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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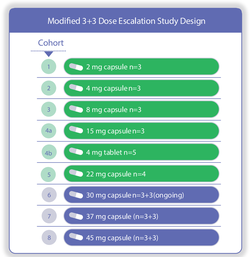
Background

PAS-004 is a small molecule allosteric inhibitor of MEK 1/2 and the first macrocyclic MEK inhibitor to enter clinical development, exhibiting good oral bioavailability (96%), metabolic stability and potency.
In a biochemical screen-testing inhibition of 99 kinases, PAS-004 was shown to be highly specific for MEK 1/2. In cancer cell growth assays, PAS-004 inhibition of in vitro NRAS mutant cell lines was greater than selumetinib and binimetinib in 5/10 cell lines tested and was comparable to trametinib. In NRAS mutant tumor xenografts studies, PAS-004 was shown to have more potent anti-tumor activity than selumetinib and binimetinib.
We report initial interim results of an ongoing first-in-human Phase I dose escalation study of PAS-004 as a monotherapy in patients with advanced refractory solid tumors.

Methods

The Phase 1 clinical trial is a multi-center, open-label, modified 3+3 dose escalation study design to evaluate the safety, tolerability, pharmacokinetic (PK), pharmacodynamic (PD), and preliminary efficacy of PAS-004 in patients with MAPK pathway driven advanced solid tumors with a documented RAS, NF1 or RAF mutation, or patients who have failed BRAF/MEK inhibition (NCT06299839). Two drug products have been tested, API in capsule in all cohorts to date (cohort 1 to 5) and a single 4mg tablet cohort (cohort 4B).

Study design: modified 3+3 cohort dose escalation at 8 different dose cohorts as a monotherapy.



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
A performance status on ECOG scale of 0 or 1
Histologically or cytologically diagnosed MAPK pathway driven advanced solid tumors
Adequate organ function at screening

Key endpoints
Toxicities graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
RECIST 1.1. based evaluation (ORR)

Data cutoff: April 02, 2025
(imaging cutoff: May 01, 2025)

Results

Demographics

As of April 2, 2025 (cut-off date), a total of 21 patients have been enrolled in 6 dose escalation cohorts (Capsules: 2mg, 4mg, 8mg, 15mg, 22mg / Tablets: 4mg). Six (28.6%) patients presented with pancreatic cancer, six (28.6%) patients presented with colorectal cancer, and five (23.8%) patients presented with melanoma.
One patient did not complete the DLT observation period and was replaced.
All patients recruited through the cut-off date had received at least two prior lines of treatments

Patient demographics and disease characteristics

Participant Characteristics		N = 21
Mean age at enrollment, years (range)		54.4 (36-74)
Sex, n (%)	Male	9 (43%)
	Female	12 (57%)
Race, n (%)	American Indian or Alaska Native	1 (4.8%)
	Black	1 (4.8%)
	White	17 (81%)
	Not Reported/Unknown	2 (9.5%)
ECOG Performance Status, n (%)	0	1 (4.8%)
	1	20 (95.2%)

Cancer Diagnosis	N = 21 n (%)
Gastroesophageal Junction Cancer	1 (4.8%)
Colorectal Cancer	6 (28.6%)
Melanoma of skin	5 (23.8%)
Non-small cell lung Cancer	1 (4.8%)
Pancreatic Cancer	6 (28.6%)
Ovarian Cancer	1 (4.8%)
Other (Metastatic Adenocarcinoma, intestinal type)	1 (4.8%)

Safety

No DLTs and no treatment-related SAEs observed through the cut-off date and the MTD has not been reached.
All adverse events (AEs) were grade 1 or 2. No drug-related grade 3, 4 or 5 AEs were reported.
No known MEK inhibitor class related AEs such as ocular toxicities, cardiotoxicities and skin toxicities were observed during the DLT observation period.
Most common drug related AEs observed through the cut-off date were gastrointestinal toxicities, including nausea, diarrhea and vomiting.

Summary of Clinical Safety: Adverse Events (AEs) at least Possibly related to PAS-004 during the DLT period

		Grade 1		Grade 2		Grade 3	Grand Total
	AE Preferred Term	Possible	Probable	Possible	Probable	Possible	
Cohort 1 - 2mg	Nausea				1		1
	Urinary incontinence			1			1
	Vomiting		1		1		2
Cohort 2 - 4mg	Dehydration				1		1
Cohort 3 - 8mg	Nausea		1				1
Cohort 4A - 15mg	Creatine phosphokinase increased	1		1			2
	Diarrhoea	1					1
Cohort 4B - 4mg tablet	Diarrhoea	1	1	1			3
	Fatigue		1				1
	Lacrimation increased		1				1
	Nail disorder		1				1
	Nausea	1	1				2
	Scleral disorder		1				1
	Vomiting	1	2				3
Cohort 5 - 22mg	Constipation		1				1
	Vomiting		1				1
Grand Total		5	12	3	3	0	23

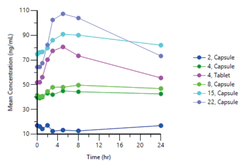
Pharmacokinetics

Preliminary PAS-004 PK analysis suggests linear PK with an estimated half-life >60h.
Exposure increases with an increase in dose and dose normalized exposure ranges overlap.
Cmax/Cmin ratio <2 at steady state, achieving potentially sufficient exposures for target engagement. This is supported by preliminary pERK inhibition observed in cohort 3 (8mg capsule), with pERK inhibition of up to 91%.

Pharmacokinetics (PK) parameters by cohort

PAS-004 Study Cohort	C_{max} (ng/mL) [mean CV%]	AUC_{0-24} (ng*h/mL) [mean CV%]	T_{max} (h) [mean CV%]	AR_{AUC} [mean CV%]
2 mg Capsule (N=3)	16.2 (89.7)	354 (95.2)	1 - 5	4.1 (16.2)
4 mg Capsule (N=3)	38.7 (94.8)	859 (101.3)	2 - 24	8.4 (37.8)
8 mg Capsule (N=3)	42.1 (100.9)	889 (118.0)	3-8	6.2 (11.3)
15 mg Capsule (N=3)	91.3 (27.6)	1990 (32.5)	2-24	4.02 (14.8)
22 mg Capsule (N=3)	108 (19.9)	2160 (16.4)	3-8	4.64 (50.6)
4 mg Tablet (N=4)	76.8 (37.9)	1550 (33.8)	3-5	4.17 (21.7)

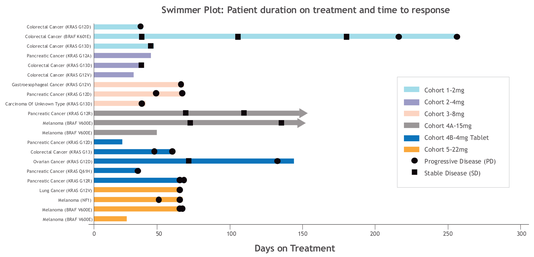
Pharmacokinetics (PK) curve at Steady State (day 22)



Efficacy

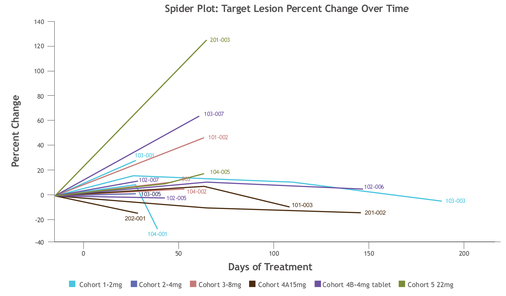
In the efficacy evaluable population (n=16), early response evaluation reveals stable disease (SD) by RECIST 1.1 was observed in 10 patients, with progression free survival of up to 159 days and overall survival of up to 253 days.

Swimmer Plot: Patient duration on treatment and time to response

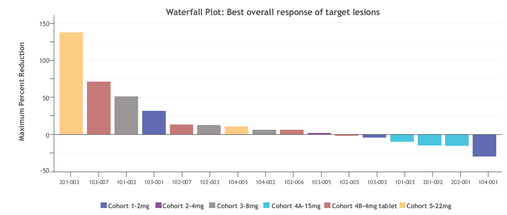


In Cohort 4A (15mg capsule), two out of three patients achieved SD and remain on therapy. One patient with Stage 4 KRAS G12R-mutated pancreatic cancer, having progressive disease while on three prior lines of therapy, achieved a tumor diameter reduction of -9.8% and remains on study for over 5 months. The second patient with Stage 4 BRAF mutated melanoma, having failed 2 prior lines of therapy including a prior MEK inhibitor + BRAF inhibitor combination therapy, achieved tumor diameter reduction of -14.9%.

Spider Plot: Target Lesion Percent Change Over Time



Waterfall Plot: Best overall response of target lesions



Conclusions

Through the cut-off date, PAS-004 is shown to be a safe and well-tolerated next-generation MEK inhibitor at all doses tested. No DLTs have been observed through the cut-off date and the MTD has not yet been reached.
PAS-004 presents a dose-dependent linear PK profile with an half-life >60h. The Cmax (peak) to Cmin (trough) ratio below 2 provides the potential to achieve sustained target inhibition.
PAS-004 has demonstrated promising preliminary clinical activity as a monotherapy in patients with heavily pre-treated refractory solid tumors. Particularly, PAS-004 has demonstrated promising clinical benefit in a re-challenge patient who failed a prior MEK inhibitor.
These findings provide a compelling rationale to continue to test PAS-004 in clinical trials for the treatment of MAPK-driven opportunities, such as advanced cancer, Neurofibromatosis Type 1 (NF1) or in patients who have failed prior treatment with a MEK inhibitor.

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