KO-947, a Potent and Selective ERK Inhibitor with Slow Dissociation Kinetics

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Abstract

The RAS/RAF/MEK pathway is activated in more than 30% of human cancers, including cancers arising from mutations in KRAS, NRAS, and BRAF. Although inhibitors of both BRAF and MEK have been approved for treatment of melanoma, acquired resistance to these inhibitors has been documented both in preclinical and clinical samples due to reactivation of ERK1/2 kinases. Here we describe the characterization of KO-947, a potent and selective inhibitor of ERK1/2 kinases, in biochemical, cellular and in vivo activity assays.

KO-947 is a low nanomolar inhibitor of ERK1/2 with limited off-target activity across a broad range of protein kinases as measured by biochemical activity assays, competition binding assays, and a probe-based competition binding assay in cell lysates. KO-947 potently inhibits ERK signaling pathways and proliferation of tumor cells exhibiting dysregulation of MAPK pathway signaling, including mutations in BRAF, NRAS, or KRAS. KO-947 also inhibits MAPK signaling and cell proliferation in clinically relevant models that are resistant to BRAF and MEK inhibitors. Results from screening a large panel of PDX models demonstrate that KO-947 induces tumor regressions in BRAF or NRAS mutated tumor models as well as in tumor models lacking BRAF/NRAS mutations but with other dysregulation of the MAPK pathway. KO-947 is differentiated from other published ERK inhibitors by an extended residence time and high plasma in cell engagement that translate into prolonged path way inhibition in vitro and in vivo. Drug properties of KO-947 enable the achievement of optimal antitumor activity with intermittent dosing, which may provide an opportunity to maximize the therapeutic window with feasible administration routes and schedules. These results demonstrate the potential clinical utility of KO-947 in MAPK pathway dysregulated tumors.

KO-947 is a potent and selective ERK1/2 inhibitor

KO-947 maintains activity in models resistant to BRAF and MEK inhibitors

KO-947 displays a long lasting effect after washout and has a slow off rate

KO-947 induces regressions in BRAF and KRAS mutant tumor models

KO-947 induces prolonged suppression of ERK signaling in vivo

KO-947 demonstrates robust activity with intermittent dosing schedules

Rationale

Aberrant signaling caused by mutations or dysregulation of the MAPK pathway is associated with numerous tumor types. Inhibitors of Raf and MEK have validated the MAPK pathway as a therapeutic target for cancer. Acquired resistance to Raf and MEK inhibitors has been documented due to reactivation of ERK1/2 kinases.

KO-947 is a potent and selective inhibitor of ERK1/2 kinases with extended residence time.

KO-947 induces tumor regression and is well tolerated in BRAF and KRAS mutant xenograft mouse models.

KO-947 is active in a subset of KRAS- or BRAF-mutant colon, lung and pancreatic PDX models.

KO-947 displays comparable anti-tumor activity with daily dosing and intermittent dosing in various xenograft mouse models.

KO-947 demonstrates potential clinical utility of KO-947 in the treatment of tumors with MAPK pathway dysregulation.

Conclusions

KO-947 is a highly potent and selective ERK inhibitor.

KO-947 demonstrates consistent and compelling activity against MAPK pathway dysregulated tumors in vivo, with tumor regressions demonstrated at tolerable doses.

KO-947 demonstrates prolonged pathway modulation enabling a flexible administration and supports flexible administration schedules up to once weekly dosing.

Pharmaceutical properties support IV formulation.

These results demonstrate the potential clinical utility of KO-947 in the treatment of tumors with MAPK pathway dysregulation.

Acknowledgements: We thank Shanghai Lantis Biotechnological Company, LTD (Shanghai, China) for their support on synthesis of ERK inhibitors.

Pharmacodynamic Modulation After a Single Oral Dose

KO-947 is a potent and selective inhibitor of ERK1/2 kinases that is able to block phosphorylation of ERK efficiently.