A phase 1/2, first-in-human, open-label, dose-escalation study of TAK-280, an investigational B7-H3 x CD3ε Conditional Bispecific Redirected Activation (COBRA) T-cell engager, in adult patients with unresectable, locally advanced, or metastatic solid tumors

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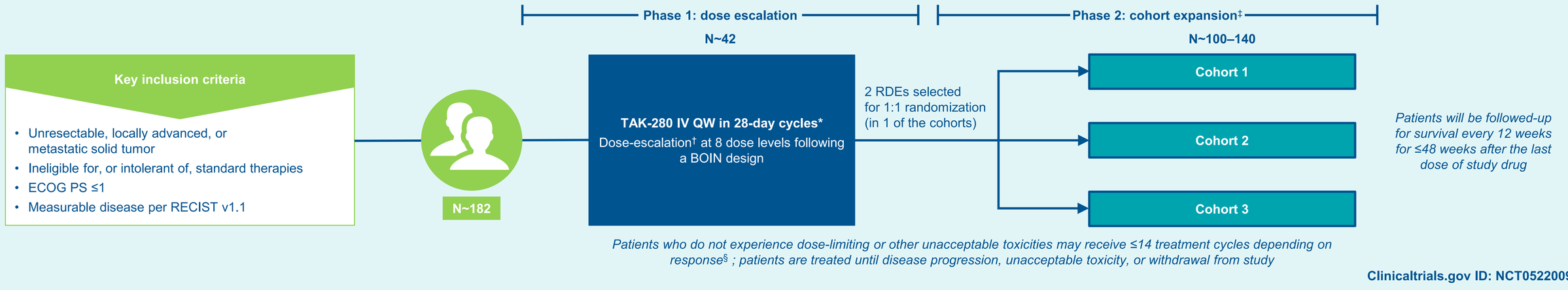
Trial design

First-in-human, open-label, phase 1/2 study of TAK-280 in patients with unresectable, locally advanced or metastatic cancers

Study objectives

Primary: To characterize the **safety**, **tolerability**, and **DLTs** of TAK-280 to determine its **MTD** (if any) and **RP2D**

Secondary: To characterize the **PK** and **potential immunogenicity,** and to evaluate the **preliminary anti-tumor activity** of TAK-280



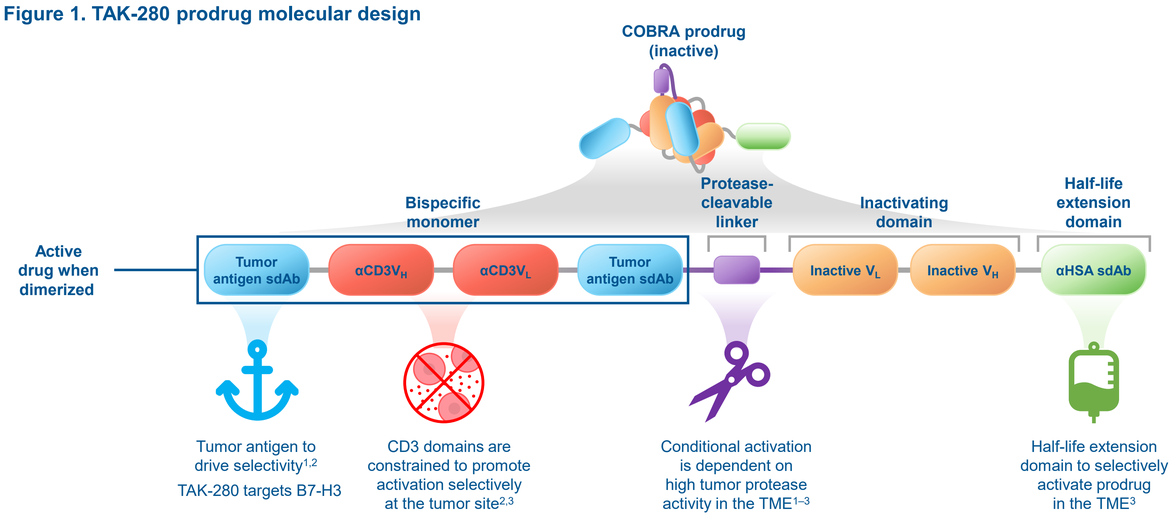
Clinicaltrials.gov ID: NCT05220098

*Initial infusion of 60 minutes, may be adjusted to shorter or longer time (but never less than 30 minutes). †Only one patient will be enrolled for the first two dose levels. ‡Indications to be confirmed based on data from the escalation phase.
§ Patients who, in the opinion of the investigator, continue to receive clinical benefit by the end of the 14 cycles with acceptable toxicity and no alternative treatment option, may continue therapy on a case-by-case basis.
BOIN, Bayesian Optimal Interval design; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; QW, once weekly; PK, pharmacokinetic; RDE, recommended dose for expansion; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose.

Background

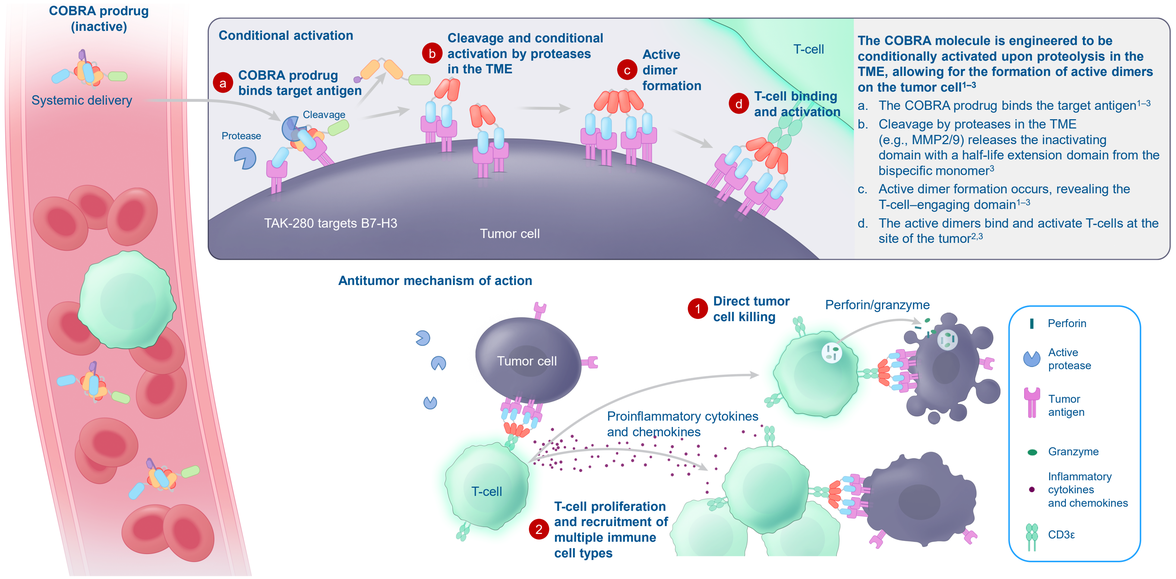
- The COnditional Bispecific Redirected Activation (COBRA) platform is designed to allow the targeting of antigens widely expressed in solid tumors that are typically not targetable with traditional T-cell engagers (TCEs)[1–3]
- Conditional T cell engagement has the potential to deliver wider therapeutic margin to treat solid tumors[1,4,5]
- TAK-280 is a novel COBRA TCE that targets the transmembrane protein B7 homolog 3 protein (B7-H3; also known as CD276)
- B7-H3 is known to be overexpressed in a range of solid tumors, including metastatic castration-resistant prostate cancer (mCRPC) and non–small cell lung cancer[6,7]

Figure 1. TAK-280 prodrug molecular design



HSA, human serum albumin; sdAb, single-domain antibody; V_H, variable domain of the heavy chain; V_L, variable domain of the light chain.

Figure 2. Conditional activation of TAK-280



1 Activated T-cells interacting with tumor cells release cytolytic granules, which may drive direct tumor-killing effects[8]
2 Activated T-cells release cytokines to drive T-cell proliferation and expend T-cells and other immune cells, potentially amplifying the tumor-killing effect[9,10]

- In its prodrug form, TAK-280 binds to B7-H3 but not to CD3ε on T-cells (**Figure 1**)
- Once in the protease-rich tumor microenvironment (TME), TAK-280 undergoes protease-mediated activation
  - Formation of active dimers through CD3ε-binding, and co-engagement of B7-H3 expressing cells is postulated to result in cytotoxic anti-tumor response[1] (**Figures 1** and **2**)
- In preclinical studies, COBRA molecules demonstrated cleavage-dependent conditionality, engagement of tumor target antigen, and induction of T-cell mediated tumor killing[3]

Study eligibility

- This phase 1/2 study is enrolling adult patients with unresectable, locally advanced, or metastatic solid tumors described in the literature to have enhanced B7-H3 expression[6] (**Summary panel** and **Table 1**)

Table 1. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
≥18 years old	History of known autoimmune disease
Histological or pathological confirmation of unresectable, locally advanced, or metastatic solid tumor described in the literature to have enhanced B7-H3 expression	Major surgery, or traumatic injury within 8 weeks before the first dose of TAK-280
Ineligible for or intolerant of standard therapies, have no approved therapy with demonstrated benefit or have exhausted all available therapies	Vaccination ≤2 weeks (or ≤4 weeks for live virus vaccine) of first dose of TAK-280
ECOG PS ≤1	Ongoing or active infection of grade ≥2, or inflammatory process unresolved for ≥4 weeks before first dose of TAK-280
Measurable disease per RECIST v1.1. (except for patients with mCRPC and bone lesions only)	Clinically significant cardiac or gastrointestinal disorders ≤6 months prior to receiving the first dose of TAK-280
Acceptable laboratory parameters	Bone marrow or solid organ transplant, or use of immunosuppressive agents, within the past 5 years
Appropriate measures taken to prevent pregnancies in female patients of child-bearing potential or in male patients with partners of child-bearing potential	Known hypersensitivity to TAK-280 or any excipient
Treated symptomatic or asymptomatic ≥14 days central nervous system (CNS) metastases with no concurrent treatment for CNS disease or leptomeningeal disease or cord compression	Second primary invasive malignancy not in remission for ≥3 years

Key study endpoints

Primary endpoint

1. Incidence of DLTs and other toxicities* during dose escalation

Secondary endpoints

1. PK parameters
2. Response assessment by the investigator (using RECIST v1.1)
3. Confirmed overall response rate (defined as rate of complete responses + partial responses)
4. Duration of response
5. Disease control rate
6. Overall survival and progression-free survival
7. Immunogenicity characterization (presence, titer, and impact assessment on exposure, safety, and efficacy)
8. Prostate-specific antigen (PSA) assessment (for patients with mCRPC only): PSA response, duration of response, time to PSA progression, and proportion of patients with PSA reduction ≥6

*Safety endpoints are evaluated according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 for non-cytokine-release syndrome (CRS) toxicities, and the American Society for Transplantation and Cellular Therapy (ASTCT) CRS consensus grading for CRS/infusion-related reaction toxicities.[11]

Study status

- Patients are being enrolled in ~16 study sites in the United States, Australia, Canada, and Spain[12]
- As of the data cutoff date of Jan 10, 2024, 18 patients have received the study drug
- Study completion is estimated for 2026[11]

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