AACR - 2025 Poster 374

OMX-0407 - a spectrum selective kinase inhibitor shows preclinical efficacy in RCC as well as Sarcomas

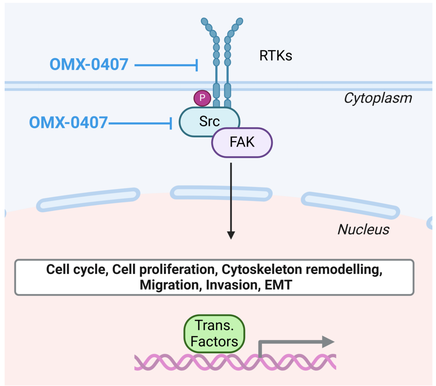
Ilona-Petra Maser, Carmen Amerhauser, Bettina Bauer, Andreas Schirmer, Moritz Zulley, Marisa Stebegg-Wagner, Alina Huth, Tillmann Michels, Tiantom Jarutat, Hannes Loferer, Stefan Bissinger

iOmx Therapeutics AG, Martinsried/Munich, Germany

Introduction

OMX-0407 is an orally bioavailable, spectrum-selective kinase inhibitor that targets key tyrosine kinases implicated in oncology. It exerts a dual MoA by (i) direct effects on tumor cells by inducing cell cycle arrest and (ii) enhancing immune cell-mediated tumor cell killing. In a patient-derived xenograft (PDX) model of human angiosarcoma (AS), OMX-0407 demonstrated dose-dependent efficacy, resulting in significant tumor inhibition. Post-study analyses revealed downregulation of phospho-proteins associated with critical signaling pathways, including those regulating the cell cycle. Beyond angiosarcoma, OMX-0407 exhibited *in vitro* anti-tumor activity in soft tissue sarcoma (STS) and renal cell carcinoma (RCC).

These preclinical findings align with Phase I clinical data (NCT05826600), in which a chemotherapy-resistant angiosarcoma patient achieved a complete and durable response. Collectively, these preclinical and clinical data support the ongoing expansion of the Phase I trial in AS and RCC.



Conclusions

- **OMX-0407, a potent and spectrum-selective kinase inhibitor, demonstrates robust anti-tumor efficacy in angiosarcoma, soft tissue sarcomas and renal cell carcinoma.**
- **Anti-tumor effects are associated with strong cell cycle arrest driven by OMX-0407-mediated inhibition of cell cycle progression and proliferation across indications.**
- **Preclinical findings are in line with the durable clinical response observed in an angiosarcoma patient during the ongoing first-in-human trial OMX-0407-101 (NCT05826600).**
- **Confirmation of *in vitro* sensitivity of STS to OMX-0407 as predicted by a proprietary predictive gene signature**
- **Mechanistic insights into OMX-0407's anti-proliferative effects will inform its further clinical development, including the recently initiated Phase Ib expansion.**

OMX-0407 Drives Potent Growth Inhibition in Angiosarcoma Cell Lines

- OMX-0407 achieved a durable, complete clinical response in an AS patient previously treated with chemotherapy in the ongoing Phase I trial (NCT05826600).
- *In vitro*, OMX-0407 demonstrates potent, dose-dependent inhibition of cancer cell growth in patient-derived angiosarcoma cell lines.
- OMX-0407 induces a dose-dependent reduction in cancer cell proliferation, accompanied by downregulation of Src-family kinase (SFK) activity.

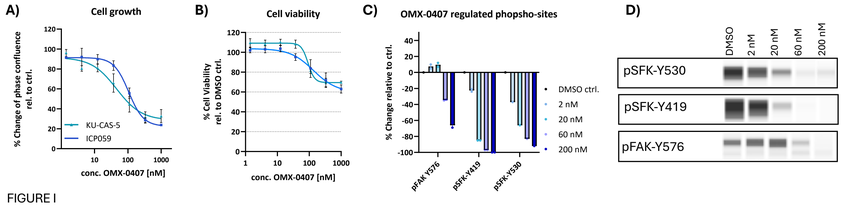


FIGURE I

Angiosarcoma cell lines were cultured and treated with the indicated doses of OMX-0407 or DMSO (vehicle control) for 48 hours. Cell confluence **A)** was assessed via a live-cell imaging system (Incucyte®) using phase contrast and fluorescence emission. **B)** Cell viability was measured using the CellTiter-Glo® assay following the manufacturer's protocol. **C)** KU-CAS-5 cell line was exposed to OMX-0407 for 4 hours. SFK-phospho-Y530, pSFK-Y419 and pFAK-Y576 were analyzed by Simple Western. **D)** Representative visualization of protein bands for analyzed p-sites in KU-CAS-5 cells.

OMX-0407 Anti-Tumor Efficacy in Human Angiosarcoma PDX Model

- OMX-0407 exhibited dose-dependent anti-tumor efficacy in a human PDX model from epithelioid AS.
- PamGene PTK functional kinase activity analysis revealed dose-dependent downregulation of several SFK-specific phosphosites associated with cancer cell proliferation and tumor cell cycle regulation.

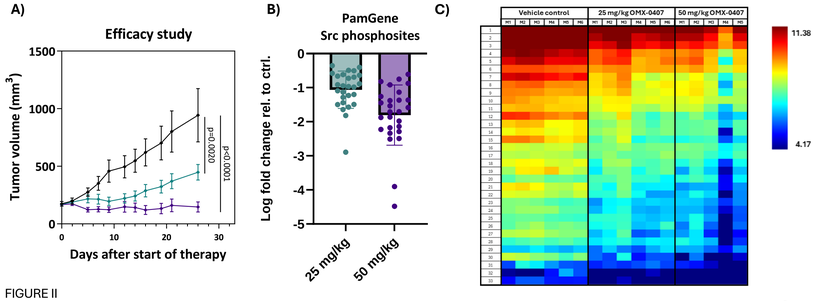


FIGURE II

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. Fresh frozen tumor fragments were lysed and analyzed by **B)** Simple Western for pSFK Y419. Fold change compared to vehicle control in tumor lysates; **C)** Clustering reveals phosphorylation patterns, with color intensity indicating the log fold change of all significant downregulated SFK-specific p-sites analyzed by PamGene kinase activity assay in tumor lysates of AS PDX study.

OMX-0407 Gene Signature Predicts Sensitivity in Sarcoma Subtypes

- A transcriptome-based signature predictive of OMX-0407 efficacy was applied to identify subsets of cancer indications with high potential for anti-tumor efficacy by OMX-0407.
- Beyond AS, multiple sarcoma subsets were predicted to be sensitive to OMX-0407.
- OMX-0407-sensitive indications consistently overlapped across cell line models (A), patient-derived xenografts (PDX) (B), and cancer patients (C).

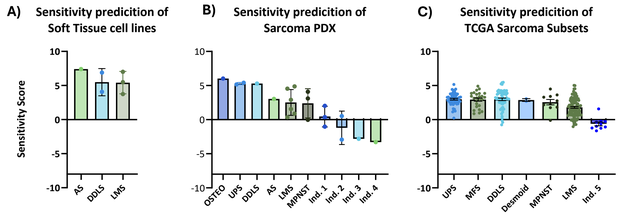


FIGURE III

Prediction of OMX-0407 sensitivity based on transcriptome signature **A)** in 6 STS cell lines **B)** of transcriptome data from 27 PDX models of 10 different STS sub indications and **C)** of transcriptome data from 265 human cancer patients TCGA database. Sensitivity score = log2(2*max inhibition[%])2 −log2(IC50abs)+2.5;sensitivity score < 0 = resistant to OMX-0407; sensitivity score > 0 = sensitive to OMX-0407

AS = Angiosarcoma, CCS = Clear cell sarcoma, DDLS = Dedifferentiated Liposarcoma, Ind. = Indication, LMS = Leiomyosarcoma, MPNST = Malignant Peripheral Nerve Sheath Tumor, MFS= Myxofibrosarcoma, Osteo= Osteosarcoma, UPS= Undifferentiated pleomorpic sarcoma

OMX-0407 Suppresses Growth of Soft Tissue Sarcoma Cell lines

- OMX-0407 induces dose-dependent inhibition of tumor cell growth, viability and significant G1-phase arrest in LMS cell lines.
- This is accompanied by the downregulation of SFK activity, associated with cancer cell proliferation and tumor cell cycle.

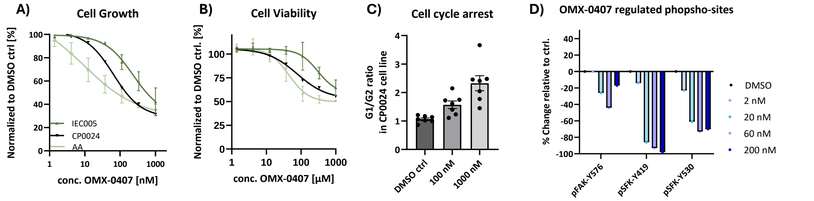


FIGURE IV

LMS cell lines were cultured and treated with the indicated doses of OMX-0407 or DMSO (vehicle control) for 48 hours. Cell confluence **(A)** was assessed via a live-cell imaging system (Incucyte®) using phase contrast and fluorescence emission. **B)** Cell viability was measured using the CellTiter-Glo® assay following the manufacturer's protocol. **C)** Cell cycle arrest was measured via PI staining analyzed with Flow cytometry, representative graph shown for CP0024 cell line. **D)** Cell lines were exposed to OMX-0407 for 4 hours, phospho-sites of indicated proteins were analyzed by Simple Western, representative semi quantitative analysis shown for CP0024 cell line.

OMX-0407 Suppressed Growth of RCC Cell Lines by Modulating Key Cell Cycle Pathways

- OMX-0407 induces dose-dependent inhibition of tumor cell growth and viability, accompanied by significant G1-phase arrest in renal cell carcinoma (RCC) cell lines.
- Tumor growth inhibition in RCC cell lines is associated with OMX-0407's efficacy in targeting SFK signaling pathways that regulate cell proliferation and the cell cycle.
- Gene Ontology (GO) pathway analysis confirms OMX-0407-dependent modulation of 257 pathways related to cell cycle regulation and cytoskeletal organization following 24 hours of treatment.

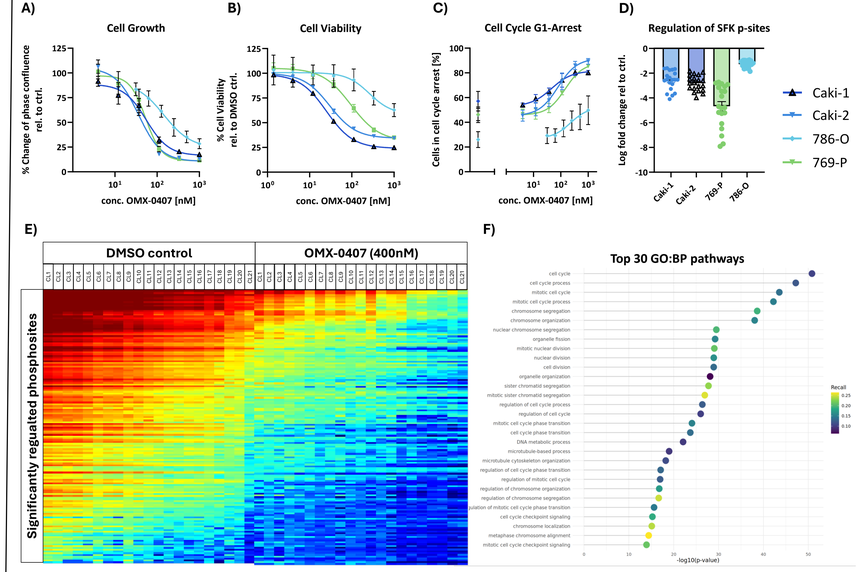


FIGURE V

Renal cell carcinoma (RCC) cell lines (Caki-1, Caki-2, 769-P, and 786-O) were *in vitro* treated with the indicated doses of OMX-0407 or DMSO (vehicle control) for 48 hours. Cell confluence **A)** and G1-arrest **C)** were assessed via flow cytometry after lentiviral transduction with fluorescence tags. **B)** Cell viability was measured using the CellTiter-Glo® assay following the manufacturer's protocol. **D)** Regulation of the top 20 Src-pathway-related phospho-sites in the indicated cell lines, analyzed by PamGene kinase activity assay. Data are shown at 20 nM OMX-0407 relative to control treatment. **E)** Clustering reveals phosphorylation patterns, with color intensity indicating the log fold change of all significant downregulated SFK-specific p-sites analyzed by PamGene kinase activity assay in 22 OMX-0407 treated RCC cell line lysates compared to untreated cells **F)** GO biological process (BP) terms which are significantly enriched among significant OMX-0407 regulated genes analyzed by RNAseq in sensitive RCC cell lines; Recall = Proportion of genes within a given pathway which are significantly modulated by OMX-0407.

Statistical analyses:

Unless otherwise indicated, data points show mean ±SEM. Significance was calculated using one-way ANOVA analysis including Tukey's multiple comparison analysis.