

## A FIRST-IN-HUMAN PHASE I STUDY OF M6223 (TIGIT INHIBITOR) AS MONOTHERAPY OR IN COMBINATION WITH BINTRAFUSP ALFA IN PATIENTS WITH METASTATIC OR LOCALLY ADVANCED SOLID UNRESECTABLE TUMORS

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**Background** T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domains (TIGIT) is an inhibitory receptor expressed on T cells, including regulatory T cells (Tregs) and natural killer (NK) cells. In the tumor microenvironment, TIGIT is often overexpressed and directly inhibits both T cell and NK cell effector function and proliferation. TIGIT is also involved in regulating Treg function. Therefore, inhibiting the TIGIT-related immunosuppressive pathway may result in antitumor activity. M6223 is an intravenously (IV) administered, human, antagonistic, immunoglobulin G1 (IgG1) anti-TIGIT antibody with an Fc mediated effector region. Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the human transforming growth factor  $\beta$  receptor II (a TGF $\beta$  "trap") fused to a human IgG1 monoclonal antibody blocking programmed death ligand 1 (PD-L1). As TIGIT and programmed death receptor 1 (PD-1) are co-expressed on T cells, dual inhibition of both immune checkpoints may enhance antitumor activity. This phase Ia study (NCT04457778) aims to determine the safety, tolerability, maximum tolerated dose and recommended dose for expansion of M6223 monotherapy and M6223 (both the once every 2 weeks [Q2W] and once every 3 weeks [Q3W] regimens) in combination with bintrafusp alfa. Secondary objectives include the evaluation of pharmacokinetics and clinical activity of M6223 with and without bintrafusp alfa.

**Methods** Eligible patients include those aged  $\geq 18$  years with: an Eastern Cooperative Oncology Group performance status  $\leq 1$ ; adequate baseline hematological, renal and hepatic function; and histologically or cytologically proven locally advanced or advanced solid tumors, for which no effective standard therapy is available. Patients previously treated with a TIGIT targeting agent or bintrafusp alfa are excluded. Patients with brain metastases are also excluded, except those without neurological symptoms  $\geq 4$  weeks before start of treatment and those receiving either a stable or decreasing dose of steroids  $< 10$  mg/day or no steroid treatment. In the monotherapy dose escalation phase, approximately 17–26 patients will receive M6223 IV at one of the six dose levels planned (10–1600 mg Q2W). In the combination dose escalation phase, 18–21 patients will receive M6223 IV at one of four dose levels planned (300, 900, 1600 mg Q2W and 2400 mg Q3W) in combination with bintrafusp alfa IV (1200 mg Q2W or 2400 mg Q3W). Dose escalation is determined by the safety monitoring committee and supported by a Bayesian 2-parameter logistic regression model. The study is currently ongoing in the United States and Canada.

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**Trial Registration** NCT04457778

**Ethics Approval** The study and the protocol were approved by the Institutional Review Board or ethics committee at each site. All patients provided written informed consent before any study procedures were performed.

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