Phase 1/2 study of the novel SUMOylation inhibitor TAK-981 in adult patients with advanced or metastatic solid tumors or R/R hematologic malignancies

Arkadiusz Z. Dudek,[1,2] Dejan Juric,[3,4] Afshin Dowlati,[5] Erlene K. Seymour,[6] Jordi R. Ahnert,[7] Bingxia Wang,[8] Dennis Huszar,[8] Allison J. Berger,[8] Sharon Friedlander,[8] Alejandro Gomez-Pinillos,[8] Igor Proscurshim,[8] Anthony J. Olszanski[9]

[1]Department of Medicine, Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, MN, USA; [2]Regions Cancer Care Center, HealthPartners, Saint Paul, MN, USA; [3]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [4]Department of Medicine, Harvard Medical School, Boston, MA, USA; [5]University Hospitals Seidman Cancer Center and Case Western Reserve University, Cleveland, OH, USA; [6]Wayne State University School of Medicine and Karmanos Cancer Institute, Detroit, MI, USA; [7]Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited; [9]Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA, USA

Background

Mechanism of action

- TAK-981 is a first-in-class, investigational, small-molecule inhibitor of SUMO-activating enzyme (SAE), which catalyzes the first step in the SUMOylation enzyme cascade **(Figure 1)**[1]
- SUMOylation is a reversible post-translational modification that regulates protein function by covalent attachment of small, ubiquitin-like modifier proteins (SUMOs) to protein substrates[2]
- SUMOylation plays a central role in regulating type I IFN-dependent innate response and functions to constrain the innate immune response, which can impair tumor immune surveillance[3,4]
- Inhibition of SUMOylation by TAK-981 promotes type I IFN-dependent innate and adaptive antitumor immune responses[5,6]

Figure 1. Mechanism of TAK-981 inhibition of the SUMOylation enzyme cascade

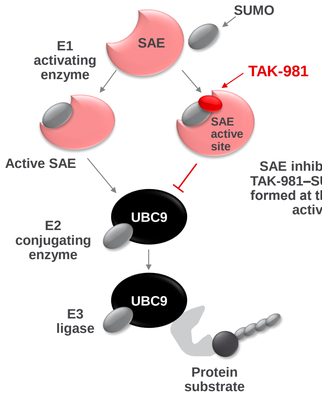


Figure adapted from Langston SP, et al. J Med Chem 2021.[1]

Preclinical data

- TAK-981 induced markers of activation and maturation, including CD40, CD80, and CD86, in ex-vivo assays of dendritic cells derived from mouse bone marrow and human peripheral blood mononuclear cells[6]
  - Increased secretion of immunomodulatory cytokines (IFNα, IFNβ, IP10, MCP1, MIP-1α, MIP-1β) was also observed
  - These processes were type I IFN-dependent
- In another ex-vivo assay, TAK-981 activated macrophages and NK cells, promoting phagocytosis and cytotoxicity in cancer cells[7]
- In-vivo studies of TAK-981 have shown T cell priming, and T cell- and type I IFN-dependent antitumor activity in syngeneic mouse models[6,8]
- Here we report the study design for the first-in-human study of TAK-981, a phase 1/2, dose-escalation and dose-expansion study (NCT03648372) evaluating the safety, tolerability, PK, and preliminary efficacy of TAK-981 in patients with advanced or metastatic solid tumors or R/R hematologic malignancies

STUDY DESIGN

Phase 1/2, open-label, dose-escalation and dose-expansion study of TAK-981.

PRIMARY STUDY OBJECTIVES

Part 1: Determine the safety and tolerability of TAK-981 and establish an RP2D.
Part 2: Evaluate the preliminary efficacy of TAK-981.

METHODS

Part 1: Dose-escalation

Patients with advanced/metastatic solid tumors or R/R lymphoma (N≈70).

TAK-981 administered by IV infusion on days 1, 4, 8, and 11 in 21-day cycles for up to 1 year*† or until unacceptable toxicity, patient withdrawal, or death.

Less intensive TAK-981 administration schedules on day 1, days 1 and 8, or days 1, 8, and 15 are permitted if clinical safety, PK, and PD data are supportive.

Part 2: Dose-expansion

Patients with selected relapsed **solid tumors (3 cohorts)** or **R/R NHL (3 cohorts)** (N≈132).

CPI-exposed non-squamous NSCLC (n=7–19)	R/R DLBCL with prior CAR-T therapy (n=7–19)
CPI-naïve cervical cancer (n=7–19)	R/R DLBCL with 2 or 3 prior lines of systemic therapy (n=10–28)
CPI-naïve MSS-colorectal cancer (n=7–19)	R/R FL with 2 or 3 prior lines of systemic therapy (n=10–28)

TAK-981 administered at RP2D identified during dose escalation for up to 1 year.*

STUDY TIMELINES

Start: October 2018; Estimated primary completion: December 2022; Estimated study completion: October 2023.[9]

*Patients with clinical benefit could continue treatment beyond 1 year with approval of sponsor; †Patients not on RP2D may be transitioned to RP2D once established.
ClinicalTrials.gov identifier: NCT03648372.[9]

Methods

Part 1: Dose-escalation

Primary objectives

- Determine safety and tolerability of TAK-981
- Establish an RP2D of TAK-981
  - Determination of RP2D based on MTD or identification of a lower, biologically effective dose (BED)
    - The BED is a dose at which there is evidence of drug-target engagement and inhibition of SUMOylation, plus: induction of cytokines/chemokines and/or type I IFN signature in tumor or blood; evidence of increased T-cell infiltration in tumor; or antitumor activity

Secondary objectives

- Assess preliminary antitumor activity of TAK-981
- Characterize PK profile of TAK-981
- Assess target engagement (TAK-981–SUMO adduct formation) and SUMOylation pathway inhibition in skin and peripheral blood cells

Patients

- Adult male or female patients (aged ≥18 years)
- ECOG PS 0 or 1
- Patients with histologically or cytologically confirmed advanced or metastatic solid tumor who have no standard therapeutic option with proven clinical benefit, or who are intolerant to or have refused standard therapeutic option

OR

- Patients with R/R lymphoma that is not amenable to therapies with proven clinical benefit, or who are intolerant to or have refused standard therapeutic options
  - Patients with low-grade lymphomas may not need to exhaust all therapeutic options; these patients are eligible if two prior systemic therapies have failed and there is no immediate need for cytoreduction

TAK-981 dosing

- Dose escalation, from a starting dose of 3 mg, guided by a 3+3 design combined with BLRM with overdose control, plus consideration of other safety, clinical, PK, and PD data
- TAK-981 administered via 1-hour IV infusion on days 1, 4, 8, and 11 of 21-day cycles
  - Alternative dosing schedules requiring fewer infusions (e.g. day 1, or days 1 and 8, or days 1, 8, and 15) permitted if clinical safety, PK, and PD data are supportive

Part 2: Dose-expansion

Primary objective

- Evaluate preliminary efficacy of TAK-981

Secondary objectives

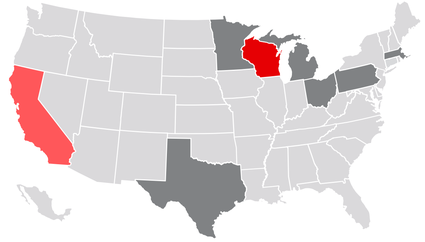
- Evaluate tumor response and progression/survival endpoints
  - ORR, TTR, DOR, DCR (assessed according to RECIST version 1.1 for solid tumors or Lugano classification for lymphomas)
  - PFS, TTP, OS
- Evaluate safety and tolerability of TAK-981
- Collect plasma concentration–time data

Patients

- Adult male or female patients (aged ≥18 years)
- ECOG PS 0 or 1
- Patients with histologically or cytologically confirmed advanced (metastatic and/or unresectable) cancer that is incurable and for which standard first-line treatment has failed, in one of six disease cohorts:
  - Non-squamous NSCLC that has progressed after prior immune CPI therapy
    - Maximum two prior lines of therapy in total
    - For patients with known driver mutations, prior treatment should include a targeted therapy
  - Recurrent or Stage IVB cervical cancer
    - ≤1 prior line of systemic therapy
    - Immune CPI-naïve
  - MSS colorectal cancer
    - ≤3 prior chemotherapy regimens
    - Immune CPI-naïve
  - R/R DLBCL that has progressed or relapsed after prior CAR-T therapy
  - R/R DLBCL that has progressed or relapsed after 2 or 3 lines of prior systemic therapy
    - ≥1 prior line must have included CD20-targeted therapy
    - No prior cellular therapy
  - R/R FL that has progressed or relapsed after 2 or 3 lines of prior systemic therapy
    - ≥1 prior line must have included CD20-targeted therapy

Enrollment

- The study is planned to enroll up to 202 patients at 8 sites in the USA
- Recruitment has closed in California



Study start: October 2018
Estimated completion: October 2023

Recruitment closed
Recruitment ongoing
Recruitment planned

References

1. Langston SP, et al. J Med Chem 2021;64:2501–20.
2. Geiss-Friedlander R and Melchior F. Nat Rev Mol Cell Biol 2007;8:947–56.
3. Decque A, et al. Nat Immunol 2016;17:140–9.
4. Marcus A, et al. Adv Immunol 2014;122:91–128.
5. Assouline SE, et al. Blood 2019;134(Supplement_1):1593.
6. Khattar M, et al. Cancer Res 2019;79(13 Suppl):3252.
7. Nakamura A, et al. Cancer Res 2019;79(13 Suppl):1523.
8. Berger A, et al. Cancer Res 2019;79(13 Suppl):3079.
9. Clinicaltrials.gov/ct2/show/NCT03648372. Accessed April 2021.

Abbreviations

BED, biologically effective dose; BLRM, Bayesian logistic regression modelling; CAR-T, chimeric antigen receptor T-cell; CPI, checkpoint inhibitor; DCR, disease control rate; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IFN, interferon; IP10, interferon-gamma-inducible protein 10; IV, intravenous; MCP1, macrophage chemotactic protein-1; MIP-1, macrophage inflammatory protein; MSS, microsatellite stable; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; NK, natural killer; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PD, pharmacodynamics; PK, pharmacokinetics; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SAE, SUMO-activating enzyme; small ubiquitin-like modifier; TTP, time to progression; TTR, time to response; UBC, ubiquitin-conjugating enzyme.

Acknowledgments

- This study is funded by Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited
- We thank all patients and their families, and investigators at all clinical sites for their participation in the study
- Medical writing support for the development of this poster, under the direction of the authors, was provided by Samantha Stanbury, PhD, and Helen Wilkinson, PhD, of Ashfield MedComms, an Ashfield Health company, was funded by Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, and complied with the GPP3 guidelines (Battisti WP, et al. Ann Intern Med 2015;163:461–4)

Disclosures

AZD reports stock/ownership in TTC Oncology, IGF Oncology, Squarex, and Martell Diagnostic; leadership roles (e.g. board of directors) TTC Oncology, IGF Oncology, Squarex, and Martell Diagnostic; and patents/royalties/other intellectual property with IGF Oncology. **DJ** reports consulting/advisory roles for Novartis, EMD Serono, Eisai, Genentech, Ipsen, Syros Pharmaceuticals, MapKure, Vibliome Therapeutics, and Petra Pharma; and research funding (received by institution) from Novartis, Genentech, Takeda, Eisai, EMD Serono, Placon, Amgen, Syros Pharmaceuticals, InventisBio, Infinity Pharmaceuticals, Takeda, and Pfizer. **AD** reports consulting/advisory roles for Abbvie/Stemcentrx, AstraZeneca, Seattle Genetics, Bristol-Myers Squibb, Takeda, Bayer, G1 Therapeutics, and Ipsen; and research funding (received by institution) from Lilly/ImClone, Amgen, Bristol-Myers Squibb, EMD Serono, Tesaro, Takeda, Mirati Therapeutics, Abbvie/Stemcentrx, United Therapeutics, Regeneron, Bayer, Seattle Genetics, Symphogen, and Ipsen. **EKS** reports employment with Flatiron Health; consulting/advisory roles for Karyopharm Therapeutics, Janssen Oncology, and Gamer Health; and research funding from Karyopharm Therapeutics. **JRA** reports consulting/advisory roles with Novartis, Eli Lilly, Orion Pharmaceuticals, Servier Pharmaceuticals, Peptomyc, Merck Sharp & Dohme, Kelun Pharmaceutical/Klus Pharma, Spectrum Pharmaceuticals Inc, Pfizer, Roche Pharmaceuticals/Genentech, Ellipses Pharma, NovellusDx, Ionctura, and Molecular Partners; research funding from Blueprint Pharmaceuticals, Bayer, Novartis, Spectrum Pharmaceuticals, Tocagen, Symphogen, BioAtla, Pfizer, Genmab, CytomX Therapeutics, Kelun, Takeda/Millennium, GlaxoSmithKline, and Ipsen; travel/accommodation/expenses from ESMO, US Department of Defense, Louisiana State University, Huntsman Cancer Institute, Cancer Core Europe, Karolinska Cancer Institute, King Abdullah International Medical Research Center (KAIMRC), and Molecular Partners; investigator roles for Spectrum Pharmaceuticals, Tocagen, Symphogen, BioAtla, Pfizer, GenMab, CytomX, Kelun-Biotech, Takeda-Millennium, GlaxoSmithKline, and IPSEN; and other disclosures with European Journal of Cancer, Vall d'Hebron Institute of Oncology, Chinese University of Hong Kong, SOLTI, Elsevier, and GlaxoSmithKline. **BW, DH, AJB, SF, AG-P,** and **IP** report employment with Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited. **AJO** reports consulting/advisory roles for Merck, Pfizer, Bristol-Myers Squibb, and Sanofi; and research funding (received by institution) from Takeda, Immunocore, Bristol-Myers Squibb, Checkmate Pharmaceuticals, Targovax, Alkermes, Astellas Pharma, GlaxoSmithKline, Kartos Therapeutics, GlycoNex, Intensity Therapeutics, Kadmon, Nektar, OncoSec, Seattle Genetics, Sound Biologics, Spring Bank, Gan & Lee, Iovance Biotherapeutics, Regeneron, Navire, and Sumitomo Group.

To request a mobile-friendly version of this poster, scan this QR code or visit: http://tago.ca/2asco

Electronic poster presentation at the virtual 2021 Annual Meeting of the American Society of Clinical Oncology (ASCO), June 4–8, 2021. Contact information: Arkadiusz.Z.Dudek@HealthPartners.com