

A phase 1, first-in-human study of OP-3136, a novel oral selective KAT6A/B inhibitor, as monotherapy in advanced solid tumors and in combination with endocrine therapy in ER+, HER2– advanced breast cancer: preliminary results

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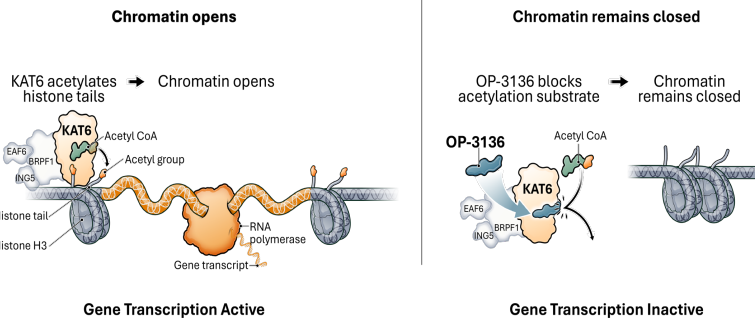
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BACKGROUND

- Histone lysine acetyltransferases (KATs) control oncogenic transcription and are frequently dysregulated in cancer.¹
- Small-molecule KAT6A/B inhibitors have shown promising clinical efficacy in estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC).²
- OP-3136 is an investigational, potent and selective oral small-molecule inhibitor of KAT6A/B, with additional activity against KAT7, and demonstrates preclinical antitumor activity, including in combination with endocrine therapy (ET).³

Figure 1. OP-3136 inhibits KAT6-mediated histone acetylation and transcription of proliferation-associated genes



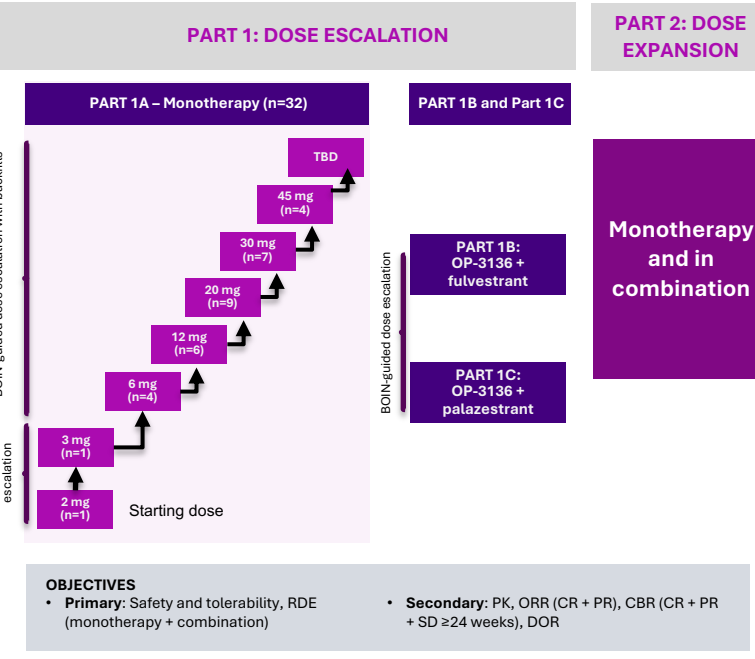
BRPF1, bromodomain and PHD finger-containing protein 1; CoA, coenzyme A; EAF6, MYST/Esa1-associated factor 6; ING5, inhibitor of growth family member 5; KAT6, histone lysine acetyltransferase 6.

- This phase 1 first-in-human study evaluates the safety, tolerability, pharmacokinetics (PK), and preliminary antitumor activity of OP-3136 as monotherapy in advanced solid tumors and in combination with fulvestrant or palaezstrant (a novel oral complete estrogen receptor antagonist [CERAN] and selective estrogen receptor degrader [SERD]) in ER+, HER2– ABC (NCT06784193).⁴
- Here we present an analysis from the monotherapy dose-escalation part of the study.

METHODS

- This phase 1 study includes dose escalation of OP-3136 as monotherapy (Part 1A) or in combination with fulvestrant (Part 1B) and palaezstrant (Part 1C), followed by dose expansion (Figure 2).
- In Part 1A (monotherapy), OP-3136 was administered orally once daily (QD) in continuous 28-day cycles across multiple dose levels (2–45 mg).

Figure 2. Phase 1 OP-3136-101 study design



Key Eligibility Criteria (Part 1A)

- Patients with advanced or metastatic solid tumors ER+, HER2– ABC, metastatic castration-resistant prostate cancer (mCRPC), or metastatic non-small cell lung cancer (mNSCLC).
- Disease progression on or intolerance to standard therapies.
- Eastern Cooperative Oncology Group (ECOG) performance status 0–1.

DEMOGRAPHICS AND DISEASE CHARACTERISTICS

- As of March 2, 2026, 32 patients were enrolled in the monotherapy dose-escalation cohort (Table 1).

Table 1. Baseline patient demographics and disease characteristics

Characteristic	Total (N=32)
Cancer type, n (%)	
ABC	21 (66%)
mCRPC	10 (31%)
mNSCLC	1 (3%)
Age, years	
Median (range)	66 (38–78)
Sex, n (%)	
Male	10 (31%)
Female	22 (69%)
Race, n (%)	
White	27 (84%)
Black or African American	2 (6%)
Asian	1 (3%)
Other*	2 (6%)
ECOG performance status, n (%)	
0	17 (53%)
1	15 (47%)
Measurable disease at baseline, n (%)	25 (78%)
Visceral disease at baseline, n (%)	19 (59%)

*Other includes not reported and unknown categories.

ABC, advanced breast cancer; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration-resistant prostate cancer; mNSCLC, metastatic non-small cell lung cancer.

- Patients included in the study were heavily pretreated.
- All patients with ABC had received prior CDK4/6 inhibitor and ET.
- All patients with mCRPC had received prior androgen receptor-targeted therapy; 7 (70%) patients received prior radiopharmaceuticals, and 7 (70%) received prior chemotherapy.

Table 2. Prior systemic therapy in the advanced/metastatic setting

Prior systemic therapy in the advanced/metastatic setting	Part 1A ABC (N=21)	Part 1A mCRPC (N=10)
No. of prior lines, median (range)	4.0 (1–8)	5.0 (1–7)
Breast cancer therapies, n (%)		
CDK4/6 inhibitor	21 (100%)	—
Endocrine therapy	21 (100%)	—
Aromatase inhibitor	18 (86%)	—
Fulvestrant	14 (67%)	—
Prostate cancer therapies, n (%)		
AR-targeted therapy	—	10 (100%)
Radiopharmaceuticals	—	7 (70%)
PARP inhibitor	—	2 (20%)
General, n (%)		
Chemotherapy or ADC	12 (57%)	7 (70%)

ABC, advanced breast cancer; ADC, antibody-drug conjugate; AR, androgen receptor; CDK4/6, cyclin-dependent kinase 4/6; mCRPC, metastatic castration-resistant prostate cancer; PARP, poly (ADP-ribose) polymerase.

SAFETY AND TOLERABILITY

Table 3. TRAEs reported in ≥10% of patients (N=32)

TRAE	Any grade, n (%)	Grade 3, n (%)
Any TRAE	31 (97%)	11* (34%)
Dysgeusia*	26 (81%)	N/A
Anemia	12 (38%)	2 (6%)
Fatigue	12 (38%)	1 (3%)
Neutropenia†	11 (34%)	9 (28%)
Nausea	8 (25%)	0
Platelet count decreased	6 (19%)	0
ALT increased	4 (12.5%)	0
Back pain	4 (12.5%)	0

*Includes preferred terms 'Dysgeusia' and 'Taste Disorder.' †Includes preferred terms 'Neutropenia' and 'Neutrophil count decreased.' ‡Grade 3 TRAEs included anemia (1 at 6 mg; 1 at 12 mg; 4 at 20 mg; 1 at 30 mg; and 2 at 45 mg); thrombocytopenia (1 at 30 mg); leukopenia (1 at 30 mg); fatigue (1 at 12 mg); syncope (1 at 12 mg). ALT, alanine aminotransferase; N/A, not applicable; TRAE, treatment-related adverse event.

References

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- ClinicalTrials.gov identifier: NCT06784193. <https://clinicaltrials.gov/study/NCT06784193>.

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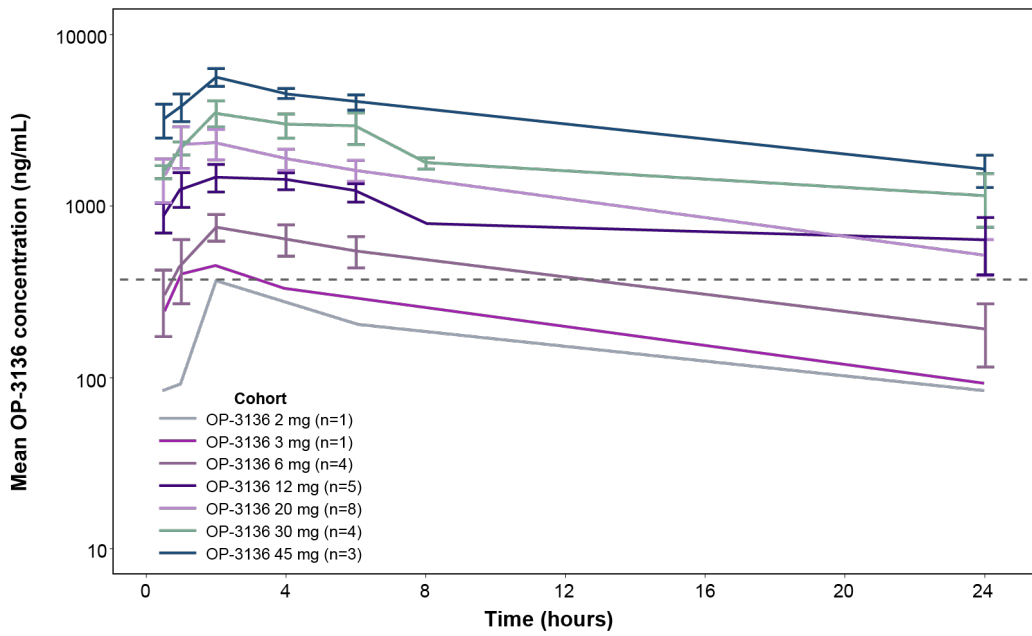
Disclosures

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PHARMACOKINETICS

- OP-3136 exhibits dose-proportional plasma exposure across the 2- to 45-mg dose range in 26 participants evaluated to date. Steady state was achieved by C1D15 (Figure 3).
- The steady-state concentrations were above effective concentration targets (determined from preclinical models) when dosed at ≥6 mg.

Figure 3. Plasma concentration-time profiles for OP-3136 across dose levels



Samples were collected on cycle 1, day 15 predose and at the indicated timepoints following OP-3136 administration. Data are arithmetic mean and SEM.

Dashed line represents efficacious C_{ave} exposure based on a 0.1 mg/kg OP-3136 dose in mouse ZR-75-1 xenograft models. C_{ave}, average plasma concentration; SEM, standard error of the mean.

- OP-3136 demonstrates rapid absorption and consistent half-life across the dose range evaluated (Table 4).

Table 4. Steady-state pharmacokinetic parameters of OP-3136

PK Parameter*	2 mg OP-3136 (n=1)	3 mg OP-3136 (n=1)	6 mg OP-3136 (n=4)	12 mg OP-3136 (n=5)	20 mg OP-3136 (n=8)	30 mg OP-3136 (n=4)	45 mg OP-3136 (n=3)
C _{max} (ng/mL)	367	445	727 (34%)	1610 (14%)	2450 (36%)	3790 (24%)	5630 (19%)
AUC ₀₋₂₄ (ng/mL·h)	3850	5110	8760 (51%)	22500 (18.6%)	27600 (30%)	48000 (39%)	72900 (21%)
C _{min} (ng/mL)	69.2	92.3	144 (101%)	401 (51%)	379 (51%)	912 (77%)	1490 (37%)
T _{max} (h)†	2.0	2.0	[2.0–2.0]	2.0 [1.0–4.0]	2.0 [1.0–6.0]	2.0 [1.0–2.0]	2.0 [1.0–2.0]
t _{1/2} (h)	12.6	11.1	10.5 (35%)	12.9 (60%)	10.5 (24%)	11.4 (44%)	13.4 (24%)

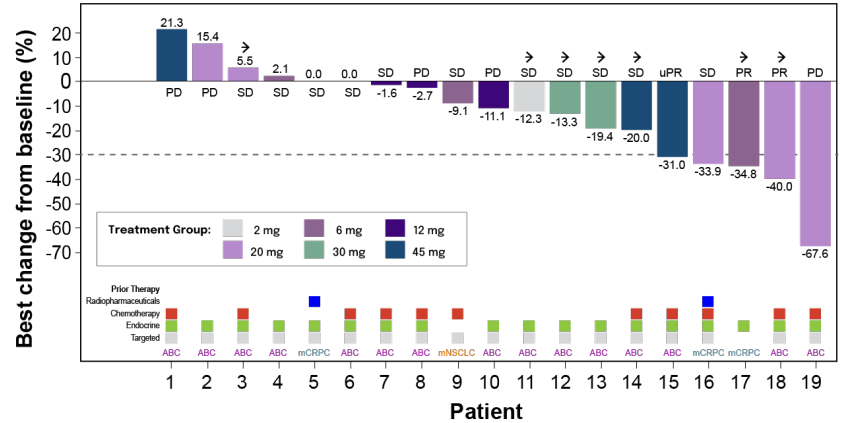
*Geomean (GeoCV%). †T_{max} = median (min–max).

AUC₀₋₂₄, area under the concentration-time curve from 0 to 24 hours; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; t_{1/2}, half-life; T_{max}, time to maximum concentration.

EFFICACY AND TARGET ENGAGEMENT

- OP-3136 monotherapy demonstrated tumor shrinkage across dose levels and tumor types (Figure 4).
- Among 19 response-evaluable patients, 13 (68%) demonstrated reduction in target lesion(s) size.
- Partial response (PR) was observed in 3 of 19 response-evaluable patients (15.8%) (2 confirmed PR [10.5%]; 1 unconfirmed PR [5.3%]): 2 patients with ABC (20 mg and 45 mg) and 1 with mCRPC (6 mg).
- Stable disease was observed in 11 patients (57.9%), including 8 with ABC, 2 with mCRPC, and 1 with mNSCLC.

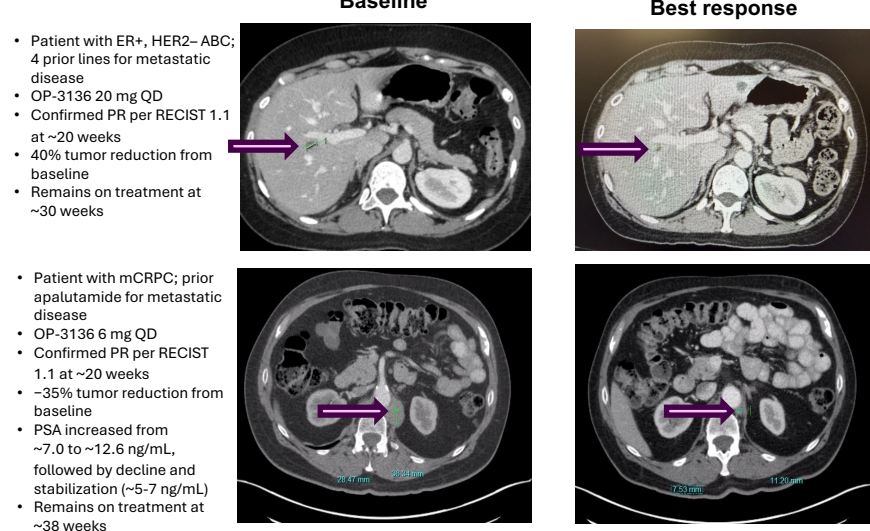
Figure 4. Best percent change from baseline in target lesions and best overall response



ABC, advanced breast cancer; mCRPC, metastatic castration-resistant prostate cancer; mNSCLC, metastatic non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; uPR, unconfirmed partial response.

- Representative cases demonstrate confirmed PRs with radiographic tumor reduction (Figure 5).

Figure 5. Computed tomography scans from patients with confirmed partial response



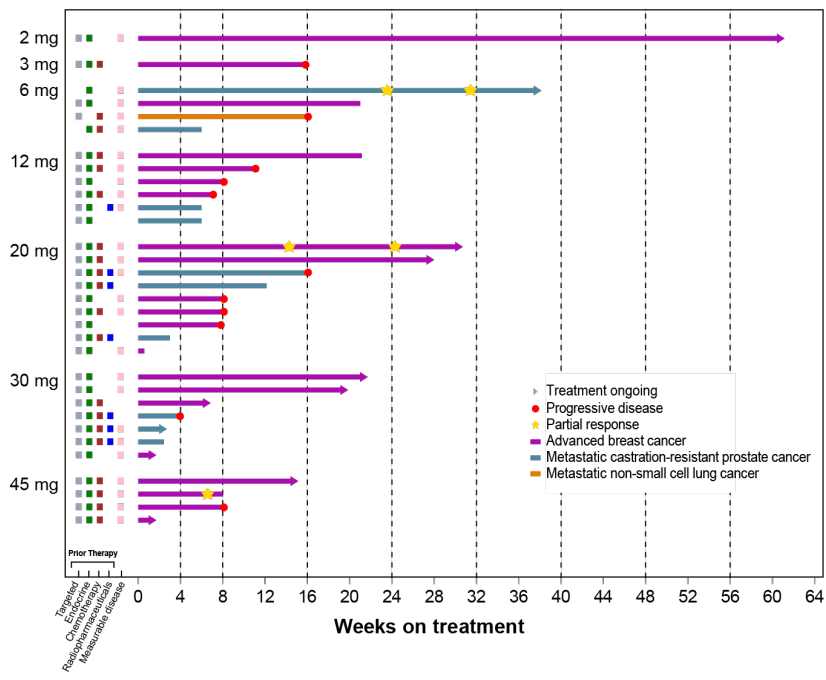
ABC, advanced breast cancer; ER+, estrogen receptor-positive; HER2–, human epidermal growth factor receptor 2-negative; mCRPC, metastatic castration-resistant prostate cancer; PR, partial response; PSA, prostate-specific antigen; QD, every day; RECIST, Response Evaluation Criteria in Solid Tumors.

CONCLUSIONS

- In the ongoing dose-escalation phase of the OP-3136-101 phase 1, first-in-human trial, OP-3136 was well tolerated as monotherapy.
 - No DLTs were observed across the evaluated daily dose range, up to 45 mg.
 - Most TRAEs were grade 1–2; there were no grade 4–5 TRAEs. TRAEs were manageable with dose modifications. No discontinuation due to TRAEs.
- PK was dose proportional across the evaluated dose range and steady state was reached by C1D15.
- Rapid and sustained reduction (~70%–90%) in H3K23ac levels was observed at all doses tested, consistent with KAT6 target engagement.
- Preliminary efficacy was observed, including tumor shrinkage in two-thirds of response-evaluable patients, with confirmed and durable responses in patients with ABC and mCRPC treated with OP-3136 monotherapy.
- Enrollment is ongoing in OP-3136 monotherapy (Part 1A) for all patients, as well as in combination with fulvestrant (Part 1B) and palaezstrant (Part 1C) in patients with ABC.

- Longest duration of treatment is 62 weeks and ongoing (Figure 6).
- 11 (34%) remain on treatment, including 9 patients with ABC and 2 with mCRPC.

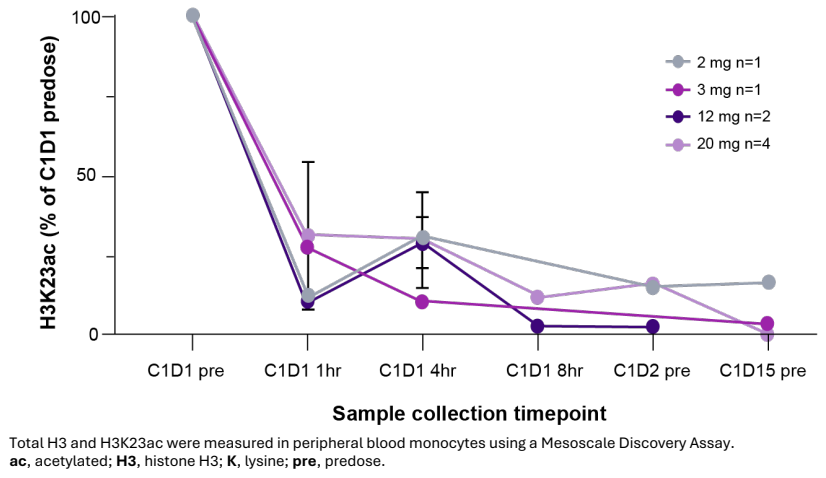
Figure 6. Duration of treatment*



*Each lane represents 1 patient. Progressive disease (PD) assessment date was used if end of treatment date was missing for patients with PD. Progression by radiographic assessment only. Data cut-off March 2, 2026.

- Lysine 23 of histone H3 (H3K23) is a direct molecular target of KAT6.
- Total histone H3 and acetylated histone H3 at lysine 23 (H3K23ac) were assessed prior to OP-3136 administration and at the indicated posttreatment timepoints (Figure 7).
- Reduction in H3K23ac levels was observed following OP-3136 dosing.

Figure 7. Acetylation of H3K23 following treatment with OP-3136



Total H3 and H3K23ac were measured in peripheral blood monocytes using a Mesoscale Discovery Assay. ac, acetylated; H3, histone H3; K, lysine; pre, predose.

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