HLX42, a Novel EGFR-Targeting ADC, for Cetuximab or TKI Resistant Cancer

Yong-Qiang Shan, Rui Liu, Ge Song, Hong-Bin Song, Jia-Hao Jiang, Chen-Qiang Jia, Teng Feng, Xiao-Yan Huang, Xiao-ling Yuan, Wan-Jen Yang, Xiao-Mu Cheng, Xin-Jing Wang, Qian Wang, Chen Hu, Chang Zhao, Qing-Yu Wang, Jason Zhu.

Shanghai Henlius Biotech, Inc., Shanghai, China.

Corresponding author e-mail: yongqiang_shan@henlius.com

Henlius

LinkedIn: Henlius

Background: EGFR is highly expressed in multiple types of solid tumors. And its aberrant expression is well recognized as a driving force in tumorigenesis and disease progression. Despite the great success of monoclonal antibody targeting EGFR and 3rd generation receptor TKIs, there is still a significant unmet medical need for effective therapies for patients who are refractory to current therapies or relapse after standard of care. ADC targeting EGFR has entered the clinical stage and shown an acceptable safety profile and preliminary clinical activity. However, conventional EGFR ADCs may be associated with significant treatment-related toxicities since EGFR is broadly expressed in normal epithelial tissues.

Methods: HLX42 is a next-generation EGFR-targeting ADC, comprised of a high-affinity humanized IgG1 antibody targeting EGFR, conjugated to a novel topoisomerase-I inhibitor payload whose cleavage and release are tumor microenvironment dependent and do not require internalization by tumor cells into lysosomes. This unique mechanism of tumor microenvironment activation and payload release allows HLX42 to possess a higher therapeutic index and better safety profile. HLX42 was examined in antigen binding, internalization and plasma stability assays; efficacy analyses were performed in CDX and PDX models of non-small cell lung cancer (NSCLC) and metastatic colorectal cancer (mCRC).

Results: *In vitro* analyses demonstrated that HLX42 possessed similar affinity and internalization rate compared to parental antibody (HLX07), and it was stable in the plasma of rats, cynomolgus monkeys and humans. In *in vivo* studies, HLX42 showed potent tumor suppression in several CDX and PDX models that were resistant to Cetuximab or EGFR TKIs or anti-PD-1 antibody. In the NCI-H1993 model, weekly administration of HLX42 at 8 mg/kg for 3 weeks resulted in 91.5% TGI compared to 79.8% TGI when treated with anti-EGFR-GGFG-Dxd. Similarly, in the EBC-1 model, weekly administration of HLX42 at 8 mg/kg for 3 weeks eradicated all lesions. All mice remained tumor free 24 days after the last dose, while tumor began to regrow in the anti-EGFR-vc-MMAE treated group. Furthermore, in the LU3075 PDX model which poorly responded to Osimertinib monotherapy, HLX42 eradicated all lesions. In another PDX model harboring EGFR exon19 deletion/T790M/C797S mutations, which exhibited complete tolerance to Osimertinib, a single dose treatment resulted in significantly complete response. After 4-week treatment in this PDX, the TGI of the IgG-linker-payload 8 mpk group was 58.1%, indicating the tumor microenvironment-specific lysis of linker-payload. HLX42 also showed strong efficacy in HT29 CRC CDX model and Cetuximab and/or anti-PD-1 resistant microsatellite stable (MSS) mCRC PDX model. In toxicology studies conducted in rats and non-human primates, HLX42 had favorable safety profile. Based on these results, the US FDA granted Fast Track Designation (FTD) to HLX42 for the treatment of patients with advanced or metastatic EGFR-mutated NSCLC whose diseases have progressed on a 3rd-generation EGFR tyrosine kinase inhibitor treatment (27/12/2023). On March 14th, 2024,

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