Supplementary Table 3. Reduction in phosphatidylinositol-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.

			Decrease, % relative to baseline							
Disease	**Dose, mg**	**Sampling day**	**pAKT (T308)**	**pAKT (S473)**	**p4EBP1 (T70)**	**pERK (T202/Y204)**	**pMEK (S217/221)**	**Ki67**	**TUNEL, fold increase**	**Tumor mutation detected[a]**
Breast carcinoma	**50 bid**	**C1D27**	71	67	80	80	NT	32	1.9	*HER2* amp
Mucinous breast cancer	**50 bid**	**C1D27**	76	76	70	74	NT	44	1.8	none
Leiomyosarcoma	**50 bid**	**C1D27**	74	70	66	69	NT	26	2.1	none
Basal cell carcinoma	**50 bid**	**C1D27**	45	45	56	42	45	48	1.4	*TP53* mut
Colon adenocarcinoma	**50 bid**	**C1D27**	57	47	62	53	NT	27	1.4	none
Rectal adenocarcinoma	**50 bid**	**C1D27**	61	68	65	62	NT	43	1.3	*TP53* mut
Chondrosarcoma	**60 bid**	**C1D28**	83	94	89	NT	NT	53	1.4	NT

Ductal breast carcinoma 1	**90 qd**	**C1D27**	64	53	55	61	52	68	1.4	*AKT1* mut, *TP53* mut
Ductal breast carcinoma 2	**90 qd**	**C1D27**	60	53	61	62	62	21	1.4	none
Ductal breast carcinoma 3	**90 qd**	**C1D27**	56	50	66	66	NT	20	1.9	*PIK3CA* mut, *HER2* amp, PTEN-def
Colorectal mucinous tumor	**90 qd**	**C1D27**	-17	-27	-35	-25	NT	-12, ns	5.7	*BRAF* mut, PTEN-def
Chondrosarcoma	**90 qd**	**C1D27**	88	75	85	88	NT	96	2.0	PTEN-def

[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.