2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Taiho Oncology, Inc.</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
TAS-117</td></tr>
<tr><td>Name of Active Ingredient:
TAS-117</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 2 Study of TAS-117 in Patients with Advanced Solid Tumors Harboring Germline PTEN Inactivating Mutations</td></tr>
<tr><td colspan="3">Principal Investigator:
PPD
Investigators:
PPD</td></tr>
<tr><td colspan="3">Study centers:
The University of Texas M.D. Anderson Cancer Center, Houston, TX, USA
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Institut Gustave Roussy, Villejuif, France
Centre Georges-Franois Leclerc, Dijon, Cote-D’or, France
Sarah Cannon Research Institute, London, United Kingdom</td></tr>
<tr><td colspan="3">Publications (reference):
Rodon J, Arkenau H-T, Funchain P, et al. Dose escalation of TAS-117 in patients with advanced solid tumors. Ann Oncol. 2022;33 (Suppl 7):S754-S755.</td></tr>
<tr><td colspan="2">Studied period (years):
Date first patient enrolled: 02 April 2021
Data cutoff for this report: 09 May 2023</td><td>Phase of development:
Phase 2</td></tr>
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Objectives:

Primary:

- **Part A**: To investigate the safety and tolerability and determine the maximum-tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) of TAS 117.
- **Part B**: To evaluate the objective response rate (ORR) in patients with solid tumors harboring germline *PTEN* inactivating mutations (including patients in Dose and Regimen Confirmation [DRC] portion in Part A) based on the independent central review (ICR).

Secondary:

- **Part A:** To characterize the pharmacokinetic (PK) profile of TAS-117.
- **Part A:** To characterize the pharmacodynamic profile of TAS-117.
- **Part B:** To evaluate the safety profile of TAS-117.
- **Parts A and B:** To evaluate ORR based on investigator assessment.
- **Parts A and B:** To evaluate disease control rate (DCR), duration of response (DOR), and progression-free survival (PFS) based on investigator assessments (ICR assessment was also to be performed in Dose and Regimen Confirmation portion in Part A and Part B).
- **Parts A and B:** To evaluate overall survival (OS).

Methodology:

This was an open-label, single-arm Phase 2 study to evaluate the safety, tolerability, PK, pharmacodynamics, and antitumor activity of TAS-117 in patients with advanced or metastatic solid tumors harboring germline *PTEN* inactivating mutations. The study was to be conducted in 2 parts:

- **Part A:** Safety lead-in (Dose Escalation and DRC) with the primary objective of investigating the safety and tolerability and determining the MTD and the RP2D of TAS-117 in patients with advanced or metastatic solid tumors irrespective of gene alterations.
- **Part B:** Single-arm Phase 2 study, with the primary objective of evaluating ORR per ICR following treatment with TAS-117 monotherapy in patients with solid tumors harboring germline *PTEN* inactivating mutations.

Using a 3 + 3 design during Dose Escalation in Part A, the MTD/RP2D was to be determined for once daily (QD) dosing and intermittent dosing (4 days on/3 days off), starting with a dose of 16 mg/day (QD) or 24 mg/day (intermittent). Enrollment into the 2 dosing cohorts was to occur in parallel. Following the selection of the recommended dose and regimen, 6 patients were to be enrolled in the DRC study part to further assess the safety and tolerability of the recommended dose and regimen. Additional patients with advanced or metastatic solid tumors harboring germline *PTEN* inactivating mutations were to be enrolled in Part B and treated with the dose and regimen confirmed in Part A.

Patients received either continuous daily dosing or intermittent dosing, with a treatment cycle defined as 21 days for both parts of the study. Patients were to be followed for safety assessments for 30 days after the last dose of study treatment.

Number of patients (planned and treated):

Part A: Planned up to 42 patients; 17 patients enrolled/treated.

Part B: Planned 54 patients; 0 patients enrolled/treated.

Diagnosis and main criteria for inclusion:

Part A (Dose Escalation): Patients ≥18 years of age with a baseline ECOG status of ≤1 who have been diagnosed with confirmed advanced or metastatic solid tumors (excluding patients with primary brain tumors) irrespective of gene alterations who have progressed after all standard treatment for advanced or metastatic disease known to provide clinical benefit or were intolerant to or ineligible for such available standard therapies.

Part A (Dose and Regimen Confirmation) and Part B: Patients ≥12 years of age with a baseline ECOG status of ≤1 (for patients ≥18 years) or Karnofsky performance status of ≥70% (for patients age ≥12 and <18 years of age) who have been diagnosed with confirmed advanced or metastatic solid tumors (excluding patients with primary brain tumors) with confirmed germline *PTEN* inactivating mutations who have progressed after standard treatment for advanced or metastatic disease, or were intolerant to or ineligible for available standard therapies.

Test product, dose and mode of administration, batch number:

TAS-117 was administered orally on an empty stomach at doses between 16-24 mg QD, or 24-32 mg/day intermittent (4 days on/3 days off).

Batch numbers assigned to patients: 71218.2, 71218.3, 71218.5, and 71218.9

Duration of treatment:

Treatment with TAS-117 continued until any of the discontinuation criteria specified in the protocol were met.

Reference therapy, dose and mode of administration, batch number:

N/A

Criteria for evaluation:

Efficacy:

Primary:

- **Part A**: N/A
- **Part B**: ORR, defined as the proportion of patients experiencing a best overall response of complete response (CR) or partial response (PR) per RECIST 1.1

Secondary:

- **Parts A and B**: ORR, DCR, DOR, PFS, and OS.

Pharmacokinetics:

Primary:

- N/A

Secondary:

- **Part A**: TAS-117 PK parameters, including C_{max}, T_{max}, AUC, and $T_{½}$.

Safety:

Safety and tolerability were to be assessed based on AE profile, clinical laboratory tests, vital signs, and 12-lead ECG as a primary endpoint in Part A and a secondary endpoint in Part B.

Dose-limiting toxicities (DLTs) graded according to CTCAE v5.0 during Cycle 1 were assessed as a primary endpoint in Part A only.

Statistical Methods:

The categorical data were summarized using frequency counts and percentages of patients, unless otherwise specified. The continuous data were summarized using the number of nonmissing observations (n), mean, standard deviation, median, minimum value, and maximum value, unless otherwise specified. T_{max} and PK parameters were summarized using coefficient of variation (CV%), geometric mean, and geometric CV%. Summary tables were presented by cohort and/or study component.

Confidence Interval (CI) for binomial proportions was estimated using the Clopper–Pearson method.

Progression-free survival was estimated using the Kaplan–Meier method. The number of events and censorings were reported. When appropriate, the median along with the corresponding log-log transformed 95% CI was estimated. Survival rates at fixed time points (eg, PFS at 6 months) were derived from the Kaplan–Meier estimate and the corresponding CI was derived based on the Greenwood formula.

Efficacy Analyses

All efficacy analyses were to be performed for each cohort (QD or intermittent cohorts) in Dose Escalation in Part A and Part B including the DRC phase in Part A (all patients with germline *PTEN* mutations) based on the Full Analysis Set.

Safety Analyses

For Part A (Dose Escalation and DRC), the primary endpoint of DLTs that occurred during Cycle 1 was graded according to CTCAE V5.0. The number and percentage of patients with a DLT were presented by dose level and overall using the DLT Evaluable Analysis Set. A listing of DLTs was provided.

Additional safety analyses included summaries of AEs, including incidence of treatment-emergent AEs (TEAEs), treatment-related AEs (TRAEs), serious adverse events (SAEs), AEs leading to discontinuation, and AEs leading to dose interruption and modification. ECGs, lab data, and other safety data were also summarized using the Full Analysis Set.

SUMMARY – CONCLUSIONS

Analyses were conducted on data from 17 patients treated in Part A (Dose Escalation: N=16; DRC: N=1) as of the clinical data cutoff date of 09 May 2023 and are presented below. Study TAS-117-201 was terminated prior to initiation of Part B due to enrollment challenges during Part A. This decision was not based on safety or efficacy concerns.

EFFICACY RESULTS:

No patients had a confirmed CR or PR, resulting in an ORR of 0%.

Seven patients had a response of stable disease, resulting in a DCR of 41.2% (95% CI: 18.4, 67.1). Duration of treatment was up to 19.1 months as of the data cutoff date for a breast cancer patient with a *PTEN* mutation in the 20-mg QD dose regimen cohort; this patient continued treatment with TAS-117 after the data cutoff date under a single-patient IND.

PK RESULTS:

TAS-117 exposures on Cycle 1 Day 1 and Cycle 1 Day 8 generally increased with increasing doses within the studied dose range of 16 mg to 28 mg. T_{max} was reached at approximately 2 hours on Cycle 1 Day 1. GeoMean CV% values of C_{max} and AUCs were from 29.2% to 180.7% on Cycle 1 Day 1 and from 34.3% to 157.2% on Cycle 1 Day 8. T_{max} on Cycle 1 Day 8 was similar to Cycle 1 Day 1 at approximately 2 to 4 hours. Two- to three-fold accumulation of C_{max} and AUC_{0-24} was observed following multiple QD dosing.

PHARMACODYNAMICS RESULTS:

No pharmacodynamics results were obtained.

SAFETY RESULTS:

Exposure

Seventeen patients received at least 1 dose of TAS-117; median (min, max) duration of treatment was 42.0 (14, 580) days. The median (min, max) relative dose intensity for the total population was 89.5% (43%, 100.0%), indicating an overall treatment compliance.

Four (23.5%) patients had a dose reduction, all of which were due to an AE; 11 (64.7%) patients had a dose interruption, 10 of which were due to an AE.

At the time of the data cutoff date, all patients had discontinued treatment with TAS-117 in this study. One patient continued treatment with TAS-117 under a single-patient IND after the clinical data cutoff date.

Adverse Events

A tabular overview of AEs is presented in Table 1.

Table 1: Overview of Adverse Events – Full Analysis Set

Patients with:	DE-QD			DE-ITD			DRC	All
	DL1 (16 mg) (N=3) n (%)	DL2 (20 mg) (N=6) n (%)	Total (N=9) n (%)	DL1 (24 mg) (N=4) n (%)	DL2 (28 mg) (N=3) n (%)	Total (N=7) n (%)	DL1 QD (16 mg) (N=1) n (%)	Total (N=17) n (%)
TEAEs	3 (100.0)	6 (100.0)	9 (100.0)	3 (75.0)	3 (100.0)	6 (85.7)	1 (100.0)	16 (94.1)
Grade ≥3 TEAEs	2 (66.7)	6 (100.0)	8 (88.9)	3 (75.0)	3 (100.0)	6 (85.7)	1 (100.0)	15 (88.2)
TRAEs	2 (66.7)	6 (100.0)	8 (88.9)	2 (50.0)	3 (100.0)	5 (71.4)	0	13 (76.5)
Grade ≥3 TRAEs	1 (33.3)	4 (66.7)	5 (55.6)	1 (25.0)	2 (66.7)	3 (42.9)	0	8 (47.1)
SAEs	1 (33.3)	4 (66.7)	5 (55.6)	2 (50.0)	1 (33.3)	3 (42.9)	1 (100.0)	9 (52.9)
Treatment-related SAEs	0	3 (50.0)	3 (33.3)	1 (25.0)	0	1 (14.3)	0	4 (23.5)
AEs Leading to Study Treatment Discon.	0	3 (50.0)	3 (33.3)	0	1 (33.3)	1 (14.3)	0	4 (23.5)
AEs Leading to Study Treatment Interruption	1 (33.3)	5 (83.3)	6 (66.7)	1 (25.0)	3 (100.0)	4 (57.1)	1 (100.0)	11 (64.7)
AEs Leading to Study Treatment Reduction	0	0	0	1 (25.0)	2 (66.7)	3 (42.9)	0	3 (17.6)
AEs with Outcome of Death	0	0	0	0	0	0	0	0

Abbreviations: AE=adverse event; DE=dose escalation; discon=discontinuation; DL=dose level; DRC=dose and regimen confirmation; ITD=intermittent dose; N=number of patients in population; n=number of patients with event; QD=once daily; TEAE=treatment-emergent adverse event; TRAE=treatment-related adverse event

Of the patients evaluable for DLTs (N=16), DLTs were reported for 2 of 3 (66.7%) patients who received the 28-mg intermittent regimen (both Grade 3 stomatitis), and for 1 of 6 (16.7%) patients who received the 20-mg QD regimen (Grade 3 neutropenic infection). Based on these data, the dose of 28

mg intermittent dosing exceeded the protocol-defined criteria for the MTD, and the MTD in the intermittent dosing regimen was determined to be 24 mg.

For QD dosing, dose escalation was stopped after the DLT observed at 20 mg QD per Sponsor and investigator consensus after review of the totality of available safety information. While the formal MTD criteria as defined by the protocol (ie, DLT ≥33%) were not reached at the 20-mg QD dose level, the investigator and the Sponsor agreed that the safety profile of TAS-117 at 20 mg QD was not favorable and agreed on 16 mg QD to be the RP2D as the dose level with the highest TAS-117 exposure and an acceptable safety profile.

Treatment-emergent AEs occurring in ≥20% of the total population were rash (58.8%), fatigue (41.2%), pruritus, decreased appetite, and hyperglycemia (29.4% each), and hypophosphatemia and diarrhea (23.5% each). Grade ≥3 AEs occurring in >1 patient in the total population included rash (17.6%), and stomatitis, dyspnea, and rash maculo-papular (11.8% each).

Treatment-related AEs occurring in ≥20% of the total population were rash (58.8%), fatigue (35.3%), and hyperglycemia and pruritus (29.4% each). Grade ≥3 treatment-related AEs occurring in >1 patient included rash (17.6%), and stomatitis and rash maculo-papular (11.8% each).

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths occurred during treatment or within 30 days after treatment discontinuation.

Treatment-related SAEs were reported for 4 (23.5%) patients and included 1 case each of Grade 2 drug reaction with eosinophilia and systemic symptoms, Grade 3 Type 2 diabetes, Grade 3 neutropenic infection, and Grade 3 hyperglycemia.

Four (23.5%) patients discontinued treatment at dose levels exceeding the RP2D due to an AE as the primary cause; these AEs included Grade 2 drug reaction with eosinophilia and systemic symptoms, Grade 1 and Grade 3 skin rash, Grade 3 stomatitis, Grade 3 rash maculo-papular, and Grade 3 skin exfoliation.

Eleven (64.7%) patients experienced an AE in the system organ class of skin and subcutaneous disorders, all of which were related to TAS-117. The most frequently reported AEs were rash (58.8%), pruritus (29.4%), and dry skin and rash maculo-papular (11.8% each). Four (23.5%) patients experienced a Grade 3 AE, and 1 patient experienced an SAE of Grade 2 drug reaction with eosinophilia and systemic symptoms that resulted in treatment discontinuation.

Hyperglycemia was reported in 29.4% of patients; all events were treatment related, and 1 Grade 3 event was serious, resulting in treatment interruption and dose reduction. An SAE of Grade 3 Type 2 diabetes mellitus resulting in treatment interruption was reported in 1 patient.

Reported hematological toxicities included treatment-emergent anemia in 17.6% of patients, and treatment-related AEs of anemia (Grade 3), neutropenia (Grade 2), and neutropenic infection (Grade 3) in 1 patient each. The AE of neutropenic infection was considered serious.

Clinical Laboratory Evaluation

Worst post-baseline CTCAE hemoglobin and platelet values were Grade 3 for 1 (5.9%) patient each. No post-baseline CTCAE results of Grade ≥3 were reported for neutrophil lab values.

Electrocardiograms

Sixteen (94.1%) patients had a maximum post-baseline QTcF interval of ≤470 msec, and 1 (5.9%) patient with a baseline QTcF interval ≤470 msec had a maximum post-baseline QTcF interval between 470-480 msec. Maximum QTcF increases >30-60 msec from baseline were reported for 3 (17.6%) patients, and a maximum QTcF increase >60 msec from baseline was reported for 1 (5.9%) patient.

CONCLUSION:

Based on the results of the Dose Escalation part of the study, the RP2D for TAS-117 was determined to be 16 mg QD. There was no confirmed response observed in the unselected tumor population enrolled in Part A. One patient with a *PTEN* mutation was ongoing on TAS-117 treatment for 19.1 months at the time of the data cutoff date. Overall, the safety and tolerability of TAS-117 was consistent with the known AKT inhibitor class side effects, and TAS-117 demonstrated a generally acceptable and manageable safety profile.

Challenges with patient enrollment resulted in the decision to terminate the study prior to initiation of Part B.

Date of the report:

02 November 2023