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- 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**).

The diagram illustrates the COBRA Prodrug (Inactive) structure and its activation mechanism. The structure consists of a Bispecific Monomer (EGFR, α CD3V_n, α CD3V, EGFR) linked to a Protease-Cleavable Linker, an Inactivating Domain (Inactive V_n), and a Half-Life Extension Domain (α HSA sdAb). The diagram illustrates the activation process:

- Active drug when dimerized:** The Bispecific Monomer (EGFR, α CD3V_n, α CD3V, EGFR) is shown.
- Tumor antigen to drive selectivity^{6,8} (TAK-186 targets EGFR):** An anchor icon indicates the EGFR target.
- CD3 domains are masked to promote activation selectively at the TME:** A red circle with a slash and dots indicates the masked CD3 domains.
- Conditional activation is dependent on high tumor protease activity in the TME⁵⁻⁷:** A scissors icon indicates the protease-cleavable linker.
- Half-life extension domain to selectively activate prodrug in the TME:** A green icon of a container indicates the half-life extension domain.

- ## References

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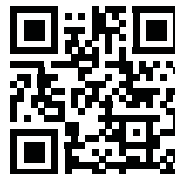
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AUC_{0-∞}, area under the plasma concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time 0 to last quantifiable concentration; AUC_{0-∞}, area under the plasma concentration-time curve for a dosing interval; CD, cluster of differentiation; CL, clearance; C_{max}, maximum observed plasma concentration; CI, confidence interval; CT, computed tomography; C₅₀, 50% cough plasma concentration; DLT, dose-limiting toxicity; EOC, 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; sAb, single-domain antibody; T_{1/2}, half-life; T_{max}, time of first occurrence of maximum observed plasma concentration; TME, tumor microenvironment; V_{max}, heavy/light chain variable domain; V_{ss}, volume of distribution at steady state.

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This poster is intended for healthcare providers

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ClinicalTrials.gov identifier: NCT04844073

*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.

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 <i>EGFR</i>	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	

- RDE
- $C_{\max}^*$, $T_{\max}^*$, AUC_{last}^* , $AUC_{\text{last}}^*/AUC_{\text{inf}}^*$, AUC_{inf}^* , C_{trough}^* , CL_{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

- Estimated study completion date: 01 November 2026