ABSTRACT
B119

Relationship of NaPi2b expression and efficacy of XMT-1536, a NaPi2b targeting antibody drug conjugate (ADC), in an unselected panel of human primary ovarian mouse xenograft models

Rebecca Mosher, Laura Poling, LiuLiang Qin, Natalya Bodyak, and Donald Bergstrom; Mersana Therapeutics Inc., Cambridge MA

Abstract

NaPi2b (SLC34A2) is expressed in many human ovarian and lung cancers. Previous human clinical trials with a NaPi2b targeting MMAE ADC have shown objective tumor responses, but have not shown a strong relationship between NaPi2b expression and the probability of response. XMT-1536 is a NaPi2b targeting ADC comprised of a novel humanized antibody conjugated with 10-15 auristatin F-HPA (AF-HPA) payload molecules via the Dolaflexin platform. 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. Previously presented preclinical studies using XMT-1536 have demonstrated efficacy *in vivo* in the NaPi2b expressing OVCAR3 ovarian cancer cell line model. Here, we describe the evaluation of XMT-1536 in a panel of patient derived xenograft models of human ovarian cancer, unselected for NaPi2b expression. The efficacy data from this study was compared to characteristics of each model, including NaPi2b expression, to predict a model for stratification of patients in XMT-1536 clinical trials.

Introduction

NaPi2b (SLC34A2), a member of the SLC34 family of sodium-dependent phosphate transporters, is expressed on the apical membranes of epithelial cells, including the intestinal brush border and the surface epithelium of the uterus and fallopian tubes. NaPi2b is also expressed in the lung on pulmonary type II pneumocytes, and bronchial epithelium. Membrane expression of NaPi2b can be detected in non-squamous, non-small cell lung carcinoma; non-mucinous ovarian carcinoma; and papillary thyroid carcinoma.[1] and internal data

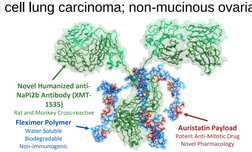


Figure 1 Graphic Rendering of XMT-1536, a NaPi2b Targeting Antibody Drug Conjugate

XMT-1536 (Figure 1) is an ADC that consists of a novel NaPi2b targeting antibody, XMT-1535, and a novel auristatin-based cytotoxic payload (Auristatin F-hydroxypropylamide, AF-HPA). A drug-antibody ratio (DAR) of 10-15 AF-HPA molecules is achieved via a biodegradable polymer conjugation platform.

Prior preclinical studies in an ovarian cell line xenograft (OVCAR3), suggested that XMT-1536 could be efficacious in this tumor type. In order to define further the preclinical effect of XMT-1536, and to model a target expression/response relationship, a series of ovarian cancer xenografts, unselected for target expression was enrolled in a “Mouse Clinical Trial”.

Methods

Primary ovarian cancer models were derived from serous ovarian or fallopian tube cancers and implanted in immunocompromised mice. Once tumors reached a stratified mean volume of 125-250 mm^3, mice were treated with 3 mg/kg IV XMT-1536 weekly for three weeks in groups of n=3. Untreated animals in groups of n=2-4 were included as a control. The study endpoint was defined as a tumor volume of 1 cm^3 or 45 days. In a case of complete response, mice were followed for a longer time course to evaluate for tumor regrowth. Growth effects were evaluated by looking at median best response relative to day 0, at any timepoint for each model.

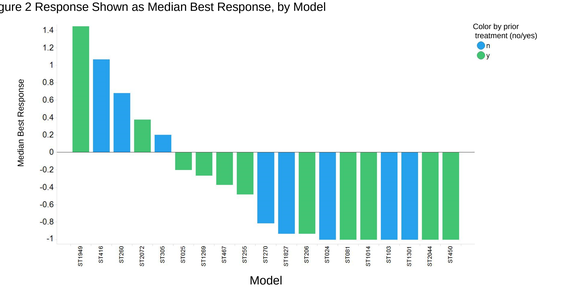
An immunohistochemistry (IHC) assay to detect NaPi2b was established using a primary anti-NaPi2b antibody, that consisted of a human/rabbit chimera of XMT-1535. IHC was initially developed as a bench method and then as an automated IHC method. The automated IHC process included manual pathologist evaluation of H-score. Tumor blocks from one untreated study animal representing each tumor model were evaluated to determine an efficacy/staining pattern relationship.

The established IHC protocol was applied to a series of human primary ovarian tumors to determine if the range of expression levels seen in xenograft models was similar to that seen in human tumors.

Results

XMT-1536 shows an anti-tumor effect in an unselected series of primary ovarian cancer xenografts

Figure 2 Response Shown as Median Best Response, by Model



Median best response (Figure 2), response calculated relative to day 0 at each timepoint for every animal, and expressed as the median value of best response for each model, showed 10/19 models with a median best response of -50% to 100%.

The enrolled models were derived both from patients who had received prior treatment and patients who were treatment naïve. Anti-tumor effect of XMT-1536 was seen in both tumor classes. Bars are colored as derived from treatment naïve (blue) tumors or post-treatment (green) tumors

XMT-1536 effect in primary ovarian cancer xenograft models was associated with NaPi2b expression

Figure 3a Median Best Response Shown in Relationship to NaPi2b IHC Expression by H-Score

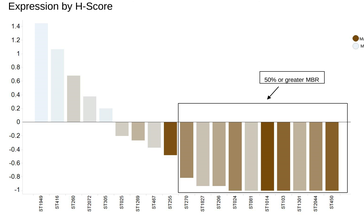
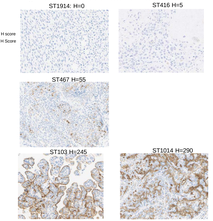


Figure 3b Representative NaPi2b IHC



Considering models with a 50% or greater median best response after XMT-1536 treatment, all had a NaPi2b IHC H-score of ≥70 (Figure 3a). Representative immunohistochemical images are shown in Figure 3b.
Amongst tumors with H-score ≥70, 10/12 (83%) models achieved 50% or greater reduction in tumor volume after XMT-1536 treatment, vs 0/7 (0%) models with H-score <70. There was an association between NaPi2b IHC H-score and tumor volume change after XMT-1536 treatment (Spearman rank coefficient 0.76).

XMT-1536 effect was sustained in some primary ovarian cancer models followed for an extended time course

Some models were continued for an extended time course. Figures 4a and 4b show examples where a sustained antitumor growth effect was seen, graphed as individual animals . Red arrows indicate dosing, at 3 mg/kg IV qw X3.
In one model, ST206, tissue obtained at the end of study was evaluated for target expression in a xenograft that showed an incomplete response. IHC performed on an untreated control xenograft and a xenograft with incomplete response at the end of study both show NaPi2b expression, Figure 4c.

Figure 4a

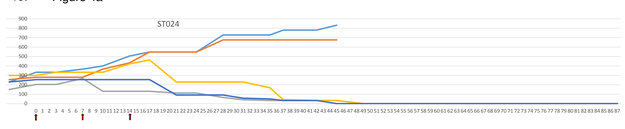


Figure 4b

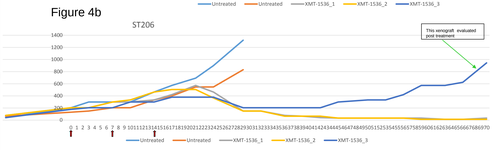
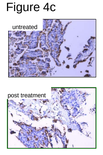


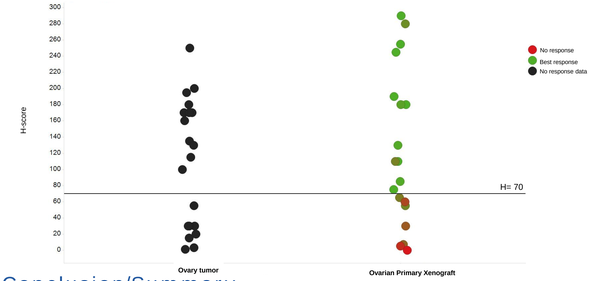
Figure 4c



NaPi2b expression in archival human tumors is seen at levels similar to primary tumor xenografts

20 human non-mucinous ovarian epithelial tumors were evaluated for NaPi2b expression by IHC, and H-scores were compared to 19 primary xenograft models of known response. 12/20 (60%) tested human tumors had an H-score ≥70. H-scores of NaPi2b expression in ovarian tumors and primary ovarian cancer xenografts are shown in Figure 5. Median best response is annotated for the primary ovarian xenografts.

Figure 5 NaPi2b IHC H-Score for human ovarian tumors and primary ovarian xenografts



Conclusion/Summary

1. **XMT-1536 is a NaPi2b targeting antibody drug conjugate with anti-tumor growth activity seen in a subset of unselected ovarian primary xenograft models (10/19).**
2. **The anti-tumor effect was sustained in some models carried past the planned study endpoint.**
3. **The anti-tumor effect of XMT-1536 was correlated with NaPi2b IHC H-score.**
4. **The range of IHC H-Score staining seen in archival human ovarian tumors was similar to that seen in primary ovarian xenografts.**
5. **12/20 Human Ovarian Tumors have a NaPi2b IHC H-score > 70; in primary ovarian xenograft models with an H-score >70, 10/12 models achieved a 50% or greater reduction in tumor size, as evaluated by median best response.**
6. **A NaPi2b IHC assay will be evaluated in a Phase 1 Clinical Trial of XMT-1536 and may have utility in enriching for ovarian cancer patients more likely to benefit from XMT-1536 treatment.**

Acknowledgements

The Authors gratefully acknowledge the contributions of START San Antonio,Texas for *in vivo* work and QualTek Molecular Laboratories Newtown, PA for IHC work.

References

1) Lin et al., Clin Cancer Res; 21(22); 5139-50. 2015