Poster texts in a responding models

ABSTRACT
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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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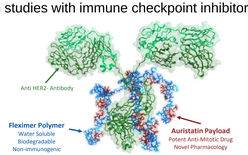
Abstract

XMT-1522 is a unique HER2 targeting antibody drug conjugate (ADC) with a high drug antibody ratio. HER2 protein overexpression, gene amplification and mutation have been described in non-small cell lung cancer. We describe the pre-clinical 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, ado-trastuzumab emtansine (T-DM1), are approved in HER2-positive breast cancer, and trastuzumab is also approved in HER2-positive gastric cancer. In NSCLC, HER2 amplification and mutation are infrequent events, occurring in ~3% of patients, and tend to be mutually exclusive (Li, 2016). Recent data suggested an effect of T-DM1 in NSCLC patients with HER2 activating mutations or amplification, but not in the broader patient population of HER2-expressing NSCLC without amplification or mutation (Li, 2018; Peters, 2018).
XMT-1522 (Fig.1) is a novel antibody drug conjugate with ~12 Auristatin F-hydroxypropylamide (AF-HPA) payload molecules per antibody that binds a HER2 epitope distinct from the binding sites of trastuzumab/T-DM1 and pertuzumab. AF-HPA is capable of controlled bystander-effect killing, resulting in efficacy in tumors with heterogeneous antigen expression, and is metabolized intra-tumorally to an active non-permeable metabolite to enable greater systemic tolerability. Prior preclinical work has demonstrated in vivo efficacy of XMT-1522 in models of HER2 wild-type NSCLC. XMT-1522 has also been shown to induce immunogenic cell death in vitro, making it a candidate for combination studies with immune checkpoint inhibitors (Bodyak, 2017)

Figure 1



Methods

Immunohistochemistry (IHC) was performed on formalin fixed paraffin embedded (FFPE) archive human tumors using the 4B5 anti-HER2 antibody on the Ventana Benchmark Ultra Instrument and on FFPE xenograft material using the Dako Herceptest on the automated Link48 system. All blocks were centrally scored according to the IHC guideline established for Gastric Carcinoma Surgical resections (Bartley, 2017; Scheel, 2018):
0: No reactivity, or membranous reactivity in <10% of cells; 1+: faint/barely perceptible membrane reactivity in ≥ 10% of cells; 2+ weak to moderate complete, basolateral or lateral membranous reactivity in ≥ 10% of tumor cells; 3+: strong complete basolateral or lateral membranous reactivity in ≥ 10% of tumor cells.
Florescence in situ hybridization (FISH) was performed and scored on human tumor material using the HER2 IQ FISH (Dako) kit according to manufacturer's instructions.

Methods (continued)

A series of primary xenograft NSCLC models (n=3 animals/model) was established in athymic Nude-*Foxn1*^{nu} mice. When tumor volume reached 150—300 mm^3 treatment was initiated with Vehicle, XMT-1522, 3 mg/kg IV q week x 3 (n=16 models) or XMT-1522 1 mg/kg IV q week x 3 (n=11 models). Group sizes were n=1 for vehicle treatment and n=3 for XMT-1522 at each dose. Outcome data were expressed as median best response (MBR) from day 0 measurement for each model. Vehicle treated blocks were collected at the study endpoint, defined as mean tumor volume of a group ≥ 1500 mm^3 or up to Day 60.

RNA was extracted from FFPE sections and analyzed using a Nanostring Panel with multiple ERBB2 probes. Data from one probe is shown. Samples were normalized in the Advanced Analysis Software Version 2.0 provided by Nanostring, using default threshold settings.

HER2 IHC and FISH Evaluation in Human NSCLC

Figure 2a

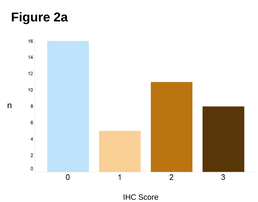


Figure 2b

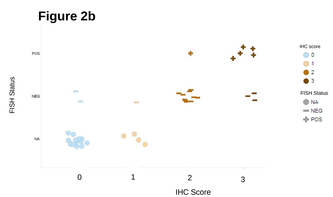
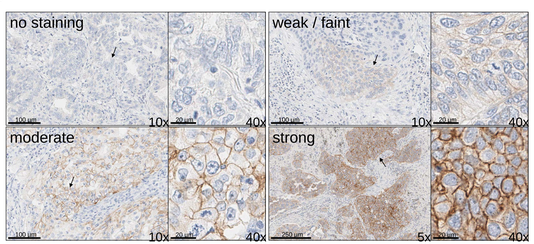


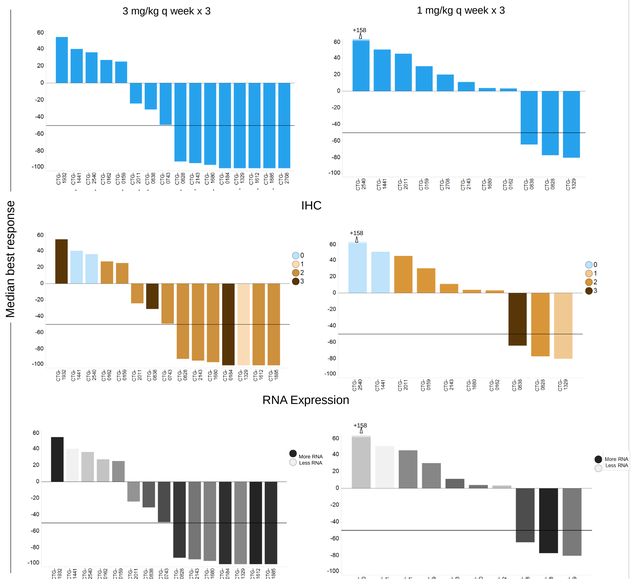
Figure 2c



HER2 IHC (Ventana) was performed in human NSCLC FFPE tumor blocks. This population of samples was selected to demonstrate the assay performance over a range of expression values, and does not represent the distribution of values that would be seen in an unselected human tumor population. The distribution of blocks examined at each expression value is shown in Figure 2a. Tumors with HER2 gene amplification tended to have higher protein expression values, although not all low protein expressing tumors were FISH tested (2b). Representative histology images are shown in Figure 2c.

Preclinical Efficacy/HER2 Expression Relationship

Figure 3

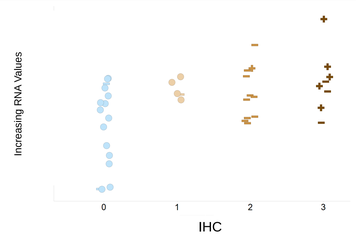


XMT-1522 at a dose of 3 mg/kg or 1 mg/kg q wk x 3 resulted in MBR > - 50 % in 8/16 or 3/11 models, respectively. Models run at both concentrations are indicated with an asterisk.

IHC (Dako) and RNA expression data were available in 15/16 or 10/11 models tested at the 3 mg/kg or 1 mg/kg respectively. MBR > -50% were seen over a range of protein expression values, but were not seen in models scored as IHC 0. Higher levels of RNA were observed more frequently in responding models. One ERBB2 high expresser by both RNA and protein assays was non-responsive, although this model was notable for a rapid growth rate.

RNA Protein Relationship in Human Lung Cancers

Figure 4



ERBB2 (Ventana) RNA Expression values were compared with IHC scores in 40 human lung NSCLC tumors. FISH status is indicated if known. A range of RNA expression values was seen in tumors across all IHC values, although some tumors that scored 0 by IHC had lower RNA values.

Summary

- **XMT-1522 is a HER2-targeted antibody-drug conjugate with high drug loading of 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 q wk x 3 yielded a median best response >-50% in 8/16 or 3/11 models respectively**
- **ERBB2 protein target expression was necessary, but not sufficient for compound activity as evaluated by median best response**
- **Models with higher RNA expression levels tended to be more responsive to XMT-1522**
- **In human tumors, HER2 RNA was expressed in an overlapping range over all protein expression levels, although some tumors that scored 0 by IHC had lower levels of RNA expression**

References:
Bartley et al, J Clin Oncol 35(4):446-464 (2017)
Bodyak et al., AACR Annual Meeting 2017 (abstract #2670)
Li et al J Thorac Oncol 11(3):414-419 (2016)
Li et al J Clin Oncol 36:2532-2537 (2018)
Peters et al Clin Can Res CCR-18-1590 (2018)
Scheel et al., Diagn Pathol 13(1):19 (2018)

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