Introduction: B7-H3, a member of the B7 family of immunomodulatory molecules, is overexpressed in a wide range of solid cancers. B7-H3 overexpression has been correlated with disease severity and poor outcome in several cancer types. Proof-of-concept studies targeting B7-H3 has demonstrated that agonist-based B7-H3 mAbs exhibited potent cytotoxicity in vitro and antitumor activity in vivo toward a range of B7-H3-expressing tumor cell lines. Based on these preliminary results, we undertook preclinical development of a B7-H3 ADC comprised of a humanized B7-H3 mAb conjugated to a potent DNA alkylating payload.

Methods: Chimeric B7-H3 mAbs were conjugated to vc-DUBA-DUocarmycin-hydroxyBenzamide Azaindole (DUBA) (ADC conjugated and provided by Synthon Biopharmaceuticals B.V.) in vitro and in vivo activity studies were conducted with tumor cell lines that overexpress B7-H3. Based on the potency analysis, together with the biological properties and immunohistochemistry (IHC) profiles of the candidates, a lead mAb was selected for preclinical development. The mAb was humanized via CDR grafting and conjugated to DUBA to yield the development candidate MGC018. In vivo and in vitro studies were then conducted with MGC018 to confirm and extend the results with the chimeric ADCs.

Results: Conforming our previous data and consistent with a growing body of literature, B7-H3 mAbs exhibited strong reactivity toward cancer cells and the vasculature of solid cancers. Chimeric B7-H3 ADCs demonstrated specific, dose-dependent cytotoxicity toward B7-H3-positive tumor cell lines and potent antitumor activity in vivo. The humanized ADC development candidates, MGC018, retained the favorable biological properties and the normal tissue-versus-tumor IHC profile of the parental mAb. MGC018 displayed cytotoxicity toward B7-H3-positive tumor cell lines in vitro, with IC50 values in the sub-μM range, and potent antitumor activity in vivo, resulting in tumor stasis and tumor regression in mouse bearing B7-H3-positive human tumor xenografts, representing breast, lung and ovarian cancers.

Conclusions: MGC018, a preclinical candidate comprised of a humanized mAb targeting B7-H3 conjugated to the potent DNA alkylating payload DUBA via a cleavable peptide linker exhibited a favorable preclinical profile, with strong reactivity toward tumor cells and tumor-associated vasculature, limited normal tissue reactivity, potent cytotoxicity in vitro and antitumor activity in vivo toward a range of B7-H3-expressing tumor cell lines representing several cancer types. Our findings support further preclinical development of MGC018 to evaluate its potential as an ADC therapeutic for B7-H3-expressing solid cancers.

Background

B7-H3: An Attractive Cell-Surface Molecule for Targeted Therapy

• B7-H3, a member of the B7 family of immune regulators, is overexpressed on many human cancers and displays high tumor-versus-normal tissue binding differential.
• B7-H3 overexpression has been correlated with disease severity and poor outcome in many cancer types.
• MGC018, a lead candidate, is a bivalent mAb:
  - Bivalent mAb (MGC018) is functionalized with enfolded mAbs via DAR (Disulfide-Attached) linkers that are not cleavable in vivo.
  - B7-H3 ADC may provide a complementary mechanism of action.
• Final Formulation (humanized mAb conjugated to DUBA) has excellent potency in vitro and antitumor activity in vivo (NACE 2015, Abstract 12017)
• Clinical: B7-H3 ADC is currently in human clinical studies with an ADC of MGC018 based on the DUBA conjugation system.

Results

MGC018 Exhibits Potent Anti-Tumor Activity

• Humanized mAb-DUBA (MGC018):
  - Humanized B7-H3 antibody conjugated to DUBA
  - Retains potent activity toward B7-H3-expressing tumor cells in vitro and in vivo

References

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Conclusions

• MGC018 (MGC018-DUBA ADC) is a favorable tumor-targeting monoclonal antibody profile.
• Potent in vitro cytotoxicity and in vivo antitumor activity toward B7-H3-positive tumor cell lines representing several cancer types.
• Cross-react with cognate receptor B7-H3 with equimolar IC50 values.
• Favorable pharmacokinetic properties in preclinical models support further development.

The preclinical profile supports continued development of MGC018 as a therapeutic ADC for the treatment of B7-H3-positive cancers.

Preclinical Development of a Duocarmycin-based Antibody-Drug Conjugate Targeting B7-H3 for Solid Cancer