Supplementary Table S3: Reduction in PI3K pathway signaling in serial tumor biopsies and effects on PI3K pathway signaling in skin collected from the same biopsy as tumor

Tumor Biopsies			Decrease Relative to Baseline (%)								TUNEL fold-increase	PIK3CA, PTEN, KRAS gene alterations	SAR245408 conc at 4 h post, ng/ml (AUC_{last}, hr*ng/ml)
Tumor histology	**Dose, mg**	**On-study sampling day**	**pAKT (T308)**	**pAKT (S473)**	**pRAS40 (T246)**	**p4EBP1 (T70)**	**pS6 (S240/S244)**	**pMEK (S217/S221)**	**pERK (T202/Y20)**	**Ki67**			
Leiomyosarcoma*	600, 21/7	C1D21 post	82	61	68	68	68	59	60	15	0.1 (ns)	None detected	59500 (8400000)
Ovarian leiomyosarcoma	600, 21/7	C1D28 post	53	NA	NA	53	NA	55	58	49	2.2	None detected	58600 (NA)
Merkel cell carcinoma*	600, 21/7	C1D21 post	77	55	50	48	70	48	59	22	1.5	None detected	20400/(NA)
Hamartoma (Cowden)*	600, 21/7	C1D21 post	76	NA	NA	62	NA	NA	NA	12 (ns)	1.2 (ns)	*PTEN R233X*	16100/356000
NSCLC	600, 21/7	C1D21 pre	79	NA	NA	73	NA	NA	70	29	1.6	*PIK3CA* ampl (~2 fold)	101000/(NA)
NSCLC (SCC)	600, 21/7	C2D21 pre	42	NA	NA	48	NA	NA	NA	37 (ns)	1.6 (ns)	None detected	114000/(NA)
Tongue (SCC)	600, CD	C1D28 post	59	NA	NA	56	NA	53	50	31	2.6	*PIK3CA E545K*	85800/(NA)
Phyllodes breast	600, CD	C1D28 post	41	NA	NA	54	NA	46	56	19	1.1 (ns)	None detected	27300/6442000
Parotid carcinoma*	900 (dose halted and reduced), 21/7	C2D21 pre	44	NA	NA	39	NA	NA	42	14 (ns)	1.4 (ns)	*PTEN C250X* mut, HER2 amplified	199000/(NA)

*Patients for whom normal skin biopsies were also available. NA = not available; ns = not significant.

Pharmacodynamic impact of SAR245408 on PI3K pathway signaling was assessed in paired tumor biopsies collected from patients administered 600mg on the 21/7 or CDD schedules. Immunofluorescence quantification of the impact on phosphomarkers at baseline (D1 pre-dose) and on D21/28 pre- or 4h post-dosing was performed. The parotid carcinoma patient was initially administered 900mg on the 21/7 schedule with subsequent dose reduction to 600mg. Total MEK and ERK were assessed in tumor biopsy samples from the tongue SCC and phyllodes breast cancer patients, with no significant changes observed. A germline *PTEN R233X* mutation was detected in the archival tissue of the phyllodes breast cancer patient based on analysis performed by the site. The hamartoma tissue was collected via skin biopsy. Modulations shown are significant, except where indicated as non-significant. Statistical analysis employed two-tailed student's *t* tests with $p<0.05$ considered as statistically significant.

Supplementary Table S3 (con't): Reduction in PI3K pathway signaling in serial tumor biopsies and effects on PI3K pathway signaling in skin collected from the same biopsy as tumor

Tumor vs. Skin		**Decrease, Relative to Baseline, %**						**TUNEL, fold-increase**	**SAR245408 conc at 4 h post, ng/ml (AUC_{last}, hr*ng/ml)**
Tumor	**Tissue**	**pAKT (T308)**	**pAKT (S473)**	**pRAS40 (T246)**	**p4EBP1 (T70)**	**pS6 (S240/S244)**	**Ki67**		
Merkel cell carcinoma	Tumor	77	55	50	48	70	22	1.5	20400 (NA)
	Skin above tumor	26	22	37	39	35	10	1.1 (ns)	
Hamartoma (Cowden)	Tumor	76	NA	NA	62	NA	12 (ns)	1.2 (ns)	16100 (356000)
	Skin above tumor	42	NA	NA	44	NA	20 (ns)	1.2 (ns)	

NA = not available; ns = not significant.

Pharmacodynamic impact of SAR245408 on PI3K pathway signaling was assessed in paired tumor and associated skin biopsies. Immunofluorescence quantification of the impact on phosphomarkers on D1 pre-dose and on D21 post-dose was performed. Modulations shown are significant, except where indicated as non-significant. Statistical analysis employed two-tailed student's *t* tests with $p<0.05$ considered as statistically significant.