Supplementary Table 1: Types of *PIK3CA* mutations in tumor types with more than 5% prevalence of *PIK3CA* mutations

Tumor type (number of patients with *PIK3CA* mutations)	**Type of *PIK3CA* mutation**	**Number (%)**
Colorectal cancer (46)	E545K	13 (28)
	E542K	16 (35)
	H1047R	3 (6.5)
	H1047L	3 (6.5)
	Other	11 (24)
Ovarian cancer (16)	E542K	5 (31)
	E545K	2 (12.5)
	H1047R	6 (37.5)
	Other	3 (19)
Head and neck squamous cancer (13)	E542K	2 (15)
	E545K	7 (54)
	H1047R	2 (15)
	Other	2 (15)
Breast cancer (21)	E542K	4 (19)
	E545K	5 (24)
	H1047R	8 (38)
	Other	4 (19)
Uterine cancer (16)	T1025A	2 (12.5)
	H1047R	4 (25)
	Other	10 (62.5)
Cervical squamous cancer (10)	E545K	6 (60)
	E542K	2 (20)
	Other	2 (20)

Supplementary Table 2: Therapies targeting PI3K/AKT/mTOR pathway

Treatment	Number of patients (%)	PR (%)	SD≥6 months/PR (%)
All	136 (100)	25 (100)	9 (100)
Single agent mTORC1 inhibitors (sirolimus, nab-sirolimus, temsirolimus)	24 (18)	1 (4)	1 (11)
mTORC1 inhibitors (sirolimus, everolimus, temsirolimus, ridaforilimus) combined with other targeted therapy	40 (29)	10 (40)	4 (44.5)
mTORC1 inhibitors (sirolimus, temsirolimus) combined with chemotherapy +/- other targeted therapy	40 (29)	11 (44)	2 (22)
Single agent PI3K inhibitors	9 (7)	1 (4)	1 (11)
Single agent dual PI3K and mTOR kinase inhibitors	6 (4)	0 (0)	0 (0)
PI3K inhibitors combined with MEK inhibitors	4 (3)	0 (0)	1 (11)
PI3K inhibitors combined with chemotherapy	7 (5)	1 (4)	0 (0)
Single agent AKT inhibitors	2 (1.5)	0 (0)	0 (0)
AKT inhibitors combined with MEK inhibitors	2 (1.5)	1 (4)	0 (0)
AKT inhibitors combined with chemotherapy	2 (1.5)	0 (0)	0 (0)

Supplementary Table 3: Characteristics of 25 patients with a PR

Tumor type	*PIK3CA* mutation	PTEN aberration	Treatment class	Drugs in combination	RECIST response (%)	PFS in months
Squamous cell cervical carcinoma	E545K, D549H	Not done	mTORC1	TT and CT	-100[1]	2.0[2] (died)
Squamous cell head and neck carcinoma	0	Loss on IHC	PI3K	CT	-70	18.4
Endometrial carcinoma	0	Loss on IHC	AKT	TT	-68	9.4
Endometrial carcinoma	H1047R	0	mTORC1	TT and CT	-65	21.6
Metaplastic breast carcinoma	H1047R	0	mTORC1	TT and CT	-64	11.8[3]
Breast carcinoma	0	Loss on IHC	mTORC1	TT	-52	12.7
Endocervical adenocarcinoma	E545K	Loss on IHC	mTORC1	TT	-52	11.0
Ovarian carcinoma	H1047R	0	PI3K	none	-50	4.6
Ovarian carcinoma	Q546K	Not done	mTORC1	TT and CT	-49	10.3
Squamous cell cervical carcinoma	E542K	Not done	mTORC1	TT and CT	-41	8.4
Squamous cell head and neck carcinoma	H1047R	Not done	mTORC1	TT	-38	2.1[3]
Squamous cell cervical carcinoma	0	Loss on IHC	mTORC1	TT and CT	-38	5.7
Endometrial carcinoma	H1047R	Not done	mTORC1	TT	-37	8.2
Breast carcinoma	H1047R	Not done	mTORC1	TT and CT	-37	8.5
Renal cell carcinoma	0	Loss on IHC	mTORC1	none	-37	6.1
Endometrial carcinoma	E545K	0	mTORC1	TT and CT	-35	2.6[3]
Lung adenocarcinoma	E542K	Not done	mTORC1	TT	-34	11.2
Ovarian carcinoma	H1047R	Not done	mTORC1	TT and CT	-34	4.6[3]
Breast carcinoma	E545K	0	mTORC1	TT	-34	5.8
Parotid gland carcinoma	0	Loss on IHC	mTORC1	TT	-33	4.3
Squamous cell head and neck carcinoma	0	Loss on IHC	mTORC1	TT	-32	11.4
Metaplastic breast carcinoma	0	Loss on IHC	mTORC1	TT and CT	-32	9.9+
Renal cell carcinoma	E545K	0	mTORC1	TT	-31	11.0+
Melanoma	0	Loss on IHC	mTORC1	TT	-30	9.5[3]
Endometrial carcinoma	0	Loss on IHC	mTORC1	TT and CT	-30	4.3

PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; PFS, progression-free survival; TT, targeted therapy; CT, chemotherapy; IHC, immunohistochemistry; + indicates ongoing treatment at the time of analysis.

[1]Not classified as a complete response due to persistence of residual ascites.

[2] Patient died without evidence of disease progression due to bowel perforation.

[3] Patient withdrew consent or lost follow-up without evidence of disease progression.

Supplementary Table 4: Therapies targeting PI3K/AKT/mTOR pathway

Treatment	Number of patients	PR (%)	P-value[1]
Patients with *PIK3CA* mutations or PTEN aberrations treated with PI3K/AKT/mTOR inhibitors	136	25 (18)	
Patients without *PIK3CA* mutations or PTEN aberrations treated with PI3K/AKT/mTOR inhibitors	458	26 (6)	<0.001
Patients with *PIK3CA* mutations or PTEN aberrations treated with other protocols than PI3K/AKT/mTOR inhibitors	67	3 (4)	0.008

[1]P-value reflects comparisons to patients with PIK3CA mutations or PTEN aberrations treated with PI3K/AKT/mTOR inhibitors