SUPPLEMENTARY MATERIAL

SUPPLEMENTARY METHODS

Statistical analysis. For concordance calculation, samples carrying the 3 hotspot mutations in paired tumor-cfDNA from the same patients were designated as concordant. Tumor samples with mutations other than the 3 hotspot mutations tested in the ctDNA were designated as wild-type for concordance calculation purpose.

Supplementary Table 1. Baseline characteristics and clinical outcomes in cfDNA and overall population in BOLERO-2

Characteristic	cfDNA population		Overall study population	
	EVE + EXE (n=357)	**PBO + EXE (n=193)**	**EVE + EXE (n=485)**	**PBO + EXE (n=239)**
Age, years (range)	61 (54-68)	60 (54-66)	62 (56-69)	61 (55-66)
Race, n (%)				
White	274 (77)	151 (78)	361 (74)	186 (78)
Asian	66 (18)	37 (19)	98 (20)	45 (19)
Other	17 (05)	5 (03)	26 (6)	8 (3)
ECOG performance status, n (%)				
0	203 (57)	114 (59)	292 (60)	142 (59)
1	140 (39)	70 (36)	175 (36)	84 (35)
2	7 (2)	4 (2)	9 (2)	7 (3)
Visceral disease, n (%)	198 (55)	108 (56)	271 (56)	135 (56)
Number of metastatic sites, n (%)				
1	106 (30)	47 (24)	154 (32)	64 (27)
2	116 (32)	77 (40)	149 (31)	84 (35)
≥3	134 (38)	69 (36)	180 (37)	91 (38)
Previous sensitivity to endocrine therapy, n (%)	300 (84)	161 (83)	409 (84)	201 (84)
Previous endocrine treatment, n (%)				
Letrozole or anastrozole	357 (100)	193 (100)	485 (100)	239 (100)
Tamoxifen	167 (47)	97 (50)	230 (47)	119 (50)
Fulvestrant	60 (17)	30 (16)	80 (17)	39 (16)
PFS events	255	171	310	200
Median PFS, months (95% CI)	6.97 (6.77-8.34)	2.83 (2.76-4.07)	7.82 (6.93-8.48)	3.19 2.76-4.14)
Hazard ratio (95% CI)	0.43 (0.35-0.52)		0.45 (0.37-0.54)	

cfDNA = cell-free DNA; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; EVE = everolimus; EXE = exemestane; PFS = progression-free survival.

Supplementary Table 2. Exploratory analysis of *PIK3CA* by mutation-site in the placebo arm

Group	N	PFS Events	Median PFS (95% CI)	Hazard ratio (95% CI)	OS Events	Median OS (95% CI)	Hazard ratio (95% CI)
WT	124	111	2.96 (2.76-4.17)		70	29.67 (21.91-40.25)	
MT	69	60	2.69 (1.51-4.11)	1.26 (1.01-1.58)	49	22.70 (15.41-32.10)	1.32 (1.02-1.71)
H1047R	43	38	4.04 (1.51-4.7)	1.15 (0.88-1.49)	28	28.48 (19.91-35.61)	1.13 (0.83-1.55)
E545K/E542K	26	22	2.22 (1.38-2.76)	1.56 (1.12-2.18)	21	13.77 (10.22-29.31)	1.72 (1.22-2.43)

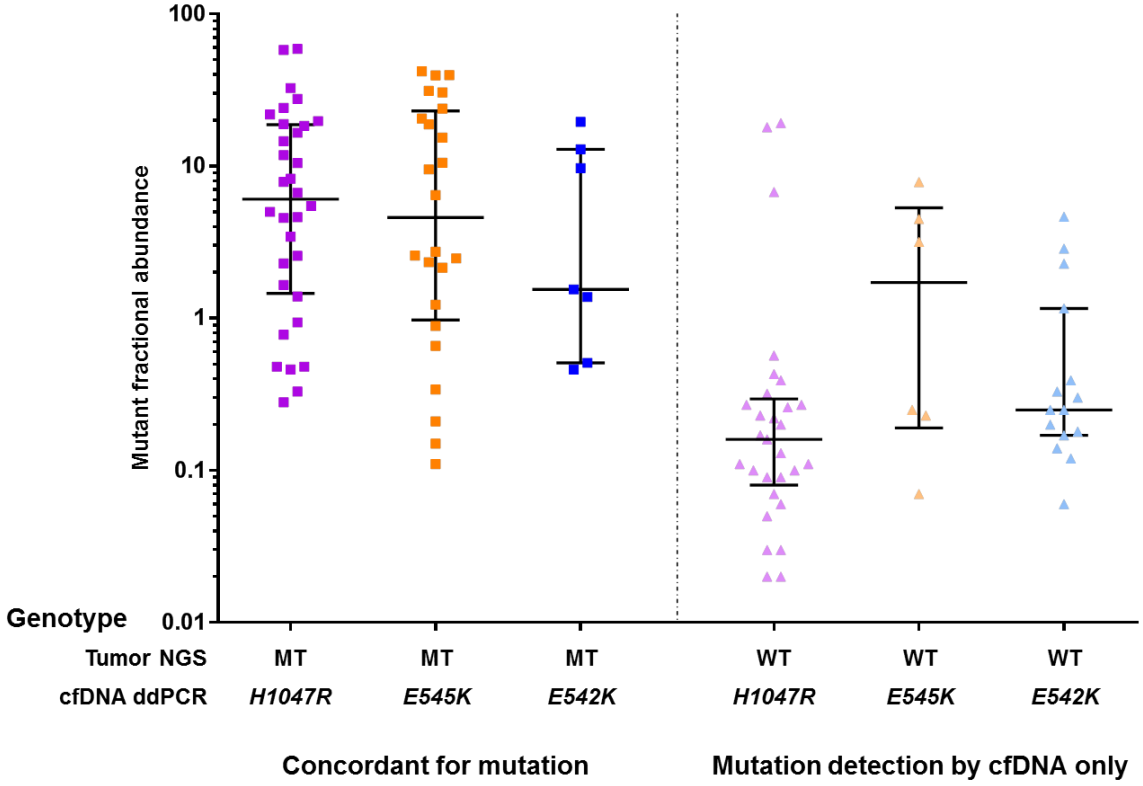
CI = confidence interval; MT = mutant; OS = overall survival; PFS = progression-free survival; WT = wild-type.

Supplementary Table 3. Multivariate analysis adjusting for sensitivity to prior hormonal therapy, visceral disease and ECOG status

PIK3CA status	Treatment	N	PFS Events	Median PFS (95% CI)	Adjusted hazard ratio (95% CI)
WT	PBO + EXE	124	111	2.96 (2.76 - 4.17)	0.39 (0.3 - 0.51)
	EVE + EXE	188	132	7.36 (6.77 - 9.69)	
MT	PBO + EXE	69	60	2.69 (1.51 - 4.11)	0.35 (0.25 - 0.49)
	EVE + EXE	169	123	6.9 (5.55 - 8.31)	

CI = confidence interval; EVE = everolimus; EXE = exemestane; MT = mutant; PBO = placebo; PFS = progression-free survival; WT = wild-type.

Supplementary Figure 1. Comparison of cfDNA *PIK3CA* mutant allele fractional abundance in tumor-cfDNA paired samples by mutation concordance



Filled shapes represent the baseline cfDNA mutant allele fractional abundance for each patient separated by mutation site and tumor NGS genotype. A dotted line separates the samples that were concordant for both tumor NGS and cfDNA ddPCR *PIK3CA* genotype and those that were discordant with *PIK3CA* mutation identified by cfDNA ddPCR only. The *y*-axis is a logarithmic scale. Error bars depict median with interquartile range. cfDNA = cell free DNA; ddPCR = droplet digital PCR; NGS = next-generation sequencing; MT = mutant; WT = wild-type.