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Abstract CT205: Updated clinical results, recommended phase 2 dose (RP2D) determination and translational study results for START-001: A phase 1/2 trial of invikafusp alfa, a first-in-class TCR b chain-targeted bispecific antibody in patients with anti-PD(L)1-resistant, antigen-rich solid tumors FREE

Ryan J. Sullivan; Claire F. Friedman; Nick Tschernia; Mercedes Herrera Juarez; Jeffrey Schlom; Yo-Ting Tsai; Renee N. Donahue; Guru P. Sonpavde; Aparna Parikh; Aurelien Marabelle; Shannon McCue; Karunya Srinivasan; Jacques Moisan; Madan Katragadda; Raj Chopra; Kevin Chin; Andrew Bayliffe; Zhen Su; Ke Liu; James L. Gulley; Lillian L. Siu

+ Author & Article Information

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Abstract

Background:

Invikafusp alfa (STAR0602), a selective, dual T cell agonist targeting Vβ6/Vβ10 T cells, is being evaluated in START-001: a multicenter Phase 1/2 monotherapy trial in patients with anti-PD(L)1-resistant, antigen-rich solid tumors (TMB-H, MSI-H/dMMR, or virally associated).

Methods:

Reported here are: 1) updated clinical results of the completed dose escalation of intravenous invikafusp, Q2W, per 3+3 design with backfill at optimal biological dose (OBD) levels; 2) first report on RP2D determination based on PK, PD, safety and anti-tumor activity; 3) new results of translational immunology studies.

Results:

As of 7 Jan 2025, 41 patients (18 with TMB-H tumors) with a median of 4 prior lines of therapies across 18 different types of antigen-rich tumors were enrolled. Updated clinical results: No new safety signals were seen since previously reported and the most common TEAE was CRS (mostly grades 1 and 2), consistent with invikafusp's MoA. Of 12 patients with TMB-H tumors who received the OBD (either 0.08 or 0.12 mg/kg) monotherapy, 9 had ≥ 1 tumor assessment at the time of submission. Overall, 6 (66.6%) of these 9 patients had disease control [confirmed partial response (cPR) + stable disease (SD)]. Four (44.4%) of these 6 had measurable tumor shrinkage per RECIST: 2 (22.2%) MSS CRC patients experienced cPR with one response lasting

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~12 months; 2 (22.2%) (1 with melanoma and 1 with pancreatic cancer) had tumor shrinkage with overall SD. Another 2 (22.2%) of 6 (1 with esophageal cancer and the other with MSS CRC) had SD. RP2D: Invikafusp peak serum concentrations (Cmax) increased proportionally with doses ≥ 0.08 mg/kg resulting in Cmax at or above the pharmacological EC90. Dose-dependent, selective expansion of peripheral Vβ6 and Vβ10 T cells was observed in all patients by flow cytometry and gene expression analyses, with maximal peak expansion at 0.08 and 0.12 mg/kg doses and decreasing expansion at 0.16 mg/kg. At the RP2D (0.08 mg/kg), CD8+ Vβ6/ Vβ10 T cells reached an average peak expansion of ~600% on Day 8. Translational studies (n=7 patients): Consistent with preclinical studies, expanded peripheral Vβ6/Vβ10 T cells exhibited an atypical central memory (TCM) phenotype with expression of cytotoxic effector molecules. Selected patients had ctDNA decrease and expansion of antigen-specific Vβ6/Vβ10 T cells with one patient with ctDNA decrease who experienced stable disease and was on trial for ~15 months. Increase in soluble markers of T cell activation (e.g., IFN-γ, sCD25) within hours after dosing were observed, with less pro-inflammatory cytokine (e.g., TNF-α and IL-6) release up to the RP2D.

Conclusions:

Invikafusp, a selective, dual T cell agonist, as monotherapy, led to clinically meaningful anti-tumor activity in anti-PD(L)-1 resistant tumors. It promoted potent and selective expansion of mainly CD8+ Vβ6/ Vβ10 T cells with a novel TCM phenotype, and led to ctDNA decrease and expansion of antigen-specific T cells. Based on these initial clinical results, US FDA granted Fast track Designation for invikafusp in TMB-H CRC and a Phase 2 trial is ongoing in antigen-rich (e.g., TMB-H & MSI-H/dMMR) tumors.

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