Preclinical Development of MGC018, a Duocarmycin-based Antibody-drug Conjugate Targeting B7-H3 for Solid Cancer

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**Abstract**

**Introduction**
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B7-H3 is a member of the B7 family of immunomodulatory molecules, is overexpressed in a wide range of solid tumors, tumor xenografts has been correlated with disease severity and poor outcome in several cancer types. MGC018 is an antibody-drug conjugate (ADC) targeted against B7-H3 and comprised of a cleavable linker, DUBA via a cleavable peptide linker, exhibited a defined as the highest non-severely toxic dose (HNSTD).

**Fractionated MGC018 dose studies were consistent with antitumor efficacy in vivo toward a range of B7-H3-expressing tumor cell lines representing several cancer types. Based on these preliminary findings and broad preclinical development of MGC018 was undertaken to support clinical development.**

**Methods:** in vivo antitumor activity toward B7-H3-positive tumor xenografts representing breast, lung, and ovarian cancers, and melanoma. Fractionated MGC018 dose studies were consistent with antitumor activity driven by the exposure (AUC) rather than peak drug exposure (Cmax). MGC018 was tolerated in cynomolgus monkeys at all dose levels tested, with 10 mg/kg, the highest dose administered, defined as the highest non-toxic severity dose (HNSTD). MGC018, a pro-candidiate 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. MGC018 demonstrated potent antitumor activity in vivo toward B7-H3 expressing tumor xenografts at clinically relevant dose levels. It was well tolerated in cynomolgus monkeys, a relevant toxicology model, at exposure levels in excess of those required for antitumor activity. Our findings support the clinical development of MGC018 to evaluate its potential as an ADC therapeutic for B7-H3-expressing solid cancers.

**Background**

**B7-H3: An Attractive Molecule for Targeted Therapy**

- Member of the B7 family of immune regulation proteins
- B7-H3 has minimal expression on normal tissues

■ MacroGenics is targeting B7-H3 by 3 modalities:
- B7-H3-directed antibodies conjugated with the potent DNA alkylating payload DUBA
- Anti-B7-H3 A387 antibodies with human tumor xenografts with high tumor burden with normal tissue binding
- Preclinical safety study conducted in cynomolgus monkeys

■ DUBA Adcs Exhibit High Clearances in Mouse Due to Rodent-specific Esterase

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**Targeting B7-H3 via Multiple Mechanisms of Action**

- **DUBA-based Linker Payload**

  - **DUBA (vinca-derived alkylating drug)**
  - **DUBA**
  - **DUBA**

- **B7-H3-DUBA ADCs Exhibit Potent In vivo Cytotoxicity**

  - **MGC018**
  - **MGC018**
  - **MGC018**

- **B7-H3 is Highly Expressed on a Range of Solid Cancers**

  - **Regression**
  - **Regression**

**Conclusion**

- **Favorable safety and toxicokinetics in a repeat-dose GLP toxicology study**
- **Limited clinical chemistry and hematology findings**
- **No microscopic correlates, resolved during recovery**

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**References**

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