FIRST-IN-HUMAN PHASE 1/2 STUDY OF THE FIRST-IN-CLASS SUMO-ACTIVATING ENZYME INHIBITOR TAK-981 IN PATIENTS WITH ADVANCED OR METASTATIC SOLID TUMORS OR RELAPSED/REFRACTORY LYMPHOMA: PHASE 1 RESULTS

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Background SUMOylation is a post-translational modification that serves as an important modulator of immune responses via its role in constraining the type I interferon (IFN-1) response. TAK-981 is a small molecule that inhibits SUMOylation and increases IFN-1-dependent innate immune responses with the potential to enhance adaptive immunity. Here, we report dose-escalation data from a TAK-981 Phase 1/2 clinical study (NCT03648372), the first clinical data for a SUMOylation inhibitor.

Methods Adults with advanced/metastatic solid tumors or relapsed/refractory lymphomas received TAK-981 IV twice-weekly (BIW; days 1, 4, 8, 11) or once-weekly (QW; days 1, 8) in 21-day cycles. Dose escalation was guided by a Bayesian Logistic Regression Model (BLRM) with overdose control, plus available pharmacokinetic/pharmacodynamic (PK/PD) data. Phase 1 objectives were to determine TAK-981 safety/tolerability and establish the recommended phase 2 dose (RP2D).

Results Seventy-six patients received TAK-981 at 10 dose levels (3–40 mg BIW; 60–120 mg QW/BW). Median age was 61 years (range, 38–79); 42 (55.3%) patients were female. Four dose-limiting toxicities were seen in 62 evaluable patients (transient grade 3 ALT/AST elevation, 60 mg BIW; grade 3 pneumonitis, 90 mg BIW; grade 3 stomatitis and grade 3 cognitive disturbance, 120 mg BIW). Per BLRM, 120 mg BIW was determined to be the maximum tolerated dose. At data cut-off, median treatment duration was 2 cycles (range, 1–12); 13 (17.1%) patients were ongoing. Table 1 summarizes TAK-981 safety. The most common ($\geq 20\%$) treatment-emergent adverse events (TEAEs) were fatigue (42.1%), nausea (39.5%), headache (31.6%), diarrhea (28.9%), pyrexia (27.6%), vomiting (23.7%), decreased appetite (22.4%). Common ($\geq 5\%$) grade ≥ 3 TEAEs were hypokalemia (9.2%), anemia (7.9%), lymphocyte count decreased (6.6%), abdominal pain (5.3%). Grade 2 cytokine release syndrome was reported in 4 (5.2%) patients; symptoms resolved within 12–24 hours with supportive oxygen and/or IV fluids. One partial response was observed at 40 mg TAK-981 BIW in a patient with relapsed/refractory HER2-negative, hormone receptor-positive breast cancer. TAK-981 exhibited linear PK, with approximately dose-proportional exposure and a mean terminal half-life of 3.8–10.8 hours at ≥ 60 mg. Evidence of dose-dependent target engagement (Figure 1), and PD (Figures 2–4) in blood were observed. The single-agent TAK-981 RP2D was 90 mg BIW.

Abstract 476 Table 1 Summary of TAK-981 safety profile

Patients with ≥ 1 event, n (%)	TAK-981 dose escalation					Total (n=76)
	≤ 75 mg BIW or QW* (n=48)	90 mg QW (n=7)	90 mg BIW (n=8)	120 mg QW (n=5)	120 mg BIW (n=8)	
Any TEAE	44 (91.6)	7 (100.0)	8 (100.0)	4 (80.0)	8 (100.0)	71 (93.4)
Drug-related TEAE	31 (64.6)	7 (100.0)	7 (87.5)	4 (80.0)	8 (100.0)	57 (75.0)
Grade ≥ 3 TEAE	21 (43.8)	5 (71.4)	6 (75.0)	3 (60.0)	6 (75.0)	41 (53.9)
Drug-related grade ≥ 3 TEAE	5 (10.4)	3 (42.9)	2 (25.0)	1 (20.0)	4 (50.0)	15 (19.7)
SAE	19 (39.6)	2 (28.6)	5 (62.5)	2 (40.0)	5 (62.5)	33 (43.4)
Drug-related SAE	3 (6.3)	0	1 (12.5)	1 (20.0)	2 (25.0)	7 (9.2)
TEAE resulting in discontinuation of TAK-981	2 (4.2)	0	4 (50.0)	1 (20.0)	2 (25.0)	9 (11.8)
Drug-related TEAE resulting in discontinuation of TAK-981	0	0	2 (25.0)	1 (20.0)	1 (12.5)	4 (5.3)
On-study deaths	4 (8.3)	0	2 (25.0)	0	0	6 (7.9)
On-study deaths related to TAK-981	0	0	0	0	0	0
DLT†	1 (2.1)	0	1	2	0	4

AE, adverse event; BIW, twice weekly; DLT, dose-limiting toxicity; QW, once weekly; SAE, serious adverse event; TEAE, treatment-emergent adverse event.
 *3 mg BIW (n=5), 6 mg BIW (n=3), 10 mg BIW (n=4), 15 mg BIW (n=3), 25 mg BIW (n=4), 40 mg BIW (n=4), 60 mg QW (n=5), 60 mg BIW (n=7), 75 mg QW (n=5), and 75 mg BIW (n=8).
 †DLTs were based on the DLT-evaluable population: 40 DLT-evaluable patients on the BIW schedule and 22 on the QW schedule.

Red lines represent mean fold-change at each dose.

Abstract 476 Figure 1

PD in patients receiving TAK-981 on the BIW schedule: target engagement.

Blood samples were collected on Cycle 1 Day 1 pre-dose and at multiple timepoints after TAK-981 administration. Target engagement in T cells was detected by flow cytometry with an antibody recognizing the TAK-981-SUMO adduct formed during the inhibition of the SUMO-activating enzyme by TAK-981; Cycle 1 Day 1 signal increased at 1 hour post-end-of-infusion compared to the background level observed pre-dose.

Red lines represent mean fold-change at each dose.

Abstract 476 Figure 2

PD in patients receiving TAK-981 on the BIW schedule: SUMOylation.

SUMOylation in T cells, detected by flow cytometry with an antibody recognizing SUMO2/3, decreased at 1 hour post-end-of-infusion on Cycle 1 Day 1 compared to pre-dose, indicating that fewer SUMO2/3 chains are formed when the SUMO-activating enzyme is inhibited.

Trial Registration Clinical Trial identification: ClinicalTrials.gov. Identifier: NCT03648372

Ethics Approval The study was approved by the Institutional Review Board or Institutional Ethics Committee of all participating institutions

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Red lines represent mean fold-change at each dose.

Abstract 476 Figure 3

PD in patients receiving TAK-981 on the BIW schedule: upregulation of CXCL10 expression.

Upregulation of mRNA levels of *CXCL10*, an IFN-I-regulated gene, in peripheral blood. Gene expression was measured using Nanostring nCounter at Cycle 1 Day 1 pre-dose and at several timepoints post-dose. Data for maximum increase at 8 or 24 hours, relative to pre-dose, is shown.

Abstract 476 Figure 4

PD in patients receiving TAK-981 on the BIW schedule: NK cell activation.

NK cell activation in peripheral blood measured by flow cytometry. Percentage of CD69-positive NK cells at Cycle 1 Day 1 pre-dose and at 24 hours post-end-of-infusion is shown by patient for each dose.

Conclusions The data generated in this study support continued TAK-981 development for treatment of solid tumors and lymphoma. The Phase 2 study expansion is ongoing in patients with advanced/metastatic non-small-cell lung, cervical, and colorectal cancer, and in relapsed/refractory non-Hodgkin lymphoma.