Development of a gene signature to predict the anti-tumor response of the salt-inducible kinase (SIK) inhibitor OMX-0407

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Introduction
SIK was identified by the iOUM genetic screening platform as a novel cell signaling modulator in cancer biology. SIKs are serine/threonine kinases belonging to the AMP-activated protein kinase family. OMX-0407, an orally available, spectrum-selective salt-inducible kinase (SIK) inhibitor, currently under evaluation in a clinical Phase I trial and was shown to inhibit tumor growth in a distinct panel of tumor models by decreasing downstream pro-survival signaling of SIK, enhancing caspase-mediated apoptosis and repolarizing the tumor microenvironment by decreasing regulatory T cell number. OMX-0407 demonstrated dose-dependent anti-tumor efficacy in murine and patient-derived xenograft (PDx) tumor models for several indications with high unmet medical need.

In a comprehensive anti-tumor viability screening, more than 200 human cancer cell lines of different indications were used to identify a selective activity profile of OMX-0407 in a subset of cancers. In-depth transcriptomic analyses were performed and used to identify and validate a predictive biomarker signature, that was successfully forecasting 83% of the selected cancer cell lines as responsive to OMX-0407 therapy. By using ex vivo and in vivo patient-derived tumor models, the response-prediction gene signature was further validated and is currently under optimization on heterogeneous tumor systems for its use in human samples. We could show a consistent overlap of OMX-0407 efficacy prediction in hundreds of cell lines of the Cancer Cell Line Encyclopedia (CCLE) database, human PDX models as well as human cancer patient data of The Cancer Genome Atlas (TCGA). Our computational model predicted a subset of indications with a high potential for anti-tumor efficacy of OMX-0407 and consequently potential clinical benefit. For OMX-0407-sensitive indications, monotherapy studies in different murine tumor models demonstrated strong in vivo anti-tumor efficacy of OMX-0407 with significantly prolonged overall survival and up to 90% tumor growth inhibition.

In summary, by screening sensitive and non-sensitive tumor cell lines and PDX models, we identified a response-prediction biomarker signature, which will contribute to the future development of OMX-0407 in specific indications and which will be assessed for its potential to select patients highly responsive to OMX-0407 therapy in clinical studies. The gene signature will be evaluated as part of the ongoing first-in-human study OMX-0407-101 (NCT055826600).

Results
Tumor cell viability screening showed distinct sensitivity profile upon OMX-0407 therapy
- Anti-tumor monotherapy efficacy screening of OMX-0407 on 225 human cancer cell lines identifies a sensitivity profile of individual cell lines towards OMX-0407.
- Sensitivity analysis of non-small cell carcinoma of the lung and renal cell carcinoma are emerging as major tumor indications responsive to OMX-0407.
- Predictive biomarkers could drive the selection of OMX-0407-sensitive patients.

Development of a transcriptome-based signature for sensitivity prediction towards OMX-0407 therapy
- OMX-0407 efficacy prediction, transcriptomic signature identified by using baseline RNA profiles of 184 human tumor cell lines.
- Machine learning-based random forest modeling revealed a subset of up- and downregulated genes, predictive for OMX-0407 sensitivity.
- Signature improvement by removal of stromal genes, filtering and prioritization of features adapted to human patient sample analysis.

Successful validation of OMX-0407 sensitivity prediction in tumor cell lines and PDX models
- Confirmation of cell line-based predictive signature in unknown cell lines with a prediction rate of 83% (24/29).
- Testing OMX-0407 sensitivity prediction hypothesis via ex vivo anti-tumor viability screening in 44 PDX models and in vivo OMX-0407 monotherapy studies in 28 PDX models compared to vehicle control.
- Ex vivo treated PDX models of RCC, mPNET and CRC indicating that, in vivo OMX-0407 sensitivity profile closely matched the in vitro sensitivity profile.

Consistent OMX-0407 sensitivity prediction using PDX models and human cancer patient data
- Consistent overlap of OMX-0407 sensitive-predicted indications between cell lines from CCLE (data not shown), PDX models as well as human cancer patient samples.
- Lung squamous non-small cell carcinoma and renal cell carcinoma show strong predicted OMX-0407 anti-tumor efficacy in PDX models as well as TCGA cancer patients.
- Predictions for cancer patients reveal a subset of indications with high potential for anti-tumor efficacy of OMX-0407.

Remarkable anti-tumor efficacy of OMX-0407 in syngeneic tumor models of different indications
- OMX-0407 demonstrates strong anti-tumor efficacy in syngeneic tumor models of indication 4; CRC, uPELC and RCC.
- OMX-0407 significantly promotes tumor growth inhibition in CRC in combination with the anti-angiogenic therapy Axitinib targeting vascular endothelial growth factor receptor 2 (VEGFR2).

Conclusion
- OMX-0407, a potent spectrum-selective salt-inducible kinase (SIK) inhibitor demonstrates outstanding anti-tumor activity in vitro as well as ex vivo in a subset of cancer cell lines and patient-derived xenograft fragments, representing different indications.
- OMX-0407 shows remarkable efficacy in monotherapy as well as in combination with VEGFR2 inhibition in tumor models of indications previously identified as highly sensitive towards OMX-0407.
- Using machine learning methods, the selective activity profile of OMX-0407 on individual cancer cell lines was used to identify and validate a predictive transcriptome-based biomarker signature.
- The predictive biomarker signature has been successfully validated in cell lines with a prediction rate of 83% and is currently being further validated in a variety of ex vivo and in vivo PDX models.
- The predictive gene signature will be evaluated in the ongoing first-in-human study OMX-0407-101 (NCT055826600), which was initiated in March 2023.