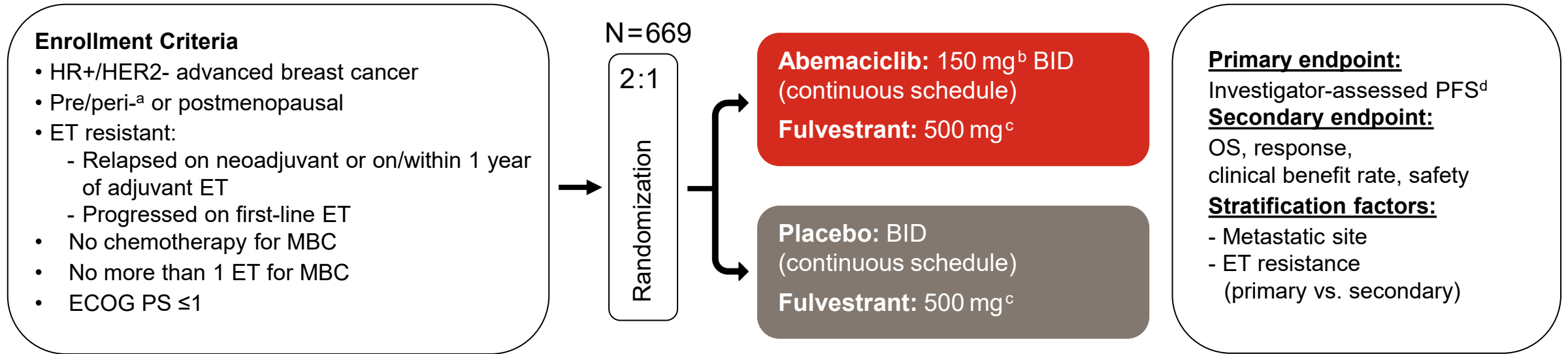


Supplemental Figure 1 - MONARCH 2 study design



Abbreviations: BID = twice daily; ET = endocrine therapy; ECOG PS = Eastern Cooperative Oncology Group Performance Status; HR+ = hormone receptor positive; HER2- = human epidermal growth factor receptor 2 negative; MBC = metastatic breast cancer; N = number; OS = overall survival; PFS = progressive-free survival

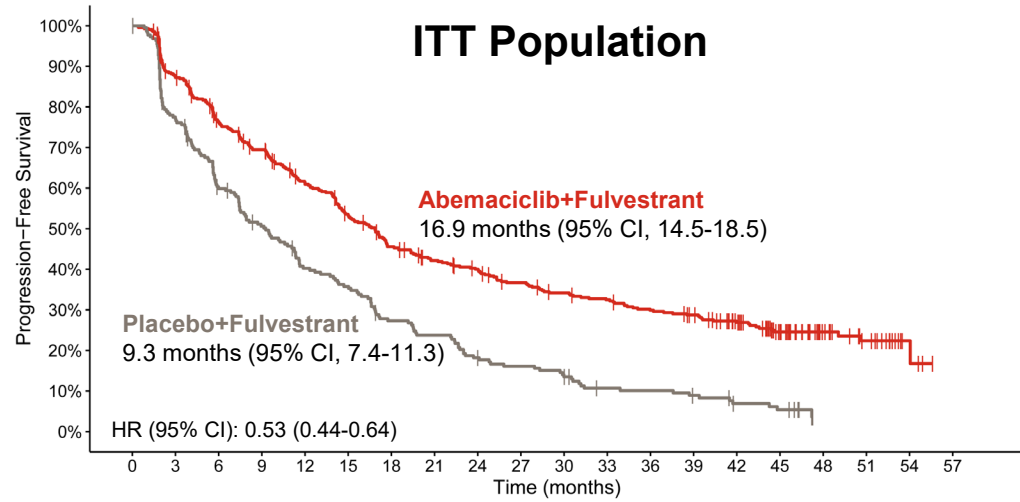
^a Required to receive gonadotropin-releasing hormone agonist

^b Dose reduced by protocol amendment in all new and ongoing patients from 200 mg to 150 mg BID after 178 patients enrolled

^c Fulvestrant administered per label

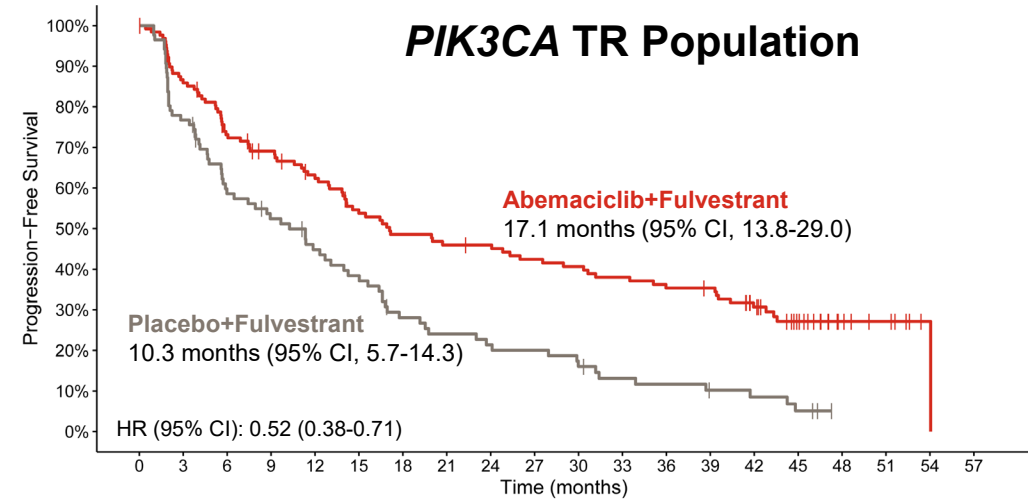
^d Statistics: 378 events for 90% power at 1-sided α of .025 assuming a true hazard ratio (HR) of .703

Supplemental Figure 2 - Progression-Free Survival: ITT and TR populations



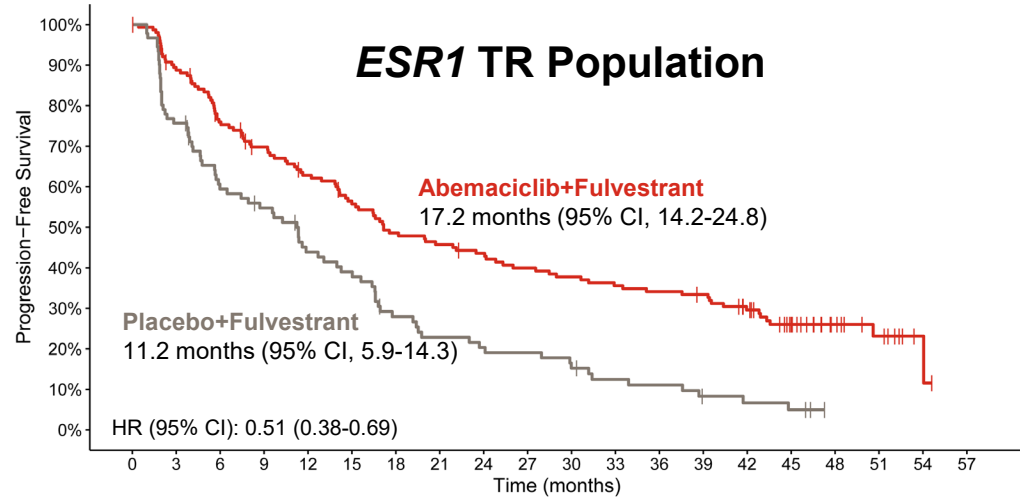
Number at risk

446	365	312	280	242	208	176	158	147	132	121	114	104	97	78	53	28	18	4	0
223	165	124	103	81	72	54	47	36	31	26	18	17	14	9	7	0	0	0	0



Number at risk

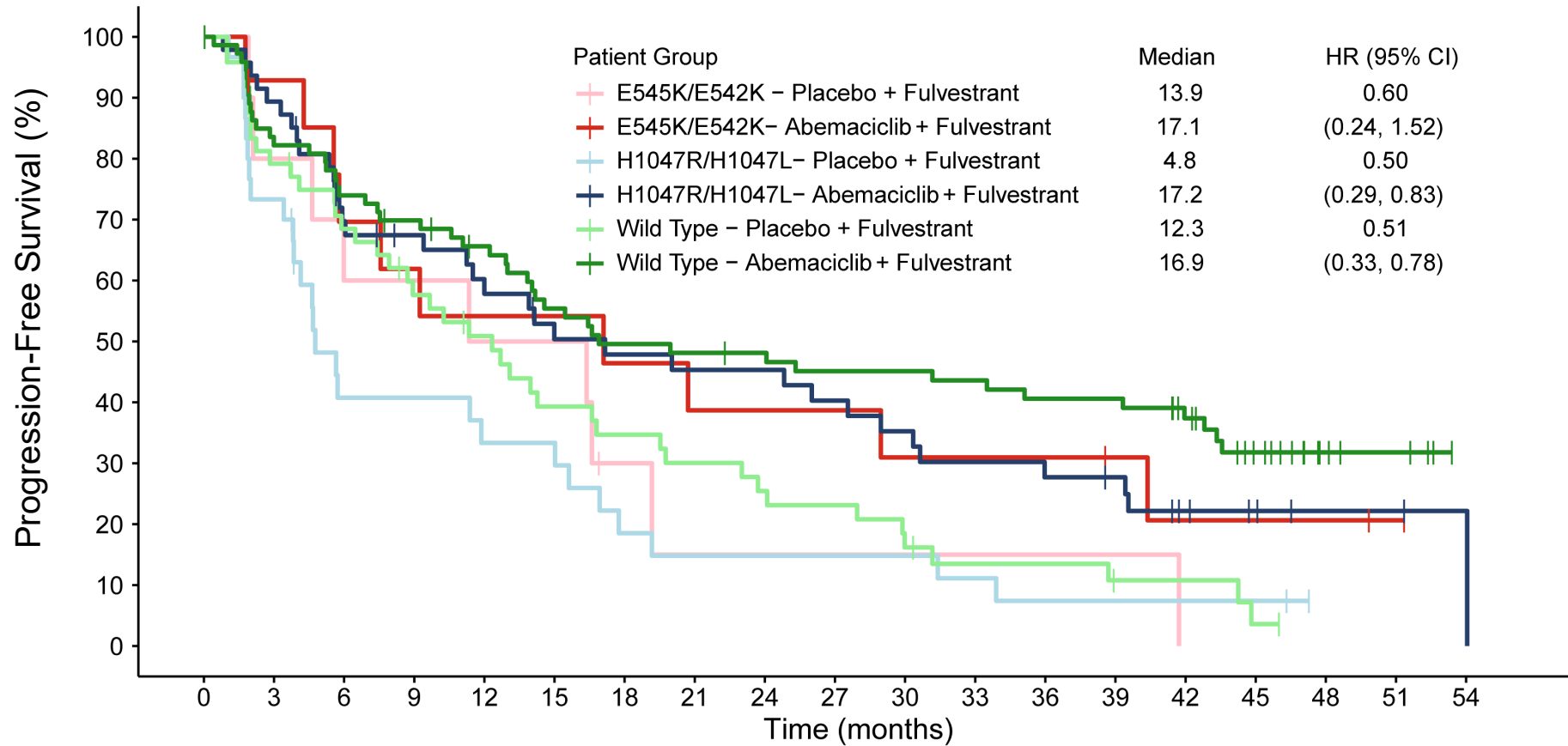
133	109	91	83	74	62	56	53	52	48	46	43	40	39	29	19	9	6	1	0
86	66	48	42	35	30	21	18	16	15	12	9	8	6	5	3	0	0	0	0



Number at risk

157	133	112	100	89	78	68	64	60	55	52	49	47	45	36	25	13	8	2	0
91	68	51	46	36	32	22	18	16	15	12	9	8	5	4	3	0	0	0	0

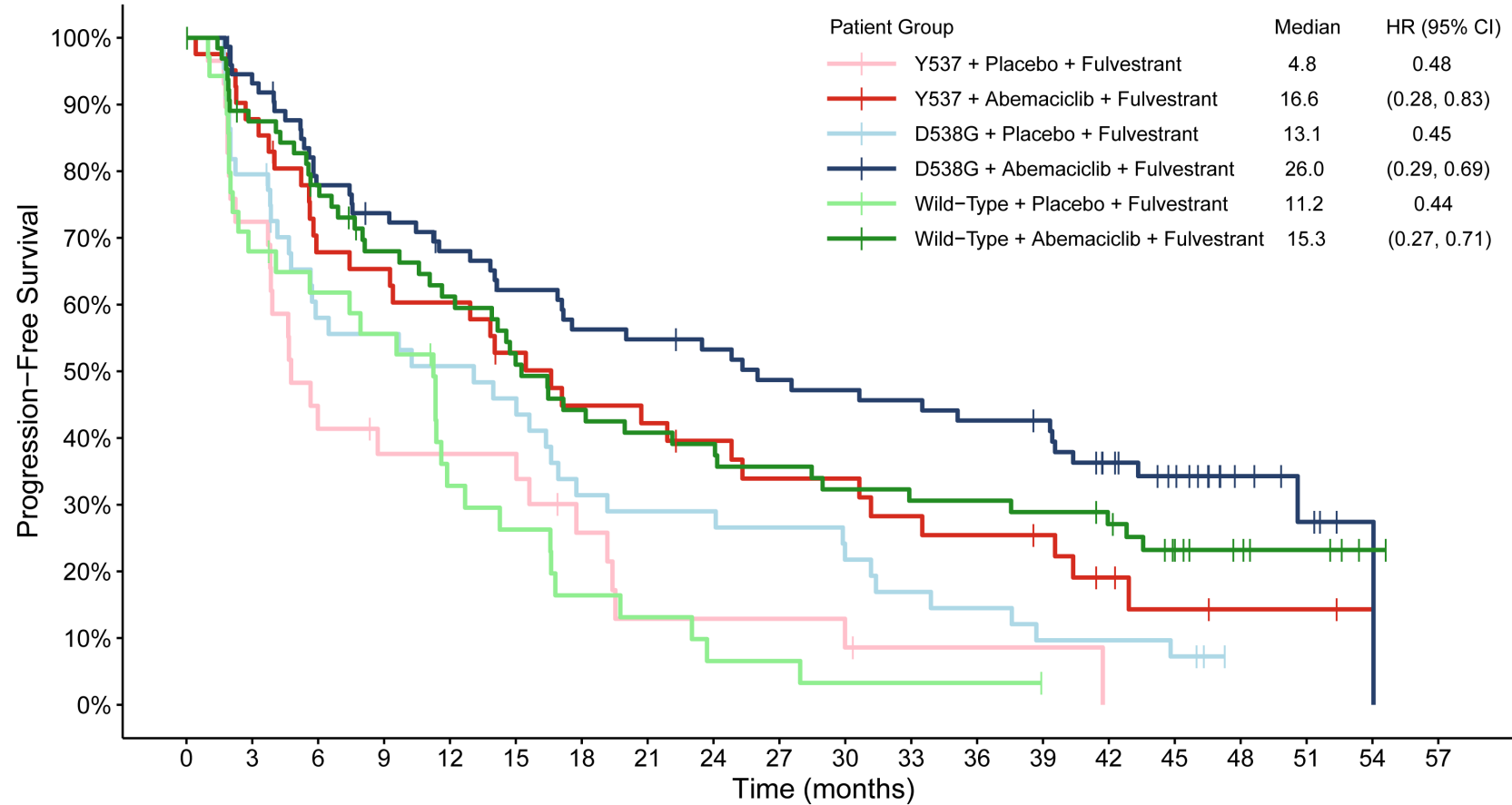
Supplemental Figure 3 – Kaplan-Meier plots of progression-free survival by mutation for patients harboring *PIK3CA* mutant vs wild-type tumors



Number at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54
—	10	8	6	6	5	5	2	1	1	1	1	1	1	1	1	0	0	0	0	0
—	14	12	9	8	7	7	6	5	5	5	4	4	4	4	3	2	2	2	1	0
—	30	22	11	11	9	9	5	4	4	4	4	4	3	2	2	2	2	0	0	0
—	50	42	31	28	25	20	19	18	18	16	14	12	11	11	10	6	4	2	2	1
—	48	38	32	26	22	17	15	13	11	10	7	5	5	3	3	3	1	0	0	0
—	75	60	54	50	45	38	34	33	32	30	30	29	27	27	22	14	6	4	0	0

**Note: Hazard Ratio were calculated between the treatment and placebo arm.
8 patients belong to both E545K/E542K and H1047R/H1047L groups**

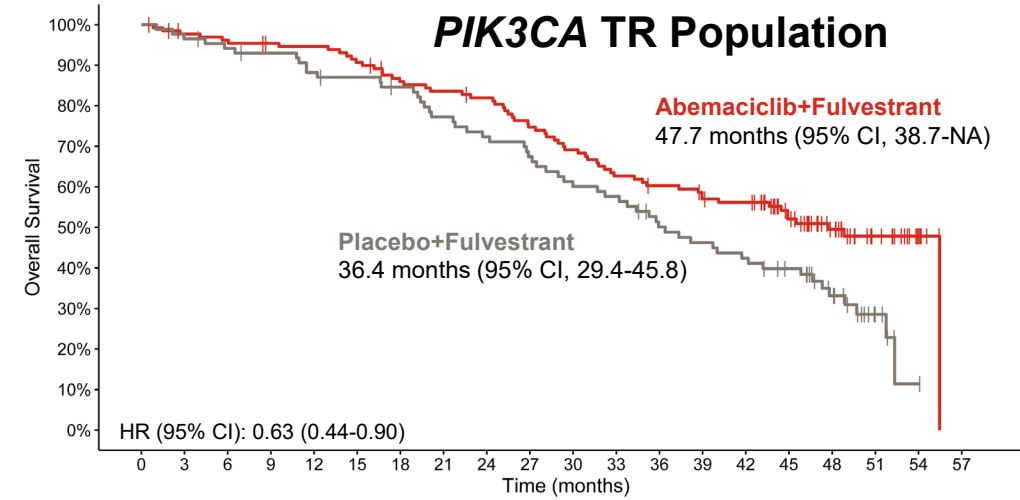
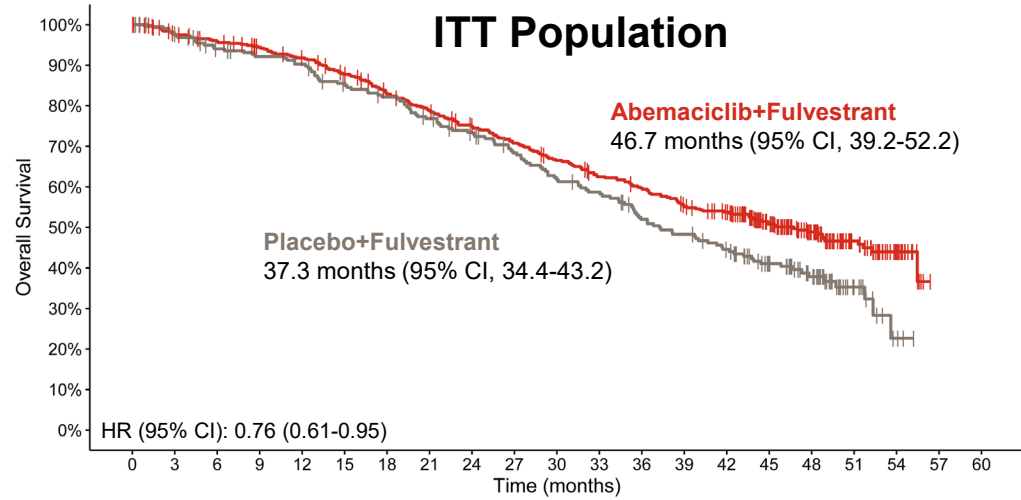
Supplemental Figure 4 – Kaplan-Meier plots of progression-free survival by mutation for patients harboring *ESR1* mutant vs wild-type tumors



Number at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Y537 + Placebo + Fulvestrant	29	21	12	10	10	10	6	3	3	3	2	1	1	1	0	0	0	0	0	0	0
Y537 + Abemaciclib + Fulvestrant	42	36	27	26	24	20	17	16	14	12	12	10	9	8	5	3	2	2	2	1	0
D538G + Placebo + Fulvestrant	44	35	24	23	21	19	13	12	12	11	9	7	6	4	3	0	0	0	0	0	0
D538G + Abemaciclib + Fulvestrant	76	68	56	52	47	42	38	37	35	32	31	30	28	27	20	15	7	4	1	0	0
Wild-Type + Placebo + Fulvestrant	35	23	20	18	10	8	5	4	2	2	1	1	1	0	0	0	0	0	0	0	0
Wild-Type + Abemaciclib + Fulvestrant	66	55	48	40	36	30	26	24	23	21	19	18	18	17	15	10	6	4	1	0	0

**Note: Hazard Ratio were calculated between the treatment and placebo arm.
44 patients belong to both D538G and Y537 mutation groups**

Supplemental Figure 5 - Kaplan-Meier plots of overall survival in the ITT vs. TR population

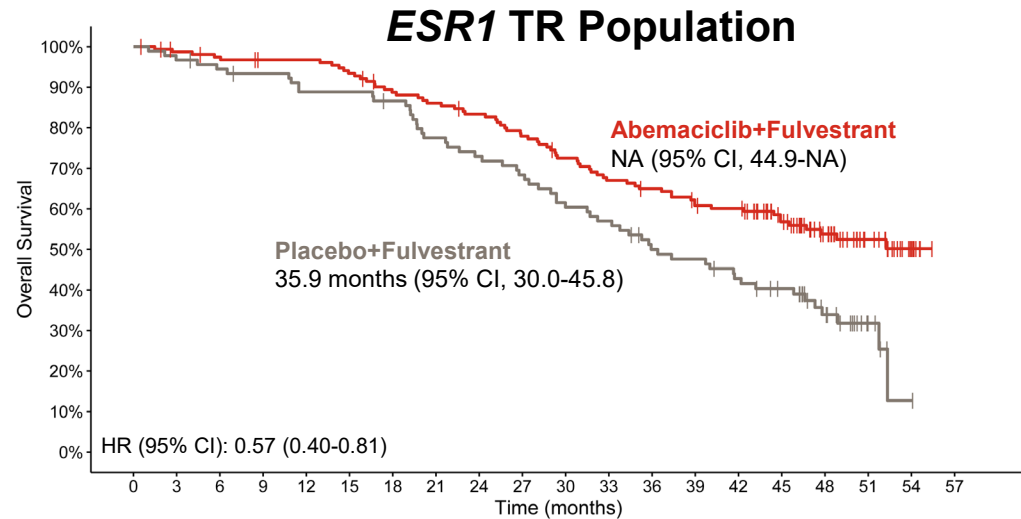


Number at risk

—	446	422	410	397	384	364	339	321	302	284	265	246	234	214	202	157	101	58	23	0	0
—	223	214	201	195	191	178	170	158	148	135	122	115	99	92	82	62	42	15	3	0	0

Number at risk

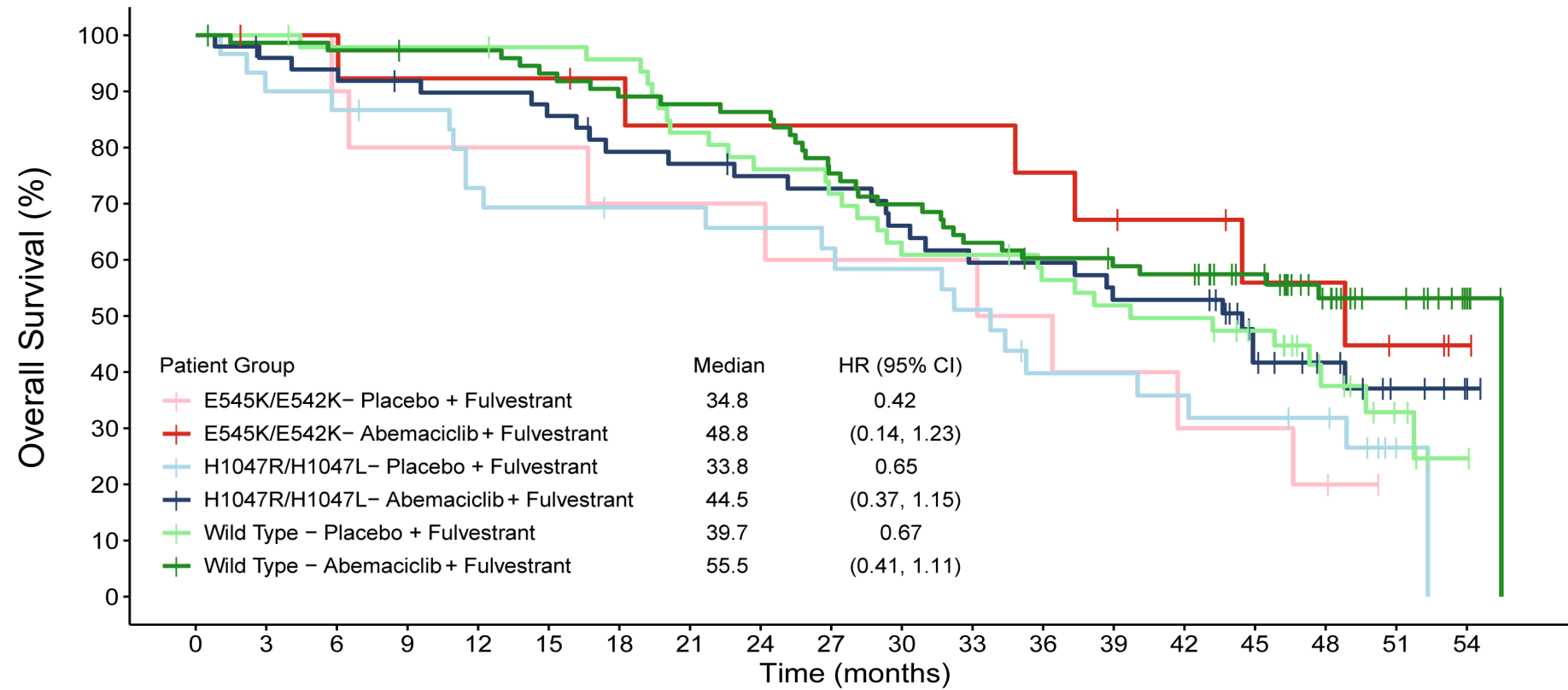
—	133	127	125	122	121	116	108	105	102	93	86	78	74	69	67	49	34	21	8	0
—	86	83	80	78	74	72	69	63	59	55	49	47	39	36	33	28	18	6	1	0



Number at risk

—	157	152	149	146	146	141	132	128	123	115	106	98	94	87	85	66	46	30	9	0
—	91	88	85	83	79	79	76	68	64	60	53	50	42	40	35	30	19	6	1	0

Supplemental Figure 6 – Kaplan-Meier plots of overall survival by mutation for patients harboring *PIK3CA* mutant vs wild-type tumors

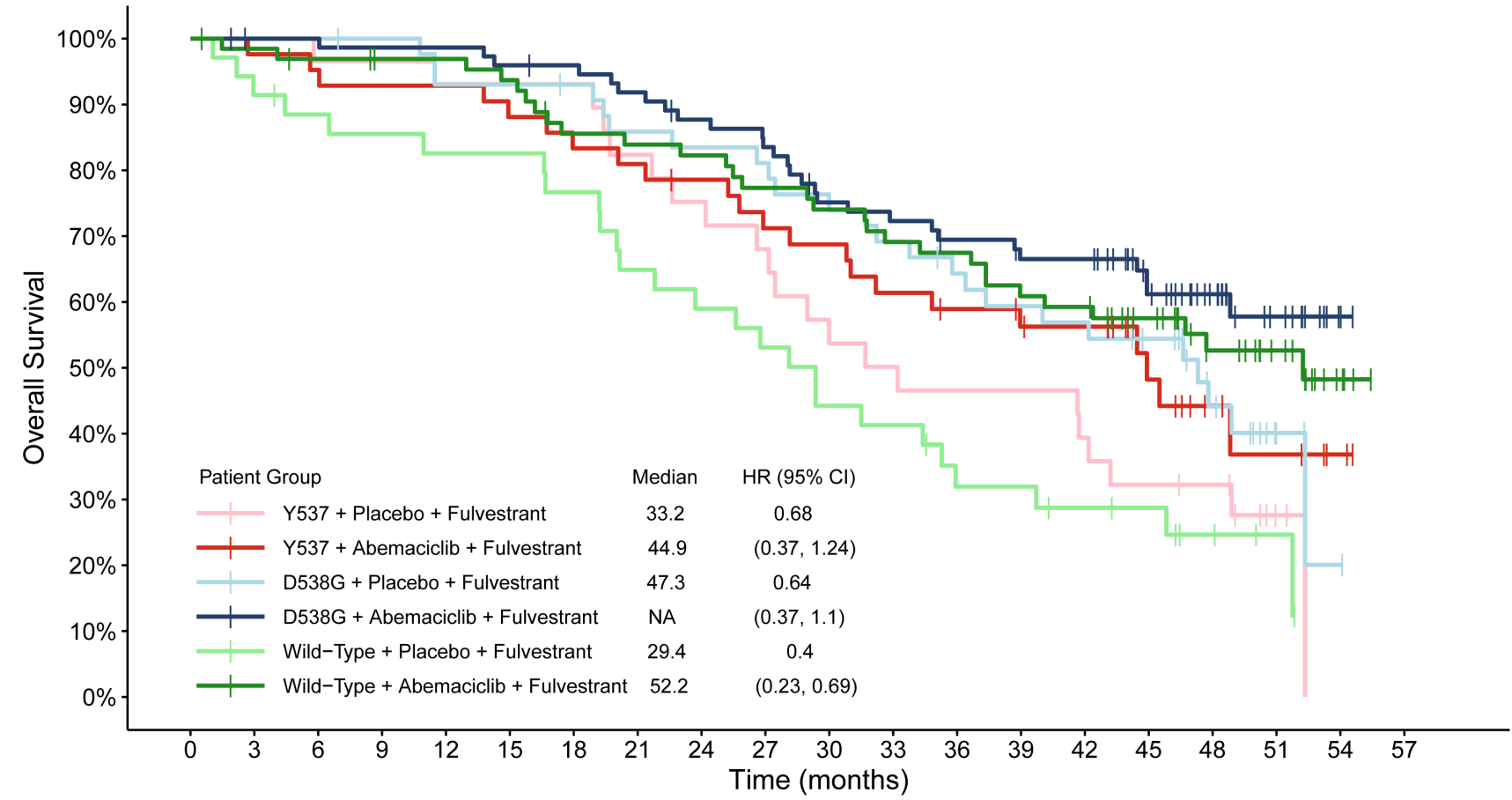


Number at risk

10	10	9	8	8	8	7	7	7	6	6	6	5	4	3	3	2	0	0
14	13	13	12	12	12	11	10	10	10	10	10	9	8	7	5	5	3	1
30	27	26	25	21	20	19	19	18	17	16	14	10	10	9	8	7	1	0
50	47	46	44	43	41	37	36	34	33	30	27	27	24	24	14	10	5	2
48	48	46	46	46	45	44	38	35	33	28	28	25	23	22	18	10	5	1
75	73	72	71	71	68	65	64	63	55	51	46	43	41	40	32	21	14	5

Note: Hazard Ratio were calculated between the treatment and placebo arm. 8 patients belong to both E545K/E542K and H1047R/H1047L groups

Supplemental Figure 7 – Kaplan-Meier plots of overall survival by mutation for patients harboring *ESR1* mutant vs wild-type tumors

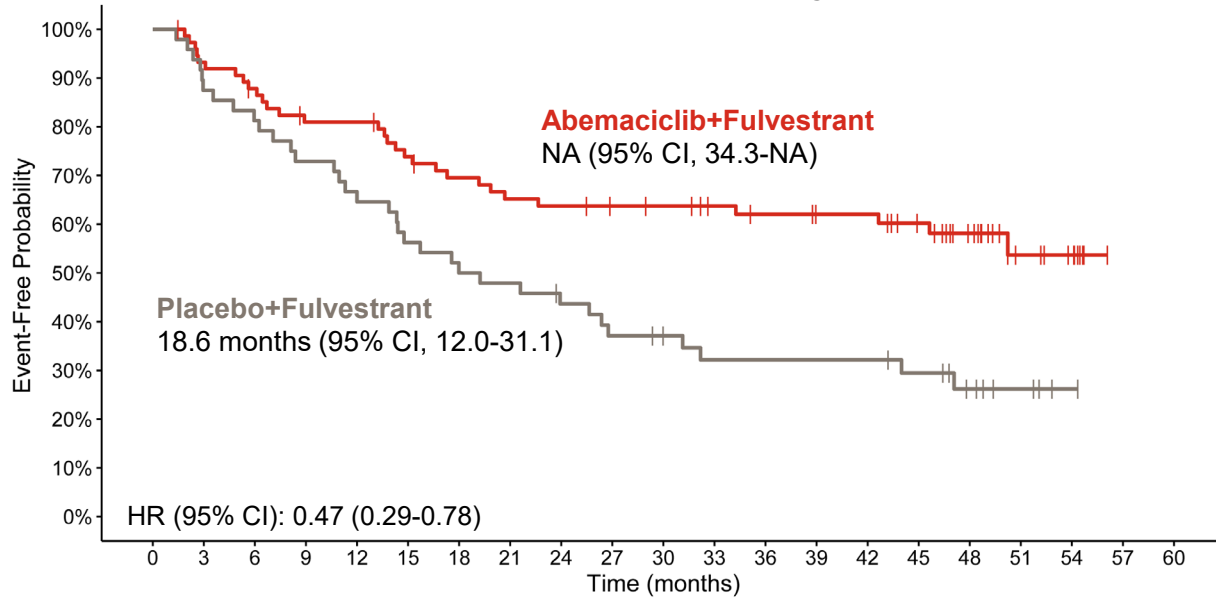


Number at risk		0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Y537 + Placebo + Fulvestrant	29	29	28	28	27	27	26	23	21	19	15	14	13	13	11	9	8	2	0	0	0
Y537 + Abemaciclib + Fulvestrant	42	41	40	39	39	37	35	34	32	29	28	25	23	21	20	12	7	5	2	0	0
D538G + Placebo + Fulvestrant	44	44	44	43	40	40	39	36	35	34	31	29	26	24	23	20	12	3	1	0	0
D538G + Abemaciclib + Fulvestrant	76	74	74	73	73	71	70	67	63	60	53	51	48	45	45	34	24	14	3	0	0
Wild-Type + Placebo + Fulvestrant	35	32	30	29	28	28	26	22	20	18	15	14	10	10	8	7	4	2	0	0	0
Wild-Type + Abemaciclib + Fulvestrant	66	64	62	60	60	58	52	51	50	47	45	42	41	37	36	29	20	14	5	0	0

Note: Hazard Ratio were calculated between the treatment and placebo arm. 44 patients belong to both D538G and Y537 mutation groups

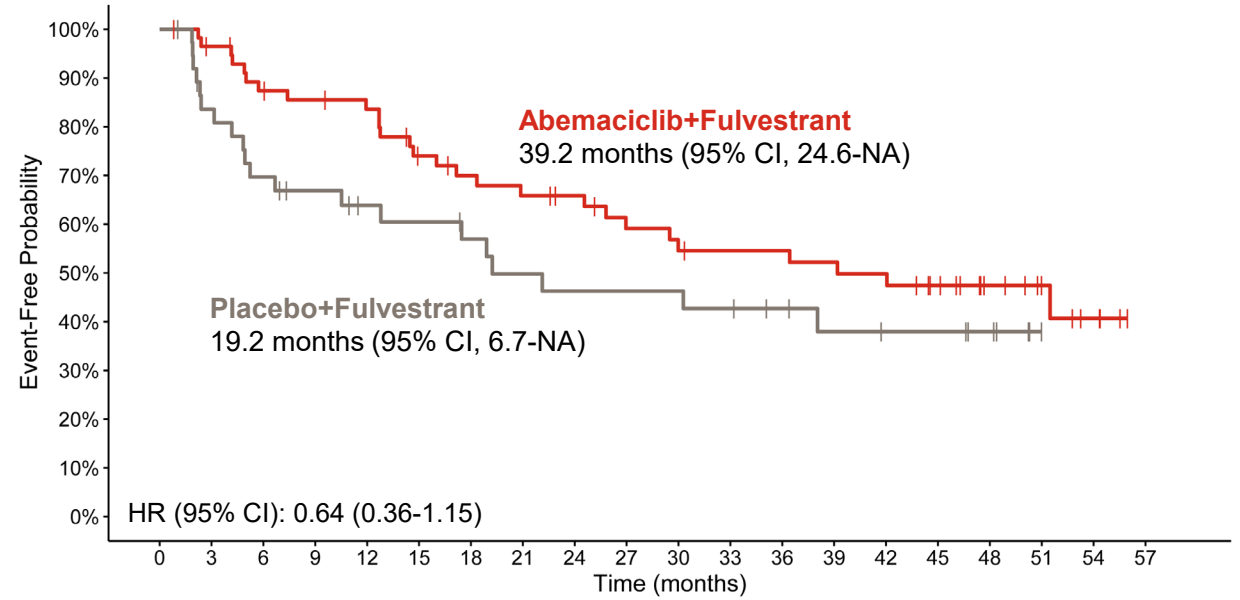
Supplemental Figure 8A: Kaplan-Meier plots of time-to-chemotherapy for patients with A) *PIK3CA*-wild-type or mutant tumors and B) *ESR1*-wild-type or mutant tumors

***PIK3CA* Wild-Type**



Number at risk	
75	69 64 58 58 52 48 45 44 42 41 38 36 34 34 29 20 10 7 0 0
48	42 39 35 32 27 24 23 20 17 15 13 13 13 13 11 7 4 1 0 0

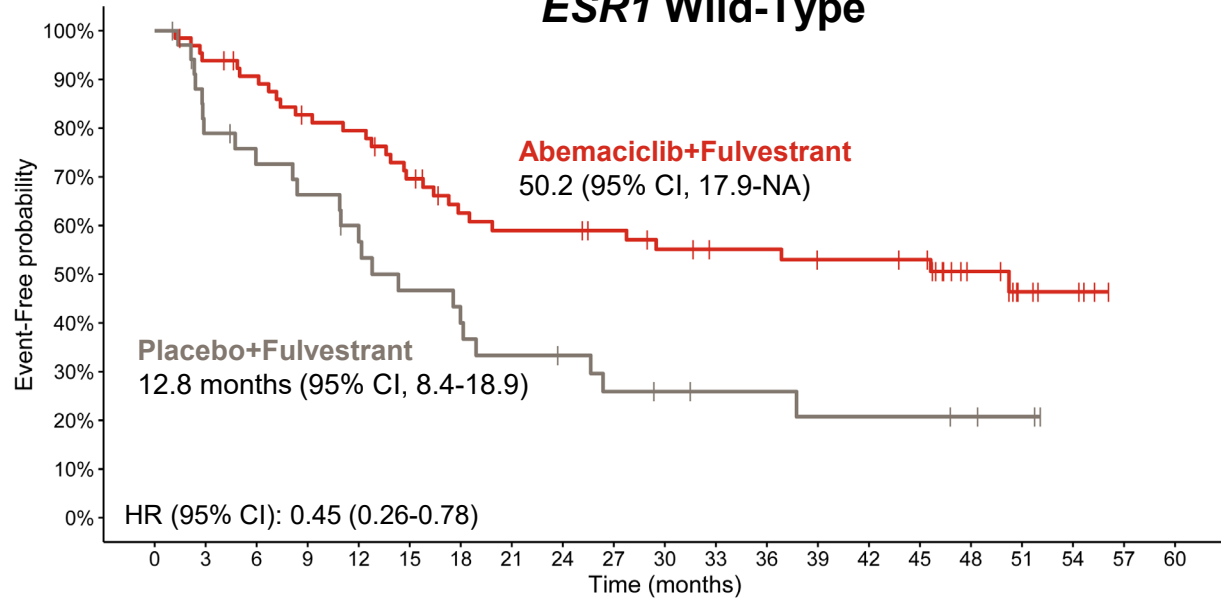
***PIK3CA* Mutant**



Number at risk	
58	54 48 46 44 37 34 32 30 26 24 23 23 22 21 17 11 7 4 0
38	30 25 22 19 18 16 14 13 13 12 10 8 7 7 5 0 0 0

Supplemental Figure 8B: Kaplan-Meier plots of time-to-chemotherapy for patients with A) *PIK3CA*-wild-type or mutant tumors and B) *ESR1*-wild-type or mutant tumors

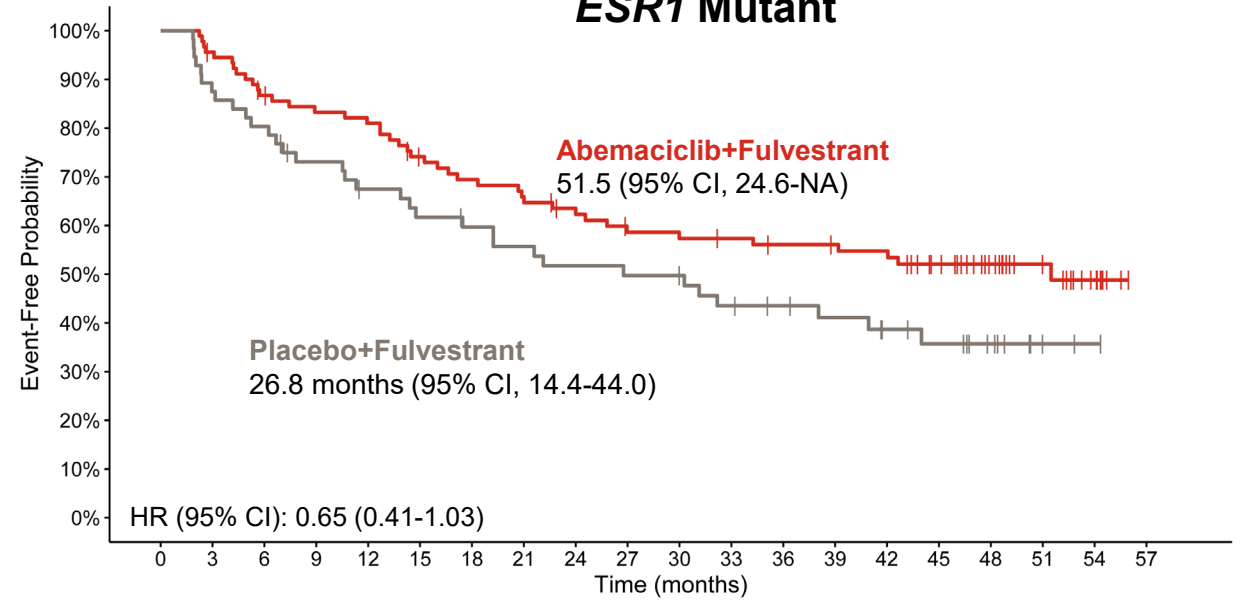
***ESR1* Wild-Type**



Number at risk

66	61	57	51	49	42	35	33	33	31	28	26	26	24	24	23	13	7	5	0	0
35	26	23	21	18	14	12	10	9	7	6	5	5	4	4	4	3	2	0	0	0

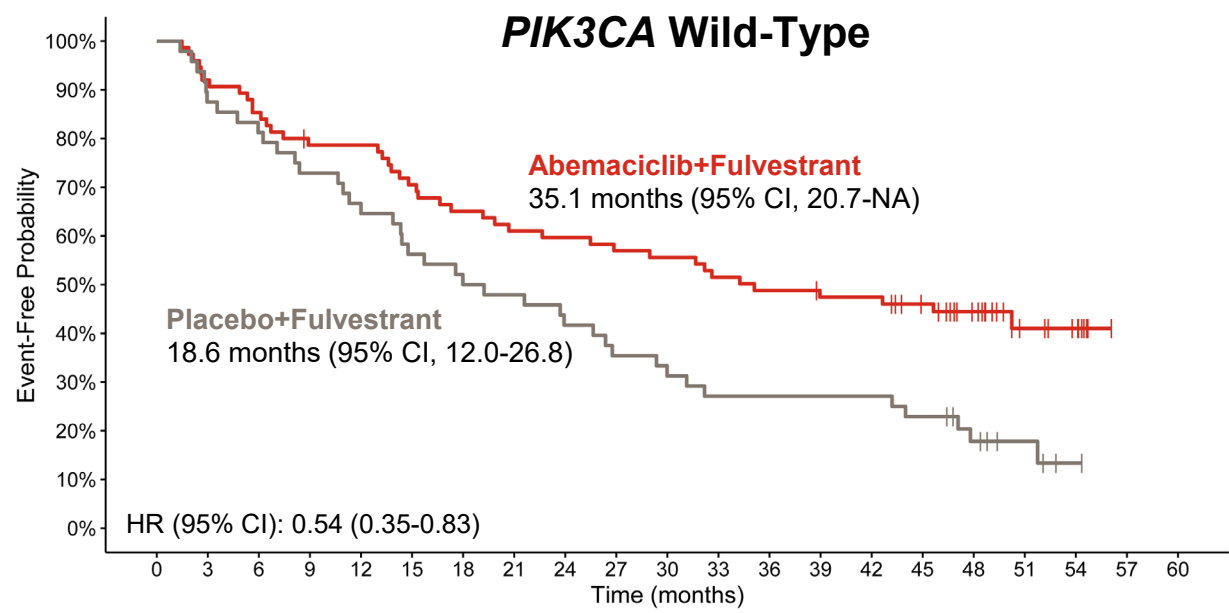
***ESR1* Mutant**



Number at risk

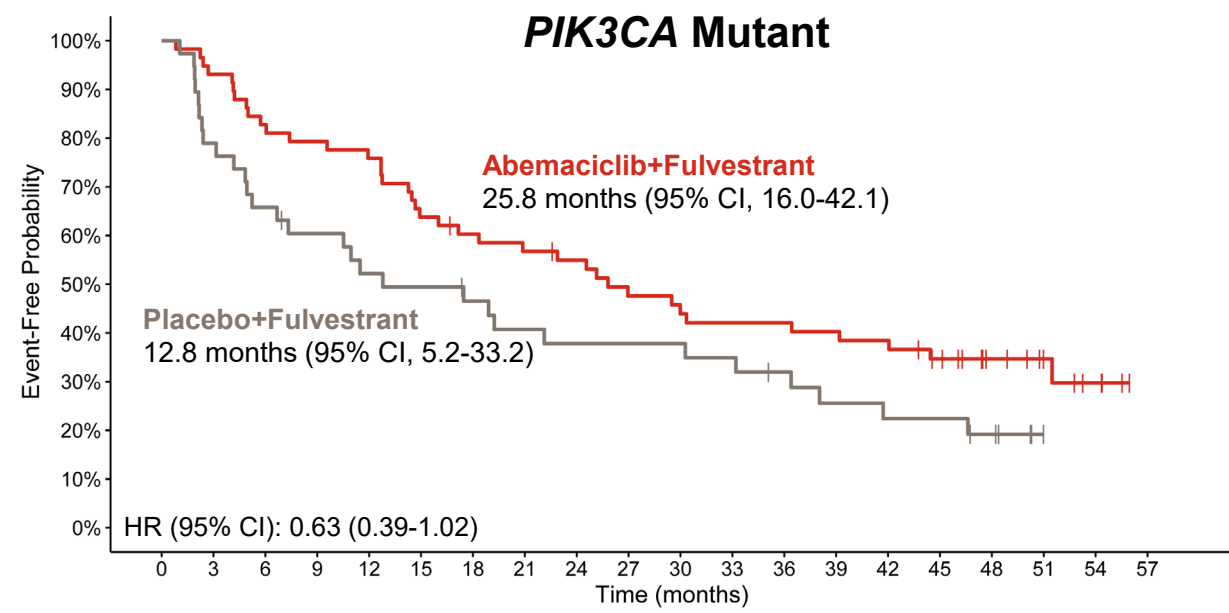
91	86	77	73	71	63	59	56	52	47	46	45	43	42	41	34	25	16	9	0
56	49	45	39	35	32	30	28	26	25	24	21	19	17	14	12	8	2	1	0

Supplemental Figure 9A: Kaplan-Meier plots of chemotherapy-free survival for patients with A) *PIK3CA*-wild-type or mutant tumors and B) *ESR1*-wild-type or mutant tumors



Number at risk

75	69	64	58	58	52	48	45	44	42	41	38	36	34	34	29	20	10	7	0	0
48	42	39	35	32	27	24	23	20	17	15	13	13	13	13	11	7	4	1	0	0

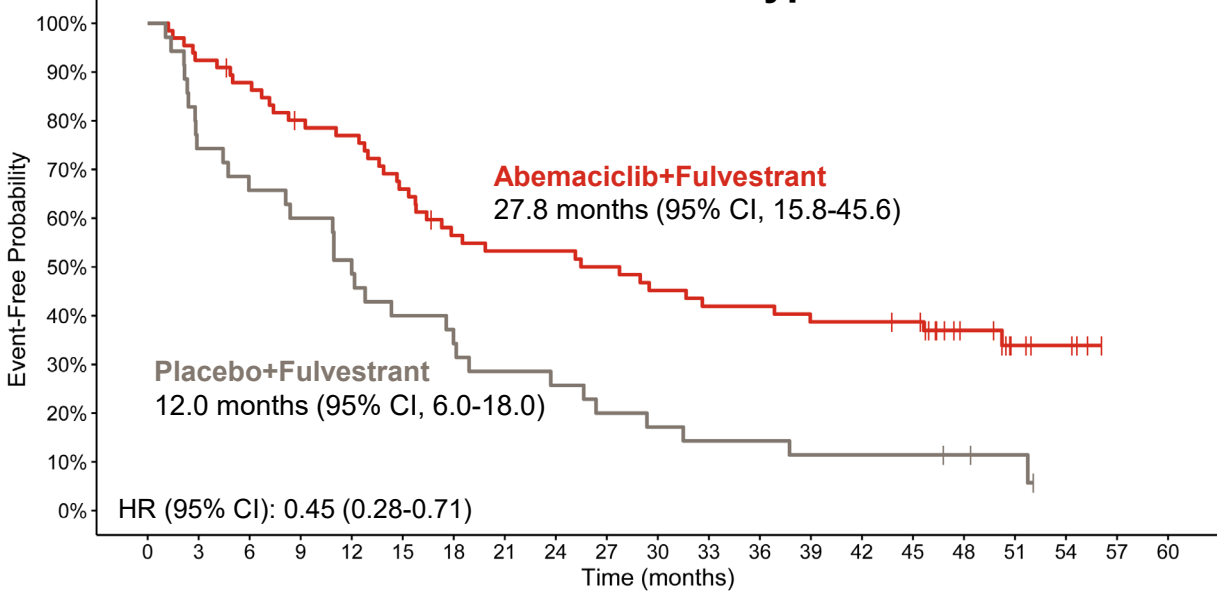


Number at risk

58	54	48	46	44	37	34	32	30	26	24	23	23	22	21	17	11	7	4	0
38	30	25	22	19	18	16	14	13	13	13	12	10	8	7	7	5	0	0	0

Supplemental Figure 9B: Kaplan-Meier plots of chemotherapy-free survival for patients with A) *PIK3CA*-wild-type or mutant tumors and B) *ESR1*-wild-type or mutant tumors

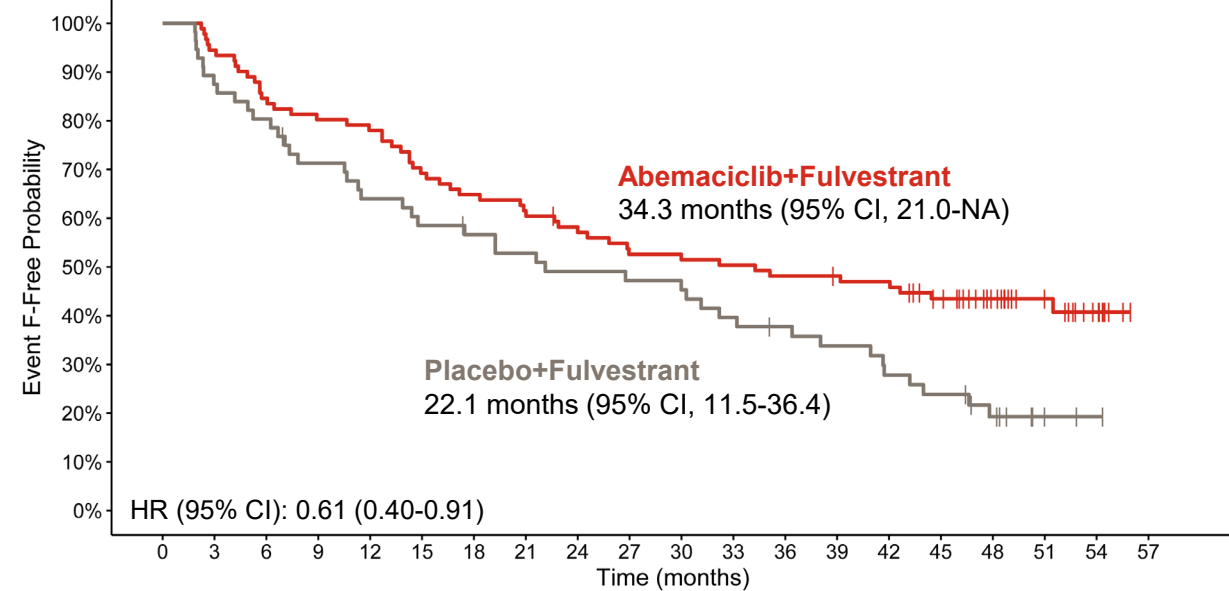
***ESR1* Wild-Type**



Number at risk

66	61	57	51	49	42	35	33	33	31	28	26	26	24	24	23	13	7	5	0	0
35	26	23	21	18	14	12	10	9	7	6	5	5	4	4	4	3	2	0	0	0

***ESR1* Mutant**

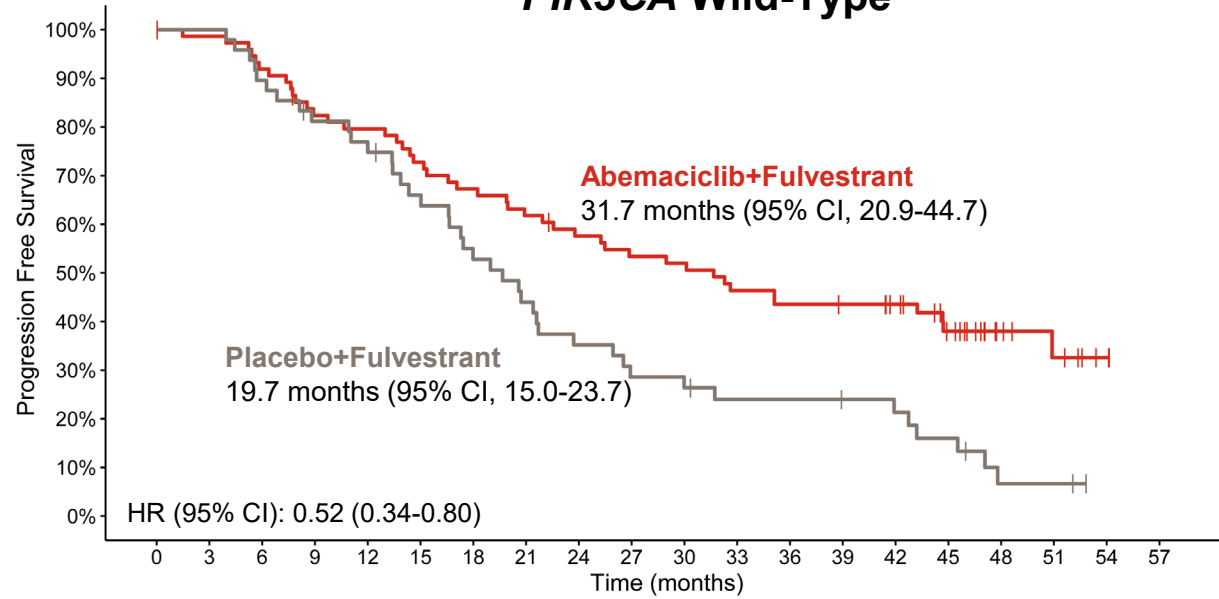


Number at risk

91	86	77	73	71	63	59	56	52	47	46	45	43	42	41	34	25	16	9	0
56	49	45	39	35	32	30	28	26	25	24	21	19	17	14	12	8	2	1	0

Supplemental Figure 10A: Kaplan-Meier plots of time to second disease progression for patients with A) *PIK3CA*-wild-type or mutant tumors and B) *ESR1*-wild-type or mutant tumors

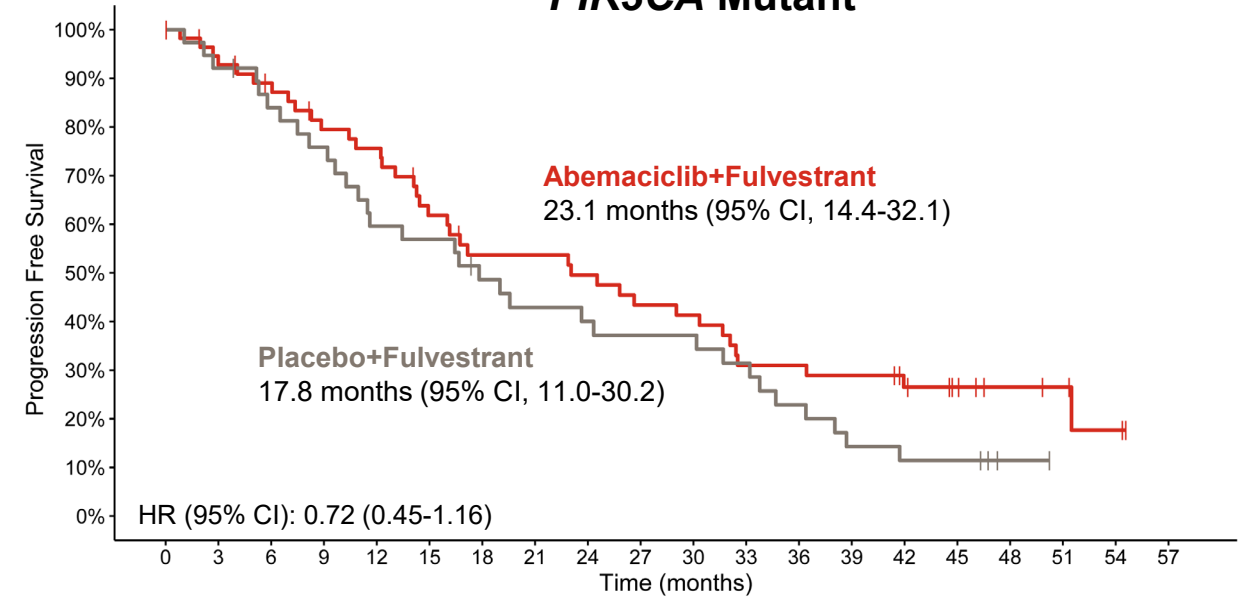
***PIK3CA* Wild-Type**



Number at risk

75	73	68	60	58	53	49	45	41	38	37	33	31	30	27	19	9	6	2	0
48	48	43	38	36	30	24	20	16	13	12	10	10	9	8	6	2	2	0	0

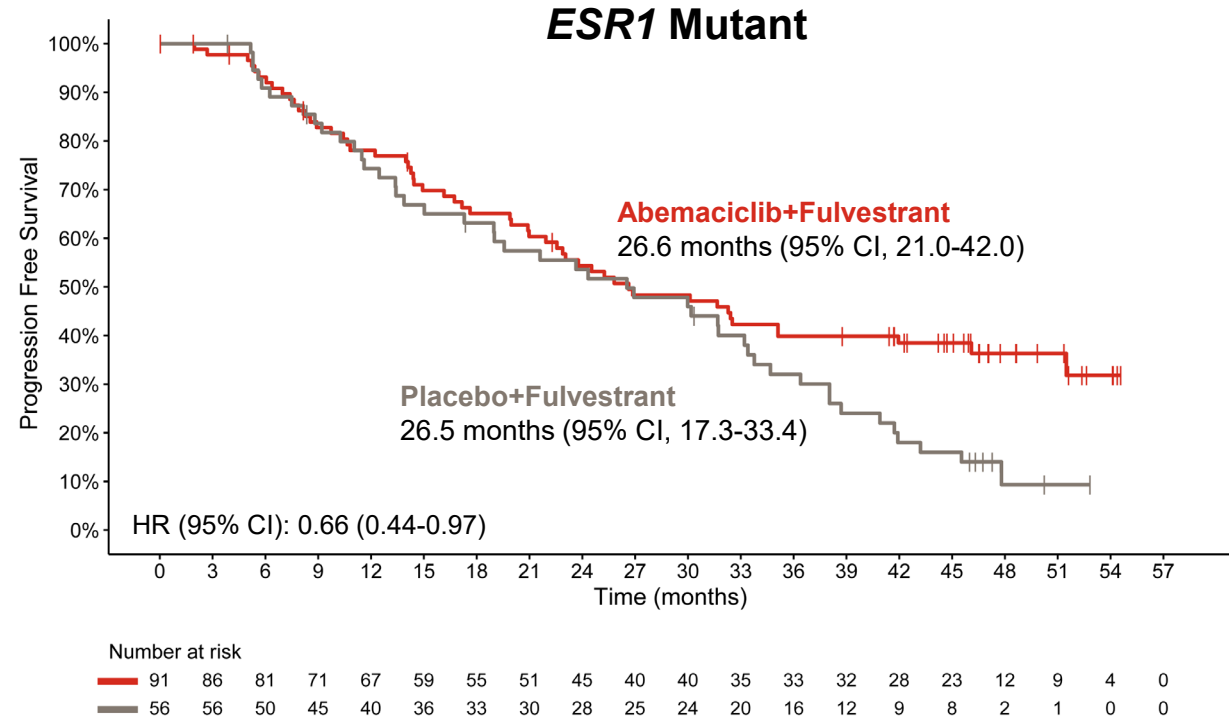
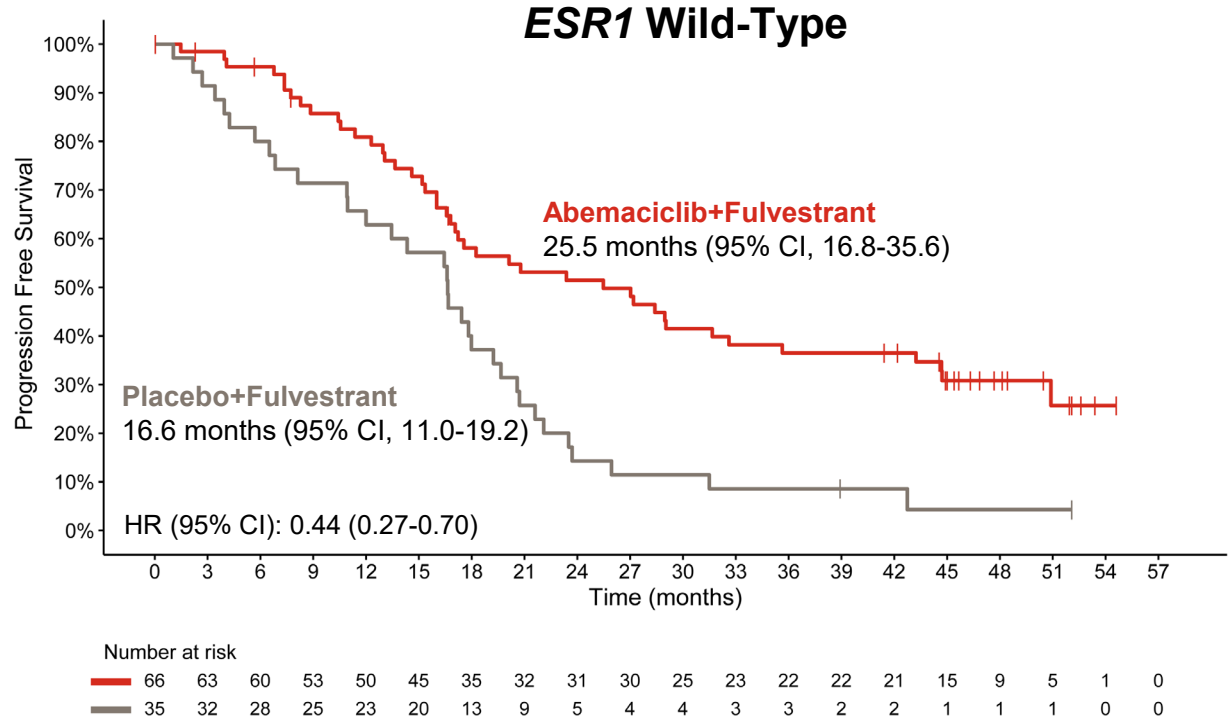
***PIK3CA* Mutant**



Number at risk

58	51	47	41	39	31	26	26	24	21	20	15	15	14	11	8	5	4	2	0
38	35	31	28	22	21	17	15	14	13	13	11	8	5	4	4	1	0	0	0

Supplemental Figure 10B: Kaplan-Meier plots of time to second disease progression for patients with A) *PIK3CA*-wild-type or mutant tumors and B) *ESR1*-wild-type or mutant tumors



Supplemental Table 1 – Table describing frequency of *PIK3CA* and *ESR1* mutations in plasma samples

<i>PIK3CA</i> Mutations	Positive	Negative	Frequency
Overall	96	123	43.8%
H1047R	78	156	33.3%
E545K	14	215	6.1%
E542K	10	224	4.3%
H1047L	3	216	1.4%
<i>ESR1</i> Mutations	Positive	Negative	Frequency
Overall	147	101	59.3%
D538G	120	146	45.1%
Y537C	42	223	15.8%
Y537S	21	247	7.8%
Y537N	20	246	7.5%

Note: Frequency = positive/(positive + negative) X 100; 8/219 (3.7%) patients had both H1047R/L and E545K/E542K mutations, 44/248 (17.7%) patients had both D538G and Y537C/S/N mutations

Supplemental Table 2 – Post-discontinuation therapy following second disease progression for patient with *PIK3CA*-wild-type or mutant tumors

Post-discontinuation therapy	<i>PIK3CA</i> Wild-Type, PL (N=48)	<i>PIK3CA</i> Wild-Type, Abema (N=75)	<i>PIK3CA</i> Mutant, PL (N=38)	<i>PIK3CA</i> Mutant, Abema (N=58)
Overall, n (%)	48 (100)	75 (100)	38 (100)	58 (100)
Chemotherapy, n (%)	17 (35.4)	19 (25.3)	15 (39.5)	15 (25.9)
Endocrine therapy, n (%)	13 (27.1)	15 (20.0)	6 (15.8)	14 (24.1)
Everolimus, n(%)	4 (8.3)	9 (12.0)	4 (10.5)	6 (10.3)
Other, n(%)	14 (29.2)	32 (42.7)	13 (34.2)	23 (39.7)
CDK4 & 6 inhibitor n(%)	7 (14.6)	3 (4.0)	3 (7.9)	3 (5.2)
non-CDK4 & 6 inhibitor, n (%)	7 (14.6)	29 (38.7)	10 (26.3)	20 (34.5)

Supplemental Table 3 – Post-discontinuation therapy following second disease progression for patient with *ESR1*-wild-type or mutant tumors

Post-discontinuation therapy	<i>ESR1</i> Wild-Type, PL (N=35)	<i>ESR1</i> Wild-Type, Abema (N=66)	<i>ESR1</i> Mutant, PL (N=56)	<i>ESR1</i> Mutant, Abema (N=91)
Overall, n (%)	35 (100)	66 (100)	56 (100)	91 (100)
Chemotherapy, n (%)	15 (42.9)	19 (28.8)	20 (35.7)	25 (27.5)
Endocrine therapy, n (%)	10 (28.6)	15 (22.7)	11 (19.6)	18 (19.8)
Everolimus, n(%)	1 (2.9)	8 (12.1)	8 (14.3)	11 (12.1)
Other, n(%)	9 (25.7)	24 (36.4)	17 (30.4)	37 (40.7)
CDK4 & 6 inhibitor n(%)	3 (8.6)	2 (3.0)	6 (10.7)	3 (4.4)
non-CDK4 & 6 inhibitor, n (%)	6 (17.1)	22 (33.3)	11 (19.6)	33 (36.3)