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First-in-Human Study of ABBV-514 as Monotherapy and in Combination With Budigalimab in Patients With Advanced Solid Tumors

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OBJECTIVE

This first-in-human study evaluates the safety, pharmacology, and preliminary efficacy of ABBV-514 as monotherapy and in combination with budigalimab, a programmed cell death protein 1 (PD-1) inhibitor, in patients with locally advanced or metastatic solid tumors

- To assess the safety, tolerability, and identify the maximum tolerated dose (MTD)/maximum administered dose (MAD)
- To evaluate the pharmacokinetics (PK) and immunogenicity
- To assess preliminary efficacy
- To evaluate blood and tumor pharmacodynamic and predictive biomarkers

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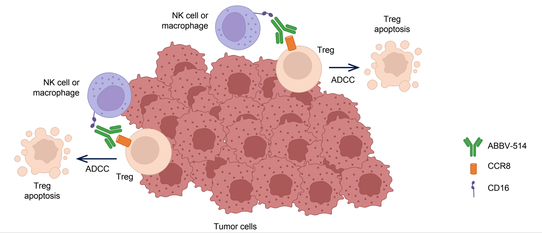
BACKGROUND

- Regulatory T-cells (Tregs) are a specialized T-cell subset that can inhibit antitumor immune responses, and high intratumoral Treg levels have been associated with negative outcomes in several types of cancer[1,2]
- Chemokine receptor (CCR)8 mediates chemotaxis and immune cell interactions and is preferentially expressed on tumor-infiltrating Tregs, relative to peripheral blood Tregs and effector T cells. Thus, it is a potential target for intratumoral Treg interference[3,4]
- ABBV-514 is an afucosylated monoclonal antibody that binds CCR8 and is designed to enhance antibody-dependent cellular cytotoxicity to deplete tumor-infiltrating Tregs
- Immune checkpoint inhibitors targeting the PD-1/PD-1 ligand 1 (PD-L1) pathway can induce robust immune activation and are effective against various tumors. However, many patients do not respond, or develop resistance[5]
- In preclinical studies, the combination of CCR8 and PD-1–targeting antibodies improved efficacy over either antibody alone in a murine model. Thus, combining CCR8 and PD-1–targeting antibodies is of interest and will be explored in this clinical study

Proposed Mechanism of Action of ABBV-514



ADCC, antibody-dependent cellular cytotoxicity; CCR8, chemokine receptor 8; NK, natural killer; Treg, regulatory T cell.

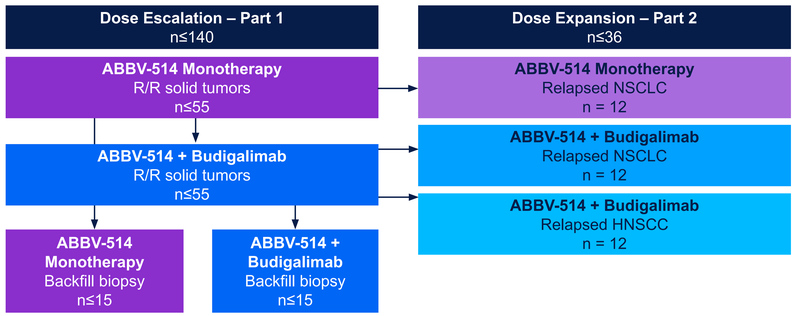
METHODS

Study Overview

Multicenter | International | Open label | **P1** Phase 1 | **176** patients planned for enrollment | **NCT05005403**

- Patients will be enrolled at approximately 80 sites across the US, Japan, Israel, Taiwan, and South Korea
  - Additional countries may be selected for the dose expansion phase
- Enrollment started in November 2021, with 35 patients enrolled as of July 2023

Study Design



HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; R/R, relapsed/refractory.

- Dose escalation starts with ABBV-514 monotherapy; the ABBV-514 and budigalimab combination begins after the first ≥2 ABBV-514 monotherapy dose levels are declared safe and ≥6 patients have been treated
  - Dose escalation is guided by a Bayesian optimal interval design, based on the cumulative number of patients experiencing a dose-limiting toxicity (DLT) assessed in the 21-day observation period after study drug administration for each dose level per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0
  - At least 6 DLT-evaluable patients are to be enrolled at the dose declared as the MTD
- Pre- and on-treatment fresh tumor biopsies will be collected from patients enrolled in the backfill biopsy cohorts. Tumor biomarkers are assessed to analyze changes in tumor microenvironment and immune landscape
- Enrollment in dose expansion will start once the MTD/MAD has been defined
- ABBV-514 (intravenous [IV]), with or without budigalimab (IV), is administered until disease progression or intolerable toxicity

Key Eligibility Criteria

- Adults (≥18 years)
- Evaluable or measurable disease per RECIST v1.1
- ECOG performance status ≤1
- No uncontrolled CNS metastases
- No active autoimmune disease or history of primary immunodeficiency

Dose Escalation – Part 1

- Patients with advanced solid tumors who are refractory to or intolerant of all existing therapies
- Patients who refused or are ineligible for standard therapies may be included
- All patients must consent to provide archival (or fresh) formalin-fixed paraffin-embedded tumor tissue

Dose Expansion – Part 2

- Patients with histologically or cytologically confirmed advanced or metastatic NSCLC or HNSCC who have received prior platinum-based chemotherapy and a PD-1/PD-L1–targeting agent
- In NSCLC cohorts, patients with known *EGFR* mutations or *ALK* rearrangements are excluded, and patients with actionable genomic alterations for which approved therapies exist must have disease progression on the targeted therapy

ALK, anaplastic lymphoma kinase; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; PD-1, programmed cell death 1; PD-L1, PD-1 ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors.

Endpoints

Safety

AE monitoring, physical examinations, vital sign measurements, ECG, and clinical laboratory testing

Serum ABBV-514 PK and Immunogenicity

C_{max}, T_{max}, $t_{1/2}$, AUC; ADA/neutralizing ADA

Efficacy

ORR (confirmed CR or PR) and CBR (confirmed CR or PR or sustained SD [occurring at ≥6 weeks from first dose and sustained for ≥24 weeks]) per RECIST v1.1, DOR, and PFS

Biomarkers

Blood PD and predictive biomarkers, including serum/plasma proteomics and cellular immunophenotyping, chemokines and cytokines, and circulating biomarkers including but not limited to ctDNA. Tumor PD and predictive biomarkers

ADA, antidrug antibody; AE, adverse event; AUC, area area under serum concentration-time curve; CBR; clinical benefit rate; C_{max}, maximum observed serum concentration; CR, complete response; ctDNA, circulating tumor DNA; DOR, duration of response; ECG, electrocardiogram; ORR, overall response rate; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; $t_{1/2}$, terminal elimination half-life; T_{max}, time to C_{max}.

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