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-1356 is a NaPi2b targeting ADC comprised of a novel humanized antibody conjugated to 10-15 auristatin F-HPA (AF-HPA) payload molecules via the DOLAFixin platform. AF-HPA is capable of controlled bystander effect killing in 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-1356 have demonstrated efficacy in vivo in the NaPi2b expressing OVCAR3 ovarian cancer cell line model. Here, we describe the evaluation of XMT-1356 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-1356 clinical trials.

Methods

Primary ovarian cancer models were derived from 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 2 mg/kg XMT-1356 weekly for three weeks in groups of 3-4. Untreated animals in groups of 4-6 were included as a control. The study endpoint was defined as a “tumor doubling time” of 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 best response relative to day 0, at any time point for each model.

An immunohistochemistry (IHC) assay to detect NaPi2b was established using a primary anti-NaPi2b antibody, that consisted of a human IgG1 chimeric clone of XMT-1356. IHC was manually developed as a bench method and then as an automated IHC method. The automated IHC process included manual pathological evaluation of H-score. Tumor blocks from one untreated study animal representing each tumor model were evaluated to determine an efficacious pathologist scoring procedure. 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-1356 shows an anti-tumor effect in a variety of mouse models.

Figure 3b: NaPi2b IHC H-score for human ovarian tumors and primary ovarian xenografts.

1. 12/20 Human Ovarian Tumors have a NaPi2b IHC H-score > 70; in primary ovarian xenograft models.

2. A NaPi2b IHC assay will be evaluated in a Phase 1 Clinical Trial of XMT-1536.

Conclusion/Summary

1. NaPi2b is a NaPi2b targeting antibody drug conjugate with anti-tumor activity seen in a subset of unselected ovarian primary xenograft models (10/15).

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 is 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 IHC H-score >70; 10/12 models achieved a 50% or greater reduction in tumor volume, 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 Translational Laboratory Network, PA for IHC work. Reference:

1) Lin et al., Clin Cancer Res; 22(2); 5139-50. 2015