First-in-human phase 1 trial of VT3989, a first-in-class YAP/TEAD inhibitor in patients with advanced mesothelioma

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Abstract

VT3989, a potent Hippo-YAP inhibitor, showed promising safety and antitumor activity in patients with advanced mesothelioma.

Background

Hippo signaling regulates transcription factors YAP and TAZ in response to diverse upstream signals. The pharmacological inhibition of a conserved cysteine is required for TEAD interaction with YAP.

First-in-class, first-in-human Phase 1 Study of VT3989

Doses and schedules being evaluated: - 28-day cycle of 1-DVT (2 cycles on, 1 week off) - First early clinical proof-of-concept of VT3989 at ≤100 mg results in less frequent/severe albuminuria which is reversible with dose reduction or interruption - Dose-optimization expansion cohorts currently evaluating different doses/schedules in 2-stage designs - Multivariate analyses underway to explore potential predictors of antitumor efficacy

Safety

Treatment-related adverse events in 2 patients (N = 44) * Albuminuria

Baseline demographics and characteristics – mesothelioma patients

VT3989 Pharmacokinetics

First early clinical proof-of-concept that VT3989 inhibition of the Hippo-YAP/TEAD signaling pathway has antitumor efficacy

Durable activity seen in patients with advanced mesothelioma +/- NF2 mutations

- Intermittent dosing of VT3989 at ≤100 mg results in less frequent/severe albuminuria which is reversible with dose reduction or interruption
- Dose-optimization expansion cohorts currently evaluating different doses/schedules in 2-stage designs
- Multivariate analyses underway to explore potential predictors of antitumor efficacy

Results

Baseline = 163 mm

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ClinicalTrials.gov NCT04665206
Presented at: 2023 World Conference on Lung Cancer, September 9-12, Singapore