**Summary**

XMT-1536 is a novel, highly potent NaPi2b-targeted antibody-drug conjugate (ADC) comprising of an average of 10 auristatin molecules conjugated to XMT-1535, a novel humanized anti-NaPi2b antibody, via the Dolafieldin linker. The auristatin payload is enzymatically cleaved upon ADC trafficking to the endosomal/lysosomal compartment, releasing a cytotoxic auristatin derivative that is capable of bystander effect killing.

In cell binding assays, XMT-1535 antibody binds to non-mucinous ovarian cancer (OC) cells with low nonspecific affinity, which is unaffected by conjugation of the Dolafieldin drug conjugate. XMT-1536 is 1.2 log10 more potent than a non-binding Dolafieldin ADC control, consistent with target-dependent cytotoxic effect.

In vivo XMT-1536 induced partial tumor regressions in the OVCAR3 OC model after a single dose of 3 mg/kg (0.21 mg/kg payload equivalent dose), and complete tumor regressions after a single dose of 5 mg/kg (0.38 mg/kg payload dose) or 3 weekly doses of 3 mg/kg. XMT-1536 was also tested in a patient-derived model of NSCLC, where it led to significant tumor growth delay and regressions.

XMT-1535 is cross-reactive with mucinous monkey NaPi2b, allowing an informative evaluation of whether XMT-1536 retains good tolerability in non-human primates. XMT-1536 was administered to cynomolgus monkeys in an exploratory single dose study up to 5 mg/kg ADC (4294 µg/m2 auristatin payload equivalents), with no observed target-mediated toxicity and limited adverse findings. Of note, there was no evidence of bone marrow toxicity, which has been observed generally forcleavable auristatin ADCs, and specifically for a recently published auristatin-based NaPi2b ADC (Lin et al., Clinical Cancer Research, 2015).

Based on these data, XMT-1536 is advancing to early clinical development for the treatment of NaPi2b-expressing tumors.

**Discussion and Conclusions**

- XMT-1535 Dolafieldin conjugation (XMT-1536) does not adversely affect ADC target binding.
- XMT-1536 is highly active in vitro.
- XMT-1536 is highly active in vivo in OC xenograft model.
- XMT-1536 is highly active in vivo in patient derived NSCLC xenograft models.
- XMT-1536 is cross-reactive with mucinous monkey NaPi2b, allowing an informative evaluation of whether XMT-1536 retains good tolerability in non-human primates.
- XMT-1536 demonstrates good efficacy in plasma and very low exposure to free drug.

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**References**