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Pharmacodynamic biomarker modulation by OMX-0407, a novel, spectrum-selective kinase inhibitor for the treatment of angiosarcoma and renal cell carcinoma

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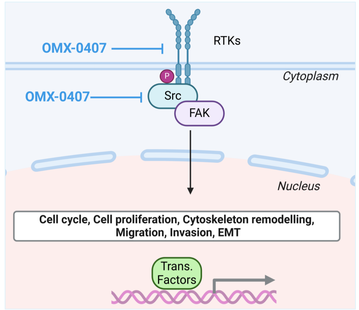
Introduction

OMX-0407 is an orally available, spectrum-selective kinase inhibitor targeting a set of oncology-relevant tyrosine kinases (TK) as well as the salt-inducible kinase (SIK) family, demonstrating a dual mode of action (MoA) in cancer. This involves OMX-0407-induced cell cycle arrest in tumor cells by de-phosphorylation and inactivation of TKs such as Src family kinases (SFK) and the SIK family, and increased sensitivity of the tumor microenvironment to immune-mediated tumor cell killing. OMX-0407 is currently undergoing early clinical testing for the treatment of angiosarcoma (AS) and clear cell renal cell carcinoma (ccRCC) (NCT05826600).

In the dose escalation phase of this study, patients with previously treated unresectable solid tumors were treated with OMX-0407 at dose levels of 10 to 140 mg twice daily (BID). Treatment was well tolerated with the main safety finding being gastro-intestinal adverse reactions. One patient with secondary radiation-induced angiosarcoma achieved a complete response at doses of up to 60 mg BID, which remains ongoing at 19 months.

A flow-cytometry-based "phosFlow" assay confirmed OMX-0407 effects on the phosphorylation of SFKs in PBMCs at doses of 60 mg and above. This was associated with the inhibition of oncology-relevant TKs as determined by functional kinase activity profiling. Treatment-related PD modulation was significantly correlated with OMX-0407 plasma levels.

This confirms that both phosFlow and kinase activity profiling successfully resolve exposure-dependent OMX-0407 activity in peripheral patient blood as pharmacodynamic biomarkers. These findings, together with safety findings and PK profiling, contributed to the selection of 100 mg BID as the preliminary recommended phase 2 dose (RP2D) for the dose expansion.



Study Design

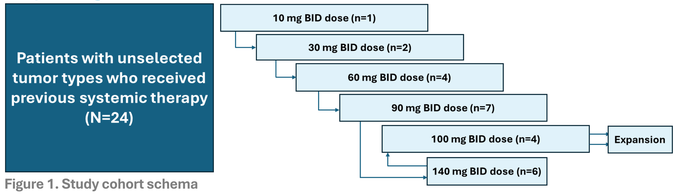


Figure 1. Study cohort schema

- In this Phase 1a/1b dose-escalation and dose-expansion study (NCT05826600), patients received continuous treatment with OMX-0407 administered in 28-day cycles (10-140 mg). On Cycle 1 Day 1, only a single morning dose was given for PK assessment; BID dosing began on Day 2.
- Key inclusion criteria: Patients with previously treated unresectable solid tumors (at least one previous line of therapy), ECOG PS of 0 to 2, and tumors evaluable by RECIST 1.1 criteria.
- The dose-escalation part utilized a 3+3 design to characterize the safety profile of OMX-0407 and determine the MTD.
- Primary outcomes in the dose-escalation (Phase 1a) part included incidence of dose-limiting toxicities; secondary outcomes included MTD, RP2D, PK, PFS and duration of response.
- A total of 24 patients were included in the Phase 1a dose-escalation phase with a mean age of 60.8 years. Half of the enrolled participants were female. Treatment was well tolerated with the main safety finding being gastro-intestinal adverse reactions.

Schedule of Assessments

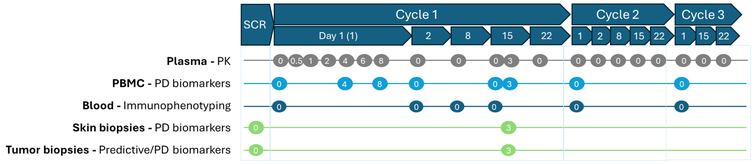


Figure 2. **Schedule of Assessments**. Circled numbers indicate time of collection (h) with respect to OMX-0407 morning dose (0h=pre am dose, 0.5h-8h=post am dose)

- Plasma samples are collected at regular intervals for OMX-0407 PK assessments, with PBMC collections at matched time-points for the assessment of peripheral pharmacodynamic biomarkers.
- Whole blood, skin and tumor biopsies are collected for the assessment of additional predictive and pharmacodynamic biomarkers (analysis ongoing, data not shown)

OMX-0407 PD effects in *in vivo* tumor mouse model

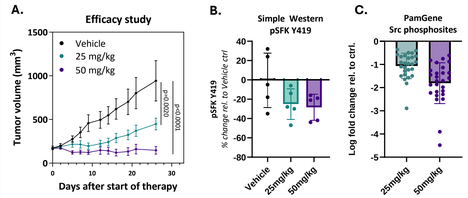


Figure 3. **A)** Human AS PDX tumor fragments were transplanted into immunodeficient NOG mice, randomized at an average tumor volume of ~150 mm³. Tumor-bearing mice were treated twice daily with OMX-0407 (25 mg/kg or 50 mg/kg) or vehicle control via oral gavage. Average tumor growth is presented as mean ± SEM for six mice per group. Statistical analysis was performed using one-way ANOVA with Tukey's multiple comparison test. **B)** Fresh frozen tumor fragments were lysed and analyzed by Simple Western for pSFK Y419. Fold change compared to vehicle control in tumor lysates. **C)** Fresh frozen tumor fragments were lysed and used for PamGene PTK activity assay. Log fold change of all significant downregulated SFK-specific phospho-sites in tumor lysates.

- OMX-0407 showed dose-dependent anti-tumor efficacy in a human epitheloid AS PDX model.
- Simple Western revealed intra-tumoral dephosphorylation of Src phospho-site SFK Y419 at both OMX-0407 doses.
- PamGene PTK profiling revealed intra-tumoral, dose-dependent suppression of SFKs involved in tumor proliferation and cell cycle regulation, incl. SFK Y419.

Dose-dependent OMX-0407 PD effects observed in human PBMCs

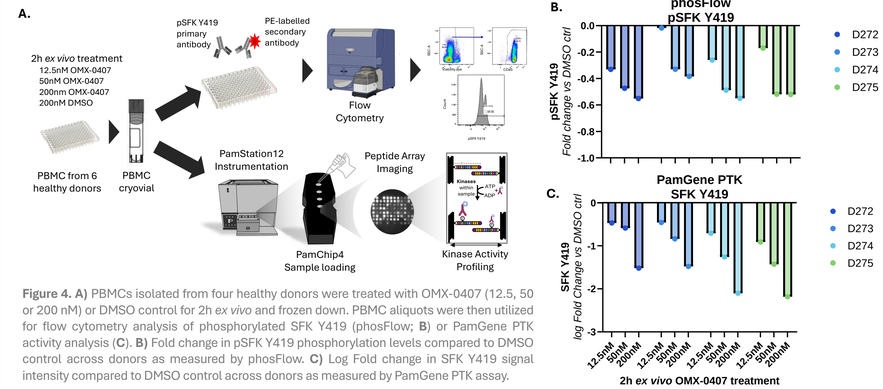


Figure 4. **A)** PBMCs isolated from four healthy donors were treated with OMX-0407 (12.5, 50 or 200 nM) or DMSO control for 2h *ex vivo* and frozen down. PBMC aliquots were then utilized for flow cytometry analysis of phosphorylated SFK Y419 (phosFlow; **B**) or PamGene PTK activity analysis (**C**). **B)** Fold change in pSFK Y419 phosphorylation levels compared to DMSO control across donors as measured by phosFlow. **C)** Log Fold change in SFK Y419 signal intensity compared to DMSO control across donors as measured by PamGene PTK assay.

- Strong dose-dependent OMX-0407 effects on SFKs were observed in *ex vivo*-treated human PBMCs using both PamGene and a flow-cytometry-based phosFlow assay assessing phosphorylation of the SFK Y419 phospho-site.
- Both assays were implemented as peripheral PD biomarkers in the first-in-human trial (NCT05826600).

Conclusions

- **In a Ph1a clinical trial, OMX-0407, a potent spectrum-selective kinase inhibitor, was well tolerated and anti-tumor activity was demonstrated for one patient with AS achieving a durable complete response.**
- **Both phospho-flow and kinase activity profiling confirmed exposure-dependent pharmacodynamic effects of OMX-0407 in patient blood at doses of 60 mg and above.**
- **Enrolment into the Ph1b dose expansion phase of the clinical study (NCT05826600) is ongoing, including patients with unresectable, metastatic AS or ccRCC who have received at least one prior line of therapy, evaluating OMX-0407 at the preliminary RP2D of 100 mg BID.**

PD effects of OMX-0407 confirmed in clinical patients

- PhosFlow and PamGene analysis confirmed pharmacodynamic OMX-0407 effects on SFKs in patient PBMCs at doses of 60 mg and above.

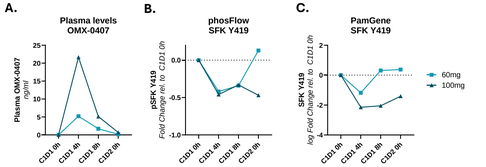


Figure 5. **Exemplary OMX-0407 plasma levels and PD results from clinical patients treated with 60 mg vs 100 mg OMX-0407. A)** Exemplary plasma OMX-0407 levels at PBMC collection timepoints on Cycle 1 Day 1. **B)** Fold change in pSFK Y419 phosphorylation levels compared to Cycle 1 Day 1 0h pre-dose timepoint as measured using phosFlow. **C)** Log Fold change in SFK Y419 signal intensity compared to Cycle 1 Day 1 0h pre-dose timepoint as measured by PamGene PTK assay.

OMX-0407 PD effects in PBMCs are correlated with drug exposure

- OMX-0407 PD effects were significantly correlated with OMX-0407 plasma levels at the C1D1 4h timepoint. For the PamGene assay, a significant correlation across all PBMC timepoints was also observed.
- This confirms that phosFlow and PamGene kinase activity profiling can successfully resolve exposure-dependent OMX-0407 activity in peripheral patient blood as PD biomarkers.
- These findings, together with safety findings and PK profiling, contributed to the selection of 100 mg BID as the preliminary RP2D for the ongoing dose expansion phase of the clinical study.
- The PamGene assay was selected as primary peripheral PD biomarker assay for the dose expansion phase.

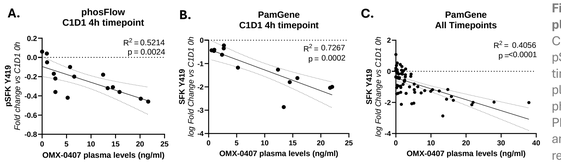


Figure 6. **Correlation analysis of OMX-0407 plasma levels and PBMC PD effects. A)** Correlation between OMX-0407 plasma levels and pSFK Y419 fold change in phosFlow at C1D1 4h timepoint. **B-C)** Correlation between OMX-0407 plasma levels and pSFK Y419 fold change in phosFlow at C1D1 4h timepoint **(B)** or across all PBMC collection timepoints **(C)**. Statistical analysis was performed using simple linear regression analysis.

Table 1. Comparison of phosFlow & PamGene technologies, highlighting benefits of PamGene technology as clinical PD biomarker.

phosFlow	PamGene
• Measurement of OMX-0407 effects on kinase phosph. status	• Measurement of OMX-0407 effects on kinase activity
• Antibody-based read-out on selected phospho-sites	• Microarray-based read-out on up to 195 phospho-sites
• Manual protocol with some batch-to-batch variation	• Automated protocol with minimal batch-to-batch variation
• Sample stability reported for a maximum of 12 weeks	• Sample stability reported for >1 year

Lasting Complete Response achieved in Angiosarcoma patient

- One previously treated patient with secondary radiation-induced metastatic cutaneous AS received OMX-0407 study treatment at doses of 10 to 60 mg BID and achieved a complete response from 30 mg BID dose, which is ongoing at 19 months.

Abbreviations:
AE, adverse event; AS, angiosarcoma; BID, twice daily; CI, confidence interval; CxDx, Cycle x Day x; DMSO, Dimethylsulfoxide; ECOG PS, Eastern Cooperative Oncology Group Performance status; FC, fold change; MoA, Mechanism of Action; MTD, maximum tolerated dose; NA, not applicable; NC, not calculated; PBMC, peripheral blood mononuclear cells; PDX, patient-derived xenograft; PD, Pharmacodynamic; PFS, Progression-free Survival, PK, Pharmacokinetics; PTK, protein tyrosine kinase; ccRCC, clear cell renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumours; SD, standard deviation; RP2D, recommended Phase 2 dose; SCR, Screening visit; SCR, Screening visit; SFK, Src family kinase; SIK, salt-inducible kinase; TK, tyrosine kinase; TRAE, treatment-related adverse event;

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