Target Expression/Efficacy Relationship of XMT-1522, a HER2-targeting Antibody Drug Conjugate (ADC), in an Unselected Series of Non-small Cell Lung Cancer (NSCLC) Primary Human Carcinoma Xenografts

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Abstract

XMT-1522 is a unique HER2 targeting antibody drug conjugate (ADC) with a high drug to antibody ratio, HER2 amplification, and an optimal metabolic linkage. In vivo efficacy, amplification and mutation have been described in non-small cell lung cancer. We describe the preclinical efficacy of XMT-1522 in an unselected series of human NSCLC primary xenografts. An immunohistochemical scoring method was established in human lung cancer specimens and this scoring algorithm was applied to representative xenograft blocks to examine a protein expression/efficacy relationship. This relationship was also evaluated by RNA expression methods.

Introduction

HER2/ERBB2 is a well validated target in tumors with HER2 gene amplification. Antibody-based therapies, trastuzumab and pertuzumab, and an ADC targeting HER2, trastuzumab emtansine (T-DM1), are approved in patients with HER2-positive breast cancer. However, gains in efficacy have been limited by resistance mechanisms in the tumor population. The distribution of blocks examined at each expression value is shown in Figure 1.

Methods

HER2/FISH scoring system was established in human NSCLC xenografts. RNA expression was assessed for a series of HER2 status selected to demonstrate the assay performance over a range of expression values. HER2/FISH scoring was performed using the IHC/FISH instrument (Ventana BenchMark Ultra) and the HER2 IHC/FISH kit along with a set of anti-HER2 antibodies. Samples were normalized in the Advanced Analysis Software Version 2.0.1, by NanoString, using default threshold settings.

XMT-1522 is a HER2-targeting antibody-drug conjugate with high drug loading (AF-HPA) and a novel antibody that does not compete with trastuzumab. Preclinical Efficacy/HER2 Expression Relationship

Methods (continued)

XMT-1522 is a novel antibody drug conjugate with a 12-AntiHER2 T-4-MonoPEG-poly-HER2 payload molecules per antibody that binds to a HER2 antibody epitope from the binding sites of trastuzumab/T-DM1 and pertuzumab. AF-HPA is capable of controlled bystander-effect killing, resulting in in vivo efficacy in tumors with heterogeneous antigen expression, and metabolically linked pathways.

Figure 2a

Methods

XMT-1522 was evaluated in syngeneic xenograft models in the Fleximer Polymer Biodegradable Water Soluble Anti HER2 Antibody Potent Anti-Mitotic Drug

Methods

HER2 IHC and FISH Evaluation in Human NSCLC

HER2 IHC (Ventana) was performed in human NSCLC FFPE tumor blocks. This population of specimens was subjected to an assay performance over a range of expression values. RNA was extracted from FFPE sections and analyzed using a NanoString Panel with multiple HER2 probes. Data from one probe is shown. Samples were normalized in the Advanced Analysis Software Version 2.0, 1.0 NanoString, using default threshold settings.

Figure 2b

Methods

XMT-1522 is a HER2-targeting antibody drug conjugate (ADC) with high drug loading (AF-HPA) and a novel antibody that does not compete with trastuzumab. In an unselected series of NSCLC Human Primary Xenografts, XMT-1522 at 3 mg/kg or 1 mg/kg x 3 resulted a median best response >50% in 8/18 or 7/14 models respectively.

ERBB2 protein target expression was necessary, but not sufficient for compound activity as evaluated by median best response

Figures 3a - 3c

Human tumors, HER2 RNA expression was related to lower levels of RNA expression

References:


Boluyt et al., AACR Annual Meeting 2017 (abstract #1587)


Acknowledgments:

The authors gratefully acknowledge the contributions of QuateK Molecular Laboratories, Newtown, CT (Fleximer & HSA) and Champions Oncology, Rockville, MD. (in vivo work).

The work performed at QuateK Molecular Laboratories, Champions Oncology, and Targos Molecular Pathology was supported by Mersana Therapeutics.