A novel, highly potent HER2-targeted antibody-drug conjugate (ADC) for the treatment of low HER2-expressing tumors and combination with trastuzumab-based regimens in HER2-drive tumors

Donald A. Bergstrom, Natalya Bodayak, Alex Yurkovetsky, Peter U. Park, Michael DeHart, Mao Yin, Laura Paling, Joshua D. Thomas, Dmitry Gustov, Dongmei Xiao, Elena Ter-Ovanesyan, LuLiang Qin, Alex Uttard, Alex Johnson, Timothy B. Lowinger.

Mersana Therapeutics, Cambridge, MA.

Abstract

Characterization of XMT-1522

- XMT-1522 demonstrates good stability of drug conjugate in plasma with t1/2 ~5 days (comparable to antibody t1/2) and 10 mg/kg. In non-human primates XMT-1522 regressions are achieved with a single 1 mg/kg dose of XMT-1522, while 10 mg/kg T-DM1 is required for studies. XMT-1522 has excellent pharmacokinetic properties and achieves complete tumor regressions at well-tolerated doses.

- Antibody-drug conjugates are effective in the treatment of HER2-amplified breast cancer and Hodgkin's lymphoma.

- XMT-1522 Key features:
  - 3-5 polymers conjugated primarily to hinge region
  - Intracellular cleavage of drug-polymer linker
  - Free Drug
  - Adimab

Adimab acknowledges Adimab, our partner for antibody discovery for HT-19.

Conclusions

- XMT-1522 is highly active in HER2-positive tumor models that are insensitive to ado-trastuzumab emtansine.
- XMT-1522 is highly active in low HER2-expressing tumor models (representing HER2+ and - tumors) where there are currently no approved HER2-targeted therapies.
- The ability to combine XMT-1522 with trastuzumab or trastuzumab-containing regimens gives the potential of achieving HER2 pathway inhibition combined with efficient delivery of cytotoxic payload.

Pharmacodynamic Studies with XMT-1522

- Comparing XMT-1522 and trastuzumab on HER2-dependent and independent signaling measured by downstream AKT phosphorylation (pAKT level of 127% of untreated control). Trastuzumab and XMT-1522 strongly inhibit HER2 signaling in cell lines with fewer than 100,000 HER2 receptors per cell.
- For HER2 dependent signaling, all cell lines were tested (Figure 10). The fold potency of XMT-1522 compared to trastuzumab is very similar. Overall, both antibodies had similar properties as trastuzumab in its ability to inhibit HER2 signaling.

- For HER2 independent signaling, all cell lines were tested (Figure 10). The fold potency of XMT-1522 compared to trastuzumab is very similar. Overall, both antibodies had similar properties as trastuzumab in its ability to inhibit HER2 signaling.

Acknowledgement

Mersana acknowledges Adimab, our partner for antibody discovery for HT-19.