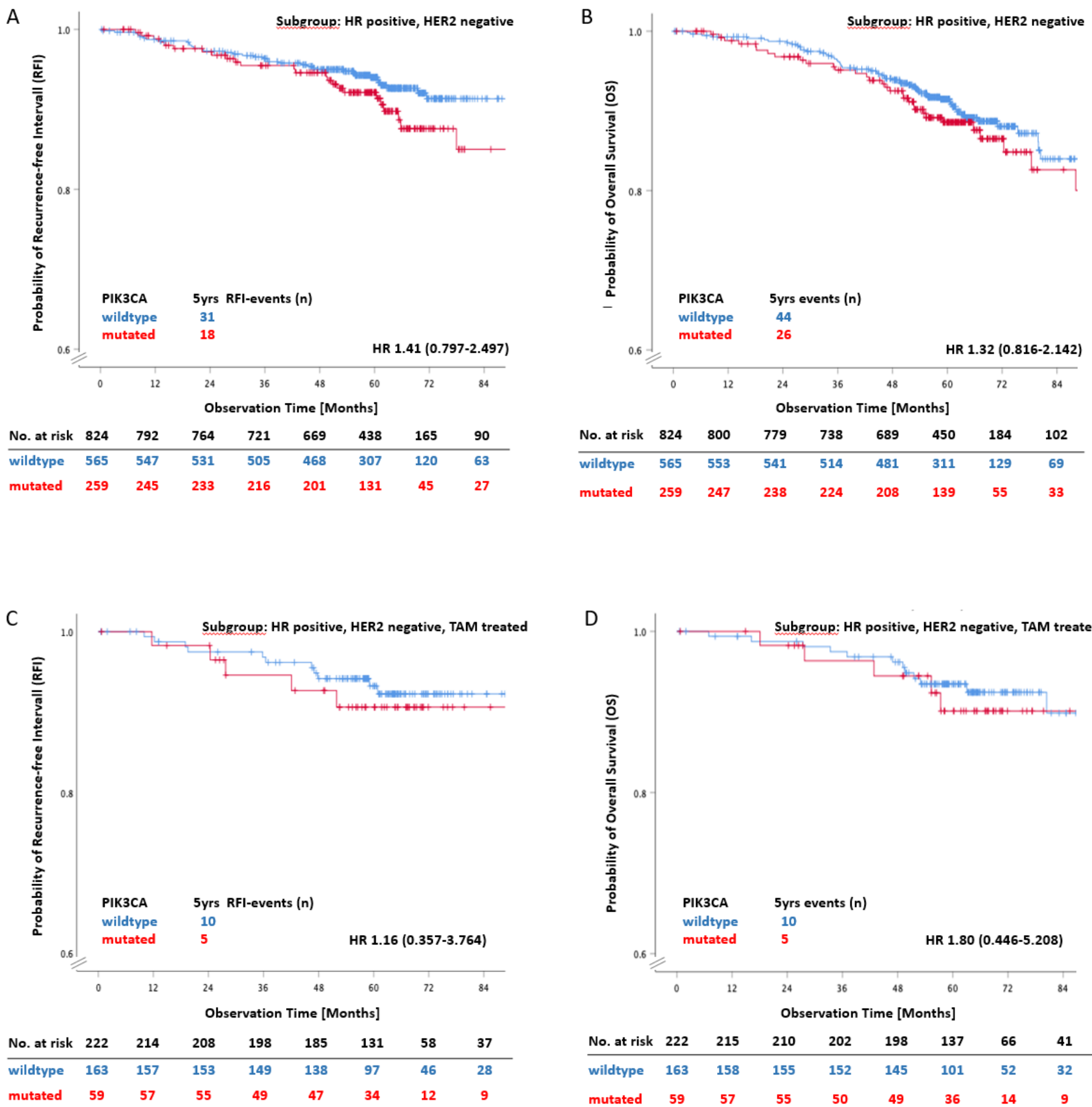


PIK3CA mutations in breast cancer

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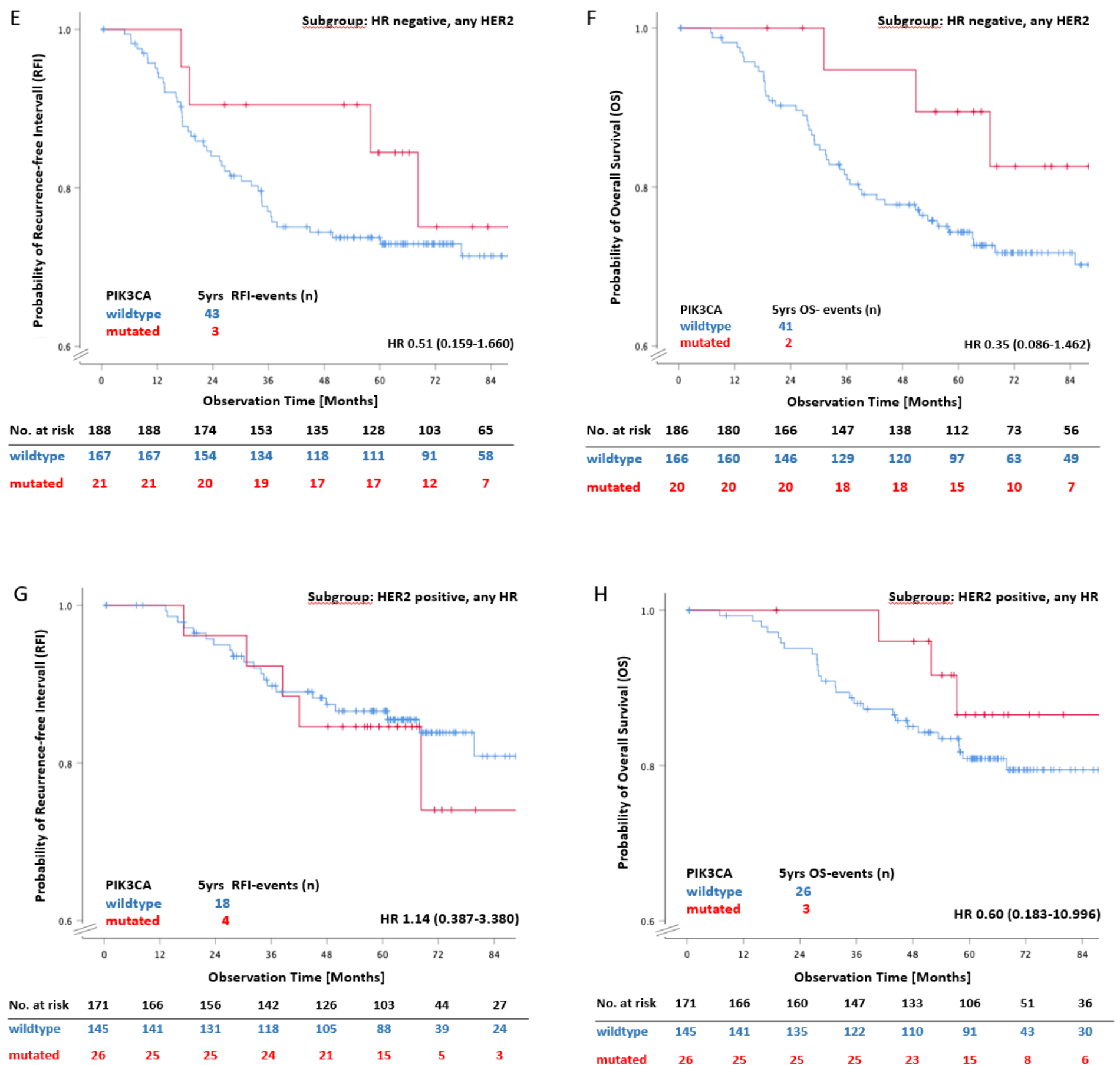
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Supplement Fig. S1 Survival estimates for RFI and OS stratified by detection of PIK3CA- mutations. The tables present the effective sample size for each interval (numbers at risk).

A, B: Patients with HR positive and HER2 negative tumours (n=824), RFI (A) and OS (B)

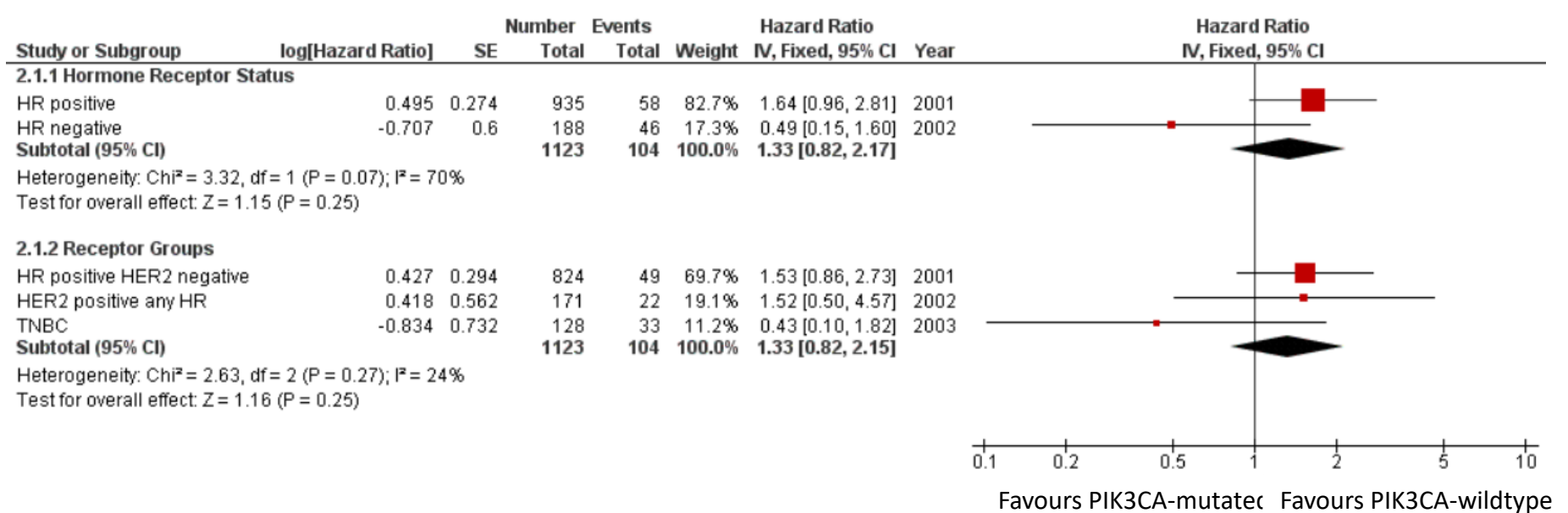
C, D: Patients with HR positive tumours and HER2 negative tumours, Tamoxifen treatment only (n=222), RFI (C) and OS (D)



Supplementary Fig. S1 Survival estimates for RFI and OS stratified by detection of PIK3CA- mutations
The tables present the effective sample size for each interval (numbers at risk)

E, F: Patients with HR negative tumours, irrespective of HER2 status (n= 188), RFI (C) and OS (D)

G, H: Patients with HER2 positive tumours, irrespective of HR status (n=171), RFI (G) and OS (H)



Supplementary Fig. S2 Forest plot for the effect of PIK3CA mutation in different subgroups on RFI

Hazard ratios for subtotals represent aggregation of the weighted subgroup, therefore results that may be different from calculations based on individual data

Supplementary Table S1 Patients characteristics and histopathological parameters of the tumours with PIK3CA mutations

Parameters	Total cohort n=1,270 (100 %)	PIK3CA - cohort n=1,123 (100%)
Age at time of diagnosis		
≤ 50 years	344 (27.1%)	293 (26.1%)
> 50 years	926 (72.29%)	830 (73.9%)
Histological type		
ductal	1039 (81.8%)	905 (80.6%)
lobular	172 (13.5%)	163 (14.5%)
others	59 (4.7%)	55 (4.9%)
Tumour size at time of diagnosis		
< 2cm	636 (50.1%)	575 (51.2%)
≥ 2 cm	634 (49.9%)	548 (48.8%)
Nodal status at time of diagnosis		
Node-negative	780 (61.4%)	688 (61.3%)
Node-positive	490 (38.6%)	435 (38.7%)
Tumour differentiation		
G1	167 (13.1%)	154 (13.7%)
G2	794 (62.5%)	703 (62.6%)
G3	309 (24.4%)	266 (23.6%)
ER status		
ER positive (≥ 1%)	1,020 (80.3%)	919 (81.8%)
ER negative (< 1%)	250 (19.7%)	204 (18.2%)
PgR status		
PgR positive (≥ 1%)	862 (67.9%)	776 (69.1%)
PgR negative (< 1%)	408 (32.1%)	347 (30.9%)
HR status (ER, PgR combined)		
HR positive	1,038 (81.7%)	935 (83.3%)
HR negative	232 (18.3%)	188 (16.7%)
HER2 Status		
HER2 negative	1,060 (83.5%)	952 (84.8%)
HER2 positive	210 (16.5%)	171 (15.2%)
IHC types		
HR positive and HER2 negative	907 (71.4%)	824 (73.4%)
HER2 positive and HR positive	133 (10.5%)	111 (9.9%)
HER2 positive and HR negative	78 (6.1%)	60 (5.3%)
TNBC	152 (12.0%)	128 (11.4%)

Supplementary Table S2 Patients characteristics and histopathological parameters of the tumours for patients treated with Aromatase Inhibitors (n=208)

Parameters	AI treated - cohort n=208 (100%)	Wildtype - cohort n=140 (100%)	PIK3CA - cohort n=68 (100%)
Age at time of diagnosis			
≤ 50 years	1 (0.5%)	1 (0.7%)	- -
> 50 years	207 (99.5%)	139 (99.3%)	68 (100.0%)
Histological type			
ductal	159 (76.4%)	101 (72.1%)	58 (85.3%)
lobular	30 (14.4%)	22 (15.7%)	8 (11.8%)
others	19 (9.1%)	17 (12.1%)	2 (2.9%)
Tumour size at time of diagnosis			
< 2cm	122 (58.7%)	80 (57.1%)	42 (61.8%)
≥ 2 cm	86 (41.3%)	60 (42.9%)	26 (38.2%)
Nodal status at time of diagnosis			
Node-negative	163 (78.4%)	113 (80.7%)	50 (73.5%)
Node-positive	45 (21.6%)	27 (19.3%)	18 (26.5%)
Tumour differentiation			
G1	61 (29.3%)	42 (30.0%)	19 (27.9%)
G2	128 (61.5%)	84 (60.0%)	44 (64.7%)
G3	19 (9.1%)	14 (10.0%)	5 (7.4%)
ER status			
ER positive (≥ 1%)	205 (98.6%)	137 (97.9%)	68 (100.0%)
ER negative (< 1%)	3 (1.4%)	3 (2.1%)	- -
PgR status			
PgR positive (≥ 1%)	177 (85.1%)	116 (82.9%)	61 (89.7%)
PgR negative (< 1%)	31 (14.9%)	24 (17.1%)	7 (10.3%)
HR status (ER, PgR combined)			
HR positive	208 (100.0%)	140 (100.0%)	68 (100.0%)
HR negative	- -	- -	- -
HER2 Status			
HER2 negative	208 (100.0%)	140 (100.0%)	68 (100.0%)
HER2 positive	- -	- -	- -
IHC types			
HR positive and HER2 negative	208 (100.0%)	140 (100.0%)	68 (100.0%)
HER2 positive and HR positive	- -	- -	- -
HER2 positive and HR negative	- -	- -	- -
TNBC	- -	- -	- -

Supplementary Table S 3 Univariate and multivariate analysis of RFI (A) and OS (B) considering PIK3CA mutation status

A											
Group		sample size (n)	events (n)	RFI [%]	95% CI	Hazard ratio univariate RFI	95% CI	p-value	Hazard ratio multivariate RFI	95% CI	p-value
ALL*	wiltype	1,123	103								
	mutated	823	79	89.8	87.6-92.0						
		300	24	90.9	87.4-94.4	0.867	0.554-1.359	0.535	1.193	0.752-1.894	0.454
HR positive, any HER2 **	wiltype	935	58								
	mutated	656	37	93.8	91.6-96.0						
		279	21	91.5	88.0-95.0	1.468	0.866-2.489	0.154	1.640	0.958-2.807	0.071
HR positive, HER2 negative **	wiltype	824	49								
	mutated	565	31	94.0	91.8-96.2						
		259	18	92.1	88.6-95.6	1.410	0.797-2.497	0.238	1.532	0.861-2.727	0.147
HR positive, HER2 negative, AIs treated only**	wiltype	208									
	mutated	140	5	96.0	92.7-99.3						
		68	8	85.7	76.5-95.0	4.231	1.409 – 2.699	0.010	4.391	1.385-13.920	0.012
HR positive, HER2 negative, TAM treated only**	wiltype	192									
	mutated	137	9	92.8	92.0-93.6						
		55	4	91.9	84.3-99.5	1.159	0.357-3.764	0.806	1.17	0.357-3.836	0.796
HR negative, any HER2 **	wiltype	188	46								
	mutated	167	43	72.9	66.0-79.8						
		21	3	84.4	68.1-99.9	0.514	0.159-1.660	0.266	0.493	0.152-1.597	0.238
TNBC **	wiltype	128	33								
	mutated	113	31	71.5	63.1-79.9						
		15	2	84.0	63.2-99.9	0.446	0.107-1.866	0.269	0.434	0.103-1.822	0.254
HER2 positive, any HR **	wiltype	171	22								
	mutated	145	18	86.6	80.7-92.5						
		26	4	84.6	70.7-98.5	1.144	0.387-3.380	0.808	1.519	0.505-4.568	0.457

B											
Group		sample size (n)	events (n)	OS [%]	95% CI	Hazard ratio univariate OS	95% CI	p-value	Hazard ratio multivariate OS	95% CI	p-value
ALL *	wiltype	1,123	129								
	mutated	823	98	87.2	84.8-89.6						
		300	31	88.2	84.3-92.1	0.870	0.581-1.303	0.500	1.081	0.714-1.638	0.712
HR positive, any HER2 **	wiltype	935	86								
	mutated	656	57	90.5	88.1-92.9						
		279	29	88.1	84.0-92.2	1.221	0.782-1.906	0.380	1.366	0.867-2.152	0.179
HR positive, HER2 negative **	wiltype	824	70								
	mutated	565	44	91.5	89.1-93.9						
		259	26	88.6	84.5-92.7	1.322	0.816-2.142	0.257	1.365	0.837-2.227	0.212
HR positive, HER2 negative, AIs treated **	wiltype	208									
	mutated	140	15	85.2	79.6-91.4						
		68	15	73.5	63.0-85.8	2.373	1.172-4.80	0.016	2.120	1.021-4.404	0.044
HR positive, HER2 negative, TAM treated only**	wiltype	192									
	mutated	137	7	94.5	90.6-98.4						
		55	4	91.7	83.9-99.5	1.524	0.446-5.208	0.501	1.601	0.463-5.533	0.457
HR negative, any HER2 **	wiltype	188	56								
	mutated	167	49	74.3	67.4-81.2						
		21	7	89.5	75.8-99.9	0.354	0.086-1.462	0.151	0.323	0.078-1.340	0.120
TNBC **	wiltype	128	30								
	mutated	113	28	74.3	66.1-82.5						
		15	2	85.7	77.8-99.9	0.483	0.115-2.027	0.320	0.451	0.107-1.903	0.278
HER2 positive, any HR **	wiltype	171	29								
	mutated	145	26	80.9	74.2-87.6						
		26	3	86.5	72.2-99.9	0.604	0.183-10.996	0.409	0.743	0.223-2.471	0.627

adjusted to:
* Tumour size, nodal status, grading, HR-status, HER2 Status, PIK3CA mutation status
** Tumour size, nodal status, grading, PIK3CA mutation status
bold: significant