757 A PHASE 1/1B DOSE ESCALATION AND COHORT EXPANSION STUDY OF MGC018 IN COMBINATION WITH LORIGERLIMAB IN PATIENTS WITH ADVANCED SOLID TUMORS (AST)

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Background The immune checkpoint molecule B7-homolog 3 (B7-H3) is highly expressed in multiple solid tumors with limited expression in normal tissue, may play an immune suppressive role, and favors cancer growth. MGC018 is an investigational anti–B7-H3 IgG1 antibody-drug conjugate with a duocarmycin-based DNA-alkylating payload that can damage DNA in both dividing and nondividing cells, causing cell death.[1] As previously presented, Phase 1 testing of single-agent MGC018 (NCT03729596) demonstrated an acceptable safety profile with manageable toxicity in 115 patients and 25% objective response rate (ORR) among 32 evaluable patients in the NSCLC and mCRPC cohorts.[2,3] Lorigerlimab is an investigational bispecific, Fc-bearing (IgG4) DART® molecule that blocks PD-1 with enhanced CTLA-4 blockade on dual PD-1/CTLA-4–expressing tumor-infiltrating lymphocytes within the tumor microenvironment, and reduced CTLA-4 blockade in normal tissues.[4] Phase 1 testing of single-agent lorigerlimab (NCT03761017) demonstrated acceptable safety in 43 patients with advanced solid tumors and encouraging antitumor activity.[5] Coblockade of PD-1 and CTLA-4 with lorigerlimab combined with targeted delivery of a cytotoxic payload via MGC018 may improve antitumor activity in B7-H3+ cancers.
Methods This is a Phase 1/1b, open-label, multicenter, dose-escalation, and cohort-expansion study of MGC018+lorigerlimab in patients with relapsed/refractory, unresectable, locally advanced/metastatic solid tumors, including mCRPC, melanoma, pancreatic cancer, HCC, ovarian cancer, and RCC for whom there is no available therapy. Eligibility criteria include ECOG performance status ≤2 and having archival tumor or fresh biopsy specimens for B7-H3 and PD-L1 immunohistochemistry (IHC) analysis, although IHC results will not be used for patient selection. The primary objective is evaluation of safety/tolerability, dose-limiting toxicities, and the maximum-tolerated dose or maximum-administered dose for MGC018+lorigerlimab. Secondary objectives include assessment of pharmacokinetics, immunogenicity, and antitumor activity (ORR, DoR, progression-free survival, overall survival) of MGC018+lorigerlimab. MGC018 and lorigerlimab are administered as sequential infusions on Day 1 of each 28-day cycle, for up to 26 cycles. Dose escalation follows a 3+3 design with MGC018 escalating from 1.0-3.0 mg/kg and lorigerlimab fixed at 6 mg/kg. Cohort expansion of MGC018 +lorigerlimab follows a Simon's 2-stage design for each tumor-specific cohort. Safety assessments are based on AEs, graded by NCI CTCAE v5.0, occurring from the first dose until 30 days after the last dose or until starting another anticancer therapy. Tumor assessments are performed every 8 weeks for the first 6 months, then every 12 weeks until progressive disease. Response evaluation is determined using RECIST v1.1 or PCWG3 (for mCRPC). Enrollment ongoing.
Trial Registration Clinicaltrials. gov NCT05293496

REFERENCES

1. Scribner JA, Brown JG, Son T, *et al*. Preclinical development of MGC018, a duocarmycin-based antibody–drug conjugate targeting B7-H3 for solid cancer. *Mol Cancer Ther*. 2020;**19**(11):2235–2244.
2. Jang S, Powderly JD, Spira AI, *et al*. Phase 1 dose escalation study of MGC018, an anti-B7-H3 antibody-drug conjugate (ADC), in patients with advanced solid tumors. *J Clin Oncol*. 2021;**39**(suppl 15):Abstract #2631.
3. Shenderov E, Mallesara GHG, Wysocki PJ, *et al*. MGC018, an anti-B7-H3 antibody-drug conjugate (ADC), in patients with advanced solid tumors: preliminary results of phase I cohort expansion. *Ann Oncol*. 2021;**32**(suppl 5):S657–S658, Abstract #620P.
4. Berezhnoy A, Sumrow BJ, Stahl K, *et al*. Development and preliminary clinical activity of PD-1-guided CTLA-4 blocking bispecific DART® molecule. *Cell Rep Med*. 2020;**1**(9):100163.
5. Sharma M, Sanborn RE, Cote GM, *et al*. A phase 1, first-in-human, open-label, dose escalation study of MGD019, an investigational bispecific PD-1 x CTLA-4 DART® molecule in patients with advanced solid tumors. *Ann Oncol*. 2020;**31** (suppl 4):S704–S705, Abstract #1020O.

Ethics Approval Trial conduct was in accordance with Good Clinical Practice and Principles in the Declaration of Helsinki. An independent ethics committee approved the protocol at each participating site. All patients provided written informed consent.

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