Supplemental Table 1: Class I PI3K isoform alterations in cancer.

Alteration Type	Cancer Type	Frequency of Alteration	Sample Size Range	References
Class IA				
***PIK3CA* (p110α)**				
Mutation	Endometrial	10.3-53.0%	29-232	1, 2
	Breast	7.1-35.5%	65-507	3-9
	Ovarian (CC)	33.0%	97	10
	Colorectal	16.9[†]-30.6%	72-195	11, 12
	Bladder	5.0-20.0%	20-130	13-16
	Lung (SCC)	20.0%	5	17
	Lung (SQCC)	2.9-16.8%	35-178	17, 18
	Lung (LCC)	11.9%	9	17
	Lung (ADC)	0.6-4.3%	57-183	3, 17, 19, 20
	Cervical	13.6%	22	2
	Glioblastoma	4.3-11.0%	91-291	21-24
	Head and neck	8.1-9.4%	32-74	25, 26
	Esophageal	5.5%	145	27
	Melanoma	5.0%	121	28
	Prostate	1.3-3.6%	55-156	3, 29-31
	Sarcoma	2.9%	207	32
	Renal (CC)	1.0-2.9%	98-417	33, 34
	Liver (HCC)	1.6%	125	35
	Megalencephaly[‡]	48.0%	50	36
Copy number gain/amplification	Head and neck	9.1-100%	11-117	37-39
	Cervical	9.1-76.4%	22-55	2, 40
	Lung (SQCC)	42.9-69.6%	28-52	17, 41, 42
	Lung (SCC)	33.3-66.7%	3-12	17, 41
	Lung (LCC)	16.7-37.5%	6-16	17, 41
	Lung (ADC)	9.5-19.1%	47-74	17, 41
	Lung (NSCLC)	12.0%	92	43
	Lymphoma (MCL)	68.2%	22	44
	Lymphoma (DLBCL)	16.7%	60	45
	Ovarian	39.8%	93	46
	Ovarian (Serous)	13.3-24.3%	60-74	47, 48
	Gastric	36.4%	55	49
	Thyroid	30.0%	110	50
	Prostate	28.1%	32	16
	Breast	8.7-13.4%	92-209	8, 9
	Glioblastoma	1.9-12.2%	139-206	21, 22
	Endometrial	10.3%	29	2
	Thyroid	9.4%	128	51
	Esophageal	5.7%	87	52
	Leukemia (CLL)	5.6%	161	53
Increased expression	Prostate	40.0%	25	16
***PIK3CB* (p110β)**				
Mutation	Breast	0.5%	183	3, 54
Copy number gain/amplification	Lung (SQCC)	56.5%	46	42
	Thyroid	42.3%	97	50
	Ovarian	5-26.9%	NA-93	46, 55
	Lymphoma (DLBCL)	20.0%	60	45
	Glioblastoma	5.8%	103	56
	Breast	4.9-5%	NA-81	55, 57

Increased expression	Prostate	46.7%	30	[58]
	Glioblastoma	3.9%	103	[56]
***PIK3CD* (p110δ)**				
Copy number gain	Glioblastoma	40.0%	10	[59]
Increased expression	Neuroblastoma	52.6%	19	[60]
	Glioblastoma	5.8%	103	[56]
***PIK3R1* (p85α, p55α, p50α)**				
Mutation	Endometrial	19.8-32.8%	108-243	[1, 61, 62]
	Pancreatic	16.7%	6	[63]
	Glioblastoma	7.6-11.3%	91-291	[22-24]
	Colorectal	4.6[†]-8.3%	108-195	[11, 63]
	Melanoma	4.4%	68	[64]
	Ovarian	3.8%	80	[65]
	Esophageal	3.4%	145	[27]
	Breast	1.1-2.8%	62-507	[3, 4, 63, 66]
	Colon	1.7%	60	[65]
Decreased expression	Breast	61.8%	458	[66]
	Prostate	17-75%*	NA	[67]
	Lung	19-46%*	NA	[67]
	Ovarian	22%*	NA	[67]
	Breast	18%*	NA	[67]
	Bladder	18%*	NA	[67]
Copy number loss	Ovarian	21.5%	93	[46]
***PIK3R2* (p85β)**				
Mutation	Endometrial	4.9%	243	[61]
	Colorectal	0.9%	108	[63]
	Megalencephaly[‡]	22.0%	50	[36]
Amplification	Lymphoma (DLBCL)	23.3%	60	[45]
Increased expression	Colon	55.0%	20	[68]
	Breast	45.7%	35	[68]
***PIK3R3* (p55γ)**				
Copy number gain	Ovarian	15.0%	93	[46]
Class IB				
***PIK3CG* (p110γ)**				
Copy number gain	Ovarian	19.3%	93	[46]
Increased expression	Breast	77.5%	40	[69]
	Prostate	72.4%	29	[70]
	Medulloblastoma	52.9%	17	[71]
***PIK3R5* (p101)**				
Mutation	Melanoma	38.2%	68	[64]
	Gastric	2.7%	37	[63]

CC, clear cell; SCC, small cell carcinoma; SQCC, squamous cell carcinoma; ADC, adenocarcinoma; LCC, large cell carcinoma; NSCLC, non-small cell lung carcinoma; MCL, mantle cell lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B cell lymphoma; HCC, hepatocellular carcinoma

[‡] Megalencephaly syndromes are a collection of sporadic overgrowth disorders characterized by enlarged brain size and other distinct features.

[†] Combined number of hypermutated and non-hypermutated colon and colorectal patient samples with mutations in the indicated gene.

* Represents the percent reduction in gene expression.

NA Sample size not available for this study.

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Supplemental Table 2: Genetically engineered mouse models of PI3K isoforms in cancer.

Genotype	Phenotype	Ref
***PIK3CA* (p110α)**		
KRas^{LA2}; ***Pik3ca$^{RBD/RBD}$***	Protected from KRas-induced lung tumors	1
Rosa26-Cre; KRas^{LA2}; ***Pik3ca$^{RBD/flox}$***	Partial regression of KRas-induced lung tumors	2
MMTV-Neu-IRES-Cre; ***Pik3ca$^{flox/flox}$***	Protected from Her2/neu-driven mammary tumors	3
Pb-Cre; Pten$^{flox/flox}$; ***Pik3ca$^{flox/flox}$***	No effect on high-grade PIN driven by *Pten* loss	4
Mx1-Cre; KRas^{G12D}; ***Pik3ca$^{flox/flox}$***	Protection from MPN induced by oncogenic KRas	5
Mx1-Cre, LSL-Shp2$^{GOF/+}$; ***Pik3ca$^{flox/flox}$***	No effect on MPN induced by Shp2 GOF	6
Pten$^{-/+}$; ***Pik3ca$^{KD/+}$***	Increased endometrial hyperplasia; reduced pheochromocytoma and thyroid tumors	7
CCSP-rtTA; ***Tet-op-PIK3CA^{H1047R}***	Develop lung tumors within 3 months	8
MMTV-rtTA; ***tetO-PIK3CA^{H1047R}***	Develop mammary tumors within 7 months	9
MMTV-Cre; ***LSL-PIK3CA^{H1047R}***	Surviving mice develop mammary tumors within 7 months	10
MMTV-Cre; ***Pik3ca$^{e20H1047R/+}$***	Develop mammary tumors within 16 months	11
WAP-Cre; ***LSL-PIK3CA^{H1047R}***	Develop mammary tumors within 36 days post-partum	10
WAP-Cre; ***LSL-PIK3CA^{E545K}***	Develop mammary tumors within 80 days post-partum	12
MMTV-Cre; p53$^{flox/+}$; ***Rosa26-Pik3ca^{H1047R}***	Develop mammary tumors within 5 months	13
MMTV-rtTA; tetO-Cre; ErbB3$^{flox/flox}$; ***tetO-PIK3CA^{H1047R}***	Delayed mammary hyperplasia but no effect on mammary tumor formation driven by PIK3CA^{H1047R}	14
MMTV-rtTA; MMTV-Her2; ***tetO-PIK3CA^{H1047R}***	Accelerated mammary tumor formation and increased lung metastasis compared to *Her2* or *PIK3CA^{H1047R}* alone	15
Pten$^{flox/flox}$; ***Pik3ca$^{Lat-H1047R/+}$***	Develop ovarian tumors within 16 weeks	16
Gpa33-CrePR2; *APC$^{LOF/LOF}$*; ***Pik3ca$^{Lat-H1047R/+}$***	Accelerated development of intestinal tumors compared to *Pik3ca^{H1047R}* or *APC^{LOF}* alone	17
Fabp1-Cre; Apc$^{Min/+}$; ***Rosa26-Pik3ca****	Increased number and size of intestinal tumors compared to *Pik3ca* or Apc$^{Min/+}$* alone	18
Fabp1-Cre; Apc$^{flox/+}$; ***Rosa26-Pik3ca****	Increased number and size of intestinal tumors compared to *Pik3ca* or Apc$^{flox/+}$* alone	18
***PIK3CB* (p110β)**		
MMTV-Her2/neuT; ***Pik3cb$^{KD/KD}$***	Reduced number of mammary tumors driven by Her2/neuT	19
Pb-Cre; Pten$^{flox/flox}$; ***Pik3cb$^{flox/flox}$***	Protection from high-grade PIN driven by *Pten* loss	4
Pten$^{-/+}$; ***Pik3cb$^{KD/+}$***	Reduced PIN and prostate cancer driven by *Pten* loss	7
(ARR)2PB-Pik3cb^{CA}	Develop VP PIN by 10 weeks and DLP PIN by 60 weeks	20
MMTV-Neu-IRES-Cre; ***Pik3cb$^{flox/flox}$***	Accelerated mammary tumor formation and increased tumor burden driven by Her2/neu	3
***PIK3CA* (p110α) and *PIK3CB* (p110β)**		
K14-Cre; Pten$^{flox/flox}$; ***Pik3ca$^{flox/flox}$***; ***Pik3cb$^{flox/flox}$***	Loss of ¾ alleles of *Pik3ca* and *Pik3cb* blocks skin lesions and mammary hyperplasia driven by *Pten* loss	21, 22
***PIK3CD* (p110δ)**		

***Pik3cd*^{KD}**	Reduced trafficking of NK cells; reduced NK cell extravasation to tumor cells	23
Mx1-Cre, LSL-Shp2$^{GOF/+}$***;Pik3cd***$^{KD/KD}$	Reduced MPN induced by Shp2 GOF	6
Lck-Cre; Pten$^{flox/flox}$***; Pik3cd***$^{-/-}$	No effect on development of T-ALL driven by *Pten* loss	24
***PIK3CG* (p110γ)**		
Lck-Cre; Pten$^{flox/flox}$***; Pik3cg***$^{-/-}$	No effect on development of T-ALL driven by *Pten* loss	24
***PIK3CD* (p110δ) and *PIK3CG* (p110γ)**		
Lck-Cre; Pten$^{flox/flox}$***; Pik3cd***$^{-/-}$***; Pik3cg***$^{-/-}$	Delayed development of T-ALL driven by *Pten* loss	24
***PIK3R1* (p85α, p55α, p50α)**		
CD19-Cre; ***Pik3r1***$^{flox/flox}$	Reduced B-cell leukemia development driven by *ex vivo* infection with BCR-ABL	25
Albumin-Cre; ***Pik3r1***$^{flox/flox}$	Develop liver tumors within 20 months	26
Pten$^{-/+}$***; Pik3r1***$^{-/+}$	Increased intestinal polyps but no change in PIN driven by *Pten* loss	27
***PIK3R2* (p85β)**		
Pik3r2$^{-/-}$	Decreased number of colon tumors induced by AOM/DSS	28
Pten$^{-/+}$***; Pik3r2***$^{-/-}$	No change in intestinal polyps or PIN driven by *Pten* loss	27
CD19-Cre; ***Pik3r2***$^{-/-}$	No effect on B-cell leukemia development driven by *ex vivo* infection with BCR-ABL	25
***PIK3R1* (p85α, p55α, p50α) and *PIK3R2* (p85β)**		
CCSP-rtTA; tetO-KRas^{G12D}***; Pik3r1***$^{flox/flox}$***; Pik3r2***$^{-/-}$ *LSL-KRas*^{G12D}***; Pik3r1***$^{flox/flox}$***; Pik3r2***$^{-/-}$	Decreased incidence of lung tumors driven by KRas	8
CD19-Cre; ***Pik3r1***$^{flox/flox}$***; Pik3r2***$^{-/-}$	Blocked B-cell leukemia development driven by *ex vivo* infection with BCR-ABL	25
CCSP-rtTA; tetO-KRas^{G12D}***; Pik3r1***$^{flox/+}$***; Pik3r2***$^{-/-}$ *LSL-KRas*^{G12D}***; Pik3r1***$^{flox/+}$***; Pik3r2***$^{-/-}$	Increased incidence of lung tumors driven by KRas	8
***PIK3C2A* (PI3K-C2α)**		
Cdh5(PAC)-CreER^{T2}***; Pik3c2a***$^{flox/flox}$	Decreased microvessel density and tumor burden of implanted tumors	29

RBD, Ras binding domain mutant; KD, kinase dead mutant; CA, constitutively active; Tg, transgene; PIN, prostate intraepithelial neoplasia; AOM/DSS, azoxymethane/dextran sodium sulfate; LOF, loss of function; GOF, gain of function; VP, ventral prostate; DLP, dorsal/lateral prostate; MPN, myoproliferative neoplasia

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Supplemental Table 3: Combination of PI3K inhibitors with other targeted therapies in the clinic.

Agent	Company	Target	Combination therapy trials			
			Agent	Target	Tumor types*	Clinical trial*
Class I pan-PI3K inhibitors						
BKM120	Novartis	Class I PI3Ks	▪ Lapatinib ▪ Fulvestrant ▪ Trastuzumab ▪ Letrozole	▪ EGFR/HER2 ▪ ER ▪ HER2 ▪ Aromatase	▪ Breast	NCT01589861 NCT01339442 NCT01132664 NCT01248494
			▪ Gefitinib ▪ Erlotinib	▪ EGFR ▪ EGFR	▪ NSCLC	NCT01570296 NCT01487265
			▪ Panitumumab	▪ EGFR	▪ Colorectal	NCT01591421
			▪ Cetuximab	▪ EGFR	▪ Head and neck	NCT01816984
			▪ Bevacizumab	▪ VEGFR†	▪ GBM ▪ Renal cell	NCT01349660 NCT01283048
			▪ INC280	▪ c-MET	▪ GBM	NCT01870726
			▪ Rituximab	▪ CD20	▪ B cell lymphoma	NCT02049541
			▪ Imatinib	▪ BCR-ABL	▪ GIST	NCT01468688
			▪ Vemurafenib ▪ Encorafenib	▪ BRAF ▪ BRAF	▪ Melanoma	NCT01512251 NCT01820364
			▪ Olaparib	▪ PARP	▪ TNBC ▪ Ovarian	NCT01623349
			▪ Abiraterone acetate	▪ CYP17	▪ Prostate	NCT01634061
			▪ Erismodegib ▪ Trametinib ▪ MEK162 ▪ Everolimus	▪ Smoothened ▪ MEK1/2 ▪ MEK1/2 ▪ mTOR	▪ Adv. solid tumors	NCT01576666 NCT01155453 NCT01363232 NCT01470209
GDC0941	Genentech	Class I PI3Ks	▪ Fulvestrant ▪ Trastuzumab	▪ ER ▪ HER2	▪ Breast	NCT01437566 NCT00928330
			▪ Bevacizumab	▪ VEGFR†	▪ Breast ▪ NSCLC	NCT00960960 NCT00974584
			▪ Erlotinib ▪ Cobimetinib	▪ EGFR ▪ MEK1	▪ Adv. solid tumors	NCT00975182 NCT00996892
PX866	Oncothyreon	Class I PI3Ks	▪ Cetuximab	▪ EGFR	▪ Colorectal ▪ SCCHN	NCT01252628 NCT01252628
			▪ Vemurafenib	▪ BRAF	▪ Melanoma	NCT01616199
XL147	Exelixis/ Sanofi-Aventis	Class I PI3Ks	▪ Trastuzumab ▪ Letrozole	▪ HER2 ▪ Aromatase	▪ Breast	NCT01042925 NCT01082068
			▪ Erlotinib ▪ MM121 ▪ XL647	▪ EGFR ▪ HER3 ▪ RTKs	▪ Adv. solid tumors	NCT00692640 NCT00704392 NCT01436565
Isoform-selective PI3K inhibitors						
BYL719	Novartis	p110α	▪ Cetuximab	▪ EGFR	▪ SCCHN	NCT01602315
			▪ LJM716	▪ HER3	▪ ESCC	NCT01822613
			▪ Encorafenib ▪ Cetuximab	▪ BRAF ▪ EGFR	▪ Colorectal	NCT01719380
			▪ Fulvestrant	▪ ER	▪ Breast ▪ Adv. solid tumors	NCT02088684 NCT01219699
			▪ Imatinib	▪ BCR-ABL	▪ GIST	NCT01735968
			▪ Letrozole ▪ Exemestane ▪ TDM-1 ▪ LEE011	▪ Aromatase ▪ Aromatase ▪ HER2‡ ▪ CDK4/6	▪ Breast	NCT01870505 NCT01870505 NCT02038010 NCT02088684
			▪ Everolimus ▪ Exemestane	▪ mTOR ▪ Aromatase	▪ Breast ▪ Kidney ▪ Pancreas	NCT02077933
			▪ AUY922	▪ HSP90	▪ Gastric	NCT01613950
			▪ Ganitumab ▪ BGJ398 ▪ MEK162	▪ IGF1R ▪ FGFR ▪ MEK1/2	▪ Adv. solid tumors	NCT01708161 NCT01928459 NCT01449058
GDC0032	Genentech	p110α	▪ Letrozole ▪ Fulvestrant	▪ Aromatase ▪ ER	▪ Breast	NCT01296555
INK1117	Intellikine/	p110α	▪ MLN0128	▪ mTORC1/2	▪ Adv. non-	NCT01899053

	Millenium				hematological malignancies	
SAR260301	Sanofi	p110β	▪ Vemurafenib	▪ BRAF	▪ Melanoma	NCT01673737
IPI145	Infinity	p110δ and p110γ	▪ Ofatumumab	▪ CD20	▪ CLL ▪ SLL	NCT02049515
			▪ Rituximab	▪ CD20	▪ Hematologic malignancies	NCT01871675
AMG319	Amgen	p110δ				NCT01300026
CAL101 (GS101)	Gilead Sciences	p110δ	▪ Rituximab ▪ Ofatumumab ▪ Everolimus ▪ Bortezomib	▪ CD20 ▪ CD20 ▪ mTOR ▪ NFκB	▪ INHL ▪ CLL ▪ MCL	NCT01088048
			▪ GS9973	▪ SYK	▪ Hematologic malignancies	NCT01796470
			▪ Everolimus	▪ mTOR	▪ MCL	NCT01088048
Dual pan-PI3K and mTOR inhibitors						
GDC0980	Genentech	PI3K and mTOR	▪ Fulvestrant	▪ ER	▪ Breast	NCT01437566
			▪ Abiraterone acetate	▪ CYP17	▪ Prostate	NCT01485861
			▪ Bevacizumab	▪ VEGFR†	▪ Breast ▪ Adv. solid tumors	NCT01254526 NCT01332604
PF04691502	Pfizer	PI3K and mTOR	▪ PD0325901	▪ MEK	▪ Adv.solid tumors	NCT01347866
BEZ235	Novartis	PI3K and mTOR	▪ Trastuzumab	▪ HER2	▪ Breast ▪ Adv. solid tumors	NCT01471847 NCT01285466
			▪ Everolimus	▪ mTOR	▪ Breast ▪ Renal cell ▪ Adv. solid tumors	NCT01482156 NCT01508104
			▪ Abiraterone acetate	▪ CYP17	▪ Prostate	NCT01717898
			▪ Letrozole	▪ Aromatase	▪ Breast	NCT01248494
			▪ Everolimus ▪ MEK162	▪ mTOR ▪ MEK	▪ Adv. solid tumors	NCT01482156 NCT01337765
XL765	Sanofi	PI3K and mTOR	▪ Letrozole	▪ Aromatase	▪ Breast	NCT01082068
			▪ Erlotinib	▪ EGFR	▪ Adv. solid tumors	NCT00777699
PF05212384	Pfizer	PI3K and mTOR	▪ PD0325901	▪ MEK	▪ Adv. solid tumors	NCT01347866
			▪ Cetuximab	▪ EGFR	▪ Colorectal cancer	NCT01925274
			▪ Bevacizumab	▪ VEFGR	▪ Colorectal cancer	NCT01937715

* Data taken from an April 2014 search of http://www.clinicaltrials.gov.

† Bevacizumab is a monoclonal antibody targeting VEGF that prevents signaling through VEFGR.

‡ T-DM1 is a conjugate of the cytotoxic agent mertansine (DM1) to the monoclonal antibody Trastuzumab targeting HER2.

TNBC, triple-negative breast cancer; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung carcinoma; ESCC, esophageal squamous cell carcinoma; SCCHN, squamous cell carcinoma of the head and neck; sqNSCLC, squamous non-small cell lung cancer; TCC, transitional cell carcinoma; INHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myelogenous leukemia; MM, multiple myeloma; CRPC, castration-resistant prostate cancer; GBM, glioblastoma multiforme