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/BIW). 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 pneumonia, 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 (≥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 (≥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.
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.

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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.

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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.

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

http://dx.doi.org/10.1136/jitc-2021-SITC2021.476