

SUPPLEMENTARY FIGURE LEGENDS

Supplementary Figure S1: Individual and mean (SD) SAR245408 pharmacokinetic

parameters. (A) C_{\max} and AUC_{0-24} on C1D21 and C1D28 for 400mg and 600mg cohorts, combined 21/7 and CDD schedules. (B) Cl/F on C1D21 and C1D28 for 30–400mg cohorts combined vs 600mg cohorts, combined both 21/7 and CDD schedules.

Supplementary Figure S2: Effect of SAR245408 on plasma fasting insulin and glucose.

(A) Plasma fasting insulin on Days 1, 8 and 21 in patients administered SAR245408. A minor effect on fasting plasma insulin was observed 2 h after dosing on Day 8 (compared with Day 1) and was significantly elevated over pre-dose at 4 h on all 3 days (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ compared with pre-dose by Student's *t*-test). (B, C) Plasma fasting insulin and glucose on Days 1, 8 and 21 in patients administered SAR245408 at 400, 600 and 900mg/day. Insulin level (milliunit per liter, mU/l) and glucose level (mg/dl) are shown for individual patients (3 per cohort, except 6 for 600mg).

Supplementary Figure S3: Inhibition of MEK-ERK pathway signaling in tumor biopsies.

(A) Immunofluorescence staining of baseline and post-dose samples for pMEK in tumor biopsies collected from 3 patients treated with SAR245408 600mg, 21/7 cohort (Merkel cell carcinoma [48% reduction], leiomyosarcoma [59% reduction] and a tongue SCC [53% reduction]). (B) Effects on ERK pathway signaling as assessed by pERK^{T202/Y204} and total ERK immunofluorescence in a tongue SCC patient administered 600mg in the CDD cohort. No *PIK3CA*, *PTEN* or *KRAS* mutations were detected in the Merkel cell carcinoma or the leiomyosarcoma. The tongue SCC sample exhibited a *PIK3CA* E545K mutation, with no detectable *PTEN* and *KRAS* mutations.