Poster 467P

Dose escalation of TAS-117 in patients with advanced solid tumors

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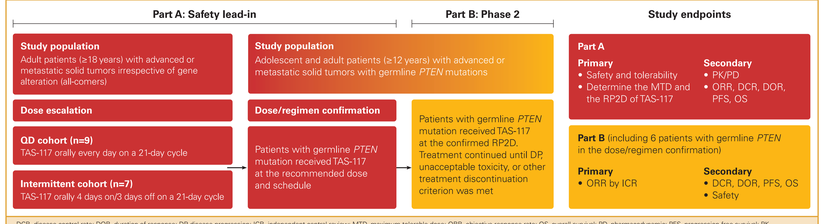
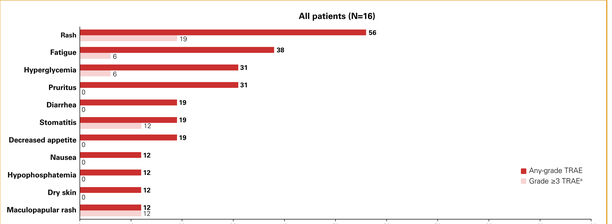
[a]At the time of research.

Figure 1. Study design[a]



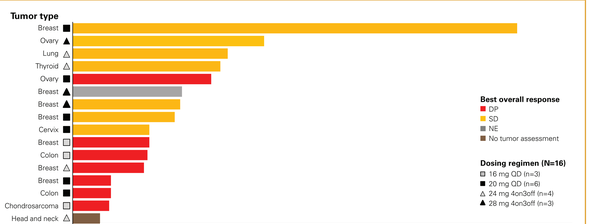
DCR, disease control rate; DOR, duration of response; DP, disease progression; ICR, independent central review; MTD, maximum tolerable dose; ORR, objective response rate; OS, overall survival; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic; *PTEN*, phosphatase and tensin homolog; QD, once daily; RP2D, recommended phase 2 dose.
[a]ClinicalTrials.gov identifier: NCT04770246.

Figure 2. Most common TRAEs (≥2 patients)



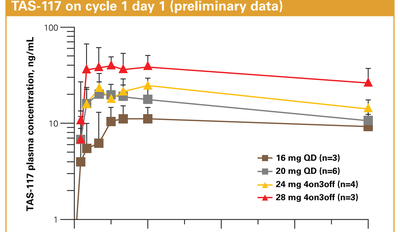
TRAE, treatment-related adverse event.
[a]No grade 5 TRAEs were reported.

Figure 4. Time on treatment by best response



4on3off, 4 days on, 3 days off; DP, disease progression; NE, not evaluable; QD, once daily; SD, stable disease.

Figure 5. Mean plasma concentration-time profiles of TAS-117 on cycle 1 day 1 (preliminary data)



4on3off, 4 days on, 3 days off; QD, once daily.

Table 1. Patient disposition

Disposition	QD cohort (n=9)	Intermittent 4on3off cohort (n=7)	Total population (N=16)
Treatment ongoing	**1 (11)**	**0**	**1 (6)**
Treatment discontinued	**8 (89)**	**7 (100)**	**15 (94)**
Clinical disease progression	1 (11)	1 (14)	2 (12)
Radiological progression	4 (44)	3 (43)	7 (44)
Adverse event	1 (11)	1 (14)	2 (12)
Withdrew consent	0	1 (14)	1 (6)
Death	1 (11)	0	1 (6)
Other	1 (11)	0	1 (6)
Missing	0	1 (14)	1 (6)

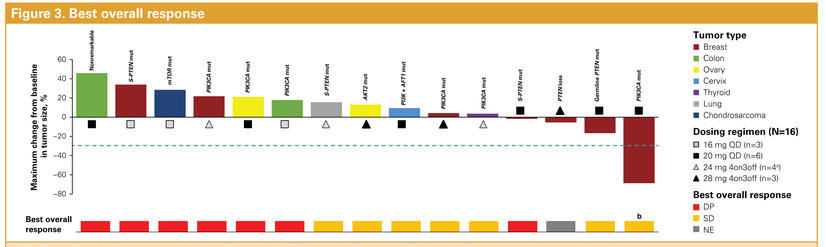
4on3off, 4 days on, 3 days off; QD, once daily; TRAE, treatment-related adverse event.

Table 2. Baseline patient characteristics

		QD cohort (n=9)	Intermittent 4on3off cohort (n=7)	Total population (N=16)
Age	Median (range), years	56 (38–82)	52 (23–70)	54 (23–82)
	<65 years, n (%)	7 (78)	6 (86)	13 (81)
	≥65 years, n (%)	2 (22)	1 (14)	3 (19)
Sex, n (%)	Female	9 (100)	4 (57)	13 (81)
	Male	0 (0)	3 (43)	3 (19)
ECOG PS, n (%)	0	3 (33)	3 (43)	6 (38)
	1	6 (67)	4 (57)	10 (62)
Race, n (%)	White	4 (44)	2 (29)	6 (38)
	Black/African American	1 (11)	1 (14)	2 (12)
	Unknown	4 (44)	4 (57)	8 (50)
Type of cancer, n (%)	Breast	4 (44)	3 (43)	7 (44)
	Colon	2 (22)	0 (0)	2 (12)
	Ovarian	1 (11)	1 (14)	2 (12)
	Cervical	1 (11)	0 (0)	1 (6)
	Head and neck	0 (0)	1 (14)	1 (6)
	Thyroid	0 (0)	1 (14)	1 (6)
	Lung	0 (0)	1 (14)	1 (6)
	Other[a]	1 (11)	0 (0)	1 (6)

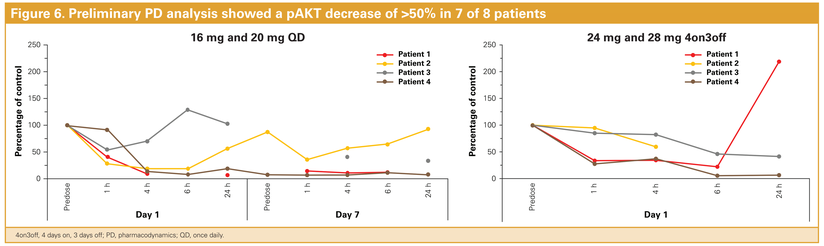
4on3off, 4 days on, 3 days off; ECOG PS, Eastern Cooperative Oncology Group performance status; QD, once daily.
[a]Chondrosarcoma of bone.

Figure 3. Best overall response



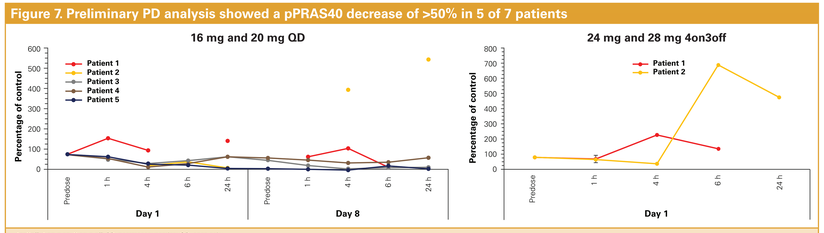
4on3off, 4 days on, 3 days off; DP, disease progression; mut, mutation; NE, not evaluable; *PTEN*, phosphatase and tensin homolog; QD, once daily; SD, stable disease.
[a]One patient with head and neck cancer with *PIK3CA* mutation withdrew consent and had no postbaseline scans (not shown in graph). [b]Unconfirmed partial response (complete response in the lymph node target lesion).

Figure 6. Preliminary PD analysis showed a pAKT decrease of >50% in 7 of 8 patients



4on3off, 4 days on, 3 days off; PD, pharmacodynamics; QD, once daily.

Figure 7. Preliminary PD analysis showed a pPRAS40 decrease of >50% in 5 of 7 patients



4on3off, 4 days on, 3 days off; PD, pharmacodynamics; QD, once daily.

Table 3. Summary of safety

Event, n (%)	QD cohort (n=9)	Intermittent 4on3off cohort (n=7)	Total population (N=16)
TEAE	**9 (100)**	**6 (86)**	**15 (94)**
Grade ≥3 TEAE	7 (78)	6 (86)	13 (81)
TRAE	**7 (78)**	**5 (71)**	**12 (75)**
Grade 3–4 TRAE[a]	5 (56)	3 (43)	8 (50)
Serious TEAE	**4 (44)**	**3 (43)**	**7 (44)**
Grade ≥3 serious TEAE	3 (33)	3 (43)	6 (38)
Serious TRAE	**3 (33)**	**1 (14)**	**4 (25)**
Grade 3–4 serious TRAE	2 (22)	1 (14)	3 (19)
AEs leading to discontinuation	**2 (22)**	**1 (14)**	**3 (19)**
AEs leading to death	**1 (11)**	**0**	**0**

4on3off, 4 days on, 3 days off; AE, adverse event; QD, once daily; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.
[a]No patient experienced a grade 5 TRAE.

Background

- Mutations in the PI3K/AKT/mTOR signaling pathway have been identified in many human cancers[1–3]
- AKT is a critical component of this pathway, and germline phosphatase and tensin homolog (PTEN)-inactivating mutations that result in AKT activation drive oncogenesis in several inherited cancer predispositions[1–5]
- TAS-117 is a highly potent and selective non–ATP-competitive allosteric AKT inhibitor that inhibits the phosphorylation of downstream substrates[6]
- A phase 1 study of TAS-117 was conducted in patients with endometrial carcinoma or ovarian clear cell carcinoma in Japan[6]
  - The recommended dose was identified as 24 mg intermittently (4 days on/3 days off)[6]
  - TAS-117 showed a manageable safety profile and clinical activity in patients from Japan
- A phase 2 study (NCT04770246) was conducted to evaluate the safety and efficacy of TAS-117 in patients from the US and Europe with advanced solid tumors
  - Part 1 of this study was designed to determine the recommended dosing regimen in these populations
  - Part 2 was designed to explore TAS-117 in patients with solid tumors harboring germline *PTEN*-inactivating mutations
  - Here we report preliminary findings from the dose escalation portion of this study in patients from the US and Europe

Methods

- This open-label, single-arm, phase 2 study enrolled adult patients with advanced or metastatic solid tumors harboring *PTEN*-inactivating mutations that progressed after all standard treatment options
- The study was conducted in 2 parts (**Figure 1**)
- Part A: dose escalation and regimen confirmation
  - The **primary objectives** were to evaluate safety and tolerability and to determine the maximum tolerable dose (MTD) and the recommended phase 2 dose (RP2D) of TAS-117
  - A 3+3 design was used to determine RP2D for a once-daily (QD) or for an intermittent dosing schedule (4 days on followed by 3 days off [4on3off])
  - The starting dosage was 16 mg/day (QD) or 24 mg/day (4on3off), and dosages were increased by 4 mg/day up to 24 mg/day and 32 mg/day, respectively
  - Dose-limiting toxicities (DLTs) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0 during the first 21-day treatment cycle
  - The dose schedule was confirmed if <33% of evaluable patients experienced a DLT
  - pAKT/tAKT and pPRAS40/tPRAS40 were assessed in circulating platelets via immunofluorescence assays as pharmacodynamic (PD) biomarkers
- Part B: single-arm phase 2 study
  - The **primary objective** was to evaluate the objective response rate according to independent central review in patients with solid tumors and *PTEN*-inactivating mutations

Results

Patient population

- As of March 31, 2022 (data cutoff), 16 eligible patients received TAS-117 on either a QD (n=9: 16 mg, n=3; 20 mg, n=6) or an intermittent 4on3off dosing schedule (n=7: 24 mg, n=4; 28 mg, n=3)
  - Treatment is ongoing for 1 patient; the remaining 15 patients discontinued owing to clinical/radiological disease progression, withdrawal of consent, or adverse event (AE; **Table 1**)
- Patient baseline demographics and clinical characteristics are shown in **Table 2**

Treatment duration

- Median duration of treatment was 49 days (range, 15–244 days)

Safety

Dose-limiting toxicities

- DLTs were reported in 3 of 16 evaluable patients
  - One patient receiving TAS-117 at 20 mg QD had grade 3 febrile neutropenia
  - Two patients receiving TAS-117 at 28-mg 4on3off dosing had grade 3 oral mucositis

Adverse events

- Treatment-related adverse events (TRAEs) were reported in 12 (75%) patients (**Table 3**)
- The most common TRAEs were rash, fatigue, hyperglycemia, and pruritus (**Figure 2**)
- No grade 5 TRAEs were reported
- Grade 3–4 serious TRAEs were reported in 3 patients and included neutropenic infection (n=1; 20 mg QD), hyperglycemia (n=1; 24-mg 4on3off dosing), and type 2 diabetes (n=1; 20 mg QD)

Tumor response

- Of the 15 patients evaluable for response, stable disease was reported in 7 patients (**Figure 3**)
  - An unconfirmed partial response was observed in 1 patient with breast cancer with a *PIK3CA* mutation
  - This patient experienced a target lesion shrinkage of 69% with 3 months of treatment
- A patient with metaplastic breast cancer with a germline *PTEN*-inactivating mutation had over 12 months of stable disease (**Figure 4**)
  - This patient experienced a target lesion tumor shrinkage of approximately 16%
- Both patients had received TAS-117 at 20 mg QD

Pharmacokinetics and pharmacodynamics

- Approximate dose-proportional exposure increases were observed within the studied dose range (**Figure 5**)
- Exploratory exposure-safety and exposure-efficacy analyses showed the following:
  - Exposures in patients with partial response or stable disease for >6 months were within the exposure range observed for other patients who received TAS-117 on the QD regimen
  - Increased exposure appeared to associate with an increased risk of DLTs within the exposure range produced by the studied dosing regimens
- Preliminary PD analyses showed a pAKT decrease of >50% in 7 of 8 patients (**Figure 6**) and a pPRAS40 decrease of >50% in 5 of 7 patients (**Figure 7**)

Recommended dosing

- Based on safety, pharmacokinetic, and PD data, the RP2D for TAS-117 was determined to be 16 mg QD

CONCLUSIONS

- Preliminary safety results support the safety and tolerability of TAS-117 in patients from the US and Europe
- Based on the results of the safety lead-in portion of this study, the recommended dose of TAS-117 is 16 mg QD
- TAS-117 treatment resulted in the following:
  - A durable clinical benefit associated with tumor shrinkage in 1 patient with metaplastic breast cancer with a germline *PTEN* mutation
  - A response in a patient with *PIK3CA*-mutated breast cancer with ≈70% tumor shrinkage

References

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