Combination of anti-HER2 ADC XMT-1522 and checkpoint inhibitor pembrolizumab for treatment of NSCLC in preclinical models

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Summary

The combination of antibody-drug conjugates (ADCs) and immunomodulatory cancer therapies is emerging as a powerful strategy for cancer treatment. Targeted delivery of a cytotoxic payload capable of inducing immunogenic cell death (ICD) can trigger both an innate and an adaptive immune response, whereby increased recruitment of effector T-cells to the tumor and formation of tumor specific immunological memory can result in a durable treatment response.

We have characterized the ability of both the free payload AF-HPA and the anti-HER2 ADC XMT-1522 to induce ICD in vitro in multiple cell lines (NCI-N87, HT-29, SKBR3), as measured by the cell surface expression of the ICD marker calreticulin (CRT) by microscopy and flow cytometry (FACS) and ATP release.

XMT-1522 as a single agent induced significant tumor regressions in two patient-derived xenograft models of HER2-expressing non-small cell lung cancer (NSCLC), resulting in a better response than either of the two monotherapies in patient-derived xenograft models of HER2 expressing non-small cell lung cancer in a mouse with a humanized immune system.

Discussion and Conclusions

- The free payload AF-HPA and the ADC XMT-1522 both induce ICD in vitro as evidenced by at least two well established ICD markers:
- ATP release
- The combination of XMT-1522 with the checkpoint inhibitor pembrolizumab resulted in a better response than either of the two monotherapies in patient-derived xenograft models of HER2 expressing non-small cell lung cancer in a mouse with a humanized immune system.
- There was no clear correlation in TILs and tumor response.

The data provide a rationale for XMT-1522 to be tested clinically as a single agent in HER2 expressing NSCLC, as well as a rationale for combination of XMT-1522 and immunomodulatory therapies in NSCLC.

References


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