Ciruelos et al., Clinical Outcomes of Alpelisib Plus Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer With *PIK3CA* Alterations Detected in Plasma ctDNA by Next-Generation Sequencing: Biomarker Analysis From the SOLAR-1 Study, SABCS 2020, PD2-06

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PD2-06

Clinical Outcomes of Alpelisib Plus Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer With *PIK3CA* Alterations Detected in Plasma ctDNA by Next-Generation Sequencing: Biomarker Analysis From the SOLAR-1 Study

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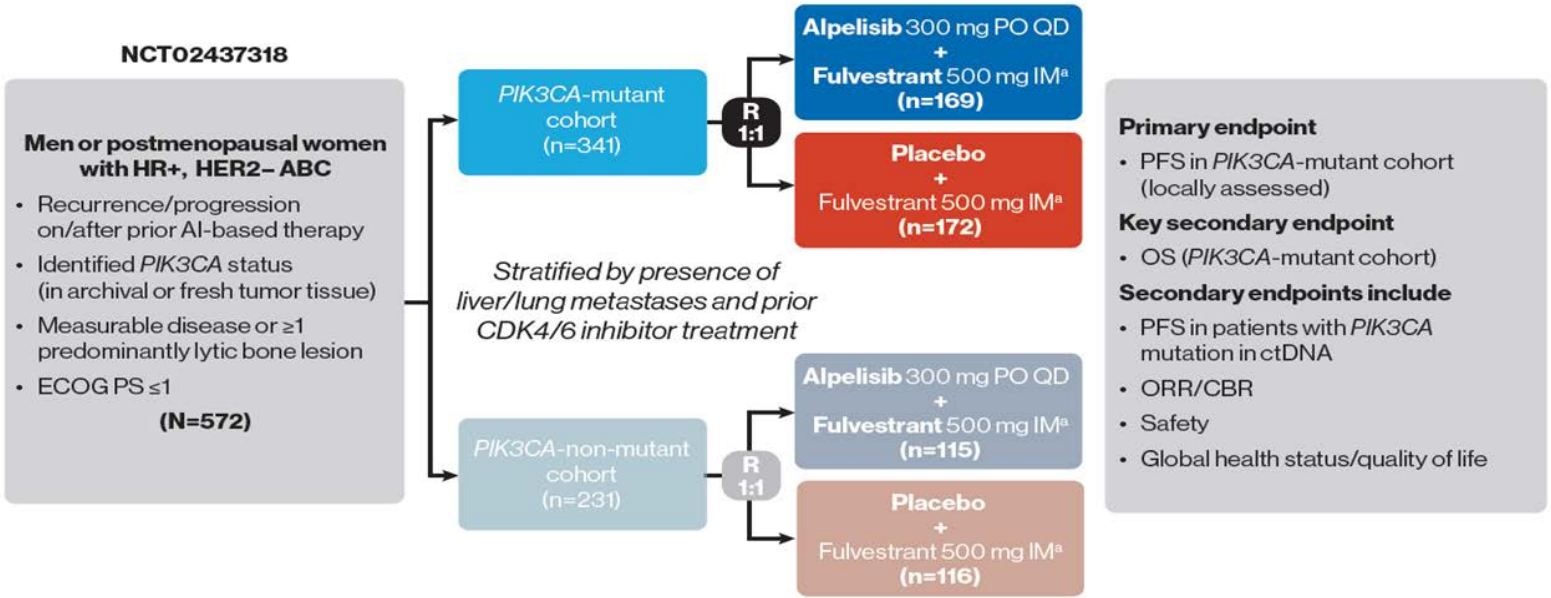
Background (1 of 3)

- Approximately 40% of cases of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC) contain mutations in the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*) gene.[1-6]
  - The majority of mutations occur in exons 9 and 20 of *PIK3CA* and are found to a lesser extent in exon 7.[7-8]
- SOLAR-1 is the first Phase III trial investigating specific inhibition of the effects of *PIK3CA* with alpelisib in combination with fulvestrant in HR+, HER2– ABC post endocrine therapy (**Figure 1**).
  - SOLAR-1 demonstrated clinical benefit in patients with HR+, HER2–, *PIK3CA*-mutated ABC in the post-endocrine therapy setting.[9-12]

Background (2 of 3)

Figure 1. Study Design



[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 kinases 4 and 6; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2–, human epidermal growth factor receptor 2–negative; HR+, hormone receptor–positive; IM, intramuscular; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PO, orally; QD, daily; R, randomization.

Background (3 of 3)

- In SOLAR-1, prospective *PIK3CA* mutation testing was performed on tumor tissue in a central laboratory using polymerase chain reaction (PCR)-based assays and patients were assigned to a cohort on the basis of this test.
  - The initial screening assay could detect 11 specific mutations in exons 7, 9, and 20.
  - In the cohort of patients with *PIK3CA* mutations, median progression-free survival (mPFS) was 11.0 months and 5.7 months in patients receiving alpelisib + fulvestrant vs placebo + fulvestrant, respectively (primary endpoint of SOLAR-1, hazard ratio [HR] 0.65; 95% confidence interval [CI], 0.50-0.85; 1-sided *P*=0.00065).[9-11]
  - In a secondary endpoint analysis, mPFS was 10.9 months and 3.7 months in patients with a *PIK3CA* mutation (as assessed retrospectively by PCR on plasma circulating tumor DNA [ctDNA] collected at baseline and analyzed retrospectively) receiving alpelisib + fulvestrant vs placebo + fulvestrant, respectively (HR 0.55; 95% CI, 0.39-0.79).[10]
- Retrospective analyses by next-generation sequencing (NGS) identified *PIK3CA* alterations in tumor tissue, and efficacy of alpelisib was demonstrated in patients whose tumors harbor *PIK3CA* alteration(s) as detected by NGS.[13,14]

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

Objective

- The objective of this exploratory biomarker analysis was to assess clinical outcomes of patients with *PIK3CA* alteration(s) as detected in plasma ctDNA through retrospective analysis by an NGS assay.

ctDNA, circulating tumor DNA; NGS, next-generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Methods

Biomarker Analyses

- Retrospectively, the full exonic region of the *PIK3CA* gene was sequenced using the Foundation Medicine panels in tumor tissue (FoundationOne® CDx 324-gene panel) and plasma ctDNA (FoundationOne® Liquid CDx 311-gene panel) collected at baseline.
  - Using NGS testing, the exploratory analysis was performed for all patients with sufficient samples (quantity/quality) independently of their tumor tissue alteration status as detected by PCR.
  - The NGS test detected additional *PIK3CA* alterations that were not detectable by the PCR assays used during SOLAR-1 screening.
    - The prospective screening assay was performed on formalin-fixed, paraffin-embedded (FFPE) tumor specimens using a validated Novartis clinical trial assay and/or the QIAGEN *therascreen*® *PIK3CA* RGQ PCR Kit. Per this prospective screening, patients with specific mutations in exons 7, 9, and 20 (C420R, E542K, E545A/D/G/K, Q546E/R, H1047L/R/Y) were enrolled in SOLAR-1.
    - For NGS testing, a *PIK3CA* alteration is defined as single or multiple genetic changes (leading or not leading to amino acid changes) or a copy number variation (amplification).
- PFS was assessed using Kaplan–Meier methodology per investigator assessment.

ctDNA, circulating tumor DNA; NGS, next-generation sequencing; PCR, polymerase chain reaction; PFS, progression free-survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Results (1 of 16)

NGS Analysis

- Of 572 patients in SOLAR-1, 381 patients (67%) across both *PIK3CA*-mutant and non-mutant cohorts had valid plasma ctDNA data.
- Of these patients, 193 (51%) had a *PIK3CA* alteration (genetic or amino acid change or copy number variation) in ctDNA (Table 1).

ctDNA, circulating tumor DNA; NGS, next-generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Results (2 of 16)

Table 1. Available Samples of Plasma ctDNA at Baseline

	Patients With a *PIK3CA* Alteration per NGS (n=193)
Number of alterations, n (%)	
Single alteration	147 (76)
Multiple alterations	46 (24)
Detectable by PCR, n (%)	
Yes	168 (87)
No	25 (13)
Exon 7 alteration, n (%)[a]	11 (6)
Exon 9 alteration, n (%)	70 (36)
Exon 20 alteration, n (%)	102 (53)

[a] No further analysis was performed on patients with alterations in exon 7 due to the low number.
ctDNA, circulating tumor DNA; NGS, next-generation sequencing; PCR, polymerase chain reaction; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Results (3 of 16)

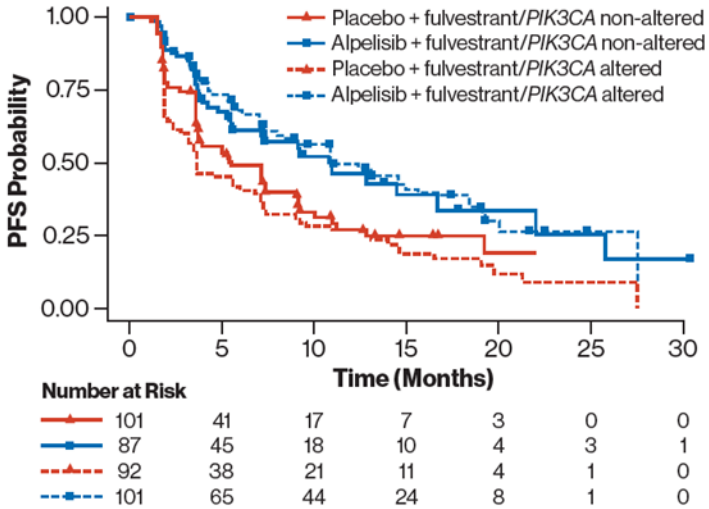
mPFS in Patients by *PIK3CA* Alteration Status in Plasma ctDNA as Detected by NGS

- In the *PIK3CA*-altered group, treatment with alpelisib + fulvestrant resulted in improved PFS compared with placebo (mPFS: 11.0 mo vs 3.7 mo; HR 0.47; 95% CI, 0.33-0.67; **Figure 2**).
- In the *PIK3CA*-non-altered group, treatment with alpelisib + fulvestrant indicated improved PFS compared with placebo (mPFS: 10.9 mo vs 5.5 mo; HR 0.60; 95% CI, 0.40-0.91; **Figure 2**)**.**

ctDNA, circulating tumor DNA; HR, hazard ratio; mo, months; mPFS, median progression-free survival; NGS, next-generation sequencing; PFS, progression-free survival; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; vs, versus.

Results (4 of 16)

Figure 2. Kaplan–Meier mPFS in Patients by PIK3CA Alteration Statusa in Plasma ctDNA as Detected by NGS



Group[a]	Events	N	mPFS (95% CI)	HR (95% CI)
Placebo + fulvestrant/ *PIK3CA* non-altered	60	101	5.5 (3.8-9.0)	0.60 (0.40-0.91)
Alpelisib + fulvestrant/ *PIK3CA* non-altered	40	87	10.9 (5.6-16.8)	
Placebo + fulvestrant/ *PIK3CA* altered	73	92	3.7 (2.9-6.8)	0.47 (0.33-0.67)
Alpelisib + fulvestrant/ *PIK3CA* altered	58	101	11.0 (7.7-16.2)	

[a]Alteration status as detected in plasma ctDNA by NGS.
CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; mPFS, median progression-free survival; NGS, next-generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Results (5 of 16)

Deeper Understanding of Alpelisib Efficacy in Patients With *PIK3CA* Non-altered Status in Plasma ctDNA

- Of the patients in the ctDNA non-altered subgroup, 38% (72/188) had *PIK3CA* alteration(s) in tissue as detected by NGS, PCR, or both (**Table 2**).

Table 2. Tissue Alterations by NGS and PCR in the Plasma ctDNA Non-altered Population

ctDNA *PIK3CA* Non-altered Population (n=188)

Tissue	Altered	Non-altered	NA
NGS, n	39	98	51
PCR, n	67	121	0

ctDNA, circulating tumor DNA; NA, not availablel; NGS, next-generation sequencing; PCR, polymerase chain reaction; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

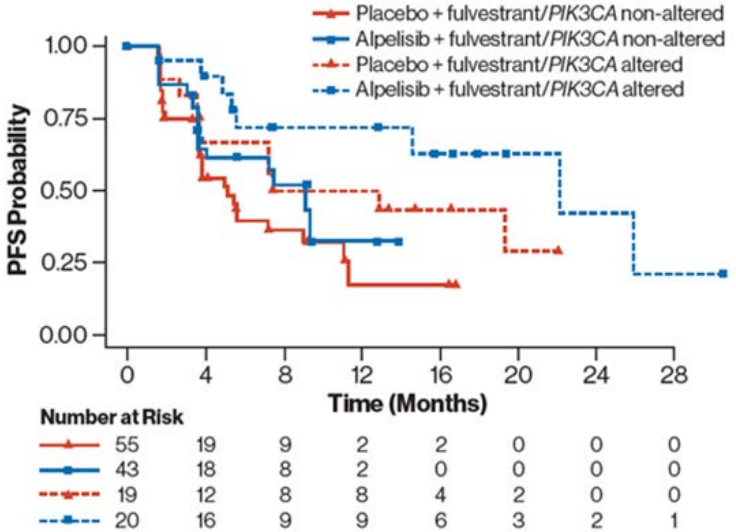
Results (6 of 16)

- For patients treated with alpelisib plus fulvestrant, those in the ctDNA non-altered subgroup with tissue alterations in *PIK3CA*, as detected by NGS, had longer mPFS (22.1mo [n=20]) than those with non-altered tissue *PIK3CA* (9.2 mo [n=43]; **Figure 3**).
  - These results should be interpreted with caution due to the low number of patients in each subgroup.
- This result suggests that when no *PIK3CA* alteration is detected in plasma ctDNA, alteration(s) in tumor tissue should be investigated to confirm the *PIK3CA* status of the tumor.

ctDNA, circulating tumor DNA; mo, months; mPFS, median progression-free survival; NGS, next-generation sequencing; PCR, polymerase chain reaction; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Results (7 of 16)

Figure 3. Kaplan–Meier mPFS in Patients Without *PIK3CA* Alteration(s) in ctDNA as Detected by NGS by Tissue Alteration Status[a]



Group[a]	Events	N	mPFS (95% CI)	HR (95% CI)
Placebo + fulvestrant/ *PIK3CA* non-altered	31	55	5.1 (3.7-9.0)	0.69 (0.38-1.27)
Alpelisib + fulvestrant/ *PIK3CA* non-altered	18	43	9.2 (3.8-NA)	
Placebo + fulvestrant/ *PIK3CA* altered	11	19	10.1 (3.6-NA)	0.54 (0.19-1.50)
Alpelisib + fulvestrant/ *PIK3CA* altered	8	20	22.1 (5.5-NA)	

[a]Alteration status as detected in plasma ctDNA by NGS.
CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; mPFS, median progression-free survival; NGS, next-generation sequencing; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Results (8 of 16)

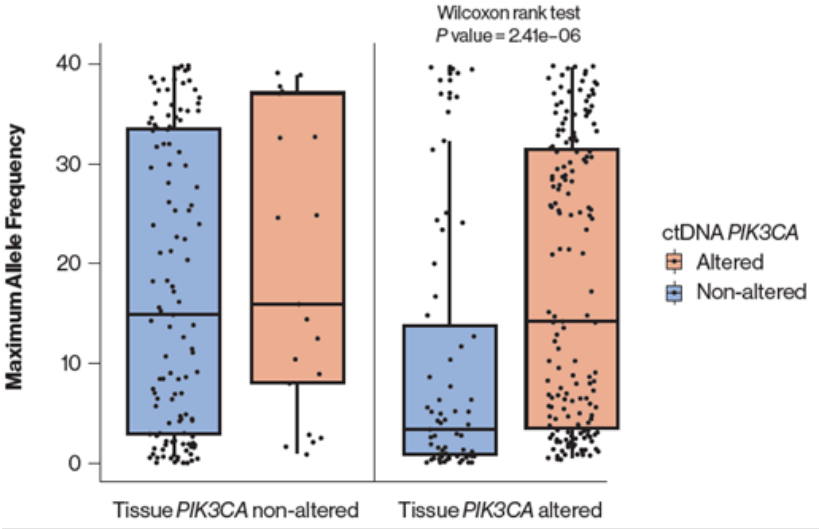
PIK3CA Alteration(s) in Tumor Tissue vs Plasma ctDNA: Investigating the Discordance

- ctDNA allele frequency
  - Patients who did not have a *PIK3CA* alteration detected in ctDNA but were found to have a *PIK3CA* alteration in tissue had lower maximum allele frequency in ctDNA (**Figure 4**).
    - Maximum allele frequency was determined, in ctDNA, using all somatic alterations, or those with an allele frequency below 40% (indicating a possible germline alteration).
    - This indicates that ctDNA may not be identifying patients with low tumor allele frequencies due to ctDNA test sensitivity.

ctDNA, circulating tumor DNA; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Results (9 of 16)

Figure 4. ctDNA Maximum Allele Frequency for Patients With *PIK3CA* Alteration or Non-alteration in Tissue by Plasma ctDNA Alteration Status



Tissue *PIK3CA*	ctDNA *PIK3CA*	n	Mean	95% CI
Non-altered	Non-altered	121	17.55	14.93-20.17
	Altered	21	20.07	13.31-26.83
Altered	Non-altered	67	9.75	6.54-12.97
	Altered	172	17.72	15.58-19.85

CI, confidence interval; ctDNA, circulating tumor DNA; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Results (10 of 16)

Tissue Allele Frequency

- In patients who were found to have a *PIK3CA* alteration in tissue but not in plasma ctDNA, tissue *PIK3CA* allele frequency was lower than that of ctDNA *PIK3CA*-altered patients (**Figure 5**).
  - This lower allele frequency may indicate differences in tumor DNA shedding.

ctDNA, circulating tumor DNA; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

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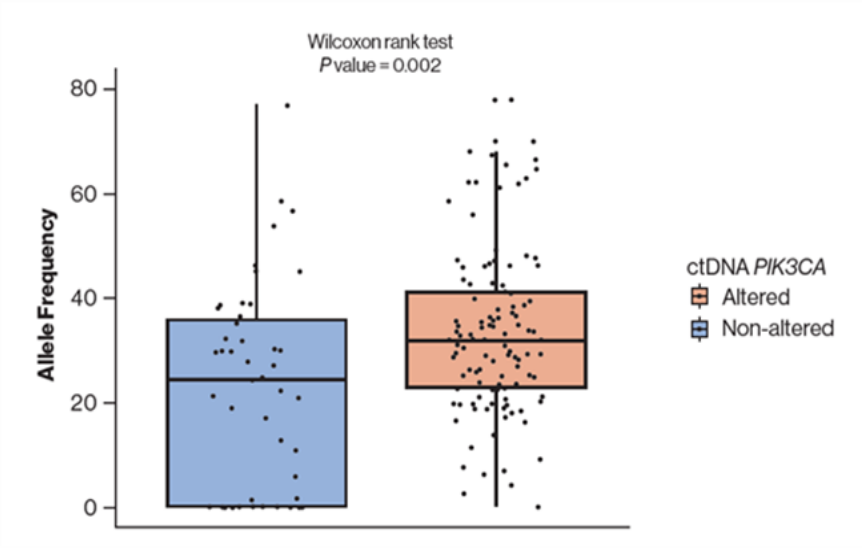
Figure 5. Tissue *PIK3CA* Allele Frequency for Patients With *PIK3CA* Alteration in Tissue by Plasma ctDNA Alteration Status



Tissue *PIK3CA*	ctDNA *PIK3CA*	n	Mean	95% CI
Altered	Non-altered	47	22.52	16.74-28.30
	Altered	114	33.07	30.11-36.04

CI, confidence interval; ctDNA, circulating tumor DNA; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Results (12 of 16)

Blood Tumor Mutation Burden

- Patients who did not have a *PIK3CA* alteration detected in ctDNA but were found to have a *PIK3CA* alteration in tissue had lower blood tumor mutation burden (**Figure 6**).
  - This observation, along with differences in maximum allele frequency, may further indicate a difference in tumor DNA shedding leading to a non-altered finding in ctDNA.

ctDNA, circulating tumor DNA; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

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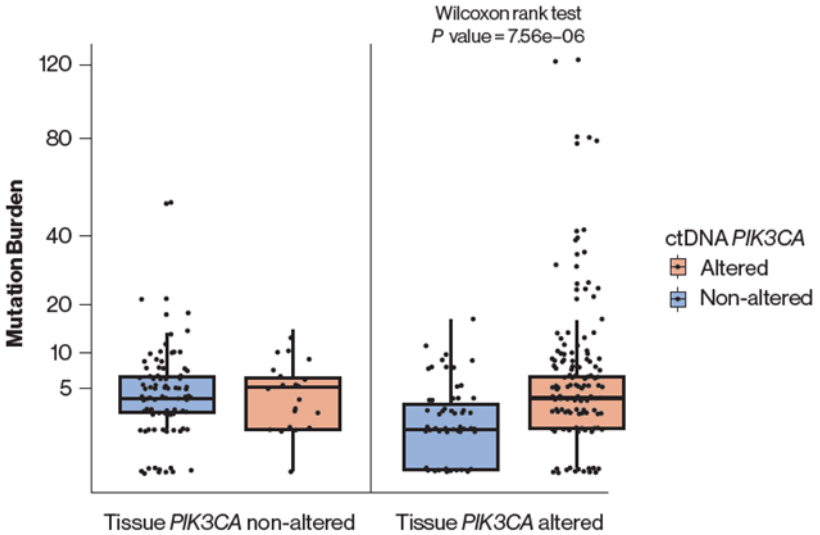
Figure 6. Blood Tumor Mutation Burden for Patients With *PIK3CA* Alteration or Non-alteration in Tissue by Plasma ctDNA Alteration Status



Tissue *PIK3CA*	ctDNA *PIK3CA*	n	Mean	95% CI
Non-altered	Non-altered	120	4.71	3.69-5.73
	Altered	21	4.70	3.07-6.33
Altered	Non-altered	67	2.58	1.80-3.37
	Altered	172	6.89	4.83-8.94

CI, confidence interval; ctDNA, circulating tumor DNA; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Results (14 of 16)

mPFS in Patients With *PIK3CA* Alteration(s) in ctDNA as Detected by NGS in Subgroups of Interest

- In patients with PCR-detectable alterations, a benefit of alpelisib + fulvestrant vs placebo + fulvestrant was observed (mPFS: 12.5 mo vs 3.6 mo; HR 0.44; 95% CI, 0.30-0.64; **Figure 7**).
- In the small group of alpelisib-treated patients with alterations not detectable by PCR, (n =13), no benefit from treatment with alpelisib + fulvestrant vs placebo + fulvestrant was observed (mPFS: 8.5 mo vs 7.4 mo; HR 1.12; 95% CI, 0.35-3.56; **Figure 7**).
- Patients with single (n=147) or multiple (n=46) *PIK3CA* alterations benefited similarly from treatment with alpelisib + fulvestrant vs placebo + fulvestrant (PFS HR for patients with single alterations: 0.43 [95% CI, 0.28-0.65]; PFS HR for patients with multiple alterations: 0.55 [95% CI, 0.25-1.20]; **Figure 7**).
  - Patients with multiple PIK3CA alterations had shorter mPFS with alpelisib (9.0 mo) than those with single alterations (12.9 mo); however, results should be interpreted with caution due to the small number of patients (n=46 with multiple alterations).

CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; mo, months; mPFS, mean progression free-survival; PCR, polymerase Chain Reaction; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; vs, versus.

Results (15 of 16)

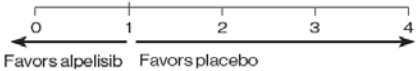
- Similar benefit was seen in patients with alterations in either exon 9 or exon 20 (PFS HR for patients with exon 9 alteration: 0.31 [95% CI, 0.16-0.61]; PFS HR for patients with exon 20 alteration: 0.51 [95% CI, 0.31-0.82]; **Figure 7**).
- Results should be interpreted with caution due to the small number of patients in some subgroups.

CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; mo, months; PFS, progression-free survival;

Results (16 of 16)

Figure 7. mPFS in Patients With *PIK3CA* Alteration(s) in ctDNA as Detected by NGS in Subgroups of Interest

	Alpelisib + Fulvestrant		Placebo + Fulvestrant		
	Events/N	mPFS, mo (95% CI)	Events/N	mPFS, mo (95% CI)	HR (95% CI)
PIK3CA: Alteration status as detected by NGS					
Altered	58/101	11.0 (7.7-16.2)	73/92	3.7 (2.9-6.8)	0.47 (0.33-0.67)
Non-altered	40/87	10.9 (5.6-16.8)	60/101	5.5 (3.8-9.0)	0.60 (0.40-0.91)
PIK3CA: Alteration status as detected by PCR[a]					
Detectable	52/88	12.5 (7.4-18.4)	66/80	3.6 (2.4-5.7)	0.44 (0.30-0.64)
Not detectable	6/13	8.5 (2.7-NA)	7/12	7.4 (1.9-13.0)	1.12 (0.35-3.56)
PIK3CA: Number of alterations					
Single	45/83	12.9 (7.4-18.5)	50/64	3.6 (1.9-6.1)	0.43 (0.28-0.65)
Multiple	13/18	9.0 (3.7-18.4)	23/28	4.6 (3.5-9.6)	0.55 (0.25-1.20)
PIK3CA: Alterations in exon 9 or exon 20					
Exon 9	18/34	15.2 (7.0-NA)	29/36	3.7 (2.9-7.4)	0.31 (0.16-0.61)
Exon 20	34/54	10.9 (5.7-18.4)	40/48	3.5 (1.9-6.1)	0.51 (0.31-0.82)



[a]Alteration detectable by PCR refers to the mutations as detected by the validated Novartis clinical trial assay and/or the QIAGEN *therascreen*® PIK3CA RGQ PCR Kit.
CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; mo, months; mPFS, median progression-free survival; NA, not applicable; NGS, next-generation sequencing; PCR, polymerase chain reaction; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

Conclusions (1 of 2)

- The data presented here indicated the clinical benefit of alpelisib + fulvestrant in patients with HR+, HER2– ABC with *PIK3CA* alterations in either plasma ctDNA or tissue FFPE as detected by NGS.
- The clinical benefit of alpelisib observed in this study is consistent with that observed in patients with *PIK3CA* alteration(s) in tumor tissue as detected by NGS and PCR
  - In subgroups of interest (including patients with PCR-detectable alterations, multiple/single alterations, and exon 9/20 alterations), a consistent PFS benefit was observed.
  - Limited benefit was observed for alpelisib + fulvestrant in the subgroup of patients with *PIK3CA* alterations not detectable by PCR.
  - Caution should be taken in interpreting these results due to the small number of patients in some subgroups.

ABC, advanced breast cancer; ctDNA, circulating tumor DNA; FFPE, formalin-fixed paraffin-embedded; HR+, hormone receptor-positive; HER2–, human epidermal growth factor receptor 2–negative; NGS, next-generation sequencing; PCR, polymerase chain reaction; *PIK3CA*, phosphatidylinositol-4,5 bisphosphate 3-kinase catalytic subunit alpha.

Conclusions (2 of 2)

- Additional analysis indicated that *PIK3CA* alteration in tissue is driving the clinical benefit observed in non-altered plasma ctDNA patients, which supports the reflex testing paradigm.
  - When no *PIK3CA* alteration is detected by ctDNA liquid biopsy, a tissue test should be performed to confirm the *PIK3CA* status of the tumor.
- Discordance between the tissue and plasma *PIK3CA* alteration results was due to both technical (test performance) and biological (ctDNA shedding) aspects.
  - Low allele frequency of mutations in tumor tissue at primary tumor or metastatic sites may lead to low representation of alterations in ctDNA, which could be lower than the detection limit of the assay.
  - Variable DNA shedding rates between tumors may also limit *PIK3CA* alteration(s) detection by ctDNA.

ctDNA, circulating tumor DNA; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha.

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