A Phase 1/2, first-in-human, open-label, dose-escalation study of TAK-186, an EGFR × CD3ε COBRA T-cell engager, in adult patients with unresectable, locally advanced, or metastatic solid tumors

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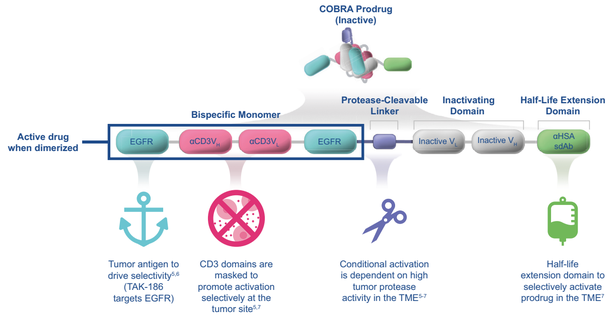
Background

- Overexpression of epidermal growth factor receptor (*EGFR*) and increased protease activity in the TME relative to healthy tissue are observed in many solid tumors, including head and neck squamous cell carcinoma, colorectal cancer, and lung cancer.[1-3]
- CD3 is a transmembrane complex of proteins expressed almost exclusively by T cells.[4]
- TAK-186 is a COnditional Bispecific Redirected Activation (COBRA) T-cell engager designed to bind to both EGFR and CD3ε following the conditional activation in the TME (**Figure 1**).

Figure 1: TAK-186 prodrug molecular design



- Upon binding of the TAK-186 prodrug to EGFR on tumor cells, the elevated levels of active proteases in the TME compared with normal tissue[6] lead to preferential cleavage of the prodrug in TME and activation of the molecule (**Figure 2**).
- The activated molecule binds to EGFR on tumor cells and associates to form active dimers.
- Dimerization of the TAK-186 molecules allows the T-cell–engaging domain to bind to and activate T cells via the CD3ε-binding domain.
- Preclinical studies have confirmed the mechanism of action of TAK-186 and support the clinical evaluation of its safety and tolerability.[6,7]

Trial Design

This is a first-in-human, open-label, Phase 1/2 study of TAK-186 in patients with unresectable, locally advanced/metastatic *EGFR*-expressing solid tumors refractory to standard therapies.

Study Objectives

- To characterize safety, tolerability, and DLTs of TAK-186
- To characterize the pharmacokinetics, pharmacodynamics, immunogenicity, and preliminary anti-tumor activity of TAK-186

Study Design

Key inclusion criteria

- Unresectable, locally advanced or metastatic malignant neoplasms (HNSCC, NSCLC, CRC, etc.)[a]
- ECOG performance status ⩽1
- Life expectancy ⩾12 weeks
- Measurable disease as per RECIST v1.1 criteria and documented by CT and/or MRI

Dose-escalation phase

TAK-186 (escalating doses) IV
Initial 60-minute infusion
30-minute infusions QW

Primary endpoint

- Characterization of safety[b]

Cohort expansion phase

- **HNSCC** IV infusion QW
- **NSCLC** IV infusion QW
- **CRC** IV infusion QW

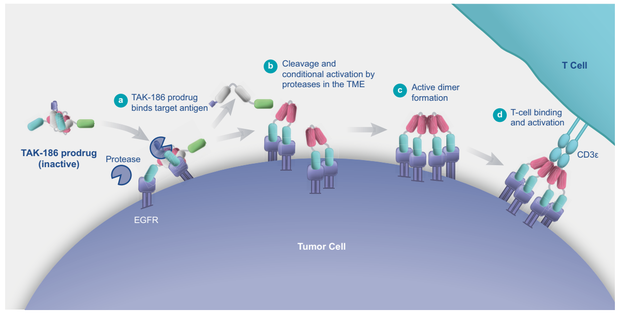
Treatment for up to 55 weeks or until discontinuation criteria are met

Follow-up at 30 days and then every 12 weeks for up to 1 year after the last treatment

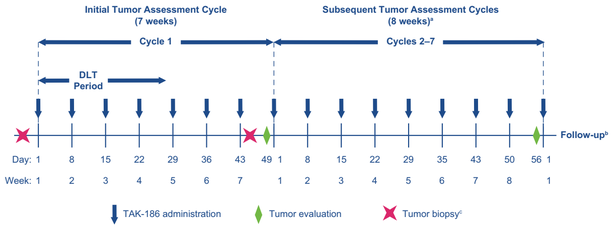
[a]Tumor evaluation will be done using RECIST v1.1 and modified RECIST v1.1.
[b]Safety data will be summarized by Common Terminology Criteria for Adverse Events v5.0 and cytokine release syndrome will be reported by American Society for Transplantation and Cellular Therapy consensus grading.

ClinicalTrials.gov identifier: NCT04844073

Figure 2: Conditional activation of TAK-186



Study schema



[a]Patients who do not experience DLT or other unacceptable toxicity may receive up to 6 additional 8-week treatment cycles (total of 7 cycles) depending on response to study treatment. The Day 49 (Cycle 1)/Day 56 (all other cycles) tumor evaluation should be reviewed before initiating the next cycle of TAK-186. The DLT evaluation period is defined as the time between the initial TAK-186 dose and Cycle 1 Day 28.
[b]All patients will be followed for survival at 30 days following last treatment, then every 12 weeks for 52 weeks until the patient has died or is lost to follow-up, or the follow-up has continued for a total of 52 weeks after the last dose.
[c]Starting in the Cohort Expansion Phase, patients must have at least 1 lesion considered capable of being biopsied. Patients starting at the 30 µg/kg dose level or higher during Dose Escalation must agree to provide fresh tumor biopsy samples during Screening and undergo a second tumor biopsy if the patient has an easily accessible lesion.

Patient eligibility criteria

Inclusion criteria	Exclusion criteria
Age ⩾18 years	History of known autoimmune disease (with exceptions)
ECOG performance status ⩽1	Major surgery or traumatic injury within 8 weeks before first dose or if wounds are still unhealed
Histologically proven, unresectable, locally advanced or metastatic solid tumors that based on prior literature reports are considered to express *EGFR*	Radiation therapy <2 weeks prior to TAK-186 initiation
Able to provide informed consent and comply with study procedures	Clinically significant cardiovascular, vascular, or gastrointestinal disease, or pulmonary compromise
Life expectancy ⩾12 weeks	Treatment with >10 mg per day of prednisone (or equivalent) or other immunosuppressive drugs within 7 days prior to the initiation of study drug
Measurable disease per RECIST v1.1	Active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to the initiation of TAK-186
Checkpoint inhibitor immune-related toxicity resolved to either Grade ⩽1 or baseline	

Primary and secondary endpoints

Primary endpoints

- Number of participants with treatment-emergent adverse events
- Number of participants with DLTs
- Number of participants with cytokine release syndrome/infusion reactions

Secondary endpoints

- RDE
- C_{max}, T_{max}, AUC_{tau}, AUC_{last}, AUC_{inf}, C_{trough}, CL, V_{ss}, and $t_{1/2}$ of TAK-186
- Number of participants with anti-drug antibodies for TAK-186 in plasma
- Preliminary anti-tumor activity of TAK-186
- Objective response rate
- Duration of response
- Progression-free survival
- Overall survival

Study status

- Status: Recruiting
- Estimated enrollment: 228
- Estimated number of sites: 35
- Estimated primary completion date: 27 September 2025
- Estimated study completion date: 01 November 2026

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Abbreviations

AUC_{inf}, area under the plasma concentration-time curve from time 0 to infinity; AUC_{last}, area under the plasma concentration-time curve from time 0 to last quantifiable concentration; AUC_{tau}, area under the plasma concentration-time curve for a dosing interval; CD, cluster of differentiation; CL, clearance; C_{max}, maximum observed plasma concentration; CRC, colorectal cancer; CT, computed tomography; C_{trough}, trough plasma concentration; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; HSA, human serum albumin; IV, intravenous; NSCLC, non-small cell lung cancer; MRI, magnetic resonance imaging; QW, once weekly; RECIST, Response Evaluation Criteria in Solid Tumors; RDE, recommended dose for expansion; sdAb, single-domain antibody; $t_{1/2}$, half-life; T_{max}, time of first occurrence of maximum observed plasma concentration; TME, tumor microenvironment; V_{HL}, heavy/light chain variable domain; V_{ss}, volume of distribution at steady state.

Disclosures

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