Phase 1a/1b study design of the novel STING agonist immune stimulating antibody conjugate (ISAC) TAK-500, with or without pembrolizumab in patients with advanced solid tumors

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Background

- Immuno-oncology has emerged as a major driver of anticancer therapeutics, including immune checkpoint inhibitors (CPIs); however, resistance to CPIs remains a challenge[1–3]
  - Reduced interferon (IFN) signaling, immune escape, altered antigen presentation, and immunosuppressive tumor phenotypes have been proposed as resistance mechanisms[1–3]
- Accordingly, a possible strategy to overcome resistance to CPIs is to stimulate innate immune cells in the tumor microenvironment
- STimulator of INterferon Genes (STING) is a cytosolic protein critical for induction of Type I IFN-dependent innate immunity[4]
- Cysteine-cysteine chemokine receptor Type II (CCR2) is expressed by tumor-infiltrating myeloid cells, including tumor-associated macrophages, which promote immune escape by limiting CD8+ T-cell infiltration, thereby decreasing the efficacy of immunotherapy[5,6]

Study design

- The study will proceed in two main sections:
  - A phased dose escalation of each treatment arm; TAK-500 as a single-agent and in combination with pembrolizumab
  - A subsequent dose expansion phase that will evaluate TAK-500 in combination with pembrolizumab

Dose escalation phase (N~72)

TAK-500

- Patients will receive single-agent intravenous (IV) TAK-500 (escalating doses) administered once every 3 weeks (Q3W) in 21-day cycles to determine the pharmacologically active dose (PAD) range
- The proposed dose range of TAK-500 is 8–480 µg/kg guided by the Bayesian Optimal Interval (BOIN) design

TAK-500 + pembrolizumab 200 mg

- An additional escalation cohort will receive IV TAK-500 in combination with IV pembrolizumab 200 mg Q3W in 21-day cycles
- The initial TAK-500 dose level (DL) will be 1–2 DLs below the single-agent predicted PAD range; dose level will be assigned at the time of enrollment

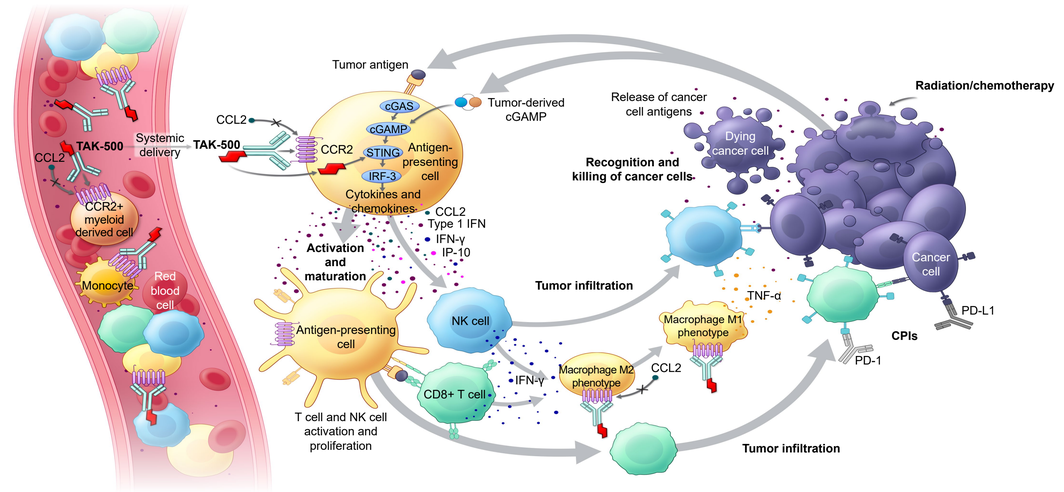
Dose expansion phase (N~34)

- Identification of minimum PAD and PAD+1 DLs in the combination arm of the dose escalation phase will trigger enrollment in the expansion cohort(s)
- Patients will receive IV TAK-500 in combination with IV pembrolizumab 200 mg, with possible exploration of Q3W versus once every 2 weeks (Q2W) administration of TAK-500

- The tumor types selected for this study were chosen based on clinical unmet need and the presence of the following biomarkers: CCR2 expression, monocyte and macrophage tumor infiltration, and STING gene signature expression as analyzed via publicly available databases

TAK-500 structure and mechanism of action

- TAK-500 is an ISAC that consists of three parts:
  - A synthetic analog of cyclic guanosine monophosphate-adenosine monophosphate (cGAMP) STING agonist payload based on TAK-676 (a potent early clinical stage STING agonist currently under phase 1 clinical evaluation [NCT04420884; NCT04879849][7,8])
  - A humanized immunoglobulin G1 anti-CCR2 antibody
  - A self-immolating maleimide-containing protease-cleavable peptide linker
- By targeting the STING pathway, and CCR2-expressing myeloid cells, TAK-500 may offer enhanced potency via improved pharmacokinetics (PK) and selective delivery. As such, TAK-500 has three possible mechanisms of action:
  - Activation of IFN response
  - Reprogramming of suppressive intratumoral CCR2+ myeloid cells to an inflammatory phenotype
  - Blockade of suppressive tumor-associated macrophage recruitment
- Through these mechanisms, TAK-500 has the potential to overcome resistance to CPIs in both CPI-refractory and immunologically cold tumors



CCL2, cysteine-cysteine chemokine ligand 2; cGAS, cyclic guanosine monophosphate-adenosine monophosphate synthase; IFN-γ, interferon gamma; IP-10, interferon gamma induced protein 10; IRF-3, interferon regulatory transcription factor 3; NK, natural killer; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; TNF, tumor necrosis factor.

Study design: **First-in-human, open-label, dose escalation and expansion, phase 1a/1b study of TAK-500, as a single-agent and in combination with pembrolizumab, in patients with select locally advanced or metastatic solid tumors**

Study objectives: **Primary:** Determine the safety and tolerability of TAK-500 when given alone or in combination with pembrolizumab
Secondary: Determine the PAD range, RP2D, antitumor activity, PK, immunogenicity, and pharmacodynamics of TAK-500 when given alone or in combination with pembrolizumab

Eligible conditions

This study is enrolling patients (N~106) with the following pathologically confirmed tumor types, whose disease has progressed on, or are intolerant to, all standard therapy:

- Gastroesophageal adenocarcinoma
- Pancreatic adenocarcinoma
- Hepatocellular carcinoma
- Non-squamous non-small cell lung cancer
- Squamous cell carcinoma of the head and neck
- Mesothelioma
- Triple-negative breast cancer

Escalation phase

n~40: **TAK-500 single-agent** (escalating doses)† IV Q3W in 21-day cycles

Determination of the minimum PAD will trigger initiation of the combination dose escalation

n~32*: **TAK-500** (escalating doses)† IV Q3W in 21-day cycles **+ pembrolizumab 200 mg** IV Q3W in 21-day cycles

Dose expansion phase

n~34: **TAK-500** IV **Q3W and/or Q2W in 42-day cycles + pembrolizumab 200 mg** IV Q3W in 42-day cycles in single tumor type expansion cohorts

Patients will receive treatment for up to 1 year

ClinicalTrials.gov identifier: NCT05070247

*In the combination arm, the number of patients will depend on the starting DL. †Dose escalation in both single-agent and combination cohorts will be guided by the BOIN design.

Study objectives and endpoints

Study objectives

Primary

- Safety and tolerability of TAK-500 as a single-agent or in combination with pembrolizumab

Secondary

- Determine PAD range and recommended phase 2 dose (RP2D)
- Characterize single- and multiple-doses of PK
- Evaluate preliminary antitumor activity
- Evaluate dose-responsive impact on tumor immune cell infiltration and activation
- Determine immunogenicity of TAK-500

Primary endpoints

- Frequency of treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to dose modifications and discontinuations
- Number of patients with dose-limiting toxicities

Secondary endpoints

- PAD range and RP2D
- PK parameters of TAK-500
- Response assessments by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 for both single-agent TAK-500 and in combination with pembrolizumab
- Immune cell infiltration and activation by immunohistochemistry or in-situ hybridization
- Changes in gene expression, including STING agonism and IFN gene signatures, between pre-treatment and on-treatment tumor biopsies
- Incidence of patients who are antidrug antibody-positive and have acquired immunogenicity

Patient eligibility

Key inclusion criteria

- Male or female participants aged ≥18 years
- Eastern Cooperative Oncology Group performance status of 0 or 1
- Patients with select pathologically confirmed (cytological diagnosis is adequate), locally advanced or metastatic solid tumors, whose disease has progressed on, or are intolerant to, all standard therapy
- At least one RECIST version 1.1 evaluable lesion
- Adequate bone marrow, renal, hepatic, pulmonary, and cardiac functions

Key exclusion criteria

- Treated with other STING agonists/antagonists, Toll-like receptor agonists, or CCR2 agonists/antagonists within the past 6 months
- Active vaping and/or smoking within 90 days of the first dose of study drug
- Treatment with any investigational products or other anticancer therapy (including chemotherapy, targeted agents, and immunotherapy) within 14 days or 5 half-lives, whichever is shorter, before the first dose of study drug
- Radiation therapy within 14 days (42 days for radiation to the lungs) and/or systemic treatment with radionuclides within 42 days before the first dose of study drug. Patients with clinically relevant ongoing pulmonary complications from prior radiation therapy are not eligible
- History of brain metastasis, unless:
  - Clinically stable following prior surgery, whole-brain radiation, or stereotactic radiosurgery
  - Off corticosteroids for central nervous system involvement
- Grade ≥2 fever of malignant origin
- Patients with either/both of:
  - Uncontrolled, known, or suspected, autoimmune disease
  - A diagnosis of congenital or acquired immunodeficiency

Enrollment and study timelines

- Recruitment is ongoing
- The study is planned to enroll ~106 patients across 7 to 10 sites in the United States
- Start date: February 1, 2022
- Estimated study completion date: April 8, 2025

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