Introduction

B7-H3 overexpression has been correlated with disease severity and poor outcome in several cancer types. Proof-of-concept studies targeting B7-H3 demonstrated that auristatin-based B7-H3 ADCs 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 potential DNA alkylation payload.

Methods: Chimeric B7-H3 mAbs were conjugated to vis-Duocarmycins (hydroxybenzamide-DUBA; 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 biophysical properties and immunohistochemistry (IHC) profiles of the candidates, a lead mAb was selected for preclinical development. The mAb was humanized by CDR grafting and conjugated to DUBA to fulfill the development criteria for MGC018. In vitro and in vivo studies were then conducted with MGC018 to confirm and extend the results with the chimeric ADCs.

Results: Confirming 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 in vitro and potent antitumor activity in vivo. The humanized B7-H3 ADC development candidates, MGC018, retained the favorable biophysical 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-nM 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 alkylation 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 suggest 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-regulatory 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.

• Membrane expression is targeted by two modalities:
  - Antibody-drug conjugate (ADC) is a fusion of an antibody with a cytotoxic payload.
  - Dual targeting (DT) is a fusion of an antibody with an antibody for a cytokine-targeted molecule.

• A B7-H3 ADC may provide a complementary mechanism of action.
• Final clinical candidate was a dual targeting-based B7-H3 mAb conjugated to a DNA alkylation payload.

B7-H3 ADC

• Dual targeting-based B7-H3 ADC comprised of a humanized B7-H3 mAb conjugated to a DNA alkylation payload.

Targeting B7-H3 via Multiple Mechanisms of Action

• B7-H3 dual targeting-based ADC comprised of a humanized B7-H3 mAb conjugated to an antibody-drug conjugate (ADC) payload (DUBA).

Results

B7-H3-DUBA ADCs Exhibit Potent in Vitro Cytotoxicity

• B7-H3-DUBA ADCs exhibit potent cytotoxicity and antitumor activity in vitro toward a range of B7-H3-expressing tumor cell lines, representing cancers of breast, lung, and ovarian cancers.

• IC50 values in the sub-nM range.

B7-H3-DUBA ADCs Exhibit Anti-Tumor Activity in Calu-6 Lung Cancer

• Humanized MGC018-DUBA (MGC018).
• Retain cytotoxicity in vitro and in vivo.

MGC018 Exhibits Favorable PK Profile

• Single-Dose Cynomolgus Monkey PK Study.

• Well tolerated in male Cynomolgus monkeys.

• MGC018: Observations in Cynomolgus Monkeys.

• Widely distributed throughout the body, with moderate exposure in male cynomolgus monkeys.

• Pharmacokinetic profile is consistent with human pharmacokinetic studies.

Conclusions

• MGC018 (MGC018-DUBA ADC):
  - Durable tumor shrinkage with a 6-week post-treatment.
  - Effective treatment across murine tumor models.

• Therapeutic index is similar to other ADCs.

References

• Loo D, Scribner J, Son T et al., http://ir.macrogenics.com/events.cfm

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

Thomas Son, Juniper A. Scribner, Jeff Hooley, Michael Chiichei, Pam Li, Tim E. Hotaling, Anushka De Costa, Yan Chen, Francine Chen, Bhaskari Barat, Ling Huang, Valentina Ciccarone, Timur Gaynyutdinov, James Tamura, Scott Koenig, Syd Johnson, Paul A. Moore, Ezio Bonvini, Deryk Loo

MacroGenics, Inc., Rockville, MD and South San Francisco, CA