A NOVEL PTK7-DIRECTED ANTIBODY-DRUG CONJUGATE (ADC) PRO1107 DEMONSTRATED BROAD ANTITUMOR ACTIVITY WITH A PROMISING SAFETY PROFILE IN PRECLINICAL MODELS

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Background Protein Tyrosine Kinase 7 (PTK7) is a member of the receptor protein tyrosine kinase family and appears to be an integral player in cancer cell stemness and tumor progression. PTK7 is overexpressed in many solid tumors with limited expression in normal tissues or organs. Historical effort has offered clinical proof-of-concept for developing PTK7-based anti-cancer therapy. PRO1107 comprises 1) a proprietary humanized monoclonal antibody specific for PTK7, 2) a novel protease-cleavable hydrophilic linker, and 3) the microtubule-disrupting agent, monomethyl auristatin E (MMAE) as the payload, at a drug to antibody ratio (DAR) of approximately 8. The linker and payload are collectively dubbed as LD343.1

Methods Homogeneity and hydrophilicity were measured by hydrophobic interaction chromatography. Binding affinity and cellular binding were evaluated in BLI and FACS assays, respectively. Internalization and in vitro cytotoxicity studies were conducted using standard methods. In vivo antitumor activity was evaluated in cell-derived xenograft (CDX) models in mice. Safety profile of PRO1107 was examined in a tolerability study in rats and a pilot non-GLP toxicity study in cynomolgus monkeys. An in-house synthesized analog of cofetuzumab pelidotin, a clinical-stage PTK7-directed DAR4 ADC, was included as the benchmarking agent in key studies.

Results PRO1107 is markedly more homogeneous and hydrophilic than cofetuzumab pelidotin. PRO1107 binds selectively and specifically to PTK7 with sub-nanomolar affinity and internalizes rapidly. PRO1107 demonstrates robust cytotoxicity against a panel of tumor cell lines as well as a strong bystander effect in vitro. PRO1107 produced potent antitumor effects that were superior to cofetuzumab pelidotin in CDX models representing lung, ovarian, and bladder cancer. In the rat tolerability study, MTD of PRO1107 (at DAR8) and cofetuzumab pelidotin (at DAR4) were approximately 30 and 15 mg/kg, respectively, suggesting a 4-fold increase in tolerated drug load. In the exploratory toxicity study in monkeys, PRO1107 was tolerated at doses up to 9 mg/kg with the main toxicity being payload (MMAE)-driven and residing in bone marrow. PRO1107 exhibited a stable PK profile that was similar to that of the unconjugated parent mAb in rats as well as favorable PK characteristics in monkeys.

Conclusions PRO1107 demonstrated very promising physiochemical properties, PK/PD, efficacy, and tolerability that were superior to cofetuzumab pelidotin in preclinical characterization. It may also carry an expanded therapeutic index compared to other antitubulin-based ADCs on conventional linker-drug platforms. PRO1107 is a highly exciting novel agent to bring forward to the clinic for the treatment of various solid tumors.

REFERENCE
1. Haidong Liu, Yang Xiao, Guobao Wang, Wanwan Shen, Lei Wang, Xiao Shang, Zhu Chen, Expanding the Therapeutic Index of MMAE-Based Antibody-Drug Conjugates (ADCs) with a Novel Linker System (LD343). SITC abstract ID: 2215. 2023