TAK-500 as a single agent and in combination with pembrolizumab in patients with advanced solid tumors: Rationale and design of a phase 1/2 study

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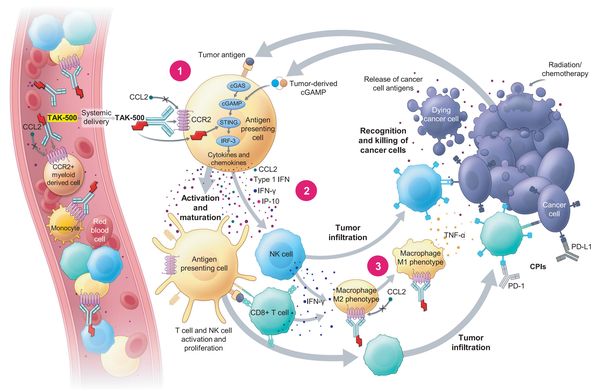
Background

- 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] thus, stimulating innate immune cells in the tumor microenvironment may overcome resistance
- STimulator of INterferon Genes (STING) is a cytosolic protein critical for induction of Type I IFN-dependent innate immunity[4]
- TAK-500 is a first-in-class immunostimulatory antibody drug conjugate (iADC) that delivers the STING agonist dazostinag (TAK-676) to cysteine-cysteine chemokine receptor (CCR2)-positive myeloid cells in the tumor microenvironment (**Figure 1**):
  - Dazostinag is a potent early clinical stage STING agonist currently under phase 1/2 clinical evaluation (NCT04420884; NCT04879849)[5,6]
- In preclinical models, treatment with the TAK-500 murine surrogate resulted in activation of innate and adaptive immunity and antitumor activity, which was increased when combined with an anti-programmed cell death protein 1 (PD-1) antibody[7,8]
- Based on these data, a phase 1/2 open-label, dose-escalation and expansion study was designed to determine the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of TAK-500 as a single agent (SA) and in combination with pembrolizumab in CCR2-enriched solid tumors (NCT05070247)
- The phase 1 portion has been previously described;[9] here we present the updated global phase 2 design

Figure 1: Mechanism of action of TAK-500



CCL2, cysteine-cysteine chemokine ligand 2; cGAMP, 2′,3′-cyclic guanosine monophosphate–adenosine monophosphate; 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-L1, programmed cell death-ligand 1; TNF, tumor necrosis factor

TAK-500 mechanism of action

- By targeting the STING pathway and CCR2-expressing myeloid cells, TAK-500 may offer enhanced potency via improved PK and selective delivery
- As such, TAK-500 has three possible mechanisms of action (**Figure 1**):
  1. Reprogramming of suppressive intratumoral CCR2-positive myeloid cells to an inflammatory phenotype
  2. Activation of IFN response
  3. 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

Study title

An open-label, dose-escalation and expansion, phase 1/2 study of TAK-500, as a single agent and in combination with pembrolizumab, in patients with specific locally advanced or metastatic solid tumors

Phase 2 study objectives

Primary: Evaluate the antitumor activity and the dose for development of TAK-500 when given alone or in combination with pembrolizumab

Secondary: Evaluate the safety and tolerability of TAK-500 when given alone or in combination with pembrolizumab

Phase 1 dose escalation

Phase 1 patient selection

The phase 1 portion is enrolling patients with the following pathologically confirmed tumor types associated with increased CCR2 expression, whose disease has progressed on or are intolerant to all standard therapy:

- Gastroesophageal adenocarcinoma
- Hepatocellular carcinoma
- Mesothelioma
- Nasopharyngeal carcinoma
- Non-squamous non-small cell lung cancer (NSCLC)
- Pancreatic adenocarcinoma (PDAC)
- Renal clear cell carcinoma (RCC)
- Squamous cell carcinoma of the head and neck
- Triple-negative breast cancer

Single-agent escalation:
TAK-500 (escalating doses)*
IV Q3W in 21-day cycles

n~52

Demonstration of minimum PAD or safety clearance of a predetermined dose level will trigger initiation of the combination dose escalation

n~30

TAK-500 + anti-PD-1 combination escalation:
TAK-500 (escalating doses)*
IV Q3W in 21-day cycles
+ pembrolizumab 200 mg
IV Q3W in 21-day cycles

Phase 2 dose expansion

Dose expansion and randomized dose exploration in single indication cohorts

TAK-500 at RDE 1 and/or RDE 2
Q3W or Q2W in 42-day cycles

± pembrolizumab 200 mg IV Q3W in 42-day cycles
in single tumor type expansion cohorts

n~231

Phase 2 patient selection

The phase 2 portion of the study will include 3 tumor types (non-squamous NSCLC, PDAC, and RCC), selected for the following criteria:

- High intratumoral CCR2 expression as determined by RNA sequencing (TCGA) and CCR2 IHC
- High myeloid infiltration in the tumor microenvironment
- Presence of active STING pathway genes as determined by RNA sequencing analysis (TCGA)

ClinicalTrials.gov identifier: NCT05070247

*Dose escalation in both single agent and combination cohorts will be guided by the Bayesian Optimal Interval design.
CCR2, cysteine-cysteine chemokine receptor type 2; IHC, immunohistochemistry; IV, intravenously; PAD, pharmacologically active dose; PD-1, programmed cell death protein; Q2W, once every 2 weeks; Q3W, once every 3 weeks; RDE, recommended dose for expansion; STING, STimulator of INterferon Genes; TCGA, The Cancer Genome Atlas

Phase 2 eligibility criteria

Patients are eligible regardless of PD-L1 expression status.

2L NSCLC
- No targetable driver mutations
- Disease progression on/after 1 prior anti-PD-(L)1
  - ≥6 weeks of exposure in metastatic setting OR progression/recurrence within 6 months of (neo)adjuvant therapy
  - Anti-PD-(L)1 therapy may be given with or without anti-CTLA4 and/or chemotherapy

3L NSCLC
- No targetable driver mutations
- Disease progression on/after 1 or 2 prior lines of chemotherapy
  - If anti-PD-(L)1 was given with chemotherapy, 2 prior lines of therapy with chemotherapy are required

2L PDAC
- Disease progression on/after 1 prior line of fluorouracil- or gemcitabine-based chemotherapy in the metastatic setting
  - (Neo)adjuvant chemotherapy qualifies as prior line if progression/recurrence occurred within 6 months of completion
- No prior anti-PD-(L)1 exposure
- Patients with MSI-H/dMMR disease are not eligible

3L RCC
- Disease progression on/after 1 prior anti-PD-(L)1
  - ≥6 weeks of exposure in metastatic setting OR progression/recurrence within 6 months of (neo)adjuvant therapy
  - Anti-PD-(L)1 therapy may be given with or without anti-CTLA4 and/or VEGFR TKI
- Disease progression on/after 1 or 2 prior lines of VEGFR TKIs
  - If anti-PD-(L)1 therapy was given with VEGFR TKI, 2 prior lines of therapy with TKIs are required

2L, second line; 3L, third line; CTLA4, cytotoxic T-lymphocyte-associated antigen-4; MSI-H/dMMR, microsatellite instability-high/mismatch repair deficient; VEGFR TKI, vascular endothelial growth factor receptor tyrosine kinase inhibitor

Phase 2 study design

Locally recurrent and metastatic non-squamous NSCLC – TAK-500 SA and TAK-500 + pembrolizumab

Dose expansion and randomized dose exploration (n~59)* — 2:1
- **2L NSCLC:** TAK-500 + pembrolizumab RDE 1: ~35 RE patients
- **2L NSCLC:** TAK-500 + pembrolizumab RDE 2: ~18 RE patients

Futility analysis: ≥5 responses in first 21 patients

Dose expansion and randomized dose exploration (n~48)* — 1:1
- **3L NSCLC:** TAK-500 SA RDE 1: ~21 RE patients
- **3L NSCLC:** TAK-500 SA RDE 2: ~21 RE patients

Final analysis

Locally recurrent and metastatic PDAC – TAK-500 SA and TAK-500 + pembrolizumab

Dose expansion and randomized contribution of parts exploration (n~90)* — 1:1
- **2L PDAC:** TAK-500 + pembrolizumab RDE 1: ~40 RE patients
- **2L PDAC:** TAK-500 SA RDE 1: ~40 RE patients

Futility analysis: ≥4 responses in first 25 patients — Final analysis

Locally recurrent and metastatic RCC – TAK-500 + pembrolizumab

Dose expansion (n~30)*
- **3L RCC:** TAK-500 + pembrolizumab RDE 1: ~30 RE patients

Final analysis

*The estimated sample size (n) accounts for ~10% dropout rate.
RE, response-evaluable

Study objectives and endpoints of phase 2 dose expansion

Study objectives

Primary objectives

- To evaluate the preliminary antitumor activity of TAK-500 in recurrent locally advanced or metastatic non-squamous NSCLC:
  - 2L NSCLC treated with TAK-500 in combination with pembrolizumab
  - 3L NSCLC treated with TAK-500 as a single agent
- To evaluate the preliminary antitumor activity of TAK-500 as a single agent and in combination with pembrolizumab in recurrent locally advanced or metastatic 2L PDAC
- To evaluate the preliminary antitumor activity of TAK-500 in combination with pembrolizumab in recurrent locally advanced or metastatic 3L RCC
- To evaluate the dose for further development of TAK-500 administered as single agent and in combination with pembrolizumab

Secondary objectives

- To determine the safety and tolerability of TAK-500 as single agent and in combination with pembrolizumab in patients with previously treated recurrent locally advanced or metastatic non-squamous NSCLC, PDAC, and RCC

Primary endpoints

- Overall response rate assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST v.1.1)[10] for both single-agent TAK-500 and in combination with pembrolizumab

Secondary endpoints

- PK parameters of TAK-500
- Disease control rate, duration of response, time to response (assessed by the investigator per RECIST v.1.1), progression-free survival, overall survival for both single agent TAK-500 and in combination with pembrolizumab
- Immune cell infiltration and activation by immunohistochemistry or in-situ hybridization
  - Patients with a safely accessible lesion will have compulsory paired tumor biopsies. Pretreatment tumor biopsies should be performed ≥2 days after the last dose of any prior antineoplastic therapy and ≤28 days before the first dose of study drug
- Incidence of patients who are antidrug antibody-positive and have acquired immunogenicity
- Frequency and severity of treatment-emergent adverse events (TEAEs) and TEAEs leading to dose modifications and discontinuations
- Number of patients with dose-limiting toxicities

Enrollment and study timelines

Current status: As of September 2023, six sites in the US are recruiting patients into the phase 1 portion of the study

First patient enrolled: April 26, 2022

Phase 2 start date (US and Global): February 2024

Projected number of sites for phase 2: Asia-Pacific: 8 sites; North America: 25 sites; Europe: 62 sites

Estimated study completion date: April 2025

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