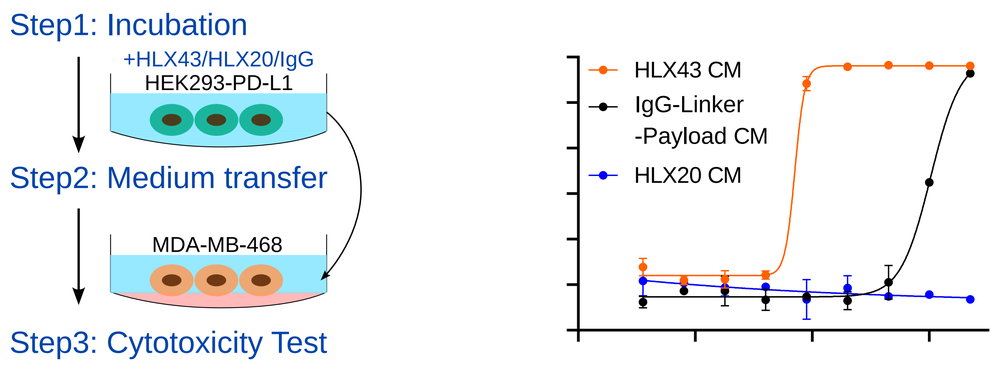
Methods: HLX43 is a PD-L1-targeting ADC, composed of an engineered version of the anti-PD-L1 humanized IgG1 antibody (HLX20), conjugated via a next-generation linker to a camptothecin-based toxin. The drug to antibody ratio is around 8. This novel linker-payload is preferentially activated for cleavage in the tumor microenvironment. And the tumor-specific release of the toxin is independent of the internalization of the ADC.* This unique mechanism of action can efficiently deliver toxin into PD-L1-expressing malignant cells, while sparing the normal cells, which will greatly reduce the systemic toxicity associated with the non-specific release of toxin in the periphery. HLX43 was examined in antigen binding, internalization, plasma stability and immunotoxicity assays. In vivo efficacy studies were performed in breast cancer CDX and PDX models from non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC).

In vitro studies demonstrated that HLX43 possessed similar affinity and internalization rate compared to parental antibody, and it showed good stability in the plasma of rats, cynomolgus monkeys and humans. HLX43 shows no immunotoxicity towards PD-L1 positive human APCs. In *in vivo* efficacy studies, HLX43 induced tumor regression in multiple PDX models, and was well tolerated, with no changes in body weight compared to control animals across all dosing groups. In the MDA-MB-231 CDX model, weekly administration of HLX43 for three times induced significant tumor regression and superior anticancer efficacy over the anti-PD-L1-GGFG-Dxd and anti-PD-L1-vc-MMAE at equivalent doses, while no body weight loss was observed. In the NSCLC PDX model, weekly administration of HLX43 for three times, HLX43 caused obvious regression of tumors. Even after stopping treatment for 3 weeks, HLX43 at 8 mg/kg groups still had durable response in lesions. After 3-week treatment in this PDX, the TGI of the IgG-linker-payload 8 mpk group was 61.6%, indicating the tumor microenvironment-specific lysis of linker-payload. HLX43 also induced significant tumor regression in HCC PDX model with (IHC1+) or without (IHC-) PD-L1 expression, meanwhile showed strong synergy with anti-VEGF antibody. In the toxicology studies in mice and cynomolgus monkeys, HLX43 was well tolerated in both species. On November 24th, 2023, the phase I clinical trial of HLX43 for the treatment of advance/metastatic solid tumors has completed the first patient dosing in China. Clinical trial information: NCT06115642

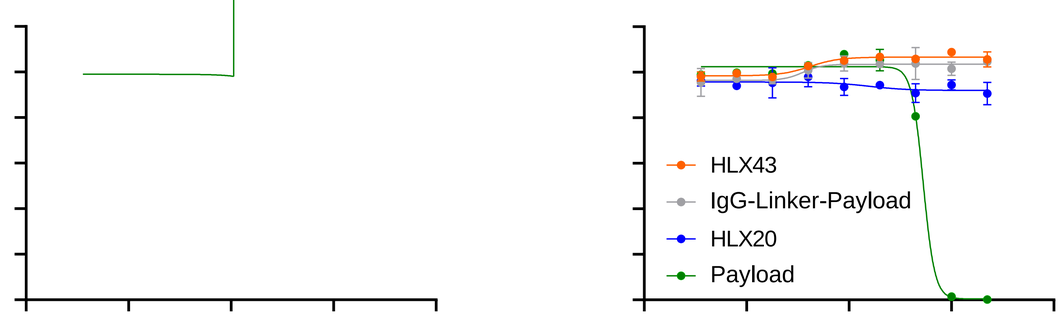
Taken together, these data strongly suggest that HLX43 is a highly promising ADC product with great clinical potential for treatment of advanced/metastatic solid tumors, especially for advanced/metastatic NSCLC and HCC patients with disease progression on standard treatments, which has urgent unmet medical needs.



(A) The binding ability of HLX43 towards PD-L1 antigen. (B) The internalization rate of HLX43 in NCI-H292 cells. (C) The ADCC effect of HLX43 in NCI-H292 cells. (D) The plasma stability of HLX43 from different animal species.



The cytotoxicity of conditional medium from HEK293-PD-L1 in MDA-MB-468 cells. CM: Condition Medium.



The immunotoxicity of HLX43 towards antigen-presenting cells (A, macrophage; B, dendritic cell)

Anti-tumor efficacy in the MDA-MB-231 CDX model(A), NSCLC PDX model(B), PD-L1:IHC1+,TPS 37.5%, HCC PDX model(C) and PD-L1:IHC-, TPS 8.3%, HCC PDX model(D).

Reference:* AACR; Cancer Res 2023;83(7_Suppl):Abstract nr 596.

Disclosures: All listed authors are employees of Henlius.