447 INTERIM RESULTS OF A PHASE 1 STUDY OF THE NOVEL ENGINEERED TOXIN BODY TAK-169 IN PATIENTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

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Background Engineered toxin bodies (ETBs) are comprised of a proprietarily engineered and de-immunized Shiga-like Toxin-I A1 subunit genetically fused to an antibody-like binding domain. ETBs can force receptor internalization, induce potent cell-kill via enzymatic and permanent inactivation of ribosomes, and may not be subject to resistance mechanisms of other therapeutics. TAK-169 is a second-generation ETB targeting CD38 in hematologic malignancies including multiple myeloma (MM).

Methods This multicenter, open-label, phase 1 study is designed to evaluate the safety, tolerability, preliminary efficacy, pharmacokinetics, and pharmacodynamics of TAK-169 monotherapy in patients with relapsed or refractory MM (RRMM). The primary objective of the expansion phase (Part 2) is to provide a preliminary evaluation of the clinical activity of TAK-169 monotherapy in patients with RRMM. The starting dose of TAK-169 in Part 1 is 50 µg/kg IV once weekly. Subsequent planned dose levels are 100, 200, 335, 500, and 665 µg/kg (NCT04017130).

Results At the data cut-off in June 2021, 4 patients with a median age of 70 years were enrolled at the initial TAK-169 dose level of 50 µg/kg. All 4 patients were heavily pretreated with at least 5 previous lines of therapy. All patients have discontinued the study, 3 due to progressive disease and 1 due to a treatment-emergent adverse event (TEAE). The TEAE was asymptomatic grade 2 reversible myocarditis diagnosed by cardiac magnetic resonance imaging (MRI) and grade 3 hs-troponin elevation in the absence of ischemia, ECG, or echocardiographic abnormalities. Comparative baselines were not available for either the cardiac MRI or hs-troponin levels. No other cardiac TEAEs have been observed with any other patient. All other related TEAEs were either grade 1 or 2 events. All patients had quantifiable drug concentrations on Cycle 1 Day 1, with the mean elimination half-life calculated as 1 hour. The geometric mean of Cmax in the 4 patients was 1.73 nM, which is lower than the EC50 of 5 nM observed in MM cell-killing assays using patient bone marrow aspirates. Number of natural killer (NK) cells in peripheral blood for the 4 patients was reduced by a maximum of 56%, 85%, 88%, and 92% after the first dose. The patient with 56% reduction in NK cells had the lowest NK cell count at baseline, along with a low percentage of CD38+ NK cells.

Conclusions These data demonstrate that, at 50 mcg/kg, TAK-169 was engaging its target CD38, leading to robust NK-cell reductions. Dose escalation is ongoing.

Trial Registration ClinicalTrials.gov identifier: NCT04017130

Ethics Approval Vanderbilt University Institutional Review Board (1313 21st Ave S, Suite 505. Nashville, TN 37232–4315) gave approval on 6/25/2021 (IRB #191752). Participants gave informed consent before taking part in the study.

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