Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. DNA Sequencing Target Gene Panel[a]

ABL1	CCND1	EPHA3	GATA2	MAP3K1	NTRK3	REL	VHL
AKT1	CCND2	EPHA5	GATA3	MAP3K13	NUP93	RET	WISP3
AKT2	CCND3	EPHB1	GNA11	MCL1	PAK3	RICTOR	WT1
AKT3	CCNE1	ERBB2	GNA13	MDM2	PAK7	RNF43	XPO1
ALK	CD79A	ERBB3	GNAQ	MDM4	PALB2	RPA1	XRCC3
ALOX12B	CD79B	ERBB4	GNAS	MED12	PARP1	RPTOR	ZNF217
APC	CDC73	ERG	GPR124	MEF2B	PARP2	RUNX1	ZNF703
APCDD1	CDH1	ESR1	GRIN2A	MEN1	PARP3	RUNX1T1	
AR	CDK12	EZH2	GSK3B	MET	PARP4	SETD2	
ARAF	CDK4	FAM123B	HGF	MITF	PAX5	SF3B1	
ARFRP1	CDK6	FAM46C	HLA-A	MLH1	PBRM1	SH2B3	
ARID1A	CDK8	FANCA	HRAS	MLL	PDGFRA	SMAD2	
ARID2	CDKN1B	FANCC	IDH1	MLL2	PDGFRB	SMAD4	
ASXL1	CDKN2A	FANCD2	IDH2	MPL	PDK1	SMARCA4	
ATM	CDKN2B	FANCE	IGF1	MRE11A	PIK3C2G	SMARCB1	
ATR	CDKN2C	FANCF	IGF1R	MSH2	PIK3C3	SMARCD1	
ATRX	CEBPA	FANCG	IGF2	MSH6	PIK3CA	SMO	
AURKA	CHEK1	FANCI	IKBKE	MTOR	PIK3CG	SOCS1	
AURKB	CHEK2	FANCL	IKZF1	MUTYH	PIK3R1	SOX10	
AXL	CHUK	FANCM	IL7R	MYC	PIK3R2	SOX2	
BACH1	CIC	FAT3	INHBA	MYCL1	PMS2	SPEN	
BAP1	CRBN	FBXW7	IRF4	MYCN	PNRC1	SPOP	
BARD1	CREBBP	FGF10	IRS2	MYD88	PPP2R1A	SRC	
BCL2	CRKL	FGF12	JAK1	MYST3	PRDM1	STAG2	
BCL2L2	CRLF2	FGF14	JAK2	NBN	PRKAR1A	STAT4	
BCL6	CSF1R	FGF19	JAK3	NCOR1	PRKDC	STK11	
BCOR	CTCF	FGF23	JUN	NF1	PRSS8	SUFU	
BCORL1	CTNNA1	FGF3	KDM5A	NF2	PTCH1	SYK	
BLM	CTNNB1	FGF4	KDM5C	NFE2L2	PTEN	TBX3	
BRAF	CUL4A	FGF6	KDM6A	NFKBIA	PTPN11	TET2	
BRCA1	CUL4B	FGF7	KDR	NKX2-1	RAD50	TGFBR2	
BRCA2	CYP17A1	FGFR1	KEAP1	NOTCH1	RAD51	TIPARP	
BRIP1	DAXX	FGFR2	KIT	NOTCH2	RAD51B	TNFAIP3	
BTG1	DDR2	FGFR3	KLHL6	NOTCH3	RAD51C	TNFRSF14	
BTK	DIS3	FGFR4	KRAS	NOTCH4	RAD51D	TOP1	
C17orf39	DNMT3A	FLT1	LMO1	NPM1	RAD52	TP53	
CARD11	DOT1L	FLT3	LRP1B	NRAS	RAD54L	TRRAP	
CASP8	EGFR	FLT4	MAP2K1	NSD1	RAF1	TSC1	
CBFB	EMSY	FOXL2	MAP2K2	NTRK1	RARA	TSC2	
CBL	EP300	GATA1	MAP2K4	NTRK2	RB1	TSHR	

eTable 1. DNA sequencing target gene panel. All genes in the targeted panel are listed, in addition to 19 gene rearrangements and 2000 whole genome single nucleotide polymorphisms. MYST3 has been renamed to KAT6A and is listed as KAT6A for subsequent analyses.

[a]Frampton GM, Fichtenholtz A, Otto GA, et al. Development and validation of a clinical cancer genomic profiling test based on massively parallel DNA sequencing. Nat Biotechnol 2013;31:1023-31.

eTable 2.Characteristics of the Entire Eligible BIG 1-98 Cohort and of the Analysis Population

	Case-Cohort Analysis Population			Eligible Cohort	
	N	Unweighted %	Weighted %	N	%
N patients	*538*	*100*	*100*	*7329*	*100*
Age at randomization, median (IQR)	61	(56-68)	60 (55-67)	61	(56-67)
Tumor size >2cm	235	44	36	2629	36
Lymph node-positive	249	46	63	4360	59
Tumor grade					
Unknown	2	0	--	165	2
1	74	14	21	1638	22
2	293	54	57	4124	56
3	169	31	22	1402	19
Luminal A/B-like status					
A-like	151	28	39	2446	33
B-like	374	70	50	3108	42
Unknown	13	2	11	1775	24
Adjuvant chemotherapy	196	36	26	1716	23
Treatment assignment and randomization option (2- or 4-group randomization)					
Tamoxifen (2-group randomization)	55	10	7	820	11
Letrozole (2-group randomization)	39	7	10	832	11
Tamoxifen	108	20	21	1422	19
Letrozole	96	18	21	1403	19
Tamoxifen -> Letrozole	125	23	22	1446	20
Letrozole -> Tamoxifen	115	21	19	1406	19
Distant recurrences after 8.1 years median follow-up	140	26	10	841	11

Characteristics of the entire eligible BIG 1-98 cohort and of the analysis population, which was based on selection of all patients experiencing a distant recurrence and a stratified random sampling of the patients' not experiencing recurrence, for whom DNA was assessable. Unweighted (as sampled) and weighted (to correct for over-sampling of recurrences) percentages of the analysis population are provided. Luminal-like status was determined using the published St. Gallen 2013 consensus. Abbreviations: IQR, interquartile range.

eTable 3.Somatic Driver Alterations and Weighted Frequencies

Short variants			Copy number alterations			
Gene	**Variant type**	**Weighted proportion (%)**	**Gene**	**Cytoband**	**Variant type**	**Weighted proportion (%)**
PIK3CA	short variant	48.8	*CCND1*	11q13	amplification	17.2
TP53	short variant	15.3	*FGF19*	11q13	amplification	14.7
MAP3K1	short variant	14	*FGF3*	11q13	amplification	14.3
GATA3	short variant	12.2	*FGF4*	11q13	amplification	13.5
CDH1	short variant	12.2	*MYC*	8q24	amplification	11.3
PTPN11	short variant	6.5	*ZNF703*	8p11	amplification	9.3
MAP2K4	short variant	5.5	*FGFR1*	8p11	amplification	8.7
SPEN	short variant	5.2	*EMSY*	11q13	amplification	7.4
PTEN	short variant	4.8	*KAT6A*	8p11	amplification	5.1
TBX3	short variant	4.2	*ERBB2*	17q12	amplification	4.8
CDKN1B	short variant	4.1	*GNAS*	20q13	amplification	4.1
AKT1	short variant	4.1	*ZNF217*	20q13	amplification	4
ARID1A	short variant	3.8	*PRSS8*	16p11	amplification	2.5
GNAS	short variant	3.7	*AURKA*	20q13	amplification	2.4
RUNX1	short variant	3.2	*ARFRP1*	20q13	amplification	2.2
ATM	short variant	3.2	*MAP2K4*	17p12	loss	2.1
PBRM1	short variant	3	*AKT3*	1q44	amplification	2
NCOR1	short variant	2.9	*MDM4*	1q32	amplification	1.9
ABL1	short variant	2.6	*IKBKE*	1q32	amplification	1.9
BRCA2	short variant	2.3	*PTEN*	10q23	loss	1.8
ERBB2	short variant	2.1	*MDM2*	12q15	amplification	1.7
SF3B1	short variant	2	*BCL2L2*	14q11	amplification	1.7
SETD2	short variant	1.9	*IGF1R*	15q26	amplification	1.6
MUTYH	short variant	1.6	*MCL1*	1q21	amplification	1.5
NF1	short variant	1.4	*SRC*	20q11	amplification	1.1
NOTCH1	short variant	1.2	*RPTOR*	17q25	amplification	1.1
PIK3R1	short variant	1				
ATRX	short variant	1				
RB1	short variant	1				
BARD1	short variant	1				

List of all driver alterations with weighted frequency of one percent or greater

eTable 4.Association With Clinicopathologic Characteristics

	Age			Tumor size			Nodal status			Tumor grade				Ki-67 (%)
	< 65 years (67%)	≥65 years (32%)	P value	≤2 cm (64%)	>2 cm (36%)	P value	Negative (63%)	Positive (37%)	P value	G1 (21%)	G2 (57%)	G3 (22%)	P value	P value
PIK3CA short variants	49%	47%	0.70	48%	49%	0.78	51%	45%	0.26	67%	48%	33%	<0.001*	0.002*
GATA3 short variants	11%	14%	0.31	12%	12%	0.90	11%	14%	0.33	8%	13%	15%	0.28	0.17
TP53 short variants	16%	13%	0.38	14%	17%	0.42	15%	16%	0.59	<1%	10%	41%	<0.001*	< 0.001*
CDH1 short variants	11%	15%	0.36	10%	17%	0.04*	14%	9%	0.18	2%	18%	6%	<0.001*	0.10
MAP3K1 short variants	14%	14%	0.9	18%	7%	0.002*	13%	16%	0.38	25%	12%	9%	0.02*	0.010*
PTPN11 short variants	7%	6%	0.85	8%	3%	0.03*	7%	5%	0.46	12%	4%	8%	0.10	0.85
PTEN short variants	4%	7%	0.13	6%	3%	0.25	4%	7%	0.24	2%	7%	2%	0.02*	0.019*
SPEN short variants	6%	3%	0.02*	1%	12%	<0.001*	6%	3%	0.01*	17%	2%	3%	<0.001*	0.09
MAP2K4 short variants	8%	1%	<0.001*	7%	3%	0.07	7%	3%	0.01*	<1%	7%	6%	0.007*	0.87
ZNF217 amplification	4%	4%	0.97	4%	3%	0.54	4%	4%	0.93	0%	4%	8%	0.02*	0.07
GNAS amplification	4%	5%	0.36	4%	4%	0.04	4%	4%	0.87	0%	4%	9%	0.006*	0.08
EMSY amplification	7%	8%	0.87	7%	8%	0.90	8%	6%	0.28	2%	7%	13%	0.02*	0.003*
MYC amplification	10%	13%	0.40	11%	13%	0.49	9%	15%	0.06	3%	9%	26%	<0.001*	0.001*
CCND1 amplification	16%	19%	0.56	18%	16%	0.60	16%	19%	0.52	10%	14%	30%	0.03*	0.001*
FGFR1 amplification	8%	10%	0.49	8%	11%	0.30	8%	11%	0.24	2%	7%	19%	<0.001*	< 0.001*
KAT6A amplification	4%	7%	0.25	6%	4%	0.42	4%	7%	0.13	<1%	5%	9%	0.003*	0.007*
ZNF703 amplification	9%	11%	0.41	8%	11%	0.33	8%	12%	0.18	2%	7%	22%	<0.001*	< 0.001*
FGF4 amplification	14%	13%	0.83	14%	13%	0.80	13%	14%	0.7	9%	11%	24%	0.07	0.001*
FGF3 amplification	14%	15%	0.92	15%	14%	0.79	13%	16%	0.48	9%	12%	25%	0.08	0.001*
FGF19 amplification	15%	15%	0.99	15%	15%	0.89	13%	18%	0.23	9%	13%	26%	0.07	< 0.001*
ERBB2 amplification	5%	5%	0.83	4%	6%	0.50	4%	5%	0.62	0%	4%	12%	<0.001*	0.01*

Associations with driver alterations present in five percent or greater weighted cohort frequency are shown. The numbers displayed are weighted proportions with the exception of N, which is the absolute number of patients per subgroup, and P values. All P values are calculated using weighted Chi-squared tests with the exception of centrally assessed Ki-67 which is analysed as a continuous variable using a weighted t-test. * P value < 0.05.

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eTable 5.Pairwise Analysis – q Values

	***PIK3CA*(m)**	***GATA3*(m)**	***TP53*(m)**	***CDH1*(m)**	***MAP3K1*(m)**	***PTPN11*(m)**	***PTEN*(m)**	***SPEN*(m)**	***MAP2K4*(m)**	***ZNF217*(A)**	***GNAS*(A)**	***EMSY*(A)**	***MYC*(A)**	***CCND1*(A)**	***FGFR1*(A)**	***KAT6A*(A)**	***ZNF703*(A)**	***FGF4*(A)**	***FGF3*(A)**	***FGF19*(A)**	***ERBB2*(A)**	***AKT1*(m)**	***ERBB2*(m)**
***PIK3CA*(m)**		0.171	0.786	0.806	0.081	0.069	0.167	0.995	1	0.828	0.529	1	0.008	0.077	0.5	0.152	0.209	0.12	0.138	0.036	0.034	0.002	0.856
***GATA3*(m)**	0.171		0.064	0.343	0.068	0.786	1	0.543	1	0.524	0.572	0.423	1	0.825	0.524	0.373	0.786	1	0.736	0.856	1	0.824	0.932
***TP53*(m)**	0.786	0.064		0	0.002	0.903	0.856	0.5	0.319	0.001	0.076	0.645	0.004	0.856	0.007	0.811	0.006	0.828	0.83	1	0.033	1	0.806
***CDH1*(m)**	0.806	0.343	0		0.308	0.307	0.975	1			0.524	0.518	0.068	1	0.822	0.308	0.929	0.796	0.796	0.856	0.387	1	0.739
***MAP3K1*(m)**	0.081	0.068	0.002	0.308		0.987	1	1			0.524	0.373	1	0.171	0.088	1	0.051	0.218	0.13	0.097	0.387	0.97	0.932
***PTPN11*(m)**	0.069	0.786	0.903	0.307	0.987		1	0.585	0.283	1	0.934	0.975	1	0.338	0.987		0.987	0.18	0.212	0.307	1		
***PTEN*(m)**	0.167	1	0.856	0.975	1	1		0.835	0.856	1	1	0.934	0.736	0.856	0.662	1	0.83	0.987	0.856	1	1		0.828
***SPEN*(m)**	0.995	0.543	0.5	1	1	0.585	0.835			0.828	0.496	1	0.796	0.97	1	1	0.932	1	1	1	1	0.796	
***MAP2K4*(m)**	1	1	0.319			0.283	0.856						1	0.5	0.751	1	0.786	0.796	0.645	0.645	0.222	0.806	
***ZNF217*(A)**	0.828	0.524	0.001			1	1	0.828			0	0.18	0.087	1	0.08	1	0.116	0.736	0.582	0.987	0.069	0.584	
***GNAS*(A)**	0.529	0.572	0.076	0.524	0.524	0.934	1	0.496		0		0.233	0.007	0.373	1		0.726	0.756	0.856	0.222	0.033	0.649	
***EMSY*(A)**	1	0.423	0.645	0.518	0.373	0.975	0.934	1		0.18	0.233		1	0	0.034	0.097	0.036	0	0	0	1	1	1
***MYC*(A)**	0.008	1	0.004	0.068	1	1	0.736	0.796	1	0.087	0.007	1		0.387	0.034	0.006	0	0.796	0.736	0.529	0		0.932
***CCND1*(A)**	0.077	0.825	0.856	1	0.171	0.338	0.856	0.97	0.5	1	0.373	0	0.387		0.097	0.19	0.068	0	0	0	0.529	0.856	0.645
***FGFR1*(A)**	0.5	0.524	0.007	0.822	0.088	0.987	0.662	1	0.751	0.08	1	0.034	0.034	0.097		0	0	0.088	0.071	0.058	0.222	0.796	
***KAT6A*(A)**	0.152	0.373	0.811	0.308	1		1	1	1	1		0.097	0.006	0.19	0		0	0.379	0.298	0.319	0.796	0.726	
***ZNF703*(A)**	0.209	0.786	0.006	0.929	0.051	0.987	0.83	0.932	0.786	0.116	0.726	0.036	0	0.068	0	0		0.053	0.042	0.034	0.281	0.802	
***FGF4*(A)**	0.12	1	0.828	0.796	0.218	0.18	0.987	1	0.796	0.736	0.756	0	0.796	0	0.088	0.379	0.053			0	0.222	1	0.796
***FGF3*(A)**	0.138	0.736	0.83	0.796	0.13	0.212	0.856	1	0.645	0.582	0.856	0	0.736	0	0.071	0.298	0.042			0	0.248	1	0.796
***FGF19*(A)**	0.036	0.856	1	0.856	0.097	0.307	1	1	0.645	0.987	0.222	0	0.529	0	0.058	0.319	0.034	0	0		0.373	0.987	0.796
***ERBB2*(A)**	0.034	1	0.033	0.387	0.387	1	1	1	0.222	0.069	0.033	1	0	0.529	0.222	0.796	0.281	0.222	0.248	0.373			0.856
***AKT1*(m)**	0.002	0.824	1	1	0.97			0.796	0.806	0.584	0.649	1		0.856	0.796		0.802	1	1	0.987			
***ERBB2*(m)**	0.856	0.932	0.806	0.739	0.932		0.828					1	0.932	0.645				0.796	0.796	0.796	0.856		

Fisher's exact test between somatic alteration pairs was applied to alterations with a weighted population frequency of five percent or greater, in addition to breast cancer alterations of interest (*ERBB2* and *AKT1* mutations). False discovery rate adjusted p values (q val) are shown. Abbreviations: m, mutation; A, amplification.

eTable 6. Prognostic Associations by Affected *PIK3CA* Protein Domain

***PIK3CA* mutation status**	**Number**	**Weighted proportion**	**Prognostic association HR (95% CI)**	**p-value**
Kinase domain mutation	103	19%	0.57 (0.33 – 1.00)	0.17
Helical domain mutation	103	20%	0.63 (0.38 – 1.04)	
Kinase and helical domain mutation	9	1%	0.48 (0.06 – 3.87)	
Other domain mutation	33	8%	0.44 (0.18 – 1.07)	
Wild type	290	51%		

The "kinase and helical domain mutations" subgroup refers to tumors harbouring both kinase and helical domain *PIK3CA* mutations. Numbers for this analysis include patients randomized to monotherapy and sequential endocrine treatment arms. Prognostic association is calculated from weighted univariate Cox Proportional Hazard models stratified by treatment arm and is mutational status versus wild type. Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

eTable 7. Predictive Associations by Affected *PIK3CA* Protein Domain

Analysis by individual protein domains				
***PIK3CA* mutation status**	**Number**	**Weighted proportion**	**Letrozole versus tamoxifen HR (95% CI)**	**Interaction P value**
Kinase domain mutation	45	16%	0.32 (0.05 – 1.88)	0.01
Helical domain mutation	63	22%	0.13 (0.04 – 0.44)	
Kinase and helical domain mutation	6	2%	1.03 (0.12 – 9.14)	
Other domain mutation	20	10%	8.56 (0.75 – 97.7)	
Wild type	164	50%	0.94 (0.46 – 1.90)	
Analysis by combined kinase and/or helical protein domain				
Kinase and/or helical domain mutation-positive	114	40%	0.18 (0.06 – 0.50)	0.002
Kinase and/or helical domain mutation-negative	184	60%	1.26 (0.65 – 2.45)	

Treatment associations by affected individual *PIK3CA* protein domains and in combined analysis. Numbers for this analysis include only patients randomized to monotherapy treatment arms. Letrozole versus tamoxifen calculations are from weighted Cox Proportional Hazard models using letrozole and tamoxifen monotherapy arms only. P values are a test of interaction between monotherapy treatment and mutation status. The Kinase and/or helical domain mutation–negative group combines wild type and other domain mutation subgroups. Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

eTable 8. Predictive Associations by Affected *PIK3CA* Mutation Hotspot

Analysis by affected *PIK3CA* mutation hotspot					
***PIK3CA* mutation hotspot**	**Functional domain**	**Number**	**Weighted proportion**	**Letrozole versus tamoxifen HR (95% CI)**	**Interaction P value**
N345	C2	10	7%	Insufficient numbers	
C420	C2	3	<1%	Insufficient numbers	
E542	helical	25	6%	0.26 (0.05 – 1.35)	
E545	helical	34	15%	0.06 (<0.01 – 0.80)	
Q546	helical	4	<1%	Insufficient numbers	
H1047	kinase	43	14%	0.30 (0.05 – 1.82)	
Non-hotspot mutation		8	3%	Insufficient numbers	
>1 hotspot per tumor		7	3%	Insufficient numbers	
Wild type		164	50%	0.86 (0.41 – 1.80)	
Analysis by combinations of common *PIK3CA* mutation hotspots					
E542, E545, H1047 mutation-positive		102	36%	0.17 (0.05 – 0.59)	0.009
E542, E545, H1047 mutation-negative		196	64%	1.13 (0.53 – 2.41)	

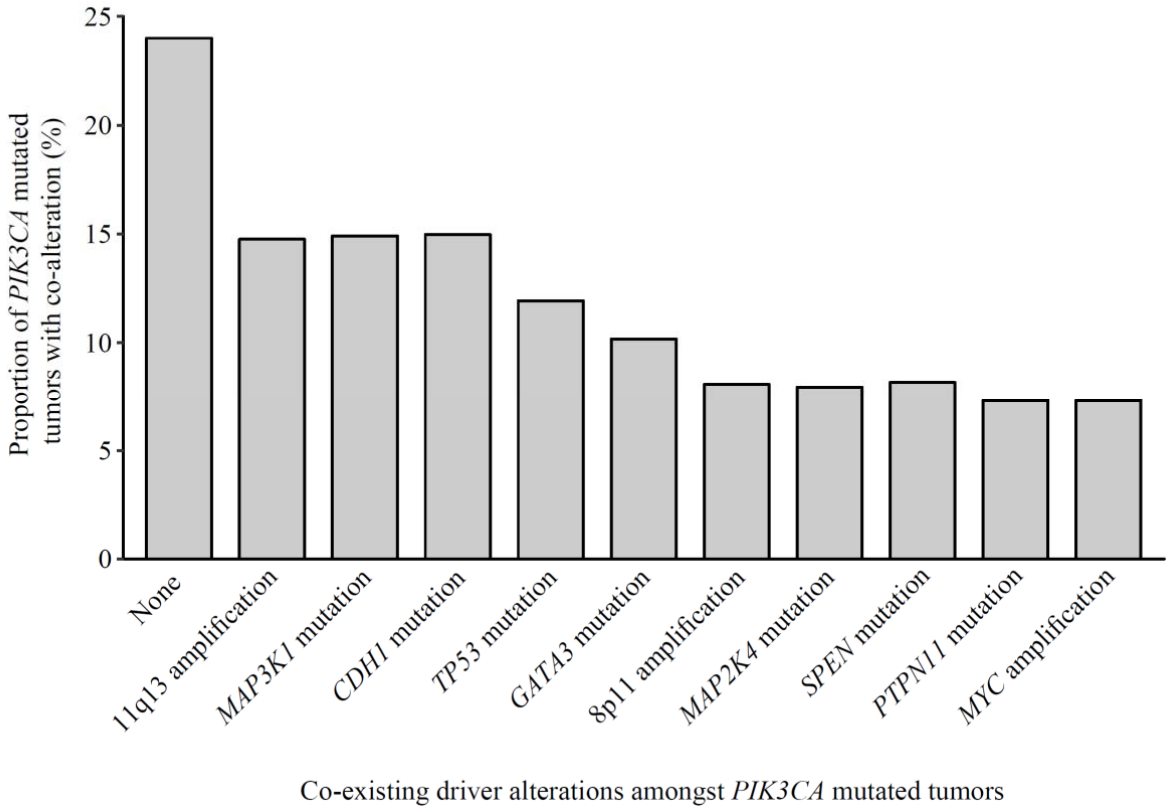
Treatment associations by affected *PIK3CA* mutation hotspot and in combined analysis of frequent mutation hotspots. Tumors were categorized into specific hotspot mutation subgroups if only one hotspot mutation was present. If more than one hotspot was present the tumor was categorized into the ">1 hotspot per tumor" subgroup. Numbers for this analysis include only patients randomized to monotherapy treatment arms. Letrozole versus tamoxifen calculations are from weighted Cox Proportional Hazard models using letrozole and tamoxifen monotherapy arms only. Interaction P values are a test of interaction between monotherapy treatment and mutation status. Exploratory Cox analysis of letrozole vs tamoxifen for the combination of infrequent hotspot mutations (N345+C420+Q546+>1 hotspot per tumor) was underpowered and is not shown (HR 4.5; 95%CI 0.40 – 51.36). Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

eTable 9. Treatment Interaction With *PIK3CA* Mutation Status in a Multivariate Cox Proportional Hazards Model

	HR (95% CI)	P value
Age (<65 vs ≥65 years)	1.37 (0.74 – 2.53)	0.31
Tumor size (≤ 2 cm vs > 2 cm)	1.54 (0.81 – 2.90)	0.19
Nodal status (positive vs negative)	2.80 (1.43 – 5.48)	< 0.01
Ki-67 level (%) (continuous)	1.03 (1.01 - 1.05)	< 0.01
Letrozole vs tamoxifen:		0.03*
PIK3CA mutation status helical and/or kinase mutation *Wild type or other mutation*	 0.27 (0.09 – 0.77) 1.15 (0.55-2.41)	

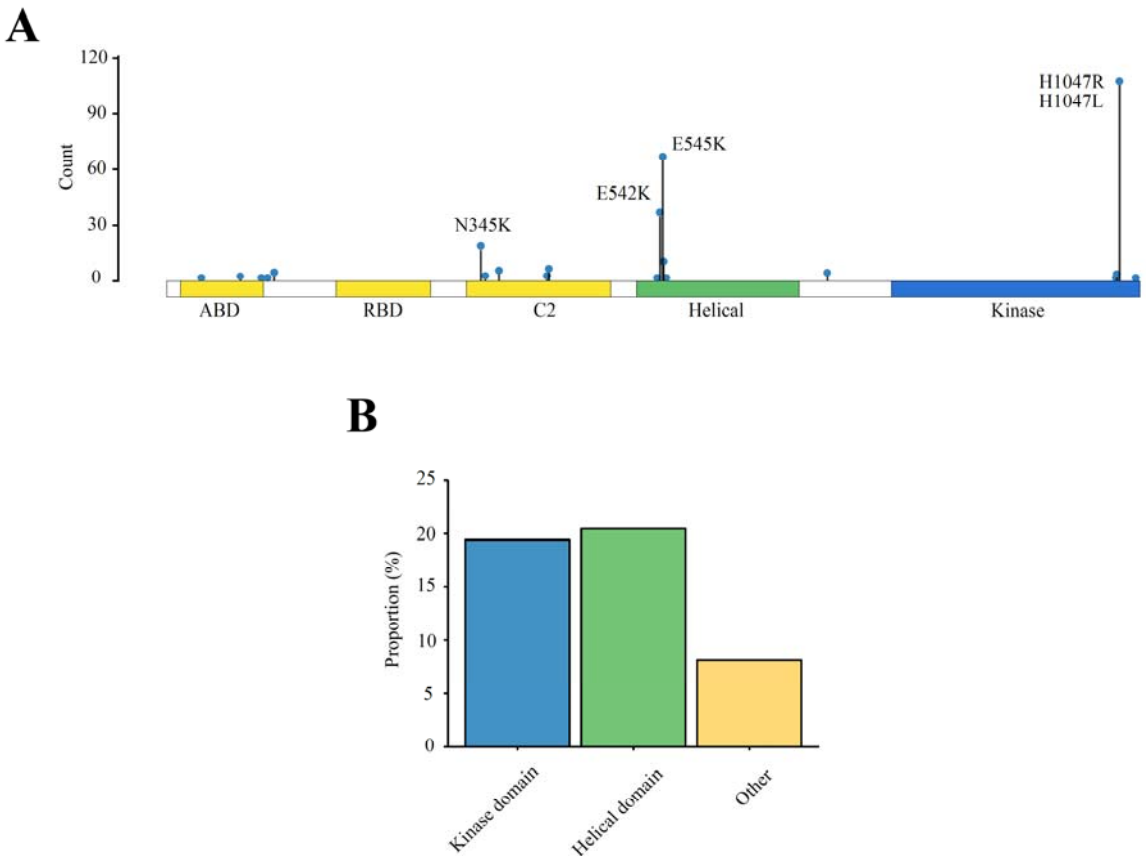
Weighted multivariate Cox proportional hazard analysis for distant recurrence-free interval with treatment interaction. All patients in the analysis cohort are included in the model. Ki-67 level was analysed as a continuous variable. Only patients treated with tamoxifen or letrozole monotherapy were included for treatment analyses. * Test for interaction between monotherapy treatment and *PIK3CA* mutation status. Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

eFigure 1. Coexistent Alterations in Tumors With a *PIK3CA* Mutation



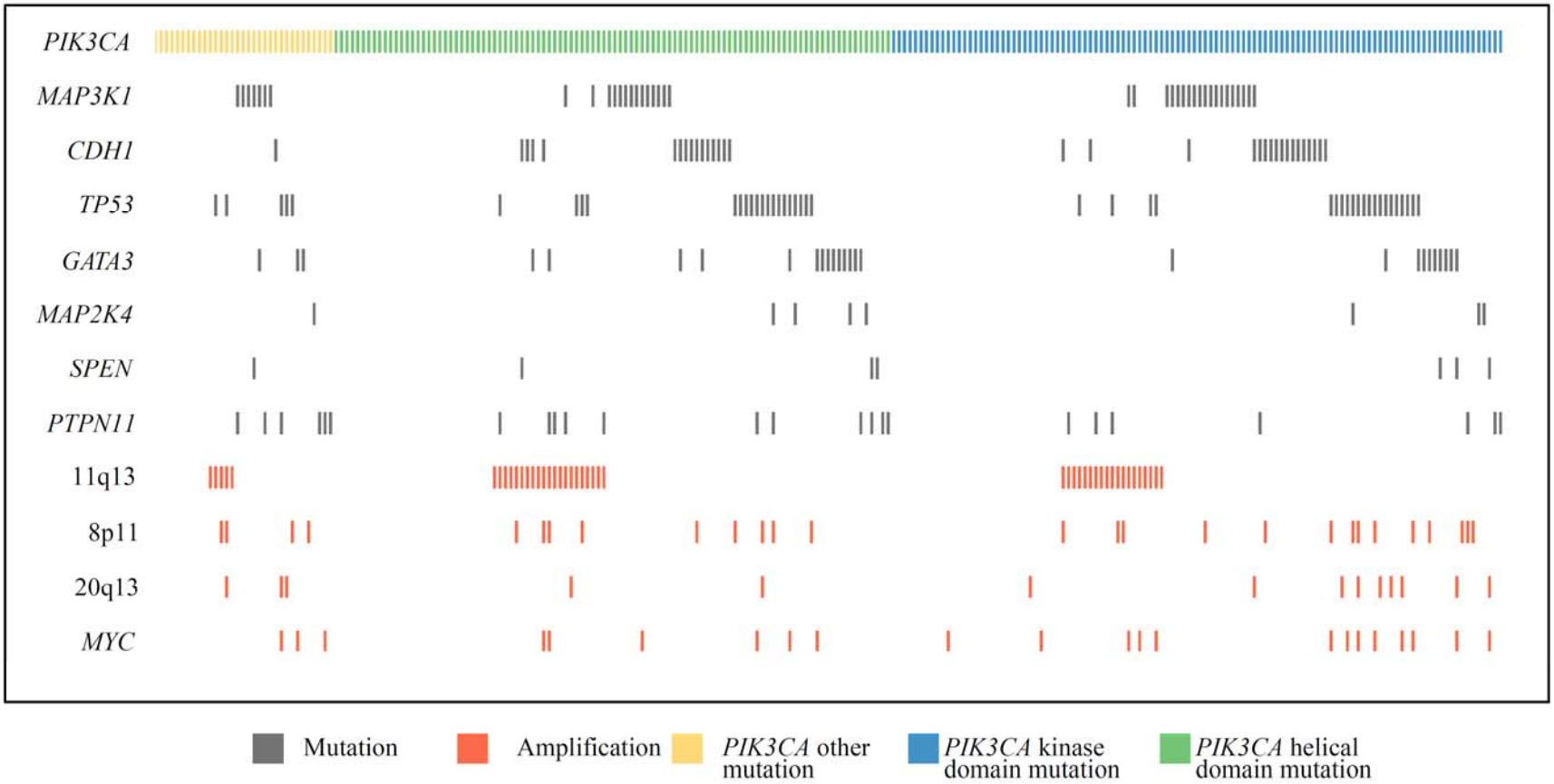
Weighted proportion of co-existent driver alterations in tumors that harbour a PIK3CA mutation.

eFigure 2. *PIK3CA* Mutations and Affected Protein Domains



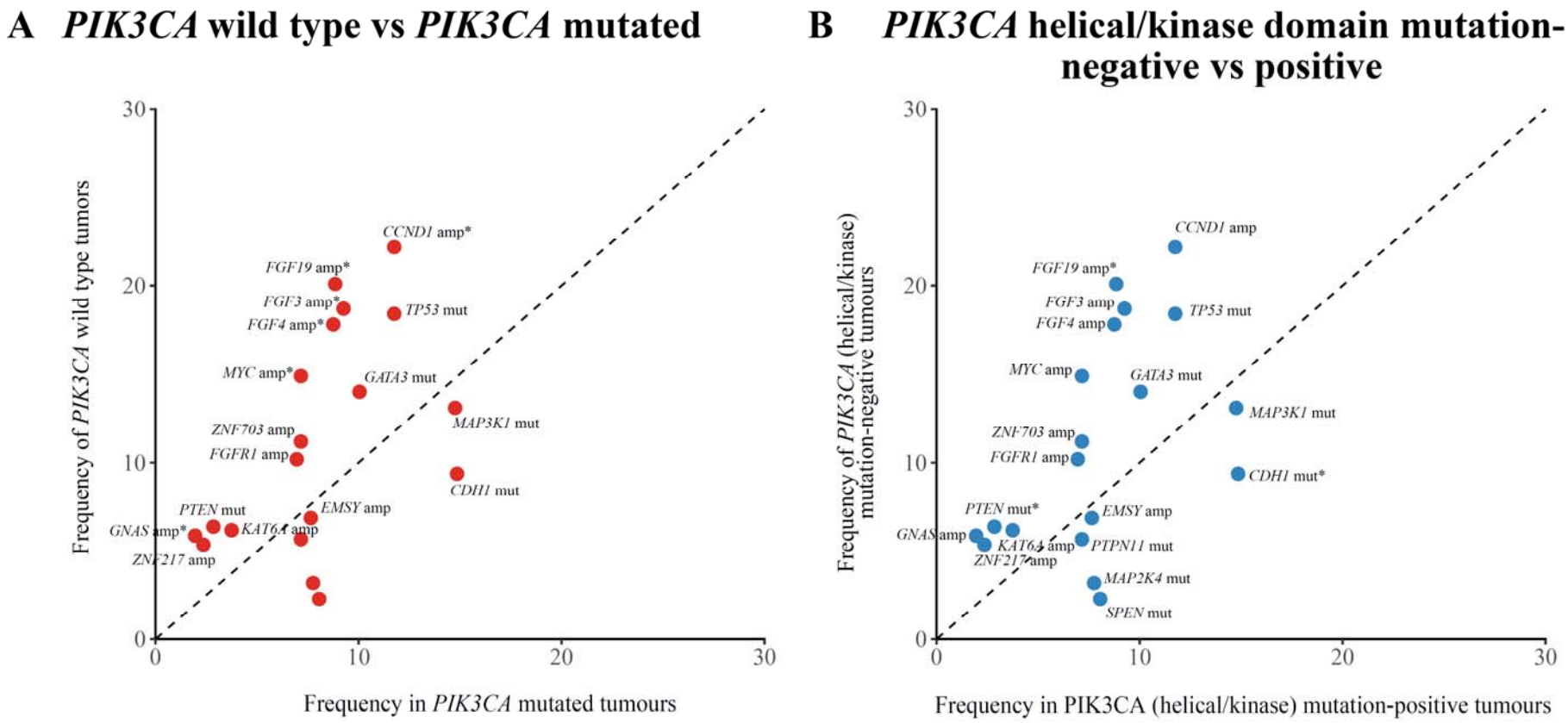
Panel A shows the distribution of *PIK3CA* mutations by affected protein domain. Count is the number of patients with a mutation at the corresponding amino acid position. Panel B shows the weighted proportions by affected protein domain, out of the whole cohort. As described in the methods, *PIK3CA* mutations were annotated as kinase domain mutation, helical domain mutation, or other mutation if it did not affect either the kinase or helical domain. Abbreviations: ABD, adaptor-binding domain; RBD, Ras-binding domain.

eFigure 3. Coalterations by Affected *PIK3CA* Protein Domain



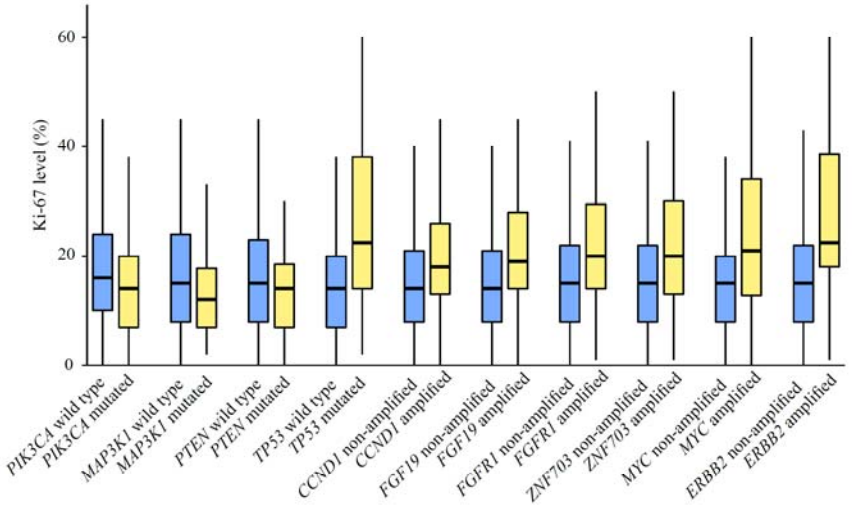
11q13 amplifications include *CCND1*, *EMSY*, *FGF3*, *FGF4*, *FGF19*; 8p11 amplifications include *FGFR1*, *ZNF703*, *KAT6A*; 20q13 amplifications include *GNAS*, *ZNF217*.

eFigure 4. Coalteration Frequencies by *PIK3CA* Genotype

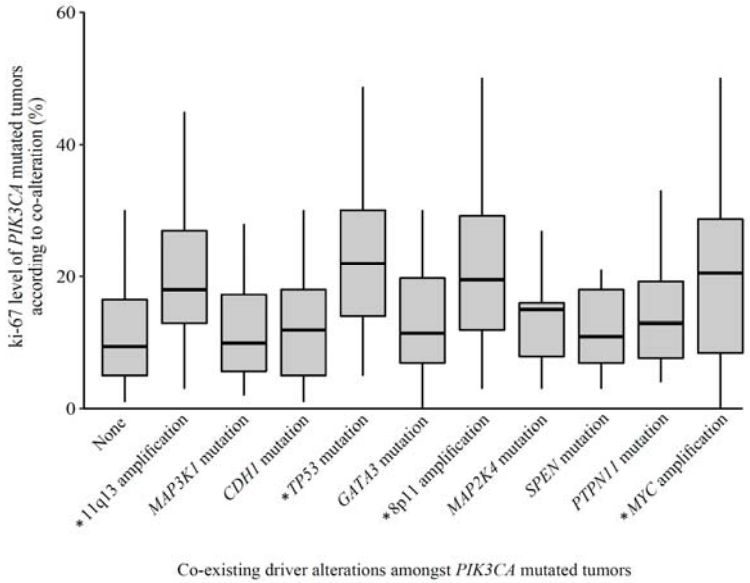


Weighted frequencies of co-existing driver alterations by *PIK3CA* genotype in A (*PIK3CA* wild type versus *PIK3CA* mutated) and B (*PIK3CA* kinase/helical domain mutation-negative vs positive). * P value of < 0.05 in weighted Chi-squared tests.

A - Ki-67 levels in all tumors by driver alteration



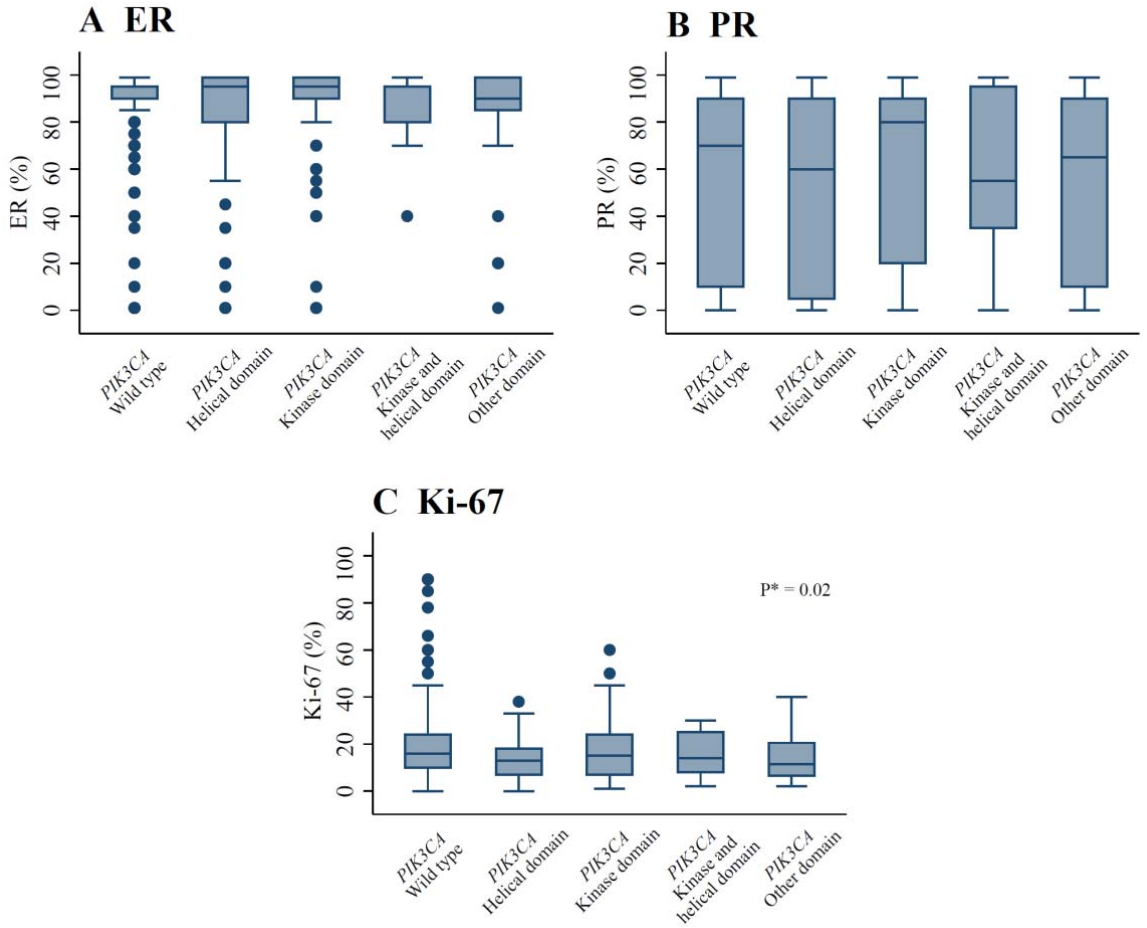
B - Ki-67 levels in tumors with a *PIK3CA* mutation by co-existent alteration



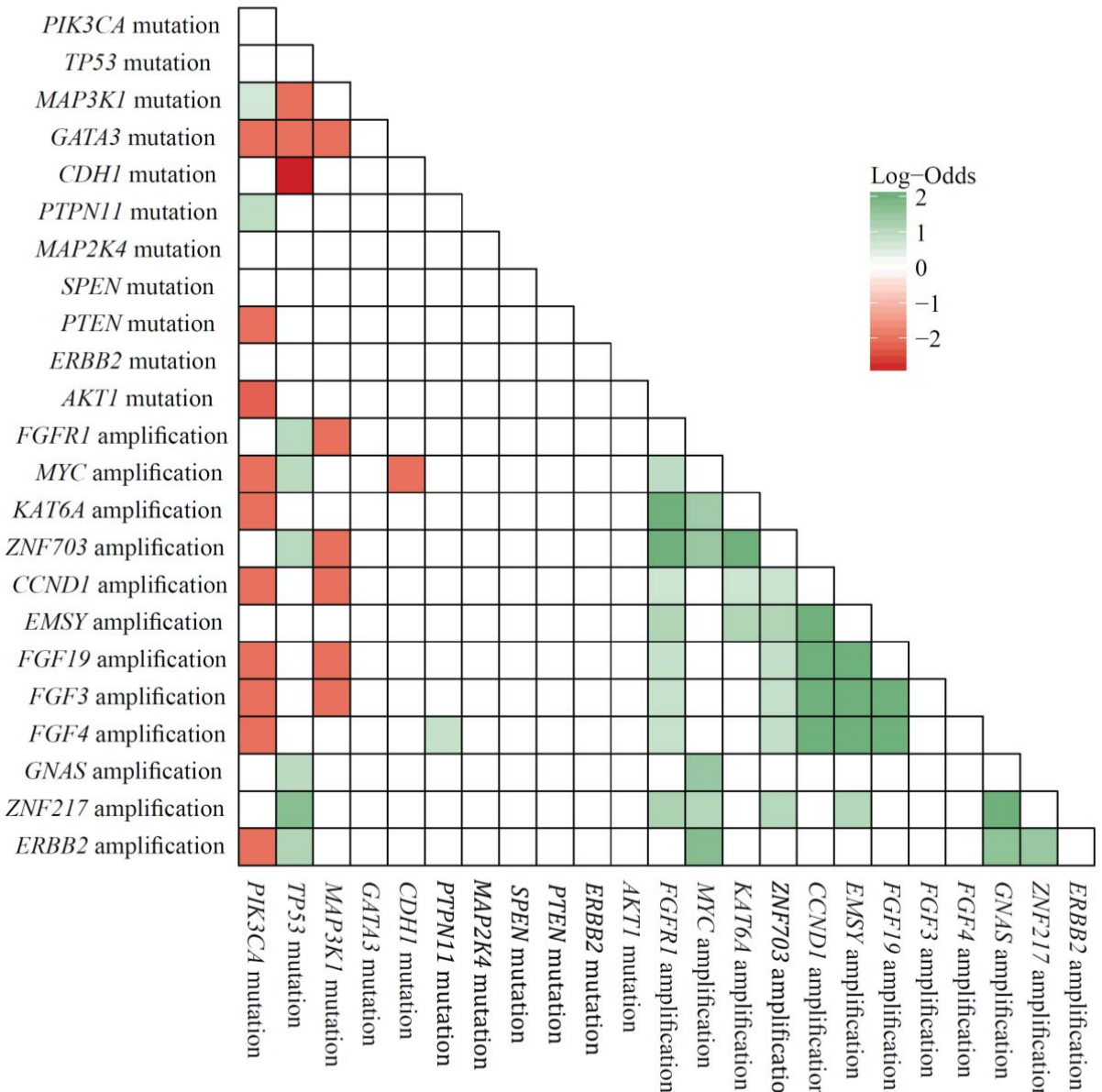
eFigure 5. Associations With Ki-67 (%) Levels

Panel A shows the association of driver alterations with centrally-assessed ki-67 level (%). All displayed boxplots of mutation versus wild type or amplification versus non-amplification are statistically significant (P value < 0.05 by weighted t-test) as shown in Table SR3. Panel B demonstrates the diversity in centrally assessed ki-67 levels (%) based on the presence or absence of co-existent driver alterations in tumors that harbour a *PIK3CA* mutation. Focal gene amplifications on chromosomes 11q13 and 8p11 are described in the text. * P value < 0.05 by weighted t-test versus subgroup of patients with tumors that harbour a PIK3CA mutation and no-coalteration ("None").

eFigure 6. Association of Pathological Characteristics by Affected *PIK3CA* Protein Domain



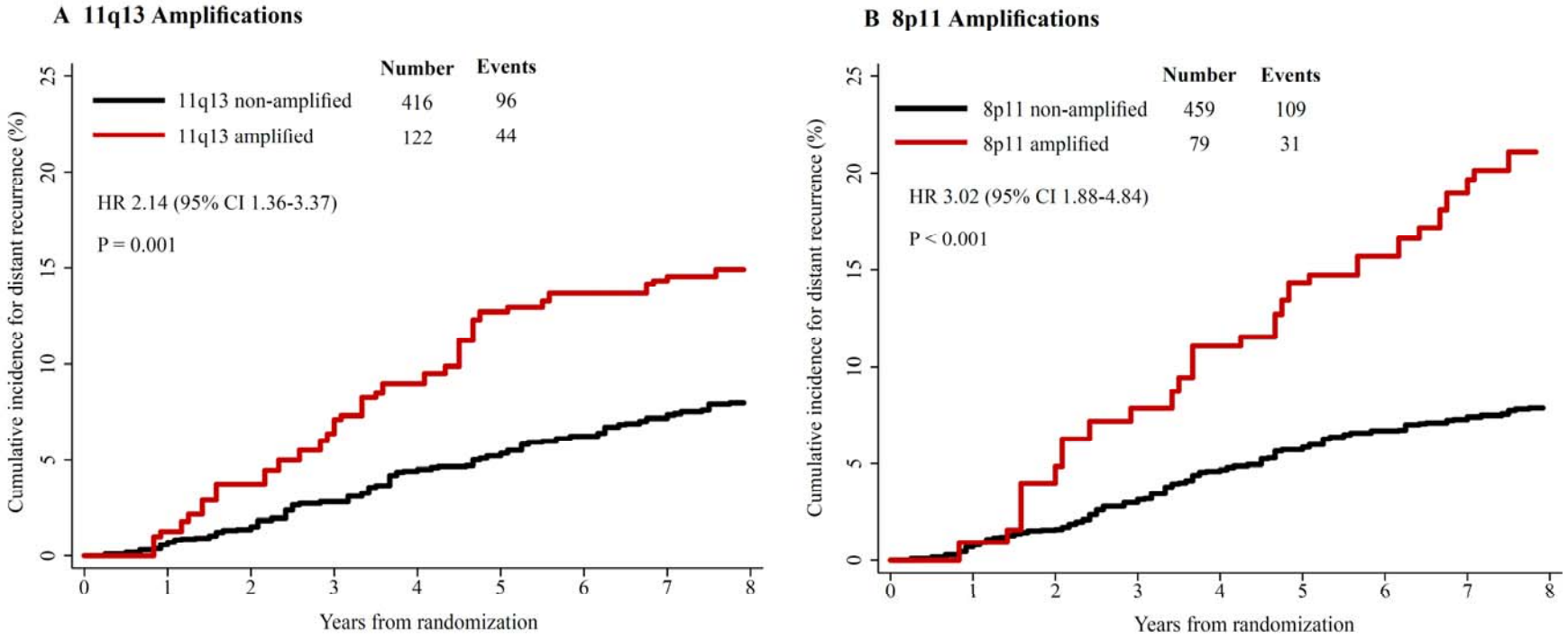
Boxplots demonstrating estrogen receptor expression (Panel A), progesterone receptor expression (Panel B), and centrally assessed ki-67 (Panel C) by affected *PIK3CA* protein domain or wild type. The *PIK3CA* Kinase and helical domain group refers to patients with both a kinase and helical domain mutation. There were no statistically significance differences between the shown groups using a Kruskal-Wallis test with a P value of < 0.05 for significance, with the exception of the P value shown. Abbreviations: ER, estrogen receptor; PR, progesterone receptor.



eFigure 7. Pairwise Analysis

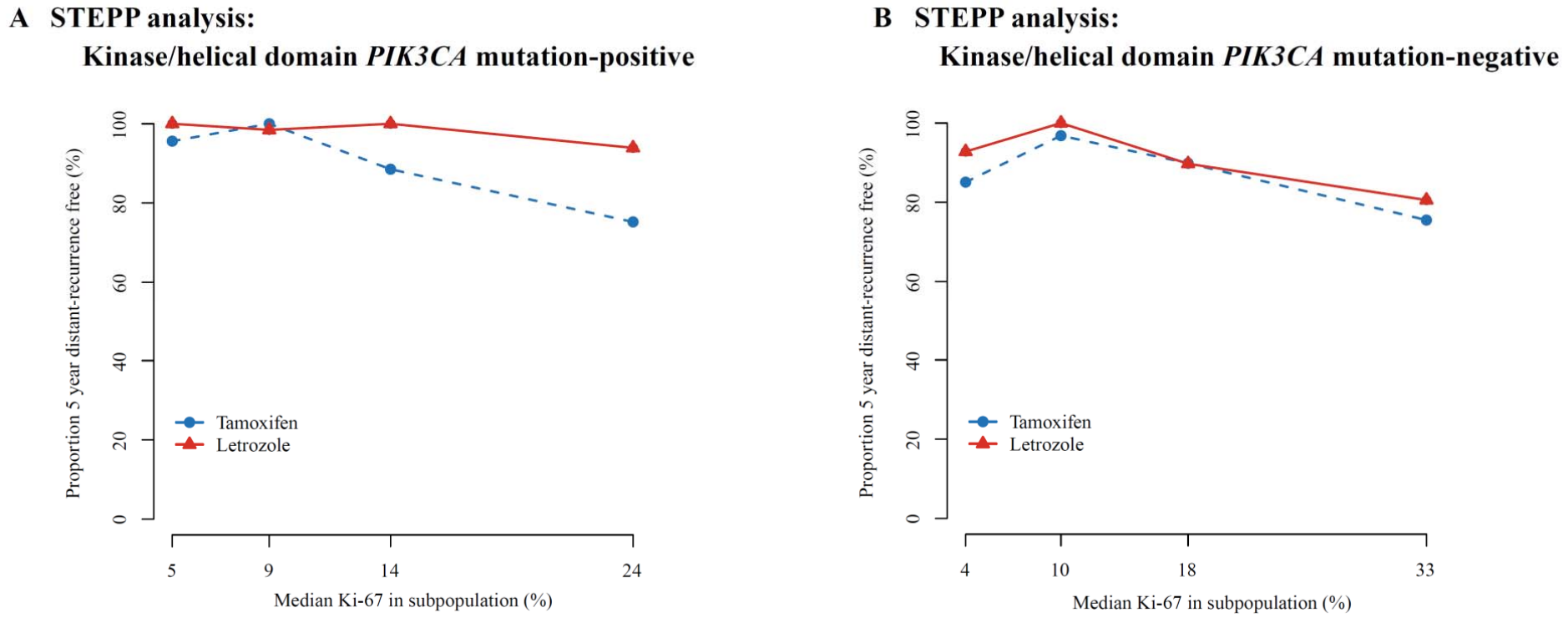
Fisher's exact test between somatic alteration pairs was applied to alterations with a weighted population frequency of 5% or greater, in addition to breast cancer alterations of interest (*ERBB2* and *AKT1* mutations), generating odds ratios and p-values. Only log-odds with a false discovery rate of < 0.2 are displayed. Log-odds are capped (2, if >2; -2 if < -2) and shown by color with green indicating an association with co-existence, and red indicating an association with mutual exclusivity.

eFigure 8. Prognostic Association of Frequent Amplicons With DRFI



Weighted cumulative incidence curves are shown for the distant recurrence (%) by 11q13 (*CCND1*, *EMSY*, *FGF3*, *FGF4*, *FGF19*) amplification status (Panel A) and by 8p11 (*FGFR1*, *KAT6A*, *ZNF703*) amplification status (Panel B). Hazard ratio, 95% confidence intervals and P values attained using weighted Cox Proportional Hazard models stratified by treatment arm. Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval.

eFigure 9. STEPP Analysis by *PIK3CA* Mutation Status



Panels A and B demonstrate the STEPP analysis of the effect of treatment with letrozole or tamoxifen on the weighted proportion of patients who are distant-recurrence free at 5 years according to overlapping subpopulations defined by median Ki-67 levels (%) by *PIK3CA* mutation status. Abbreviations: STEPP, Subpopulation Treatment Effect Pattern.

