Phase I Dose-Escalation Study of the Safety and Pharmacokinetics of PAS-004, a macrocyclic MEK inhibitor, for the treatment of patients with MAPK pathway driven advanced solid tumors

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Poster #1050P

Background

Inhibitors of MAPK kinase (MEKi) have been approved in the treatment of cancer since 2013, initially as monotherapy and then in combination with BRAF inhibitors for metastatic melanoma. MEKi, however, carry a significant risk of off-tumor, on-target toxicities, including eye, GI, and cardiac.

PAS-004 is an allosteric inhibitor of MEK 1/2 and the first macrocyclic MEK inhibitor in clinical development, developed with the intent of long-term chronic use. The macrocyclic structure was intended to increase bioavailability and prolong half-life; the lack of a reactive alcohol reduces active metabolites. Preclinical data (ASCO 2025) showed high selectivity for MEK and potent tumor growth inhibition (TGI) in RAS-mutant cell lines.

Here we show interim results from an ongoing dose-escalation study of PAS-004 as monotherapy in patients with advanced cancer.

Methods

Study design

- Phase 1, open-label, 3+3 dose escalation trial (NCT06299839)
- PAS-004 is given once daily (fasted, qAM), continuously from Day 8, with no dosing holiday
- Two drug formulations have been tested: API in capsule (cohort 1 to 8) and tablet formulation (cohort 4B and 9)
- Enrollment is ongoing, including a pilot food-effect sub-study

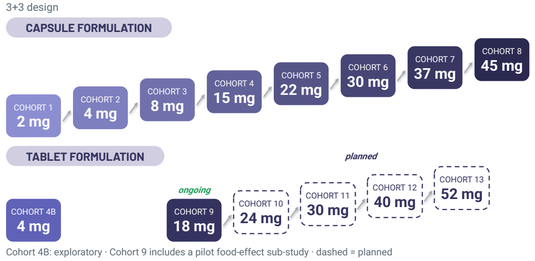
Objectives

- To evaluate the safety and tolerability when administered as a single dose (Day 1) and as multiple doses (28-day treatment cycles)
- To evaluate the pharmacokinetic (PK) profile and the pharmacodynamic (PD) effects
- To evaluate the preliminary anticancer activity
- To define the preliminary recommended Phase 2 dose (RP2D)

Key eligibility criteria

- ≥18 years of age
- Performance status on ECOG scale of 0 or 1
- Histologically or cytologically diagnosed MAPK pathway driven advanced solid tumors with a documented RAS, NF1 or RAF mutation, or patients who have failed BRAF/MEK inhibition

Data cut-off (safety and imaging): 15 Sept 2026



Cohort 4B: exploratory · Cohort 9 includes a pilot food-effect sub-study · dashed = planned

Results

Demographics

Table 1. Patient demographics and disease characteristics

Characteristic	N = 37
Age, years, median (range)	57 (36–73)
Sex, female / male, n	20 / 17
Geography, US / EU, n	19 / 18
Prior lines of treatment, median (range)	3 (1–8)
KRAS mutation, n (%)	17 (46)
BRAF mutation, n (%)	13 (35)
NRAS mutation, n (%)	4 (11)
NF1 mutation, n (%)	2 (5)
RAF mutation, n (%)	1 (3)

Tumor type	n (%)
Colorectal	14 (38)
Melanoma	11 (30)
Pancreas	6 (16)
Ovarian	2 (5)
NSCLC	2 (5)
Other	2 (5)

Safety

No dose-limiting toxicities (DLTs) were observed in dose escalation; MTD not reached.

All treatment-related adverse events (TRAEs) were Grade 1 or 2; no reports of serious MEKi class effects (eye, cardiac).

No TRAEs led to drug discontinuation or withdrawal from study; dose reductions not permitted on study.

No related serious adverse events (SAEs) were reported.

In 4 patients treated for >300 days (including 2 ongoing), no reports of rash or GI toxicity.

Table 2. Overall safety summary of treatment-related events (N = 37)

Event, n (%)	PAS-004, all doses (N = 37)
Any TEAE related to study drug (TRAE)	**17 (45.9)**
Grade 3 TRAE	0
Grade 4/5 TRAE	0
Serious TRAE	0
Discontinuation due to TRAE	0

Table 3. Treatment-related adverse events (TRAEs) reported in ≥ 5% of participants by cohort, n (%)

		PAS-004 capsule								Tablet	
Related adverse event	Participants n (%) of 37	2 mg n=3	4 mg n=3	8 mg n=3	15 mg n=3	22 mg n=4	30 mg n=6	37 mg n=4	45 mg n=3	4 mg n=5	18 mg n=3
Any related adverse event	**17 (46)**	**2**	**1**	**1**	**2**	**1**	**2**	**1**	**2**	**4**	**1**
Nausea	5 (14)	1	—	1	—	—	1	—	—	2	—
Vomiting	4 (11)	1	—	—	—	1	—	—	—	2	—
Rash*	4 (11)	—	—	—	1	—	1	—	1	—	1
Blood CPK increased	4 (11)	—	—	—	1	—	—	1	2	—	—
Diarrhea	2 (5)	—	—	—	1	—	—	—	—	1	—

* Rash is a composite of the preferred terms rash, rash maculo-papular and dermatitis acneiform

Pharmacokinetics

Steady-state (Day 22) exposure increased proportionally with dose across dose ranges, with a long half-life (approximately 58h) and C_{max}/C_{min} between 1-1.5 in every cohort.

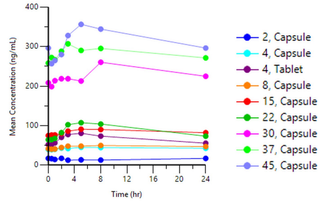


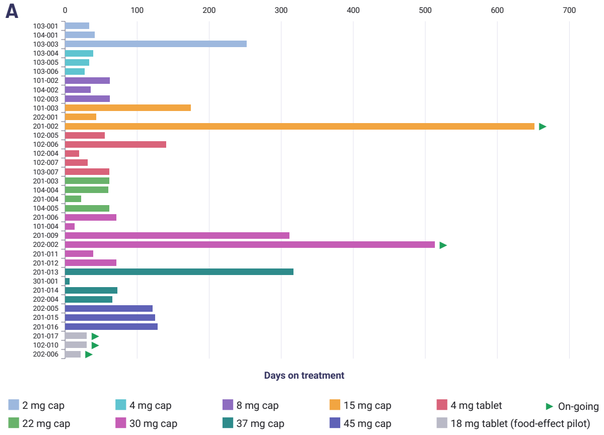
Figure 1. Mean steady-state (Day 22) plasma concentration–time profiles by dose level (mg) and formulation

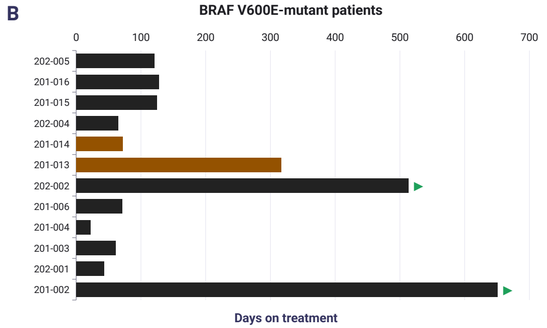
Table 4. Steady-state (Day 22) PK parameters by dose level

Dose level	C_{max} (ng/mL)	AUC_{0-24} (ng·h/mL)	C_{max}/C_{min} ratio	$T_{1/2}$ (h)
2 mg capsule	16.2	354	1.18	58.9
4 mg capsule	38.7	859	1.12	ND
8 mg capsule	42.1	889	1.21	68.6
15 mg capsule	91.3	1,990	1.18	60.6
22 mg capsule	108	2,160	1.49	42.9
30 mg capsule	249	5,480	1.16	67.1
37 mg capsule	313	6,690	1.20	69.0
45 mg capsule	356	7,620	1.23	58.0
4 mg tablet	76.8	1,550	1.41	57.6

Steady state = Day 22 · ND = not determined

Efficacy





Swim lanes for all enrolled patients (panel **A**) and for all patients with BRAF V600E-mutant disease (panel **B**) show a number of patients with prolonged stable disease. BRAF V600E patients were mostly melanoma (**black**) but included colorectal cancer patients (**brown**). Patients 201-002 and 202-002 both have metastatic, recurrent melanoma that had progressed on the combination of trametinib and dabrafenib. Both continue on study (►) at this time. No objective partial or complete responses (per RECIST 1.1) have been observed.

Conclusions

PAS-004 demonstrates linear PK over a wide dosing range, with a long half-life of approximately 58 hours and a Cmax/Cmin ratio of less than 1.5.

PAS-004 is well tolerated, with no related Grade 3 AEs, no discontinuations due to related AEs, no observed MEKi eye or cardiac class effects, and no reported GI or skin toxicity in patients on drug for prolonged periods of time.

Prolonged stable disease in patients with BRAF-mutant melanoma who have progressed on BRAFi/MEKi combination suggests PAS-004 can provide clinical benefit that is worth exploring, potentially in combination with other anti-cancer agents.

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Disclosure: Dr Rodriguez is employed by NEXT Oncology and reports consulting fees from Werewolf Therapeutics, Syneos, Cardinal Health, and Telix Pharmaceuticals.

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