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OMX-0407: A novel spectrum-selective small molecule kinase inhibitor is active in the treatment of angiosarcoma

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Background

- **OMX-0407, an orally available spectrum-selective kinase inhibitor that targets key oncology-relevant tyrosine kinases and salt-inducible kinases, is being developed as a first-in-class treatment for solid tumor indications with high unmet medical need, such as squamous NSCLC, urothelial bladder cancer, RCC and AS.**
- **OMX-0407 has demonstrated a dual mode of action by directly inducing cell cycle arrest in tumor cells (through potent inhibition of downstream signaling cascades necessary for cancer cell proliferation; Figure 1) and sensitizing the tumor environment to immune cell-mediated tumor cell killing.[1]**
- **Treatment with OMX-0407 in experimental animals has shown dose-responsive, de-phosphorylation, single-agent efficacy in multiple tumor types. *Ex vivo* analyses showed a dose-responsive, de-phosphorylation of SFKs associated with cell proliferation and cell cycle proteins. Furthermore, the anti-tumor activity of OMX-0407 has been evaluated in an *in vivo* PDX model of human AS, derived from a 9-year-old female diagnosed with epithelioid AS. OMX-0407 demonstrated dose-dependent efficacy in the PDX model, with significant tumor growth inhibition at both doses tested (25 mg/kg and 50 mg/kg), resulting also in intra-tumoral de-phosphorylation of SFKs.**
- **Functional kinase activity analysis demonstrated dose-dependent downregulation of several SFK-specific phosphorylation sites associated with cancer cell proliferation and regulation of the tumor cell cycle. OMX-0407-mediated pharmacodynamic modulation of Src phosphorylation site pSFK-Y530 was confirmed by Simple Western analysis.[2]**
- **Here, we report findings from the dose-escalation part of a Phase 1a/1b study.**

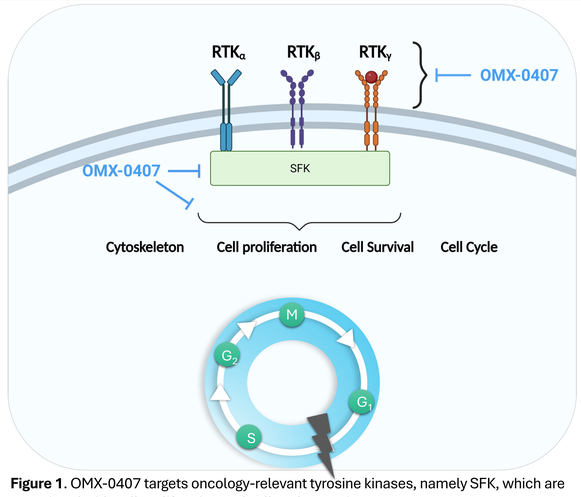

Figure 1. OMX-0407 targets oncology-relevant tyrosine kinases, namely SFK, which are associated with cell proliferation and cell cycle proteins

OMX-0407 Shows Anti-Tumor Efficacy in Human AS PDX Model

- **OMX-0407 exhibits dose-dependent anti-tumor efficacy in a human AS PDX model from a 9-year-old female with epithelioid AS, as a single-agent (Figure 2A).**
- **OMX-0407 therapy in AS PDX tumors results in intra-tumoral de-phosphorylation of SFKs, as seen in protein expression levels of pSFK Y530 (Figure 2B), but also in a functional kinase activity screen, where all SFK-specific phosphorylation sites were dose-dependently downregulated upon treatment with OMX-0407 (Figure 2C).**

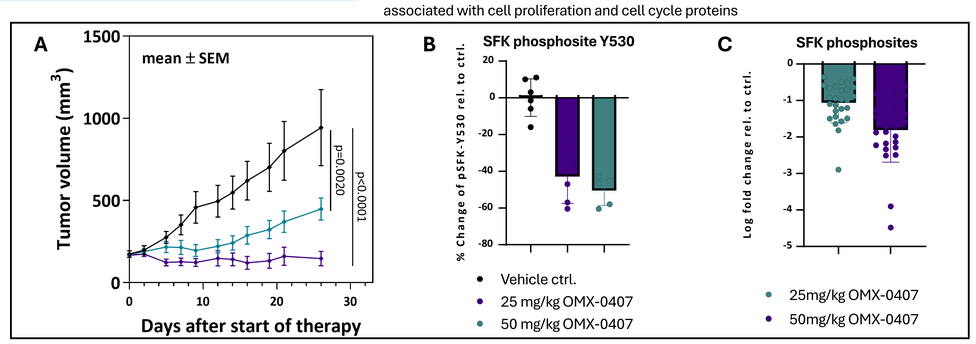

Figure 2.
A) Human AS PDX tumor fragments were transplanted into immunodeficient NOG mice, randomized at an average tumor volume of ~150 mm^3. Tumor-bearing mice were treated twice daily with OMX-0407 (25 mg/kg or 50 mg/kg) or vehicle control via oral gavage. Average tumor growth is presented as mean ± SEM for six mice per group. Statistical analysis was performed using one-way ANOVA with Tukey's multiple comparison test.
B) Semiquantitative analysis of phospho-SFK-Y530 in AS PDX tumors (sampled on the day of necropsy, 26 days after therapy initiation) after Simple Western, normalized to vehicle control-treated animals.
C) Log fold change of all significant downregulated SFK phosphosites in tumor lysates of OMX-0407 treated animals relative to vehicle control.

Study design[2]

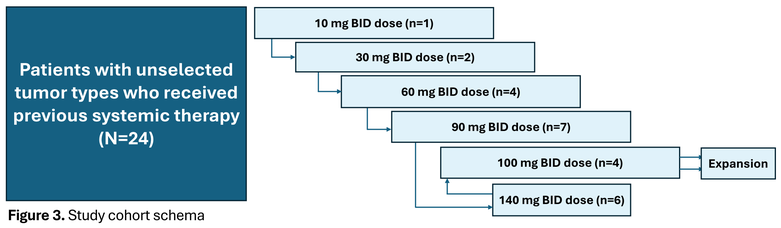

Figure 3. Study cohort schema

- **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 mg, 30 mg, 60 mg, 90 mg, 100mg and 140 mg BID doses; Figure 3).**
- **Key inclusion criteria: Patients were required to have 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.**
- **Primary outcomes were incidence of dose-limiting toxicities (at each dose level) in the dose-escalation (Phase 1a part) and objective response rate with OMX-0407 in patients with RCC, NSCLC, UC and AS in the dose expansion (Phase 1b part); secondary outcomes included MTD and recommended dose for Phase 2 based on toxicities, pharmacokinetics, duration of response and progression-free survival.**
- **The dose-escalation part utilized a 3+3 design to characterize the safety profile of OMX-0407 and determine the MTD.**

Results

Baseline Characteristics

- **At data cutoff (30 Oct 2024) for the total safety population, mean age was 60.79 years and half of the enrolled participants were female (Table 1).**

	10 mg BID (n=1)	30 mg BID (n=2)	60 mg BID (n=4)	90 mg BID (n=7)	100 mg BID (n=4)	140 mg BID		Total (N=24)
						Sub-cohort A (n=3)	Sub-cohort B (n=3)	
Age (years)								
Mean (SD)	70.00 (NC)	70.50 (2.121)	53.25 (9.777)	59.57 (15.884)	55.25 (24.240)	67.33 (7.095)	65.00 (9.000)	60.79 (14.213)
95% CI	NA	51.44, 89.56	37.69, 68.81	44.88, 74.26	16.68, 93.82	49.71, 84.96	42.64, 87.36	54.79, 66.79
Sex								
Female (n, %)	1 (100)	2 (100)	3 (75)	2 (28.6)	2 (50)	1 (33.3)	1 (33.3)	12 (50)

Table 1. Baseline patient characteristics

Response

- **One patient with secondary radiation-induced metastatic cutaneous AS (Figure 4), treated at doses of 10 to 60 mg BID, achieved a complete response at 30 mg BID:**
  - **This was ongoing at the time of data cut, with a current duration of response of 16 months.**
  - **The patient had received previous chemotherapy with doxorubicin, cyclophosphamide and paclitaxel.**

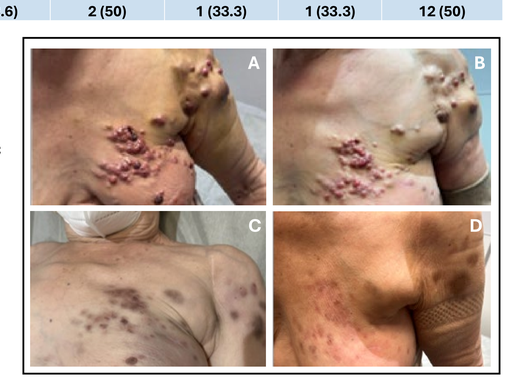

Figure 4. Patient with secondary cutaneous AS resistant to previous chemotherapy (doxorubicin, cyclophosphamide, paclitaxel) treated with OMX-0407. **A)** Baseline. **B)** Cycle 2/Day 1: Dose escalation from 10 mg to 30 mg/BID. **C)** Cycle 4/Day 1: 30 mg/BID dose. **D)** Cycle 10/Day 1: 60 mg/BID dose (since C9D1)

Safety

- **Treatment was well tolerated: TRAEs were mild to moderate, with the most common being gastrointestinal in nature (Figure 5); only 1 Grade ≥3 TRAE of anemia was reported in 1 patient at the 140 mg BID dose in sub-cohort A.**
- **Dose-limiting toxicities: One case of facial swelling secondary to drug allergy at the 90 mg BID dose, and one case of fatigue at the 140 mg BID dose in sub-cohort B.**

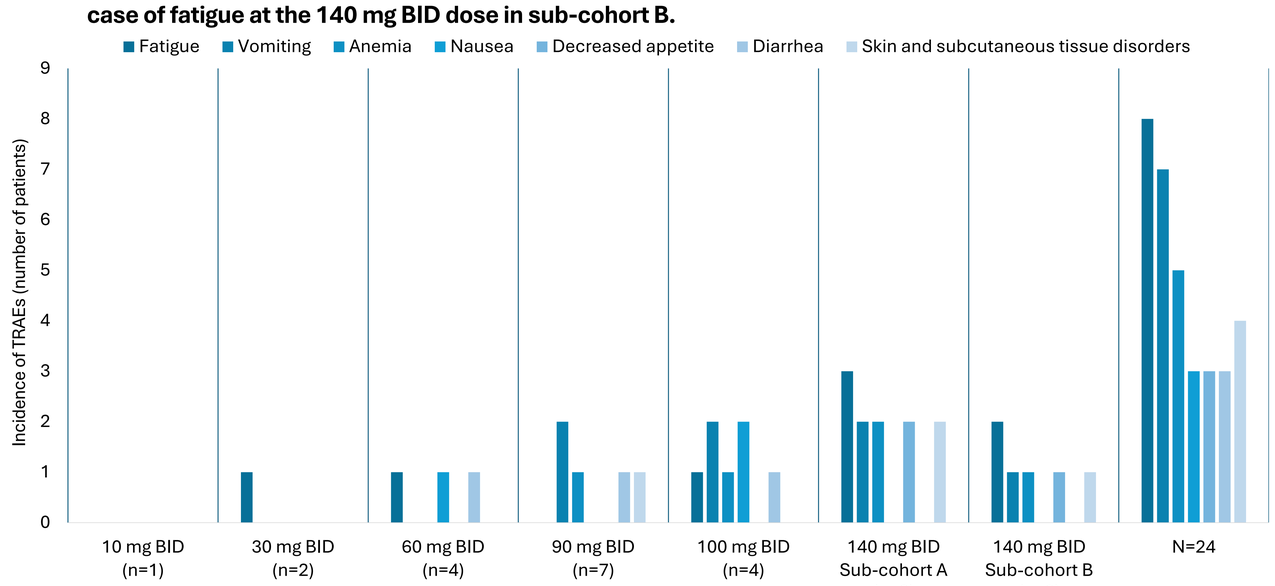

Figure 5. Grades 1–2 TRAEs occurring in >10% of patients (safety population)

Conclusions

- **In our study, OMX-0407, a potent and spectrum-selective kinase inhibitor, was well tolerated and demonstrated anti-tumor activity, with one patient with AS achieving a durable complete response.**
- **Our preclinical findings support inhibition of tumor cell proliferation by OMX-0407 as a highly relevant mode of action, with significant impact on AS in an *in vivo* model.**
- **OMX-0407 will be further evaluated clinically in the dose-expansion Phase 1b part of this study in all subtypes of AS, as well as other indications preclinically identified as sensitive to OMX-0407.**

Abbreviations
AE, adverse event; AS, angiosarcoma; BID, twice daily; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance status; MTD, maximum tolerated dose; NA, not applicable; NC, not calculated; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; PDX, patient-derived xenograft; RECIST, Response Evaluation Criteria in Solid Tumours; SD, standard deviation; SFK, Src family kinase; TRAE, treatment-related adverse event; UC, urothelial cancer.

References
1. Maser IP, et al. OMX-0407, a spectrum selective kinase inhibitor shows preclinical and clinical efficacy in Angiosarcoma, an indication of high unmet medical need. Poster presented at the 36th EORTC-NCI-AACR Symposium, October 2024, Barcelona, Spain; 2. A Study of OMX-0407 in Patients With Previously Treated Solid Tumours That Can't be Removed Surgically (NCT05826600). Available at https://clinicaltrials.gov/study/NCT05826600?term=OMX-0407&rank=1 (last accessed November 2024).

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