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A phase 2 study of TAS-117 in patients with advanced solid tumors harboring germline *PTEN*-inactivating mutations

Jordi A. Rodón,[1] Pauline Funchain,[2] Theodore W. Laetsch,[3] Christian F. Singer,[4] Hendrik-Tobias Arkenau,[5] Sant P. Chawla,[6] Alice Hervieu,[7] Claire Friedman,[8] Ikuo Yamamiya,[9] Mei Liu,[9] Abdel-Baset Halim,[9] Karim A. Benhadji,[9] Osamu Takahashi,[9] Suzette Delaloge[10]

[1]Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson Cancer Center, Houston, Texas, US; [2]Cleveland Clinic, Cleveland, Ohio, US; [3]Children's Hospital of Philadelphia, and University of Pennsylvania, Philadelphia, Pennsylvania, US; [4]Medizinische Universität Wien, Vienna, Austria; [5]Sarah Cannon Research Institute, London, UK; [6]Sarcoma Oncology Research Center, Santa Monica, California, US; [7]Centre Georges-François Leclerc, Dijon, France; [8]Memorial Sloan Kettering Cancer Center, New York City, New York, US; [9]Taiho Oncology Inc, Princeton, New Jersey, US; [10]Institut Gustave Roussy, Villejuif, France

Background

PI3K/AKT/mTOR pathway in cancer

- PI3K/AKT/mTOR is a commonly disrupted signaling pathway in cancer and AKT is a central component in this pathway[1,2]
- Activated AKT regulates numerous substrates involved in cell survival, proliferation, and cell cycle progression[1–3]
- *PTEN* is a tumor suppressor gene and *PTEN* mutations lead to activation of the AKT pathway[2]

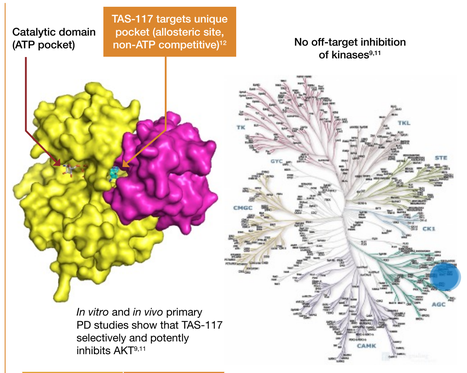
Disease background (solid tumors with germline *PTEN*-inactivating mutations)

- Germline *PTEN*-inactivating mutations resulting in AKT activation are a driving oncogenic event in multiple clinical phenotypes such as Cowden syndrome[2–4]
- Germline *PTEN* mutations are found in approximately 80% of patients with Cowden syndrome[4]
- Cowden syndrome is an extremely rare disease (1 in 200,000 births[2,4]) and is associated with increased lifetime risk of cancer, such as breast, thyroid, renal, and endometrial cancer (estimated lifetime risks of 85.2%, 35.2%, 34.0%, and 28.2%, respectively)[5]
- *PTEN* mutations appear to drive an earlier onset of cancer, including forms which can present in pediatric patients, e.g., thyroid cancer and malignant melanoma, indicating a need for clinical surveillance from birth[5,6]
- There are currently no approved molecular targeted therapies for the disease and an unmet medical need is extremely high in adult and pediatric patients

TAS-117

- TAS-117 is a novel oral allosteric AKT inhibitor with highly potent and selective inhibition, and inhibits phosphorylation of downstream substrates (mTOR, PRAS-40, Bad, FoxO1, and GSK-3)[7–9]
- *In vitro* studies show that TAS-117 inhibits cellular phosphorylation of AKTs as well as intracellular signaling pathways downstream of AKTs[7–9]
- As of May 2020, a total of 74 patients have been treated with TAS-117 in Japan;[9] the Japanese recommended dose was identified as 24 mg intermittently (4 days on/3 days off)[10]
- TAS-117 showed clinical activity against endometrial carcinoma and ovarian clear cell carcinoma in a Japanese phase 1 study[10]
- The most frequently reported TRAEs are maculopapular rash, stomatitis, hyperglycemia, decreased WBC and neutrophil counts, pyrexia, nausea, and pruritus, most of which were mild to moderate in severity[10]

TAS-117: Highly potent and selective AKT inhibitor



In vitro and *in vivo* primary PD studies show that TAS-117 selectively and potently inhibits AKT[8,11]

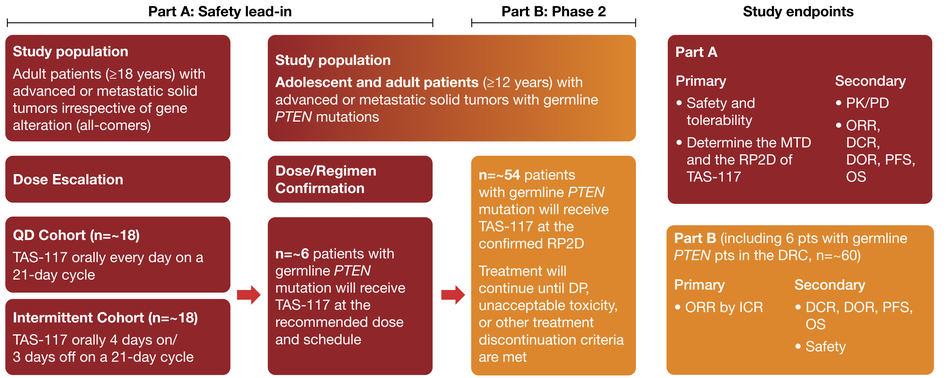
Enzyme (IC_{50})	TAS-117
AKT1 full length	4.8 nM
AKT2 full length	1.6 nM
AKT3 full length	44 nM

TAS-117
Tested against 302 kinases

Study rationale and objectives

- The aim of this phase 2 study (NCT04770246) is to evaluate the safety, tolerability, PK, PD, and antitumor activity of TAS-117 in patients with advanced solid tumors harboring germline *PTEN*-inactivating mutations
- Because germline *PTEN*-inactivating mutations are rare, the study was designed as a tumor-agnostic trial to target multiple types of cancer harboring these mutations
- Preclinical evidence suggests that cancers with AKT activation have increased sensitivity to AKT inhibition[13]
- Two cases of exceptional tumor response have been observed in patients with metastatic breast cancer with germline *PTEN* mutations and who were treated with a specific AKT inhibitor[4]
- The hypothesis is that patients with advanced or metastatic cancer in the context of a germline *PTEN*-inactivating mutation could benefit from TAS-117 monotherapy
- Adolescent (≥12 years of age) and adult patients with germline *PTEN* mutations will be enrolled. According to FDA guidance, adolescent patients weighing ≥40 kg may receive the same fixed dose administered in adults[14]
- The results of a PK simulation in adolescent patients weighing ≥40 kg (based on PK data from the Japanese phase 1 study)[10] were comparable with PK results of adult patients[9]
- In this study, simplified dose escalation will be conducted to identify an optimal dose and regimen for the global population

Study scheme (NCT04770246)



Study design

- This is an open-label, single-arm, phase 2 study to evaluate the safety, tolerability, PK, PD, and antitumor activity of TAS-117 in patients with advanced solid tumors harboring germline *PTEN*-inactivating mutations
- The study is being conducted in two parts:
  - Part A: Safety lead-in (Dose Escalation and Dose and Regimen Confirmation)
  - Part B: Single-arm phase 2 study
- **Part A Dose Escalation** consists of 2 cohorts (QD cohort and Intermittent cohort)
  - MTD/RP2D will be determined for two dosing regimens: QD dosing and intermittent dosing (4 days on/3 days off), by using a 3 + 3 design (n=~32 all-comer patients)
- **Part A Dose and Regimen Confirmation**
  - Safety and tolerability of the selected RP2D will be further assessed and confirmed for Part B (n=~6 patients with germline *PTEN* mutation)
- **Part B single-arm phase 2 study**
  - Efficacy and safety of TAS-117 at the confirmed RP2D will be evaluated in patients with advanced solid tumors harboring germline *PTEN*-inactivating mutations (n=~54)

Patient eligibility criteria

Key inclusion criteria

- ECOG performance status 0 or 1 (for patients ≥18 years of age) or KPS of ≥70% (for patients ≥12 and <18 years of age)
- Has progressed after standard treatment for advanced or metastatic disease or was intolerant to or ineligible for available standard therapies

Dose Escalation in Part A (all-comers)

- **≥18 years of age**
- **Histologically or cytologically** confirmed advanced or metastatic solid tumors
- Patients with solid tumors **irrespective of gene alterations**
- Patients with at least one **measurable or non-measurable lesion** per RECIST 1.1

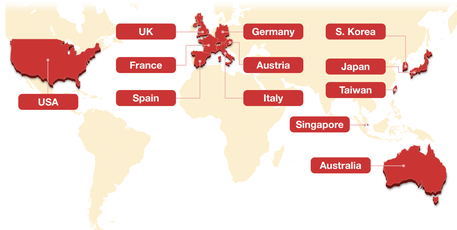
Dose and Regimen Confirmation in Part A and phase 2 (Part B)

- **≥12 years of age.** Patients aged ≥12 and <18 years must have a body weight of ≥40 kg
- **Histologically** confirmed advanced or metastatic solid tumors
- Patients with **locally confirmed germline *PTEN*-inactivating mutations** determined from a blood sample
- Patients with at least one **measurable lesion** per RECIST 1.1

Key exclusion criteria

- History of or current evidence of active interstitial lung disease or pneumonitis
- Current evidence of diabetes mellitus that requires insulin therapy
- Prior treatment with PI3K/AKT/mTOR pathway inhibitors
- Patients with primary brain tumor
- Patients with meningeal carcinomatosis, leptomeningeal carcinomatosis, spinal cord compression, or symptomatic or unstable brain metastasis
- Patients with prior active malignancies must be excluded unless a complete remission was achieved prior to enrollment and no additional therapy is required or anticipated to be required during the study

Planned study sites



Part A (safety lead-in)

Recruitment is planned at **9 sites**, across **4 countries** (Austria, France, UK, USA)

Estimated enrollment: approximately **42 participants**

The first patient was enrolled in April 2021.

Part B (phase 2)

Recruitment is planned at approximately **70 sites**, across **12 countries** (Australia, Austria, France, Germany, Italy, Japan, Singapore, S. Korea, Spain, Taiwan, UK, USA)

Estimated enrollment: approximately **54 participants**

Part B will be initiated in April 2022.

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Abbreviations

AKT, v-akt murine thymoma viral oncogene homolog; ATP, adenosine triphosphate; Bad, B-cell leukemia/lymphoma 2–associated death promoter; DCR, disease control rate; DOR, duration of response; DP, disease progression; DRC, dose and regimen confirmation; ECOG, Eastern Cooperative Oncology Group; FDA, Food and Drug Administration; FoxO1, forkhead box protein O1; GSK-3, glycogen synthase kinase 3; IC_{50}, half-maximal inhibitory concentration; ICR, independent central review; KPS, Karnofsky performance status; MTD, maximum tolerated dose; mTOR, mechanistic target of rapamycin; ORR, overall response rate; OS, overall survival; PD, pharmacodynamic; PFS, progression-free survival; PI3K, phosphoinositide 3-kinase; PK, pharmacokinetic; pt, patient; *PTEN*, phosphatase and tensin homolog; QD, once daily; RP2D, recommended phase 2 dose; PRAS-40, proline-rich AKT substrate of 40 kDa; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TRAE, treatment-related adverse event; WBC, white blood cell.

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Contact information

Osamu Takahashi, MD, PhD, 609-250-7336

clinicaltrialinfo@taihooncology.com

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