Supplementary Figure and Table Legends

Supplementary Figure 1: Mean (±SE) SAR245409 plasma concentration–time profiles on days 1 and 27 of cycle 1.
N = number of patients on day 1 for each group. Error bars represent the standard error of the mean. Lower limit of quantification = 1 ng/mL.
bid, twice daily; qd, once daily

Supplementary Figure 2: Effects of SAR245409 on plasma fasting insulin and fasting glucose

A) Plasma fasting insulin on days 1, 8 and 27/28 in patients administered SAR245409. * P<0.05, ** P<0.01, *** P<0.0001 vs pre-dose by Student's t-test.

B) Comparison of individual patient glucose level (mg/dL) on days 1, 8 and 27/28 in patients administered SAR245409 by dose cohort.

   bid, twice daily; qd, once daily.

Supplementary Figure 3: Reduction in extracellular signal-regulated kinase (ERK) pathway signaling by SAR245409 in paired tumor biopsies
Effects on A) ERK pathway signaling (pERK and total ERK) and B) mitogen-activated protein kinase kinase (MEK) in paired tumor biopsies from two patients with breast ductal carcinoma administered SAR245409 at the daily MTD of 90 mg, assessed by immunofluorescence staining. Representative fields were captured at 400x magnification to document staining in panel A of $pERK^{T202/Y204}$ (green) and total ERK (red) and in panel B for $pMEK^{S217/S221}$ (red) and 4',6-diamidino-2-phenylindole [DAPI] (blue). Significant impact on $pERK^{T202/Y204}$ (61–62% reduction) was observed in both patient samples. Likewise, $pMEK^{S217/S221}$ was reduced by 52–62%.

Supplementary Figure 4: Effect of SAR245409 on skin lesions of a ductal breast carcinoma patient

Photographs of mastectomy region in a patient with AKT1-mutant ductal breast carcinoma showing improvement in skin lesions following initiation of SAR245409.
C, cycle; D, day.

Supplementary Table 1: Adverse events that occurred in ≥10% of patients

Reported event terms were coded using MedDRA dictionary version 15.0. AEs defined according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

AE, adverse event; bid, twice daily; qd, once daily.

Supplementary Table 2: Grade 3/4 adverse events that occurred in ≥2% of patients

Reported event terms were coded using MedDRA dictionary version 15.0. At each level of summarization, a patient was counted once for the most severe event if the patient reported one or more events. AEs defined according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.
AE, adverse event; bid, twice daily; qd, once daily.

Supplementary Table 3: Reduction in phosphoinositide 3-kinase and mammalian target of rapamycin complex 1 (mTORC1)/mTORC2 pathway signaling in paired tumor biopsies

Change relative to baseline at cycle 1, day 27/28, either pre-dose or 2–6 hours post-dose of pAKT, p4EBP1, pERK, pMEK, Ki67 (proliferation) and TUNEL (apoptosis) in tumor biopsies for 12 patients receiving twice-daily and once-daily MTD of SAR245409. All modulation shown is significant, except when indicated as non-significant (ns) as assessed using criteria detailed in Supplemental Methods. Minimum mutational analysis included exon sequencing of *PIK3CA, PTEN*, *KRAS2* and *BRAF* genes, except for the basal cell carcinoma patient, where *KRAS2* was not analyzed, and for the colorectal mucinous tumor (90 mg qd) patient and the chondrosarcoma (90 mg qd) patient, where *PTEN* was not sequenced. Impact on additional markers was evaluated for the patient with chondrosarcoma (60 mg bid): post-dose decreases of 52% and 84% for $pPRAS40^{T246}$ and $pS6^{S240/244}$ were observed, respectively.

[a] All changes captured in this column are mutations, except for *HER2* amp (amplification) and PTEN-def (PTEN-deficiency as assessed by immunohistochemistry).

amp, amplification; bid, twice daily; C, cycle; D, day; def, deficient; 4EBP1, eIF4E-binding protein-1; ERK, extracellular-signal-regulated kinase; HER2, human epidermal growth factor receptor 2; MEK, mitogen-activated protein kinase kinase; mut, mutation; NT, not tested; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog; qd, once daily.