KO-947, a potent ERK inhibitor with robust preclinical single agent activity in MAPK pathway dysregulated tumors


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Abstract summary

KO-947 is a potent and selective ERK1/2 inhibitor with robust preclinical activity in MAPK pathway dysregulated tumors. KO-947 is a 10nM inhibitor of ERK with at least 50-fold selectivity against a panel of 450 kinases that blocks ERK signaling and proliferation of tumor cells exhibiting dysregulation of MAPK pathway signaling at low nanomolar concentrations. KO-947 is differentiated from other published ERK inhibitors by an extended residence time that translates into prolonged pathway inhibition. The drug profoundly suppresses ERK signaling for up to six days after a single dose and induces regressions in Ras- and Raf-mutant melanoma, NSCLC and pancreatic cancer models on administration schedules ranging from daily to weekly. PKD screening confirms and extends these findings to include Ras and BRAF-mutant colorectal, gastric and cervical carcinoma models, and robust activity is also seen on a weekly schedule in squamous cell carcinoma models lacking BRAF/RAS mutations. The favorable ADMET 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 flexible administration modes and schedules. These results demonstrate the potential clinical utility of KO-947 in MAPK pathway dysregulated tumors.

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 displays robust activity with intermittent dosing schedules

KO-947 is highly active in PDX models of esophageal squamous cell carcinoma

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

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

KO-947 induces prolonged suppression of ERK signaling in vivo

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

Conclusions

KO-947 is a highly potent and selective ERK inhibitor

KO-947 displays consistent and compelling antitumor activity in both adenocarcinomas with activating mutations in the MAPK pathway and in squamous cell carcinomas that are wild type for BRAF and RAS, with robust tumor regressions demonstrated at tolerable doses.

The wide effective dosing interval and pharmaceutical properties of KO-947 support IV formulation for clinical use.

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

KO-947 is shortly to enter Phase I clinical testing.