2022 ASCO® ANNUAL MEETING

Alpelisib + fulvestrant in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) advanced breast cancer (ABC): Biomarker analyses by next-generation sequencing from the SOLAR-1 study

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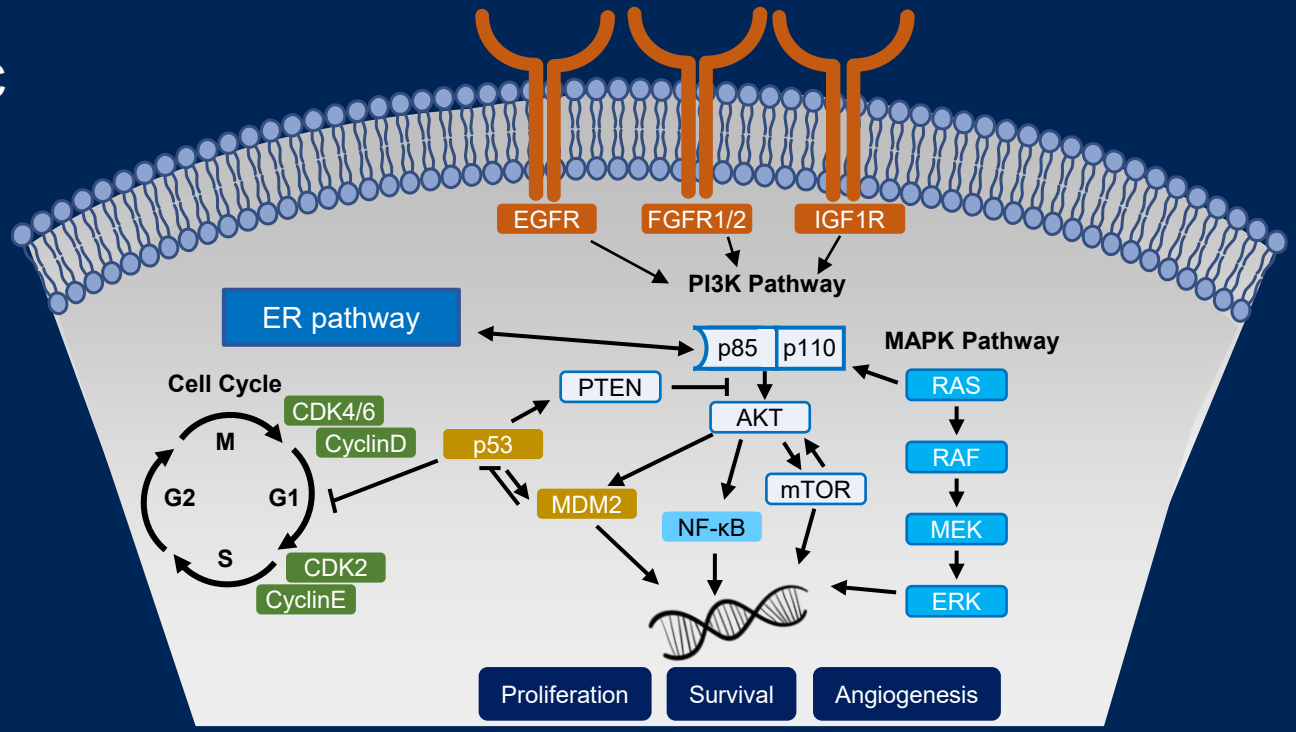
The PI3K Pathway Is Part of a Complex Signaling Network That Is Altered in Breast Cancer

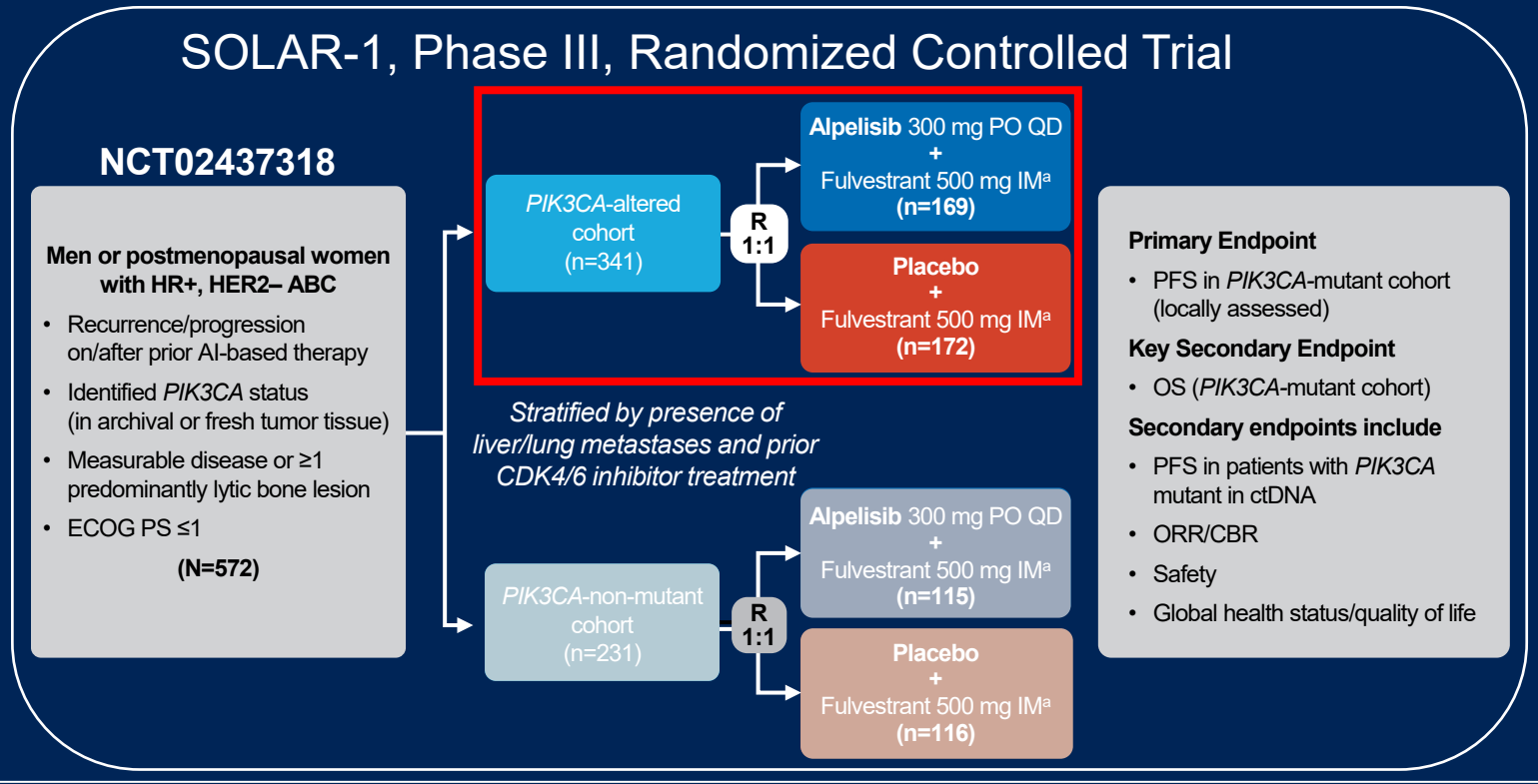
- Approximately 40% of HR+, HER2– ABC patients have mutations in *PIK3CA*, one of the most frequently mutated genes in breast cancer, which encodes the α subunit of PI3K (p110α)[1-5]
  - —*PIK3CA* mutations can contribute to endocrine therapy resistance and are linked to worse overall survival in metastatic breast cancer[6-8]



ABC, advanced breast cancer; AKT, protein kinase B; EGFR, epidermal growth factor receptor; CDK 2/4/6, cyclin-dependent kinase 2/4/6; ER, estrogen receptor; ERK, mitogen-activated protein kinase 1 (MAPK1); ET, endocrine therapy; FGFR1/2, fibroblast growth factor receptor 1/2; G1, gap 1; G2, gap 2; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor positive; IGF1R, insulin like growth factor 1 receptor; FUL, fulvestrant; M, mitosis; MAPK, mitogen-activated protein kinase; MDM2, MDM2 proto-oncogene; MEK, mitogen-activated protein kinase kinase 7 (MAP2K7); mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; PI3K, phosphatidylinositol-3-kinase; p53, tumor protein p53; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RAF, raf1 proto-oncogene, serine/threonine kinase; RAS, rat sarcoma virus; S, synthesis.

1. Cancer Genome Atlas Network. *Nature*. 2012;490(7418):61-70; 2. Di Leo A, et al. *Lancet Oncol*. 2018;19(1):87-100; 3. Mollon L, et al. AACR 2018 (poster 1207); 4. Moynahan ME, et al. *Br J Cancer*. 2017;116(6):726-730; 5. Tolaney S, et al. AACR 2019 (abstract 4458); 6. Mosele F, et al. *Ann Oncol*. 2020;31(3):377-386; 7. Fu X, et al. *Breast Cancer Res*. 2014;16(5):430; 8. Sobhani M, et al. *J Cell Biochem*. 2018;119(6):4287-4292.

Alpelisib, a *PIK3CA* Inhibitor, Is Effective for Treating Patients With HR+, HER2–, *PIK3CA*-Altered ABC

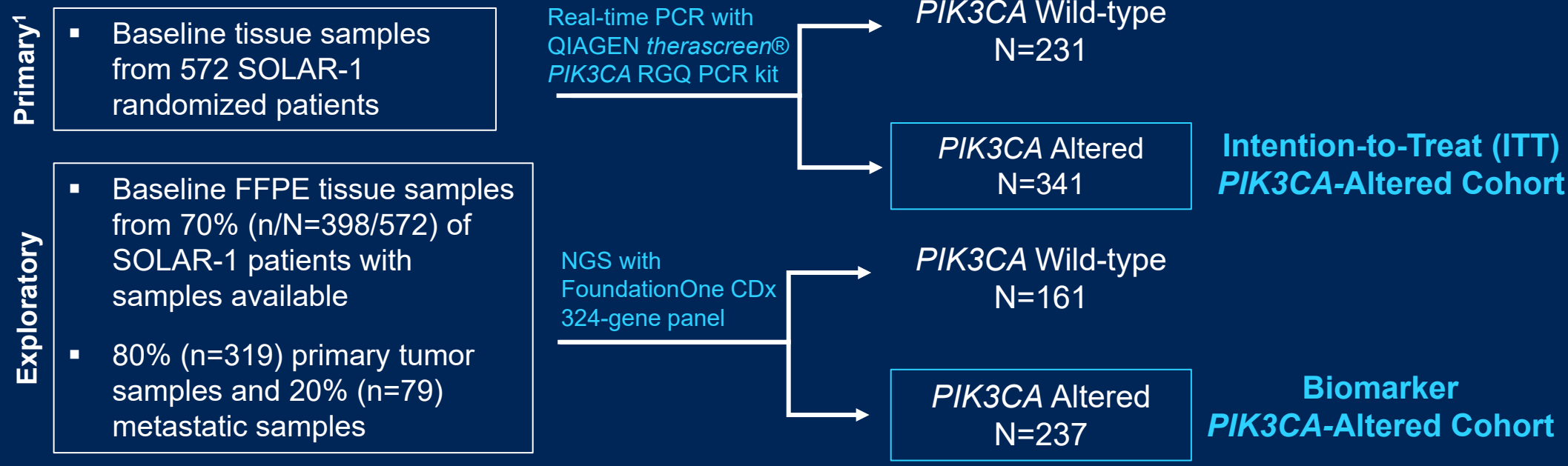


- Alpelisib is an oral and selective inhibitor and degrader of altered PI3Kα[1,2]
  - In SOLAR-1, mPFS for patients treated with alpelisib + FUL was 11.0 months compared with 5.7 months in patients treated with placebo + FUL (HR 0.65; 95% CI, 0.50-0.85; 1-sided *P*<0.001)[3]

- Alpelisib plus fulvestrant (FUL) is approved for use in men or postmenopausal women with *PIK3CA*-mutated, HR+, HER2– locally advanced or metastatic breast cancer after disease progression following ET monotherapy (Europe) or an ET-based regimen (USA)[4,5]

[a]Fulvestrant given on Day 1 and Day 15 of the first 28-day cycle, then Day 1 of subsequent 28-day cycles.
ABC, advanced breast cancer; AI, aromatase inhibitor; CBR, clinical benefit rate; CDK4/6, cyclin-dependent kinase 4/6; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; FUL, fulvestrant; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; IM, intramuscular; ORR, overall response rate; OS, overall survival; (m)PFS, (median) progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PO, orally; QD, daily; R, randomization.
1.Rugo HS, et al. *Ann Oncol.* 2020;31(8):1001-1010; 2. Fritsch C, et al. *Cancer Res.* 2018;78(13 suppl): Abstract 3934 (poster); 3. André F, et al. *N Engl J Med.* 2019;380(20):1929-1940; 4. Piqray (alpelisib) [summary of product characteristics]. Dublin, Ireland: Novartis Europharm Limited; 2020; 5. Piqray (alpelisib) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021.

Exploratory Retrospective Biomarker Analysis With SOLAR-1 Baseline Tumor Samples

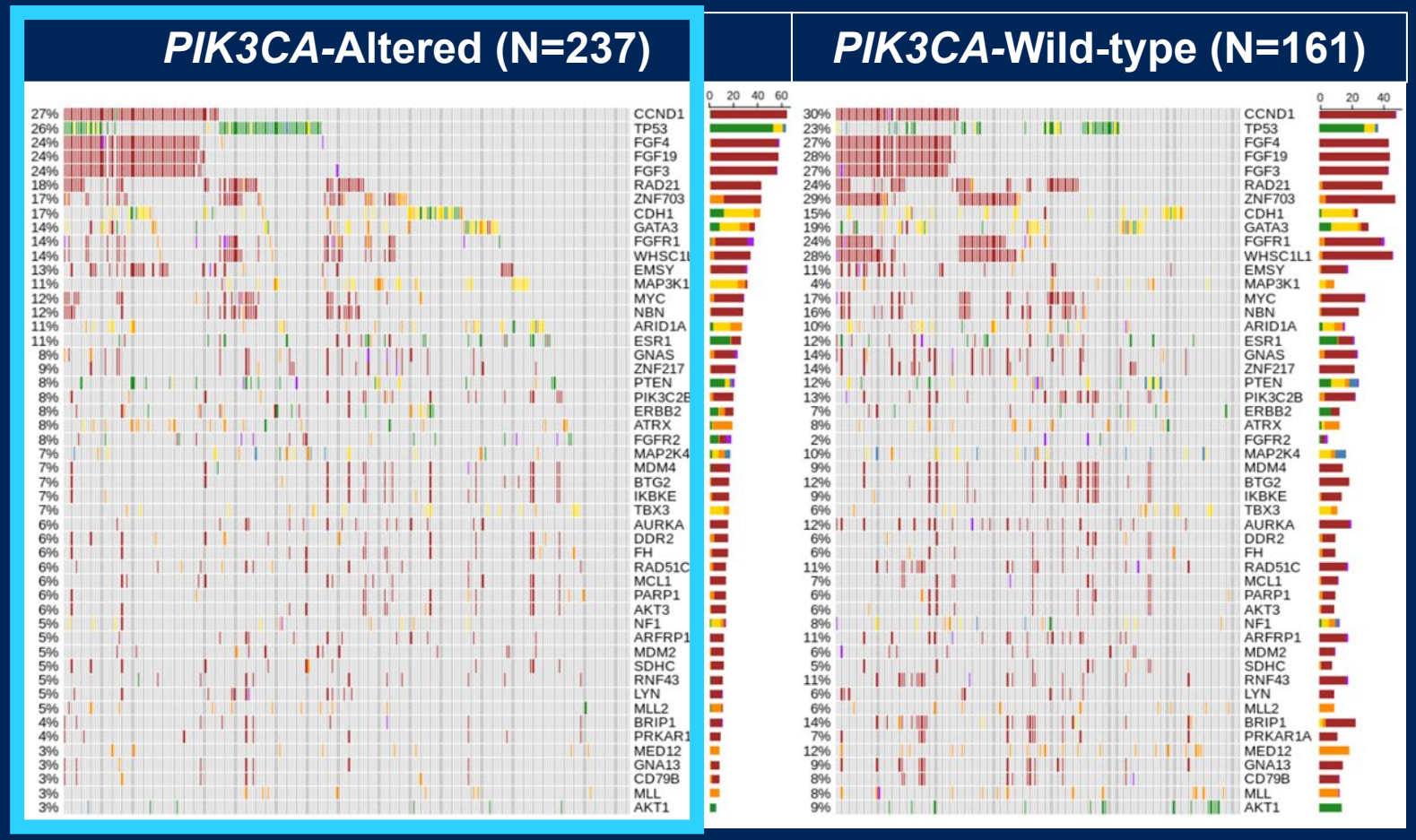


- Clinical benefit was assessed using progression-free survival (PFS) and hazard ratio (HR)
- HR (95% CI) was estimated using a multivariate Cox PH model by adjusting multiple clinical covariates including age, ECOG PS, bone lesion, lung/liver metastases, and prior CDK4/6 inhibitor treatment
- No multiple testing adjustments were made in this subgroup analysis

CDK4/6, cyclin-dependent kinase4/6; CDx, companion diagnostic; ECOG PS, Eastern Cooperative Oncology Group performance status; FFPE, formalin-fixed, paraffin-embedded; HR, hazard ratio; ITT, intention-to-treat; NGS, next-generation sequencing; PCR, polymerase chain reaction; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; RGQ, Rotor-Gene Q.

1. André F, et al. *N Engl J Med*. 2019;380(20):1929-1940.

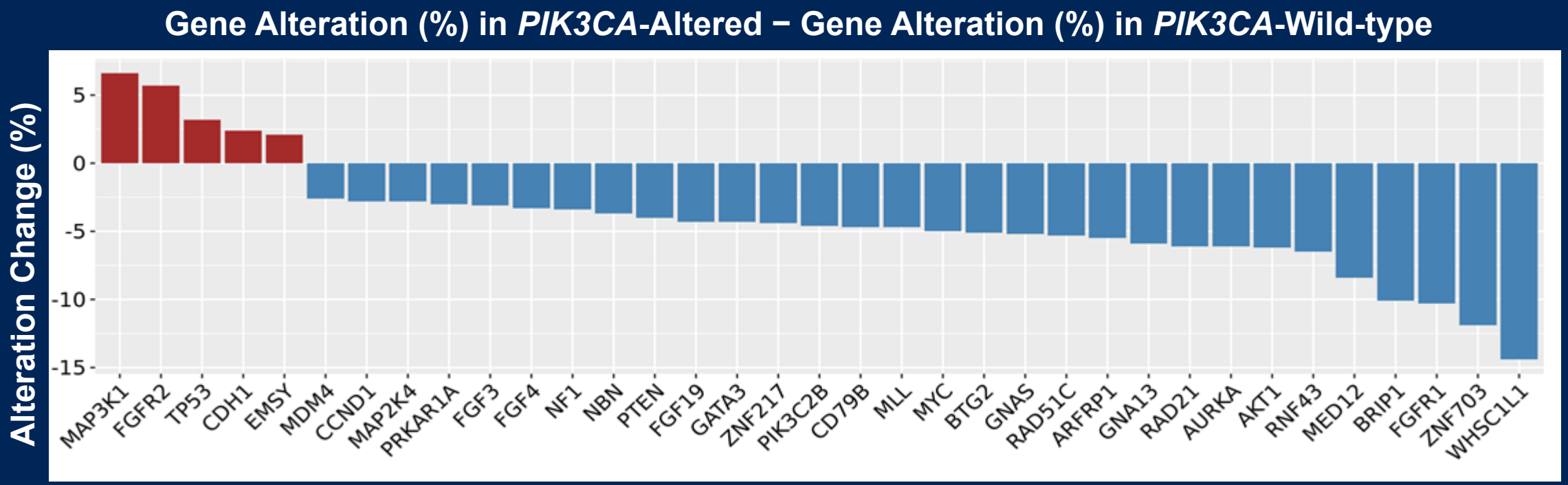
Genes Are Differentially Altered in *PIK3CA*-Altered and -Wild-type Biomarker Populations



- NGS sequencing of baseline tumor samples from patients randomized in SOLAR-1

FUL, fulvestrant; NGS, next-generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; SV, sequence variant.

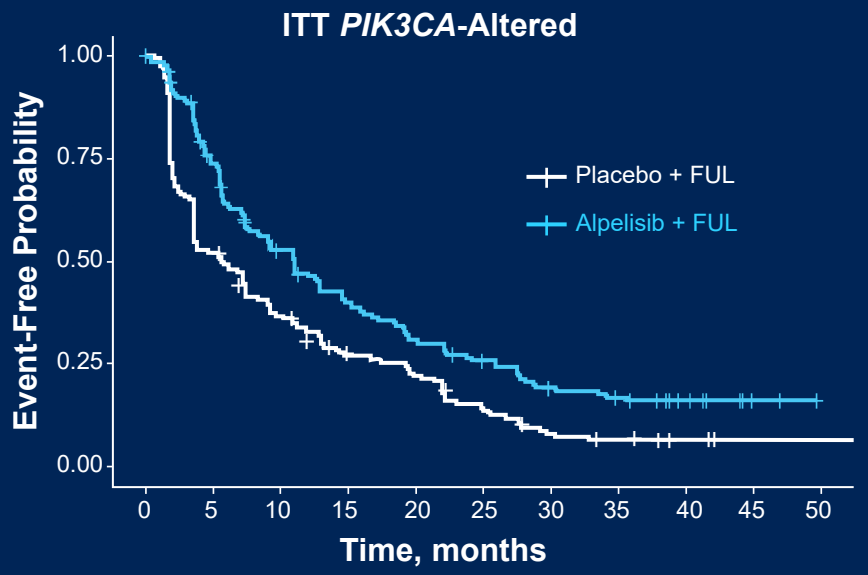
Differences in Alteration Prevalence Between *PIK3CA*-Altered and -Wild-type Biomarker Populations

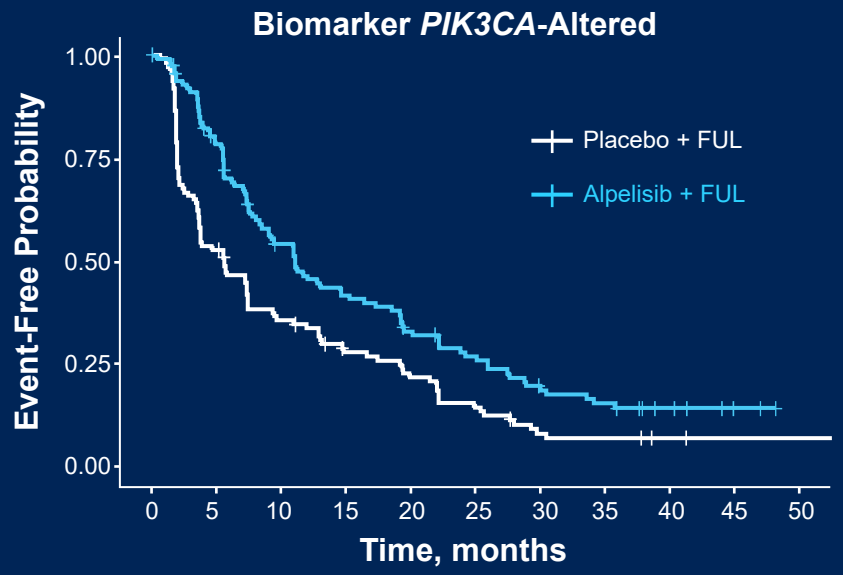


- Includes 35 genes with >2% gene alteration change between *PIK3CA*-altered and *PIK3CA*-wild-type

PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Efficacy of Alpelisib + FUL in Patients With Altered *PIK3CA* Is Similar in the SOLAR-1 ITT and Biomarker Populations





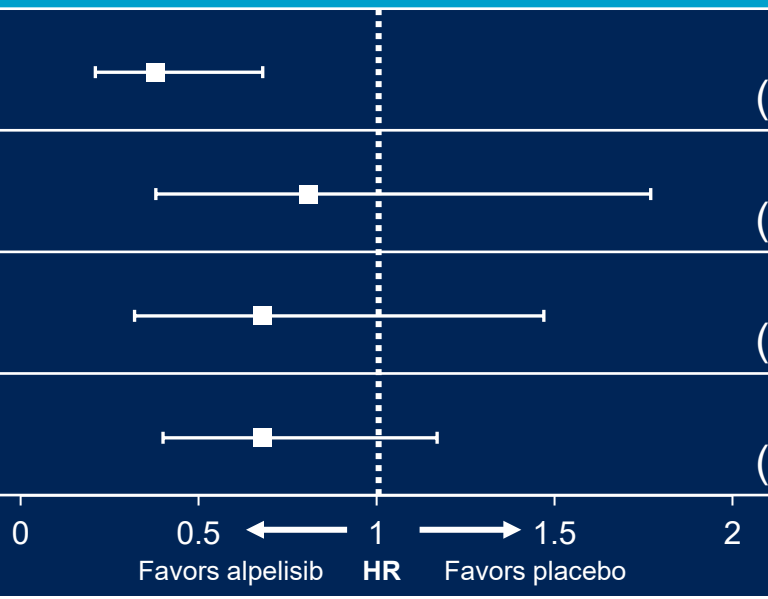
- Biomarker *PIK3CA*-altered population includes 70% of the ITT *PIK3CA*-population

Median PFS in Patients With Altered *PIK3CA*					
	Placebo + FUL		Alpelisib + FUL		
Cohort	n/N	mPFS, mo (95% CI)	n/N	mPFS, mo (95% CI)	HR (95% CI)
ITT *PIK3CA*-Altered	149/172	**5.7** (3.7-7.4)	124/169	**11.0** (7.5-14.5)	0.59 (0.43-0.81)
Biomarker *PIK3CA*-Altered	101/117	**5.6** (3.6-7.4)	90/120	**11.0** (8.3-15.2)	0.56 (0.42-0.76)

FUL, fulvestrant; HR, hazard ratio; ITT, intention-to-treat; mPFS, median progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Clinical Benefit Across TMB Quartiles of Patients Treated With Alpelisib + FUL

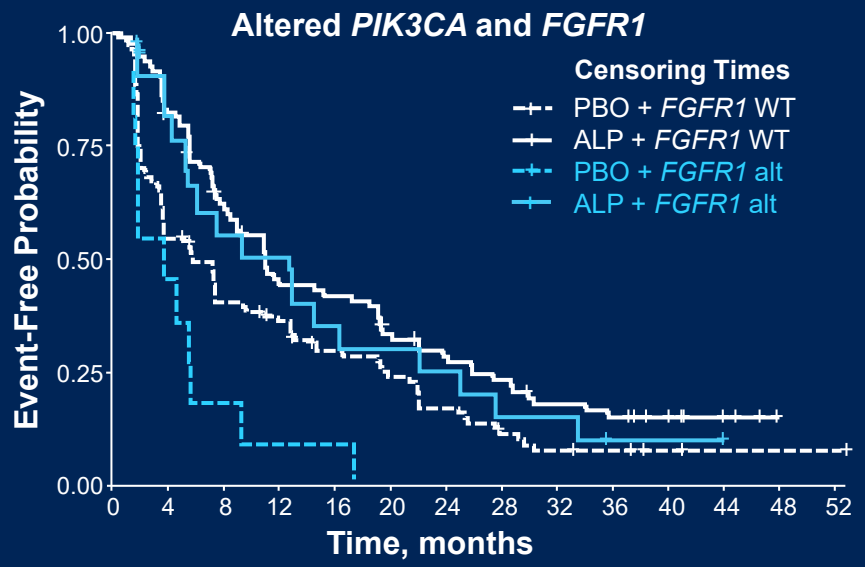
Quartile	Placebo + FUL[a]		Alpelisib + FUL[a]		HR by Quartile	HR (95% CI)
	n/N	mPFS, mo (95% CI)	n/N	mPFS, mo (95% CI)		
Quartile 1 0-<2.52 mut/mb	26/30	3.2 (1.8-7.4)	24/32	18.5 (7.7-22.1)		0.38 (0.21-0.68)
Quartile 2 2.52-<3.78 mut/mb	14/17	12.8 (3.7-22.1)	13/18	12.0 (4.5-33.5)		0.81 (0.38-1.77)
Quartile 3 3.78-<5.04 mut/mb	14/15	3.6 (1.8-7.4)	14/16	10.9 (3.8-11.2)		0.68 (0.32-1.47)
Quartile 4 ≥5.04 mut/mb	31/37	5.1 (1.9-7.4)	27/35	7.4 (5.5-17.3)		0.68 (0.40-1.17)

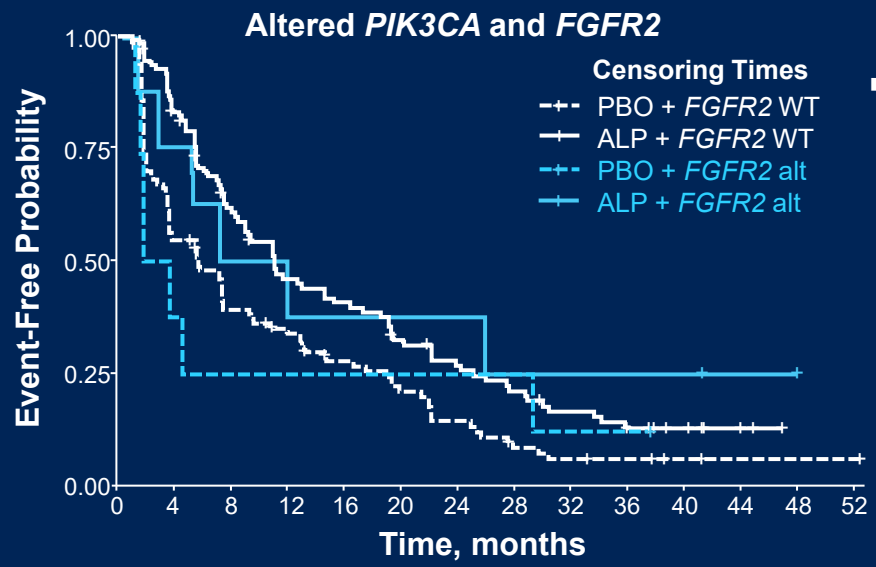


- Clinical benefit was most pronounced in patients treated with alpelisib with a low TMB (Quartile 1), and there was a trend toward clinical benefit in patients with a higher TMB

[a]TMB data available for 200 of 237 patients with *PIK3CA*-altered tumors. Data should be interpreted with caution because of the small sample size.
FUL, fulvestrant; HR, hazard ratio; mb, megabase; mPFS, median progression-free survival; mut, mutations; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; TMB, tumor mutational burden.

Improved Alpelisib Benefit Observed in Patients With Altered *FGFR1* and/or *FGFR2*



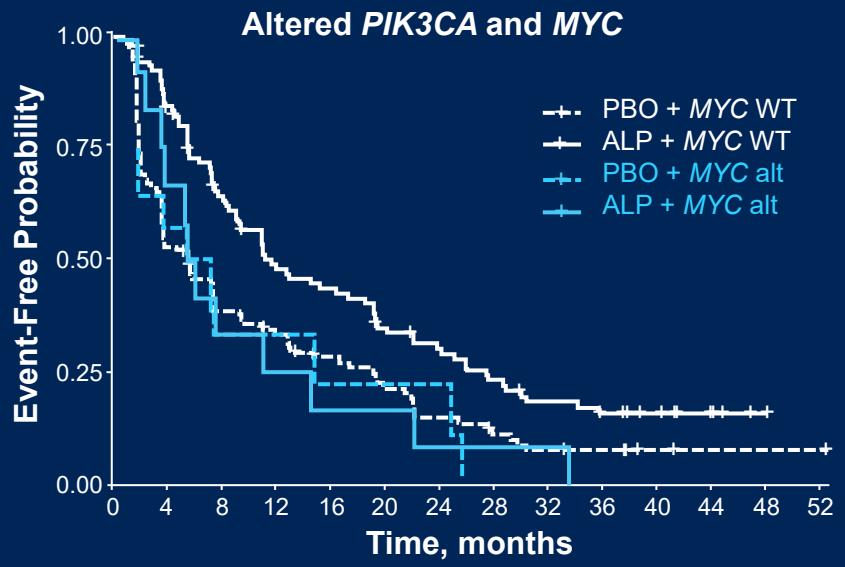


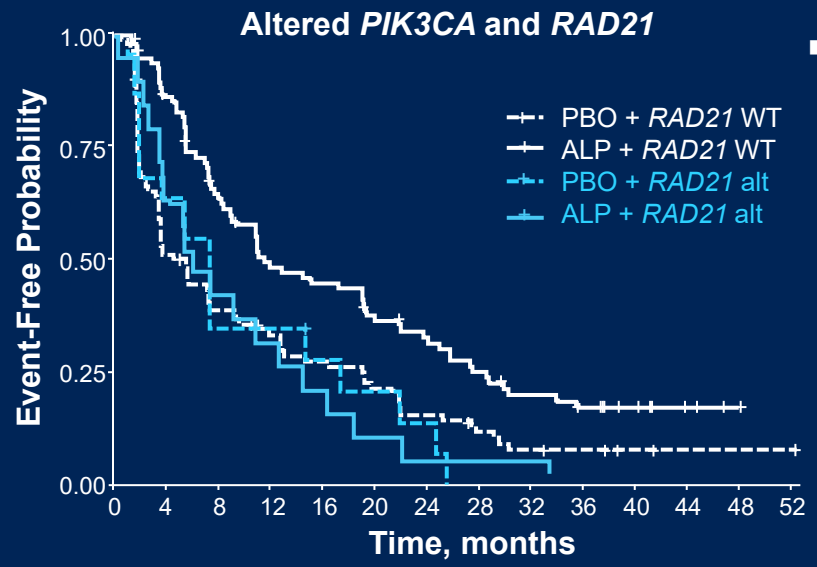
- Trend toward improved clinical benefit in patients treated with alpelisib + FUL who had altered *FGFR1* and/or *FGFR2,* despite an association of *FGFR1/2* alterations with resistance to endocrine therapy and CDK4/6 inhibitors[1,2]

Median PFS in Patients With Altered *PIK3CA* and *FGFR1/2*					
	Placebo + FUL		Alpelisib + FUL		
Gene	n/N	mPFS, mo (95% CI)	n/N	mPFS, mo (95% CI)	HR[a] (95% CI)
FGFR1 WT	90/106	5.8 (3.6-7.4)	72/98	11.0 (8.1-18.5)	0.54 (0.39-0.75)
FGFR1 Alt[b,c]	11/11	3.8 (1.6-5.6)	18/22	12.7 (5.3-22.1)	0.36 (0.16-0.77)
FGFR2 WT	94/108	5.7 (3.6-7.4)	84/111	11.0 (8.3-16.4)	0.55 (0.41-0.75)
FGFR2 Alt[b,d]	7/9	2.8 (1.4-29.2)	6/9	9.6 (1.5-NA)	0.28 (0.09-0.88)

[a]HR was calculated by adjusting additional biomarker variables TMB and PTEN Loss. [b]Data should be interpreted with caution due to the small sample size. [c]14% of patients had alterations in *FGFR1*. [d]8% of patients had alterations in *FGFR2*.
ALP, alpelisib; Alt, altered; CDK4/6, cyclin-dependent kinase4/6; *FGFR1/2*, fibroblast growth factor receptor 1/2; FUL, fulvestrant; HR, hazard ratio; mPFS, median progression-free survival; PBO, placebo; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; WT, wild-type.
1. Formisano L, et al. *Nat Commun.* 2019;10(1):1373; 2. Mao P, et al. *Clin Cancer Res*. 2020;26(22):5974-5989.

Limited Alpelisib Benefit Observed in Patients With Altered *MYC* and/or *RAD21*





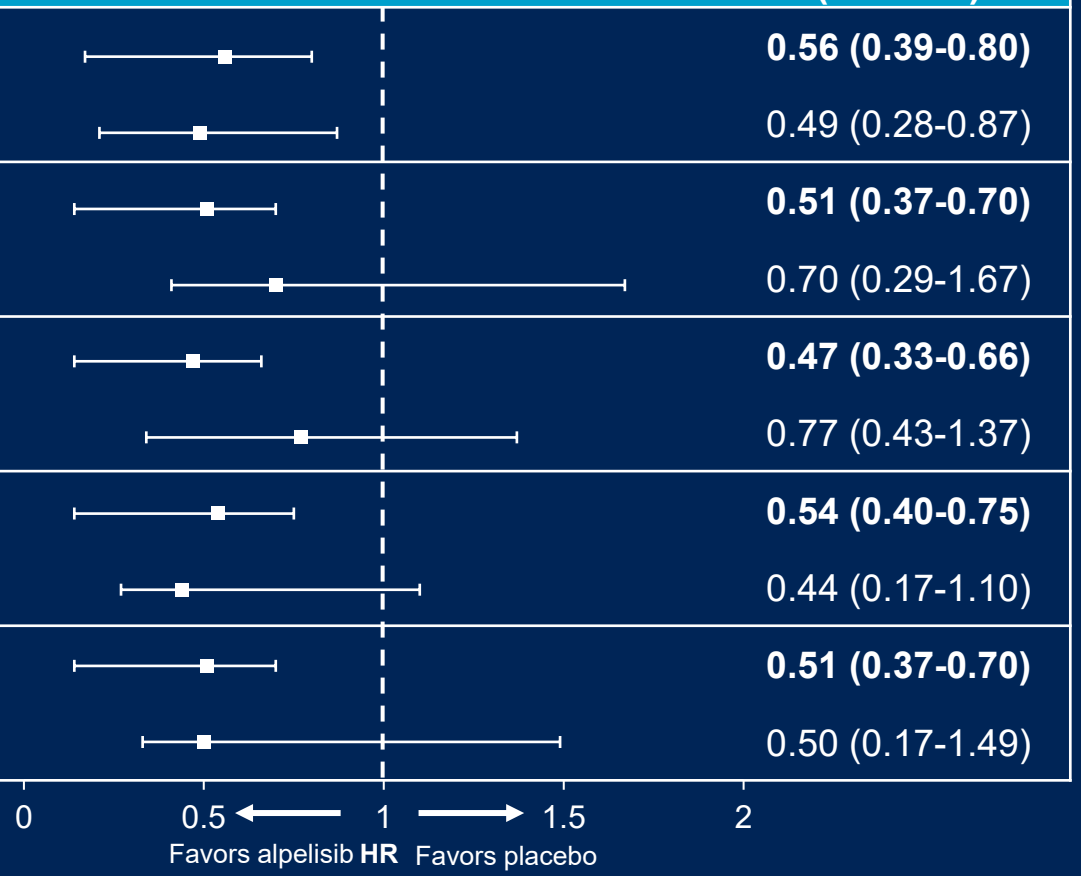
Median PFS in Patients With Altered *PIK3CA* and *MYC* or *RAD21*					
	Placebo + FUL		Alpelisib + FUL		
Gene	n/N	mPFS, mo (95% CI)	n/N	mPFS, mo (95% CI)	HR[a] (95% CI)
MYC WT	89/102	5.6 (3.6-7.4)	78/107	11.6 (9.0-19.1)	0.49 (0.35-0.67)
MYC Alt[b,c]	12/15	6.4 (1.8-14.8)	12/13	5.8 (2.3-14.6)	1.01 (0.45-2.28)
RAD21 WT	82/94	5.1 (3.6-7.4)	71/100	11.6 (9.0-19.3)	0.46 (0.33-0.64)
RAD21 Alt[b,d]	19/23	7.2 (1.9-14.8)	19/20	6.1 (3.6-12.7)	1.02 (0.54-1.95)

- Trend toward reduced clinical benefit in patients with *PIK3CA*-altered tumors who were treated with alpelisib + FUL and had altered *MYC* and/or *RAD21*
  - Aligns with previous reports that amplification of *MYC* conferred resistance to PI3K inhibition[1] and *RAD21* expression was associated with poor overall survival[2]

[a]HR was calculated by adjusting additional biomarker variables TMB and PTEN Loss. [b]Data should be interpreted with caution due to the small sample size. [c]*MYC* was altered in 12% of patients with altered *PIK3CA*. [d]*RAD21* was altered in 18% of patients with altered *PIK3CA*.
ALP, alpelisib; Alt, altered; FUL, fulvestrant; HR, hazard ratio; mPFS, median progression-free survival; PBO, placebo; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *MYC*, MYC proto-oncogene bHLH transcription factor; *RAD21*, RAD21 cohesin complex component; WT, wild-type.
1. Ilic N, et al. *Proc Natl Acad Sci U S A*. 2011;108(37),E699-E708; 2. Xu H, et al. *Breast Cancer Res*. 2011;13(1):R9.

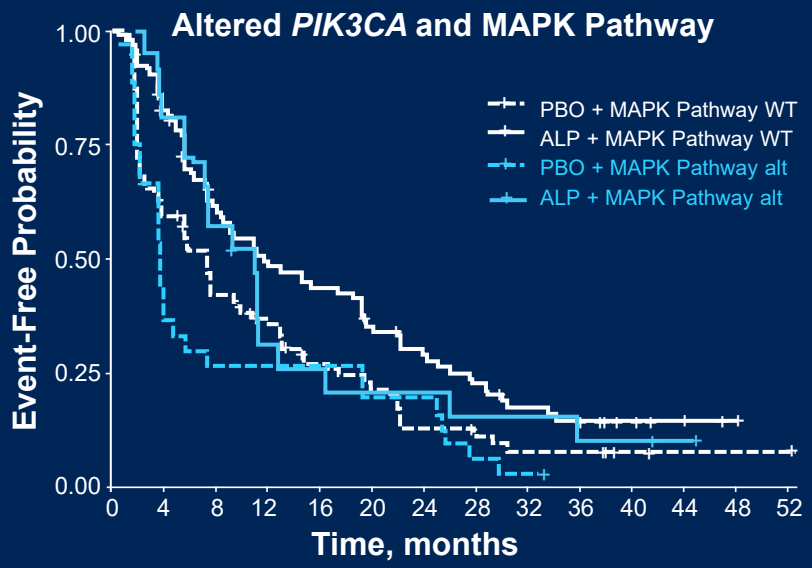
Alpelisib + FUL Is Effective Regardless of Gene Alteration Status

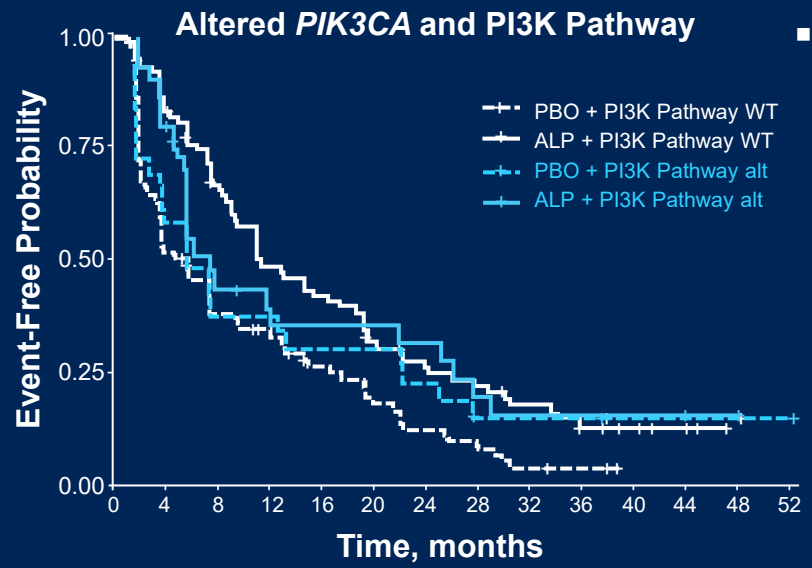
Gene	Placebo + FUL		Alpelisib + FUL		HR by Gene and Treatment	HR[a] (95% CI)
	n/N	mPFS, mo	n/N	mPFS, mo		
***TP53* WT**	**69/81**	**7.3**	**69/94**	**12.0**		**0.56 (0.39-0.80)**
TP53 Alt[b]	32/36	3.7	21/26	8.5		0.49 (0.28-0.87)
***ESR1* WT**	**90/105**	**5.5**	**78/107**	**11.0**		**0.51 (0.37-0.70)**
ESR1 Alt[b]	11/12	6.5	12/13	12.0		0.70 (0.29-1.67)
***CCND1* WT**	**75/84**	**5.7**	**67/89**	**11.2**		**0.47 (0.33-0.66)**
CCND1 Alt[b]	26/33	3.6	23/31	9.2		0.77 (0.43-1.37)
***MAP3K1* WT**	**90/104**	**5.5**	**81/107**	**10.9**		**0.54 (0.40-0.75)**
MAP3K1 Alt[b]	11/13	7.7	9/13	17.3		0.44 (0.17-1.10)
***ARID1A* WT**	**90/102**	**5.5**	**85/109**	**10.9**		**0.51 (0.37-0.70)**
ARID1A Alt[b]	11/15	12.4	5/11	22.1		0.50 (0.17-1.49)



[a]HR was calculated by adjusting additional biomarker variables TMB and PTEN Loss. [b]Data should be interpreted with caution due to the small sample size.
Alt, altered; *ARID1A*, AT-rich interaction domain 1A; *CCND1*, cyclin D1; *ESR1*, estrogen receptor 1; FUL, fulvestrant; HR, hazard ratio; *MAP3K1*, mitogen-activated protein kinase kinase 1; mPFS, median progression-free survival; *TP53*, tumor protein p53; WT, wild-type.

Alpelisib + FUL Is Effective When the MAPK and/or PI3K Pathway Are Altered





- Clinical benefit was observed in patients with mutations in the MAPK or PI3K (in addition to *PIK3CA*) pathway
  - MAPK pathway genes assessed included *ERBB2, NF1, ERBB3, KRAS, EGFR, BRAF, MAP2K1*[1]
  - PI3K pathway genes assessed included *PTEN, AKT1, AKT2, AKT3, TSC1, TSC2, PDK1, MTOR, RPTOR, RICTOR*

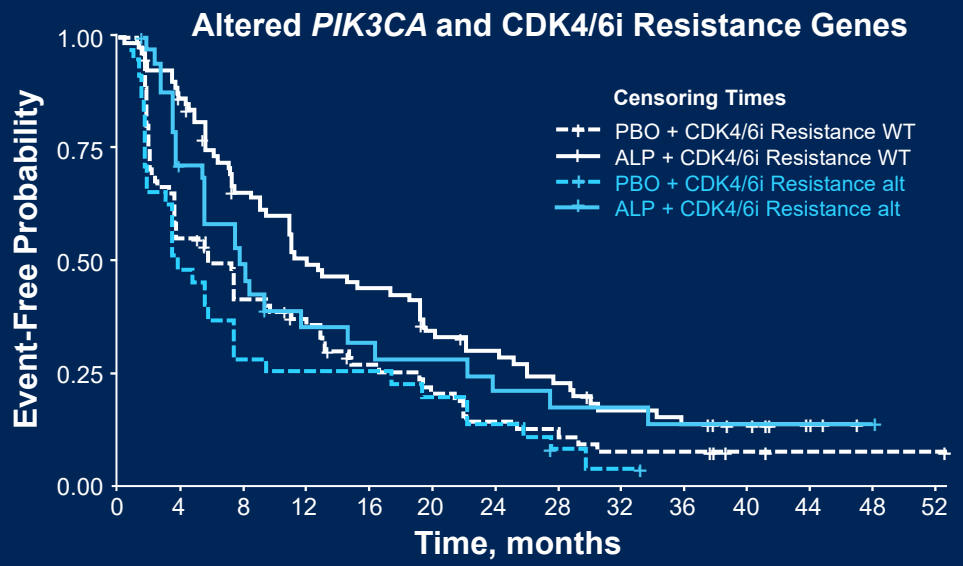
Median PFS in Patients With Altered *PIK3CA* and MAPK or PI3K Pathway

Gene	Placebo + FUL		Alpelisib + FUL		HR[a] (95%CI)
	n/N	mPFS, mo (95%CI)	n/N	mPFS, mo (95%CI)	
MAPK WT	72/87	7.2 (3.7-9.6)	72/97	11.6 (8.1-19.2)	0.56 (0.40-0.79)
MAPK Alt[b]	29/30	3.6 (2.1-5.7)	18/23	10.9 (5.5-12.7)	0.43 (0.23-0.80)
PI3K WT	77/88	5.5 (3.5-7.4)	67/88	11.2 (9.0-18.5)	0.48 (0.34-0.68)
PI3K Alt[b]	24/29	5.8 (2.8-13.1)	23/32	7.5 (5.3-22.1)	0.68 (0.38-1.23)

[a]HR was calculated by adjusting additional biomarker variables TMB and PTEN Loss. [b]Data should be interpreted with caution due to the small sample size.
AKT, protein kinase B; ALP, alpelisib; Alt, altered; *BRAF*, BRAF proto-oncogene; EGFR, epidermal growth factor receptor; *ERBB2*, erb-b2 receptor tyrosine kinase 2; *ERBB3*, erb-b2 receptor tyrosine kinase 3; FUL, fulvestrant; HR, hazard ratio; *KRAS*, KRAS proto-oncogene; *MAP2K1*, MAP2K1 mitogen-activated protein kinase kinase 1; MAPK, mitogen-activated protein kinase; mPFS, median progression-free survival; mTOR, mammalian target of rapamycin; *MYC*, MYC proto-oncogene; NF1, neurofibromin 1; PBO, placebo; PDK, pyruvate dehydrogenase kinase; PI3K, phosphatidylinositol-3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *RAD21*, RAD21 cohesin complex component; *RICTOR*, RPTOR independent companion of MTOR complex 2; *RPTOR*, regulatory associated protein of MTOR complex 1; *TSC*, TSC complex subunit 1; WT, wild-type.

1. Razavi P, et al. *Cancer Cell*. 2018;34(3):427-438.e6.

Clinical Benefit of Alpelisib + FUL Remains in Patients With Altered CDK4/6i Resistance Genes



- Clinical benefit was observed in patients with mutations in CDK4/6i resistance genes
  - CDK4/6i resistance genes included in the analysis were *PTEN, AURKA, NF1, ATM, ATR, RB1, CDK4, CDKN2A/B/C*

Median PFS in Patients With Altered *PIK3CA* and CDK4/6i Resistance Genes

Gene	Placebo + FUL		Alpelisib + FUL		HR[a] (95% CI)
	n/N	mPFS, mo (95% CI)	n/N	mPFS, mo (95% CI)	
CDK4/6i Resistance WT	67/81	**5.7** (3.6-9.6)	64/87	**12.0** (9.0-19.2)	**0.53** (0.37-0.76)
CDK4/6i Resistance Alt[b]	33/35	**3.8** (1.9-7.2)	26/33	**7.7** (5.3-14.6)	**0.52** (0.30-0.89)

[a]HR was calculated by adjusting additional biomarker variables TMB and PTEN Loss. [b]Data should be interpreted with caution due to the small sample size.
AKT, protein kinase B; ALP, alpelisib; Alt, altered; *ATM*, ATM serine/threonine kinase; *ATR*, ATR serine/threonine kinase; *AURKA*, aurora kinase A; *CDK4*, cyclin dependent kinase 4; *CDKN2A/B/C*, cyclin dependent kinase inhibitor 2A/B/C; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; FUL, fulvestrant; HR, hazard ratio; mPFS, median progression-free survival; *NF1*, neurofibromin 1; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *PTEN*, phosphatase and tensin homolog; *MYC*, MYC proto-oncogene bHLH transcription factor; *RAD21*, RAD21 cohesin complex component; *RB1*, RB transcriptional corepressor 1; WT, wild-type.

Summary

- Alpelisib had clinical benefit regardless of the mutation status of selected genes, MAPK pathway genes, PI3K pathway genes, or genes implicated in CDK4/6i resistance
- Patients with low TMB treated with alpelisib had longer mPFS than patients treated with placebo
- Improved benefit was observed in patients with altered *FGFR1* and/or *FGFR2*, whereas limited benefit was observed in patients with altered *MYC* and/or *RAD21*
- The results in this analysis are hypothesis generating because of the small sample size
- A differential gene alteration landscape was observed in *PIK3CA*-altered and *PIK3CA*-wild-type populations; further analyses will be reported in the future

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