Background Recently, the iOTarg genetic screening platform identified SIK3 as a novel cell signaling modulator in cancer biology. SIKs are serine/threonine kinases belonging to the AMP-activated protein kinase family. OMX-0407, a single-digit nanomolar inhibitor is 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 SIK3, enhancing caspase-mediated apoptosis and repolarizing the tumor microenvironment by decreasing regulatory T cells. 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.

Methods 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 optimized and validated on heterogenous tumor systems for its use in human patient samples.

Results 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 (TGCA). Our computational model predicted a subset of indications with a high potential for anti-tumor efficacy of OMX-0407 and therefore projected clinical benefit.

For OMX-0407-sensitive indications, monotherapy studies in human PDX models and different murine tumor models with low anti-PD-1 therapy responsiveness, demonstrated dose-dependent in vivo anti-tumor efficacy of OMX-0407 with significantly prolonged overall survival and up to 90% tumor growth inhibition.

Conclusions 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 (NCT05826600).

Trial Registration NCT05826600

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