

## A PHASE II, OPEN-LABEL TRIAL OF BINTRAFUSP ALFA (M7824) IN SUBJECTS WITH THYMOMA AND THYMIC CARCINOMA (TRIAL IN PROGRESS)

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**Background** Development of immunotherapy for TETs has been challenging due to the rarity of the disease, association with paraneoplastic autoimmune disorders, and a propensity toward development of serious immune-related adverse events.<sup>1–2</sup> The safety and efficacy of combination immunotherapy is under investigation.

Transforming growth factor  $\beta$  (TGF- $\beta$ ), a tightly regulated cytokine involved in tumor eradication, can paradoxically become a tumor promoter when excessively produced and activated by malignant cells through enhancement of an immunosuppressive tumor microenvironment and immune evasion.<sup>3</sup> Robust TGF- $\beta$  gene expression signature indicating high TGF- $\beta$  activity and signaling competency, and increased circulating plasma TGF- $\beta$  levels are seen in many cancers.<sup>3</sup> In TETs, a small, retrospective study found high TGF- $\beta$  expression in the majority of thymic carcinomas and in a subset of thymomas. High TGF- $\beta$  expression was associated with worse clinical outcomes (median overall survival 30 months versus 63 months).<sup>4</sup> Consequently, TGF- $\beta$  inhibition is an attractive strategy to block the multifaceted immunosuppressive mechanisms of tumor cells.

Bintrafusp alfa (BA) is a bifunctional fusion protein that consists of the extracellular domain of the human TGF- $\beta$  receptor II and an immunoglobulin G1 antibody blocking PD-L1. Preclinically, combination immunotherapy with a TGF- $\beta$  inhibitor and a PD-L1 antibody has been shown to reduce TGF- $\beta$  signaling in stromal cells, facilitate T-cell penetration into the tumor, and cause tumor regression.<sup>3–4</sup>

**Methods** This NIH IRB-approved phase 2, open-label clinical trial (NCT04417660) is evaluating the clinical activity of BA in patients with relapsed TETs.

Participants with unresectable thymoma or thymic carcinoma that has progressed after at least one platinum-containing chemotherapy, with measurable disease and no history of autoimmunity (except well-controlled autoimmune thyroid disease, pure red cell aplasia or vitiligo) receive BA (1200 mg, IV) once every two weeks until disease progression or development of intolerable adverse events. Response is assessed every six weeks by RECIST v1.1. At 12 months, participants with an ongoing response or stability may discontinue BA and reinstitute treatment if disease progression is observed. Blood and tumor tissue (optional) are collected to study changes in immune cell subsets, soluble factors and cytokines, and evaluate changes in the tumor immune microenvironment.

The primary endpoint is to determine the objective response rate. A Simon optimal two-stage phase II trial design is used, and the accrual ceiling is set at 38 participants. Enrollment is ongoing.

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Trial Registration Clinicaltrials.gov Identifier: NCT04417660

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**Ethics Approval** All patients provided written, informed consent for participation in this clinical trial that was approved by the National Institutes of Health Institutional Review Board (ClinicalTrials.gov Identifier: NCT04417660; NCI Clinical Trial ID: 20-C-0097).

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