Optimization of lead antibody selection for XMT-1522, a novel, highly potent HER2-targeted antibody-drug conjugate (ADC)

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Summary

XMT-1522 is an anti-HER2 ADC that incorporates HT19, a novel human anti-HER2 antibody optimized for cytotoxic payload delivery. Several parameters such as cell binding, internalization rate, cytotoxicity, antibody-dependent cell-mediated cytotoxicity (ADCC), downstream signaling, affinity, NHP cross-reactivity, normal human tissue cross-reactivity and in vivo efficacy were used to screen a wide range of antibodies to select a lead candidate optimized for use in ADC applications. In addition, HT19 was selected to be non-competitive for HER2 binding with existing therapies - trastuzumab or pertuzumab, to allow for potential combinability. In vivo efficacy as an ADC was not necessarily predictive of typical screening parameters such as in vitro cytotoxicity, internalization or binding affinity.

ADC In vitro cytotoxicity – not necessarily predictive of in vivo efficacy

The lead antibodies were affinity matured, and despite increases in affinity, this phenomenon was observed with all the antibody hits. HT19 showed antibody-dependent cell-mediated cytotoxicity activity. When administered as the unaffinity matured antibody in the NCI-N87 gastric cancer xenograft model it had biological activity at 20 mg/kg as well as at 3 mg/kg. Consistent with the hypothesis that a non-competitive ADC is combinable with current anti-HER2 regimens, the combination of XMT-1522 with trastuzumab and/or pertuzumab showed more rapid internalization, more complete HER2 degradation, and significantly greater anti-tumor activity in the NCI-N87 gastric cancer xenograft model relative to XMT-1522 alone or the combination of pertuzumab + trastuzumab.

In Vivo Lead Selection, Dolaflexin ADCs

The lead antibody HT19 inhibits the HER2 signaling pathways

In vivo efficacy for the ADCs. All ADCs of affinity matured leads were comparable in all endpoints and significantly greater anti-tumor activity in the NCI-N87 gastric cancer xenograft model relative to XMT-1522 alone or the combination of pertuzumab + trastuzumab.

Discussion and Conclusions

• In vivo data is crucial to select lead mAb for ADC
• In vitro cytotoxicity is not necessarily predictive of in vivo efficacy
• Affinity maturation did not translate into increases in ADC in vivo efficacy for the ADCs. All ADCs of affinity matured leads were inferior to parental versions
• High off rate could be a factor in high in vivo efficacy
• Lead antibody HT19 shows ADCc activity
• Lead antibody HT19 inhibits the HER2 signaling pathways
• Lead antibody HT19 binds to a different epitope of HER2 than each trastuzumab or pertuzumab and therefore is combinable with trastuzumab and pertuzumab
• The combination of XMT-1522 with trastuzumab and/or pertuzumab showed more rapid internalization, more complete HER2 degradation, and significantly great anti-tumor activity in the NCI-N87 gastric cancer xenograft model relative to XMT-1522 alone or the combination of pertuzumab + trastuzumab.

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