

SAFETY AND ANTI-TUMOR ACTIVITY OF TCR-ENGINEERED AUTOLOGOUS, PRAME-DIRECTED T CELLS ACROSS MULTIPLE ADVANCED SOLID CANCERS AT LOW DOSES – CLINICAL UPDATE ON THE ACTENGINE® IMA203 TRIAL

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Background Adoptive cell therapy demonstrated significant clinical benefit in patients with hematological malignancies but results in most solid tumors have been less encouraging so far.

In the IMA203 trial we are treating advanced solid cancer patients utilizing TCR-engineered T cells (TCR-T) directed against an HLA-A*02-restricted peptide derived from the highly prevalent cancer testis antigen PRAME. This target was selected due to homogenous expression and exceptionally high target peptide density per tumor cell (assessed by quantitative mass spectrometry), two features we hypothesize to be critical determinants of anti-tumor activity in TCR-T trials.

Methods This ongoing first-in-human, dose escalation, multi-indication trial enrolls HLA-A*02:01- and PRAME-positive recurrent and/or refractory solid cancer patients, who failed all available standard treatments. Eligible patients undergo leukapheresis and an autologous TCR-T product is manufactured. After lymphodepletion with fludarabine and cyclophosphamide, T cells are infused, followed by low-dose IL-2. The primary objective of the trial is to assess the safety and tolerability of IMA203. Secondary objectives are to evaluate the anti-tumor activity and pharmacodynamics using molecular and immunological methods.

Results As of August 15, 2021, 16 heavily pre-treated patients received IMA203 T cells across multiple escalating dose levels (DL). Absolute IMA203 doses infused ranged from 0.08 to 0.81×10^9 transduced CD8 T cells per patient, which to our knowledge did not lead to anti-tumor responses in other TCR-T trials. Treatment-emergent adverse events after IMA203 infusion were transient and manageable. Most common events were expected cytopenias (G1-4), CRS and ICANS (both G1-2) and 1 DLT in DL2 (reported earlier). All evaluable patients (N=12) achieved disease control (i.e. best overall response: stable disease [SD] or partial response [PR]) and 6 patients demonstrated PRs according to RECIST1.1 with 2 of these PRs being confirmed. While all 3 patients treated at DL1 (median dose: 0.11×10^9) experienced SD, a PR was observed in 6/9 patients treated beyond DL1 (median dose: 0.30×10^9). Responses were seen in patients with synovial sarcoma (N=3), malignant melanoma (N=2) and head and neck cancer (N=1). Robust engraftment of T cells was observed in all patients and tumor infiltration by TCR-modified T cells was demonstrated in patients with evaluable on-treatment biopsies.

Conclusions To our knowledge IMA203 is the first TCR-T product candidate that induced frequent tumor responses across multiple solid cancers using transduced T cells at doses below 1 billion and has a manageable safety profile. The next

step is to assess response rates at higher dose levels and durability of responses.

Trial Registration NCT03686124

Ethics Approval The study was approved by the institutional review board/ethics committee as required for each participating site.

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