A phase 1 dose-escalation study of intravenously administered TAK-676, a novel STING agonist, alone and in combination with pembrolizumab in patients with advanced or metastatic solid tumors

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Background

- Immuno-oncology therapies, including immune CPIs, are revolutionizing cancer treatment; however, primary and secondary resistance to CPIs remains a significant problem[1,2]
  - CPI resistance is associated with reduced IFN signaling, altered antigen presentation, and an immunosuppressive tumor phenotype[1,2]
- Stimulating innate immune cells to develop a proinflammatory tumor environment that activates Type 1 IFN signaling and downstream adaptive antitumor immune mechanisms may help to overcome such resistance
- Stimulator of Interferon Genes (STING) is a key mediator of Type 1 IFN-dependent innate immune modulation and may be an important target for therapeutic antitumor immunity[3]
- Intratumoral STING agonists evaluated clinically present significant logistical challenges and preclinical experiments have shown a bell-shaped response curve where antitumor effects are abrogated at higher doses[4,5]

TAK-676 is a novel STING agonist which is administered as an IV infusion, and this agent is currently under investigation in a phase 1 trial as monotherapy and in combination with pembrolizumab in patients with solid tumors (NCT04420884).

Study design

- This is a phase 1, open-label, dose-escalation study of TAK-676 as a single agent and combined with pembrolizumab **(central summary panel)**
- The trial comprises a single-patient safety lead-in with single-agent IV TAK-676 0.1 mg, followed by dose escalation using a 3+3+3 rule for the first dose level
- Subsequent dose escalation follows an adaptive BLRM design with overdose control
- Dose escalation will start in the combination arm when ≥2 dose levels in the single-agent arm have been evaluated and are considered safe
- In both arms, patients will receive IV TAK-676 on days 1, 8, and 15 in 21-day cycles
- In the combination arm, patients will also receive IV pembrolizumab 200 mg on day 1 of each cycle

Study objectives

Primary

Determine the safety and tolerability of TAK-676 alone and in combination with pembrolizumab

- Primary endpoints are the frequency and severity of TEAEs, number of patients with DLTs, and rates of SAEs and TEAEs leading to dose modification or treatment discontinuation (NCI-CTCAE version 5.0)

Secondary

- Determine the pharmacologically active dose and recommended phase 2 dose of TAK-676 alone and in combination with pembrolizumab
- Characterize PK of TAK-676 alone and in combination with pembrolizumab
- Assess preliminary antitumor activity per modified RECIST version 1.1 (as evaluated by investigators) of TAK-676 alone and in combination with pembrolizumab
- Evaluate the induction of STING/IFN agonism gene signature in peripheral blood

Exploratory

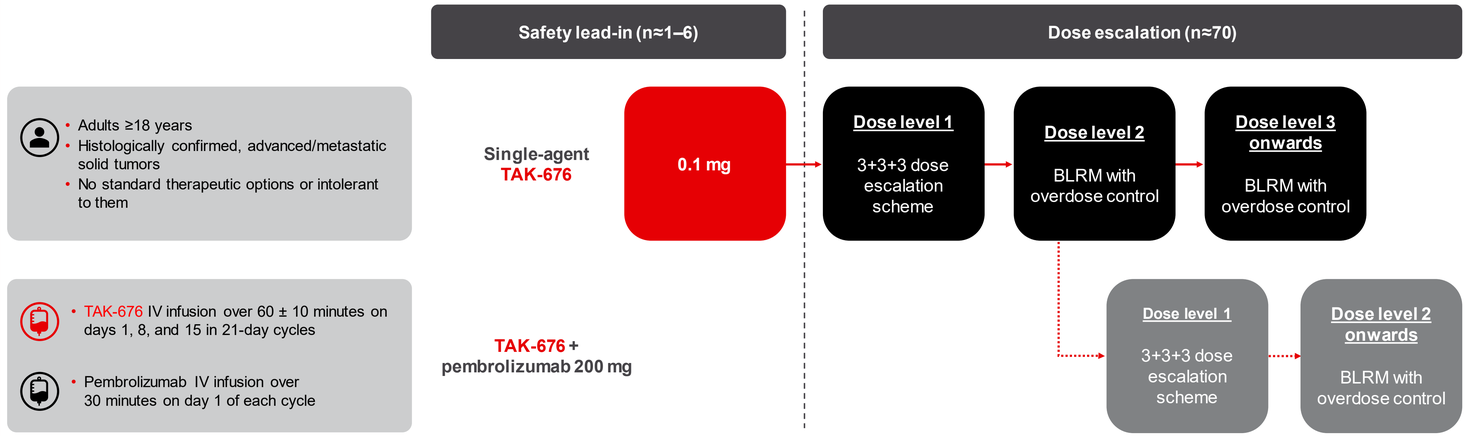
- Evaluate the relationships between STING pathway induction and TAK-676 dose/exposure, and between STING pathway induction and immune cell activation
- Assess the relationship between TAK-676 exposure, immune cell activation, and clinical response
- Evaluate the relationship between baseline and on-treatment effects of TAK-676 within the tumor and tumor microenvironment via analysis of gene expression, including degree of STING pathway induction and impact upon immune cell activation, infiltration, and overall immune contextureTo characterize germline DNA variants for correlations with clinical outcome and PK, including future pharmacogenomic exploration of polymorphisms in drug-metabolizing enzymes and/or transporters to understand their impact on TAK-676 PK
- To collect PK time-matched triplicate ECG data to contribute to concentration QTcF analysis for evaluation of the effect of TAK-676 on QTcF interval

STUDY DESIGN

Multicenter, open-label, phase 1 dose-escalation study of TAK-676 +/– pembrolizumab

PRIMARY STUDY OBJECTIVE

Determine the safety and tolerability of TAK-676, alone and in combination with pembrolizumab



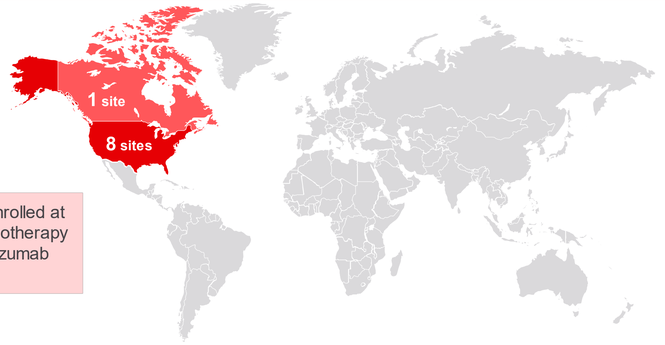
STUDY TIMELINES

Start: July 2020; Estimated study completion: March 2023[6]

ClinicalTrials.gov identifier: NCT04420884

Study locations

- The study is planned to enroll ~76 patients at 9 sites across North America (USA and Canada)
- Recruitment is ongoing



As of May 7, patients are being enrolled at the 5th dose level of TAK-676 monotherapy and the 2nd dose level of pembrolizumab combination therapy

Key eligibility criteria

- Adult patients with histologically confirmed (cytological diagnosis is acceptable), advanced or metastatic solid tumors:
  - Who have no standard therapeutic options or are intolerant to them (TAK-676 single-agent arm)
  - Who have no standard therapeutic options or are intolerant to them including tumors that have relapsed, are refractory, or are naïve to anti-PD-1/PD-L1 therapy (TAK-676 + pembrolizumab arm)
- ECOG PS 0–1
- Life expectancy >12 weeks
- Adequate bone marrow, renal, hepatic, and cardiac function
- At least one RECIST version 1.1 evaluable lesion

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Abbreviations

BLRM, Bayesian logistic regression model; CPI, checkpoint inhibitor; DLT, dose-limiting toxicity; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; IFN, interferon; IV, intravenous; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PK, pharmacokinetics; QTcF, QT interval with Fridericia correction method; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; STING, Stimulator of Interferon Genes; TEAE, treatment-emergent adverse event.

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Disclosures

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