Overall Survival With Palbociclib And Fulvestrant in Women With HR+/HER2– ABC: Updated Exploratory Analyses of PALOMA-3, a Double-Blind, Phase 3 Randomized Study

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Translational Relevance

The long-term effect of cyclin-dependent kinase 4/6 inhibition plus endocrine therapy for advanced breast cancer (ABC) is an important area of research, and circulating tumor DNA (ctDNA) may provide valuable prognostic information. In PALOMA-3, palbociclib plus fulvestrant improved median overall survival (OS) versus placebo plus fulvestrant after 44.8 months of follow-up. In this updated exploratory analysis of the PALOMA-3 clinical trial, a continued improvement in median OS with palbociclib plus fulvestrant versus placebo plus fulvestrant was observed (34.8 vs 28.0 months). Favorable OS in the palbociclib group was also observed across most subgroups regardless of ESR1, PIK3CA, or TP53 mutation status. These findings support the palbociclib plus fulvestrant regimen as a standard of care in patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) ABC and show that ctDNA analysis can provide prognostic information.

Abstract

Purpose: To conduct an updated exploratory analysis of overall survival (OS) with a longer median follow-up of 73.3 months and evaluate the prognostic value of molecular analysis by circulating tumor DNA (ctDNA).

Patients and methods: Patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) advanced breast cancer (ABC) were randomized 2:1 to receive palbociclib (125 mg orally/d; 3/1 week schedule) and fulvestrant (500 mg intramuscularly) or placebo and fulvestrant. This OS analysis was performed when 75% of enrolled patients died (393 events in 521 randomized patients). ctDNA analysis was performed among patients who provided consent.

Results: At the data cutoff (August 17, 2020), 258 and 135 deaths occurred in the palbociclib and placebo groups, respectively. The median OS (95% CI) was 34.8 months (28.8–39.9) in the palbociclib group and 28.0 months (23.5–33.8) in the placebo group (stratified hazard ratio 0.81; 95% CI, 0.65–0.99). The 6-year OS rate (95% CI) was 19.1% (14.9–23.7) and 12.9% (8.0–19.1) in the palbociclib and placebo groups, respectively. Favorable OS with palbociclib plus fulvestrant compared with placebo plus fulvestrant was observed in most subgroups, particularly in patients with endocrine-sensitive disease, no prior chemotherapy for ABC, low circulating tumor fraction, and regardless of *ESR1, PIK3CA,* or *TP53* mutation status. No new safety signals were identified.

Conclusions: The clinically meaningful improvement in OS associated with palbociclib plus fulvestrant was maintained with >6 years of follow-up in patients with HR+/HER2– ABC, supporting palbociclib plus fulvestrant as a standard of care in these patients.

Trial Registration: ClinicalTrials.gov Identifer: NCT01942135

Introduction

Palbociclib is a first-in-class orally active cyclin-dependent kinase 4/6 (CDK4/6) inhibitor that is approved for the treatment of patients with hormone receptor–positive/human epidermal growth factor receptor 2–negative (HR+/HER2–) advanced breast cancer (ABC) (1). Findings from the PALOMA-3 study in women with HR+/HER2– ABC showed that palbociclib plus fulvestrant significantly prolonged progression-free survival (PFS) compared with placebo plus fulvestrant (11.2 vs 4.6 months, respectively; hazard ratio [HR], 0.50 [95% CI, 0.40–0.62]; 1-sided *P*<0.0001) (2,3). At a median follow-up of 44.8 months, the final protocol-specified overall survival (OS) analysis demonstrated a longer OS with palbociclib plus fulvestrant compared with placebo plus fulvestrant that was not statistically significant (34.9 vs 28.0 months, respectively; HR, 0.81 [95% CI, 0.64–1.03]; 1-sided *P*=0.0429) (4). Moreover, sensitivity to prior endocrine therapy, nonvisceral disease, no prior chemotherapy for ABC, and an Eastern Cooperative Oncology Group performance status of 0 were identified as significant positive prognostic factors for OS. Patients without prior chemotherapy for ABC had longer median OS in the palbociclib arm versus placebo arm, while patients with prior chemotherapy for ABC had a similar OS among treatment arms (5).

With CDK4/6 inhibitors plus endocrine therapy now considered a standard of care for the treatment of HR+/HER2– ABC (6), a clinical need exists to identify patients who may be at risk of progressing early while receiving palbociclib plus endocrine therapy. Other than estrogen receptor and progesterone receptor expression, no clinical biomarkers presently exist for palbociclib treatment sensitivity or resistance (7). Additionally, there is limited information

regarding associations between genetic mutations and clinical outcome in ABC (8). However, circulating tumor DNA (ctDNA) is rapidly being incorporated in the clinical setting and during medication development as a preferred liquid biopsy diagnostic to analyze the genetic features of tumors (8-10).

This updated exploratory analysis reports OS results from PALOMA-3 with a longer median follow-up of 73.3 months and evaluated the prognostic value of genomic abnormalities identified by ctDNA.

Materials and Methods

Study Design and Patients

Detailed methodology of the PALOMA-3 clinical study has been previously described (11). Briefly, PALOMA-3 is a double-blind, multicenter, phase 3 study that included premenopausal or postmenopausal women with HR+/HER2– ABC whose disease had progressed on endocrine therapy. Patients were allowed up to one prior line of chemotherapy for ABC. Patients were excluded if they had active, uncontrolled, or symptomatic brain metastases or symptomatic visceral spread or were at risk for life-threatening complications. All patients provided written informed consent prior to enrollment. The study was approved by the institutional review board at each study center, and conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki, with monitoring by an academic steering committee.

Randomization and Masking

Patients were randomized 2:1 to receive palbociclib (125 mg orally per day for 3 weeks, followed by 1 week off) and fulvestrant (500 mg intramuscularly every 14 days for the first three injections followed by every 28 days) or matching placebo and fulvestrant. Patients were randomly assigned by the investigator or research staff via a centralized interactive web- and voice-based randomization system, which also generated the random allocation sequence. For each stratification level, random assignments to the treatments were made in a block size of six. Patients were assigned based on three stratification factors: sensitivity to prior hormonal therapy, menopausal status, and presence of visceral metastases. The patients, investigators, and research staff were all blinded to treatment group assignment.

Outcomes

Investigator-assessed PFS was the primary endpoint of the study, and OS was a key secondary endpoint. Overall survival was defined as the time from the date of randomization to the date of death due to any cause. In the absence of confirmation of death, survival time was censored to the last date the patient was known to be alive. Here we report the final unplanned exploratory OS analysis with 393 events in 521 randomized patients (75% of the total study population; data cutoff date: August 17, 2020) with a median follow-up of 73.3 months. The median OS was estimated using the Kaplan-Meier method; 95% CIs and hazard ratios were estimated using Cox proportional hazard models.

Plasma samples were collected and stored for ctDNA analyses at baseline and the end of treatment. A custom, amplicon error–corrected sequencing approach was used for ctDNA analyses, as previously reported (8,12). The targeted panel of 17 targetable driver and CDK4/6–related genes included all exons (*RB1*, *CDK4*, *CDK6*, *CDKN1A*, *CDKN1B*, and *NF1;* exons 5–8 of *TP53*) and hot spots (*ERBB2*, *PIK3CA*, *AKT1*, *ESR1*, *FGFR1*, *FGFR2*, *FGFR3*, *KRAS*, *HRAS,* and *NRAS*). The allele fraction cutoff for calling gene mutations as positive was 0.5% allele frequency for whole genes and 0.3% for hot spots. Progression-free survival and OS rates were assessed among treatment arms in patients with circulating tumor fraction above or below a cutoff of 10% (high and low purity), as previously reported (8).

Adverse events (AEs) were reported and severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0. Safety findings were summarized descriptively.

Data Availability

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data.

See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Results

A total of 521 patients were randomized into the study (347 patients in the palbociclib plus fulvestrant group and 174 patients in the placebo plus fulvestrant group). As previously reported (3), patient demographics and baseline clinical characteristics were generally similar between the treatment groups. As of the data cutoff date of August 17, 2020, 393 deaths had occurred; 258 deaths in the palbociclib plus fulvestrant group and 135 deaths in the placebo plus fulvestrant group. The median duration of follow-up was 73.3 months (95% CI, 73.0–74.0). A total of 18 patients remained on study treatment, including 15 patients (4.3%) in the palbociclib plus fulvestrant group and three patients (1.7%) in the placebo plus fulvestrant group (Supplementary Figure S1).

The median OS was 34.8 months (95% CI, 28.8–39.9) in the palbociclib plus fulvestrant group and 28.0 months (95% CI, 23.5–33.8) in the placebo plus fulvestrant group (stratified HR, 0.81 [95% CI, 0.65–0.99]; Figure 1). The 5-year OS rate (95% CI) was 23.3% (18.7–28.2) in the palbociclib group versus 16.7% (11.2–23.3) in the placebo group; the 6-year OS rate was 19.1% (14.9–23.7) versus 12.9% (8.0–19.1) in the palbociclib and placebo groups, respectively. In the subgroup of patients who had not received prior chemotherapy for advanced breast cancer (n=344), the median OS was 39.3 months (95% CI, 34.5–44.4) in the palbociclib plus fulvestrant group and 29.7 months (95% CI, 23.8–35.5) in the placebo plus fulvestrant group (HR, 0.72 [95% CI, 0.55–0.94]; Supplementary Figure S2A). In the subgroup of patients who had received prior chemotherapy for ABC (n=177), the median OS was 24.6 months (95% CI, 21.3–30.0) in the palbociclib plus fulvestrant group and 24.3 months (95% CI, 18.9–36.3) in the placebo plus

fulvestrant group (HR, 0.97 [95% CI, 0.69–1.36]; Supplementary Figure S2B). Favorable OS with palbociclib plus fulvestrant compared with placebo plus fulvestrant was observed in most of the subgroups evaluated (Figure 2).

ESR1, *PIK3CA*, and *TP53* gene mutation data by ctDNA analysis were available for 331 patients at Day 1 and 195 patients at the end of treatment. Among the 331 patients at Day 1, there were 160/331 (48.3%) patients with any detected mutation and 171/331 (51.7%) of patients with no detected mutation. Similar to previously reported in O'Leary et al 2021 (8), *ESR1*, *PIK3CA*, and *TP53* gene mutations were reported in 72 (21.8%), 55 (16.6%), and 51 (15.4%) patients, respectively, at Day 1. At the end of treatment mutations were reported in 61 (18.4%), 52 (15.7%), and 41 (12.4%) patients.At Day 1 or the end of treatment mutations were reported in 97 (29.3%), 71 (21.5%), and 57 (17.2%) patients. The most prevalent *ESR1* mutation variants were D538G, Y537S, E380Q, and Y537N. Herein, data are presented for mutational status subgroups defined based on the presence of a mutation at either Day 1 or at the end of treatment.

Palbociclib plus fulvestrant provided a PFS benefit regardless of *ESR1* mutation status at Day 1 or end of treatment (Figure 3A). In patients without *ESR1* mutations, the median PFS was 11.1 months (95% CI, 7.5–13.9) with palbociclib plus fulvestrant compared with 5.4 months (95% CI, 3.4–7.6) with placebo plus fulvestrant (HR, 0.60 [95% CI, 0.43–0.83]). In patients with *ESR1* mutations, the median PFS was 11.3 months (95% CI, 9.2–14.3) in patients receiving palbociclib

plus fulvestrant versus 3.6 months (95% CI, 1.9–5.4) in patients receiving placebo plus fulvestrant (HR, 0.25 [95% CI, 0.15–0.43]).

ESR1 mutations were prognostic for OS (HR, 1.58 [95% CI, 1.22–2.06]; Figure 3B) and were highly associated with shorter OS (<4 years vs ≥4 years; odds ratio [OR], 0.36 [95% CI, 0.19–0.68] Supplementary Table S1). Regardless of *ESR1* mutation status at Day 1 or end of treatment, palbociclib plus fulvestrant provided OS benefit versus placebo plus fulvestrant (Figure 3C). In patients without *ESR1* mutations, the median OS was 32.8 months (95% CI, 27.4–46.1) with palbociclib plus fulvestrant and 28.0 months (95% CI, 23.6–36.3) with placebo plus fulvestrant (HR, 0.81 [95% CI, 0.59–1.11]). In patients with *ESR1* mutations, the median OS was 27.7 months (95% CI, 20.4–36.1) with palbociclib plus fulvestrant and 20.2 months (95% CI, 15.3–27.1) with placebo plus fulvestrant (HR, 0.59 [95% CI, 0.37–0.94]).

Palbociclib plus fulvestrant provided a PFS benefit compared with placebo plus fulvestrant regardless of *PIK3CA* status (Figure 4A). In patients without *PIK3CA* mutations, the median PFS was 11.3 months (95% CI, 9.2–14.1) in patients receiving palbociclib plus fulvestrant and 3.8 months (95% CI, 3.4–7.2) in patients receiving placebo plus fulvestrant (HR, 0.48 [95% CI, 0.35–0.66]). Palbociclib plus fulvestrant also improved median PFS compared with placebo plus fulvestrant in patients with *PIK3CA* mutations (10.9 months [95% CI, 5.6–12.7] vs 3.5 months [95% CI, 1.9–11.2], respectively; HR, 0.55 [95% CI, 0.31–0.99]).

Additionally, *PIK3CA* mutations were prognostic for OS (HR, 1.44 [95% CI, 1.08–1.92]; Figure 4B) and were numerically associated with shorter OS (<4 years vs ≥4 years; OR, 0.55 [95% CI, 0.29–1.08]; Supplementary Table S1). Palbociclib plus fulvestrant provided an OS benefit compared with placebo plus fulvestrant regardless of *PIK3CA* mutation status (Figure 4C). Among patients without *PIK3CA* mutations, the median OS was 32.8 months (95% CI, 27.2–42.3) in patients receiving palbociclib plus fulvestrant and 26.6 months (95% CI, 23.4–33.0) in patients receiving placebo plus fulvestrant (HR, 0.78 [95% CI, 0.58–1.04]). In patients with *PIK3CA* mutations, the median OS was 27.7 months (95% CI, 16.9–40.1) with palbociclib plus fulvestrant and 18.3 months (95% CI, 12.9–29.5) with placebo plus fulvestrant (HR, 0.73 [95% CI, 0.42–1.25]).

Regardless of *TP53* mutation status, palbociclib plus fulvestrant was associated with improvement in PFS compared with placebo plus fulvestrant (Figure 5A). In patients without *TP53* mutations, the median PFS was 12.1 months (95% CI, 9.5–14.3) in the palbociclib plus fulvestrant group versus 5.4 months (95% CI, 3.6–7.3) in the placebo plus fulvestrant group (HR, 0.49; 95% CI, 0.36–0.67). In patients with *TP53* mutations, the median PFS was 5.7 months (95% CI, 1.9–11.4) with palbociclib plus fulvestrant compared with 1.8 months (95% CI, 1.7–3.5) with placebo plus fulvestrant (HR, 0.50 [95% CI, 0.27–0.91]).

TP53 mutations were prognostic for OS (HR, 2.19 [95% CI, 1.61–2.99] Figure 5B) and were highly associated with shorter OS (<4 years vs ≥4 years; OR, 0.23 [95% CI, 0.09–0.60]) and prior chemotherapy in the metastatic setting (OR, 1.95 [95% CI, 1.09–3.49]; Supplementary Table

S1). Palbociclib plus fulvestrant also provided an OS benefit versus placebo plus fulvestrant regardless of *TP53* mutation status (Figure 5C). In patients without *TP53* mutation, the median OS was 36.1 months (95% CI, 27.7–43.1) with palbociclib plus fulvestrant and 28.0 months (95% CI, 23.4–33.1) with placebo plus fulvestrant (HR, 0.76 [95% CI, 0.57–1.00]). In patients with *TP53* mutation, the median OS was 23.0 months (95% CI, 12.3–27.7) with palbociclib plus fulvestrant and 16.4 months (95% CI, 7.8–24.7) with placebo plus fulvestrant (HR, 0.83 [95% CI, 0.46–1.52]). *TP53* mutations were more frequent among patients who received prior chemotherapy for ABC in both the palbociclib and placebo groups (24.3% and 23.3%, respectively) compared with patients who did not receive prior chemotherapy (13.1% and 15.4%, respectively). No difference in the frequency of *PIK3CA* and *ESR1* mutations was observed in patients with or without prior chemotherapy in ABC.

Survival analyses by mutational burden demonstrated that a low-circulating tumor fraction (<10%) was associated with longer PFS in the palbociclib plus fulvestrant group compared with the placebo plus fulvestrant group (median PFS [95% CI], 13.6 months [11.3–16.6] vs 5.5 months [3.7–9.1]; HR, 0.46 [95% CI, 0.33–0.64; Supplementary Figure S3A). Similar results were observed with OS (44.5 months [35.6–51.6] vs 28.0 months [23.4–36.3]; HR, 0.61 [95% CI, 0.45–0.83]; Supplementary Figure S3B).

Neutropenia was the most frequently reported AE in the palbociclib plus fulvestrant group, as previously reported (palbociclib vs placebo: any grade, 84.3% vs 3.5%; grade 3, 57.7% vs 0;

grade 4, 11.9% vs 0; Supplementary Table S2).(4,11) Other frequently reported AEs in the palbociclib plus fulvestrant group included leukopenia (any grade, 60.3%), infections (55.1%), fatigue (43.8%), nausea (36.2%), and anemia (32.2%). Febrile neutropenia was reported in 1.2% of patients in the palbociclib plus fulvestrant group and was not reported in the placebo plus fulvestrant group.

After discontinuing from study treatment, 267 patients (76.9%) in the palbociclib plus fulvestrant group and 144 patients (82.8%) in the placebo plus fulvestrant group received subsequent systemic anticancer therapy (Supplementary Table S3). Generally, patients in the palbociclib plus fulvestrant group received fewer subsequent chemotherapies, endocrine therapies, mechanistic target of rapamycin (mTOR) kinase inhibitors, or CDK4/6 inhibitors than patients in the placebo plus fulvestrant group.

Discussion

With over 6 years of median follow-up in the PALOMA-3 trial, this analysis demonstrated a clinically meaningful improvement in OS of 6.8 months with palbociclib plus fulvestrant versus placebo plus fulvestrant in patients with HR+/HER2– ABC who progressed on prior endocrine therapy. The prolonged OS benefit was particularly evident in patients with no prior chemotherapy in the advanced or metastatic disease setting. The lack of difference in OS among patients with prior chemotherapy may be due to patients with prior chemotherapy having tumors with a higher frequency of *TP53* mutations and less endocrine sensitivity. Additionally, PFS and OS were generally more favorable with palbociclib plus fulvestrant

compared with placebo plus fulvestrant across subgroups, including patients with low circulating tumor fraction and regardless of *ESR1, PIK3CA,* or *TP53* mutation status as detected by ctDNA. However, although a PFS and OS benefit was observed regardless of mutation status, patients without the mutations had a better prognosis and outcome. Moreover, no new safety signals were identified. These findings support the continued benefit of palbociclib plus fulvestrant as a standard of care in patients with HR+/HER2– ABC, regardless of *ESR1, PIK3CA,* or *TP53* mutation status.

The current median OS of 34.8 months in the palbociclib plus fulvestrant group compared with 28.0 months in the placebo plus fulvestrant group (stratified HR, 0.81 [95% CI, 0.65–0.99]) are consistent with the results from the previous final protocol-specified OS analysis, which also demonstrated a trend toward improved OS with palbociclib plus fulvestrant versus placebo plus fulvestrant (34.9 vs 28.0 months, respectively; HR, 0.81 [95% CI, 0.64–1.03]) (4). In patients with HR+/HER2– ABC, it is often difficult for treatments to demonstrate a significant OS improvement in clinical studies. Adequate power for the statistical analysis of OS is challenging to achieve when evaluating diseases associated with long postprogression survival (13). Moreover, clinical studies often allow patients in the placebo group to cross over to receive active treatments after disease progression, confounding the interpretation of OS results (14).

However, OS findings from abemaciclib (interim) and ribociclib phase 3 studies of patients with HR+/HER2– ABC who did not receive prior chemotherapy for ABC are available (15,16). In the MONARCH 2 study, at a median follow-up duration of 47.7 months, abemaciclib plus fulvestrant

improved median OS compared with placebo plus fulvestrant (46.7 months vs 37.3 months, respectively; HR, 0.76 [95% CI, 0.61–0.95]).(15) In the MONALEESA-3 study, at a median follow-up duration of 56.3 months, the median OS was 53.7 months with ribociclib plus fulvestrant and 41.5 months with placebo plus fulvestrant (HR, 0.73 [95% CI, 0.59–0.90]) (16). Each of these study results were statistically significant. Moreover, while some survival data were still immature, a US Food and Drug Administration pooled analysis of CDK4/6 inhibitors for HER2– ABC demonstrated an HR of 0.77 (95% CI, 0.67–0.89) for OS between pooled CDK4/6 inhibitors plus fulvestrant versus placebo plus fulvestrant groups from PALOMA-3, MONARCH 2, and MONALEESA-3 (17). Together, these findings suggest CDK4/6 inhibitors provide a survival benefit for patients with HR+/HER2– ABC.

Previous analyses using ctDNA data from patients in the PALOMA-3 study have demonstrated that high-circulating tumor fraction of >10% is associated with a shorter median PFS compared with circulating tumor factor ≤10% in the palbociclib plus fulvestrant group (9.2 vs 13.6 months; HR, 1.62 [95% CI, 1.17–2.24]) (8). The current analysis of PALOMA-3 further suggests a most significant benefit in patients with a low mutational burden (≤10%) who were treated with palbociclib plus fulvestrant compared with placebo plus fulvestrant. *TP53* mutations and *FGFR1* amplification were also associated with a shorter PFS (HR, 1.84 [95% CI, 1.27–2.65] and HR, 2.91 [95% CI, 1.61–5.25], respectively) (8). Additionally, previous analyses have shown that approximately 31% of patients receiving palbociclib plus fulvestrant acquire mutations in growth factor receptors and signal transduction pathways, including 6% of patients acquiring *PIK3CA* mutations and 9% acquiring *ESR1* mutations (12). However, the present analysis is the

first CDK4/6 inhibitor study to our knowledge to evaluate the effect of tumor mutation profiles using ctDNA analyses on OS.

In the present analysis, regardless of mutation status, palbociclib plus fulvestrant prolonged OS compared with placebo plus fulvestrant. Moreover, palbociclib plus fulvestrant improved PFS versus placebo plus fulvestrant regardless of *ESR1*, *PIK3CA*, or *TP53* mutation status. Overall, findings were similar whether mutations were analyzed at Day 1, at end of treatment, or at Day 1 and end of treatment combined. These findings are consistent with results from a previous analysis, which demonstrated that palbociclib plus fulvestrant prolonged median PFS versus placebo plus fulvestrant both in patients with *ESR1* mutations (9.4 months vs 3.6 months; HR, 0.43 [95% CI, 0.25–0.74]) and without *ESR1* mutations (9.5 months vs 5.4 months; HR, 0.49 [95% CI, 0.35–0.70]) (18). Our findings are also consistent with results from the MONARCH 2 study where abemaciclib plus fulvestrant improved PFS compared to placebo plus fulvestrant in patients regardless of *ESR1* or *PIK3CA* mutation status (19). In the current analysis, patients with *ESR1* mutations gained a greater benefit from palbociclib plus fulvestrant measured by both PFS and OS. Future research is warranted to further characterize genomic features that may affect the efficacy of palbociclib plus fulvestrant.

Limitations of this study include that is is an exploratory analysis. This study is also limited by the small numbers of patients included in some of the subgroups analyzed. Nevertheless, with >6 years of median follow-up in patients with HR+/HER2– ABC, palbociclib plus fulvestrant

demonstrated longer OS compared with placebo plus fulvestrant, including in most of the subgroups assessed and regardless of *ESR1*, *PIK3CA*, or *TP53* mutation status.

Conclusions

In patients with HR+/HER2– ABC who had progressed on prior endocrine therapy, the clinically meaningful improvement in OS with palbociclib plus fulvestrant was maintained with >6 years of follow-up, regardless of genomic alterations, and no new safety signals were identified. These findings support palbociclib plus fulvestrant as a standard of care in patients with HR+/HER2– ABC. Moreover, *ESR1, PIK3CA,* and *TP53* mutational status can provide prognostic value in this clinical setting.

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Contributors

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Figure Legends

Figure 1. Kaplan-Meier curves of overall survival in all patients in the intent-to-treat population.

FUL=fulvestrant; PAL=palbociclib; PBO=placebo; HR=hazard ratio; OS=overall survival.

Figure 2. Overall survival by subgroup.

P value determined from a 1-sided unstratified log-rank test; 1-sided *P*-value from log-rank test reflects the sign of the test statistic (z-Score).

ABC=advanced breast cancer; ECOG=Eastern Cooperative Oncology Group; EOT=end of treatment; FUL=fulvestrant; ITT=intent-to-treat; PAL=palbociclib; PBO=placebo.

Figure 3. Outcomes by *ESR1* mutation status in ctDNA at Day 1 or end of treatment.

A) progression-free survival by treatment, **B)** overall survival regardless of treatment, and **C)** overall survival by treatment.

ctDNA=circulating tumor DNA; *ESR1*=estrogen receptor 1; FUL=fulvestrant; HR=hazard ratio; mut=mutation; OS=overall survival; PAL=palbociclib; PBO=placebo; PFS=progression-free survival; WT=wild type.

Figure 4. Outcomes by *PIK3CA* mutation status in ctDNA at Day 1 or end of treatment.

A) progression-free survival by treatment, **B)** overall survival regardless of treatment, and **C)** overall survival by treatment.

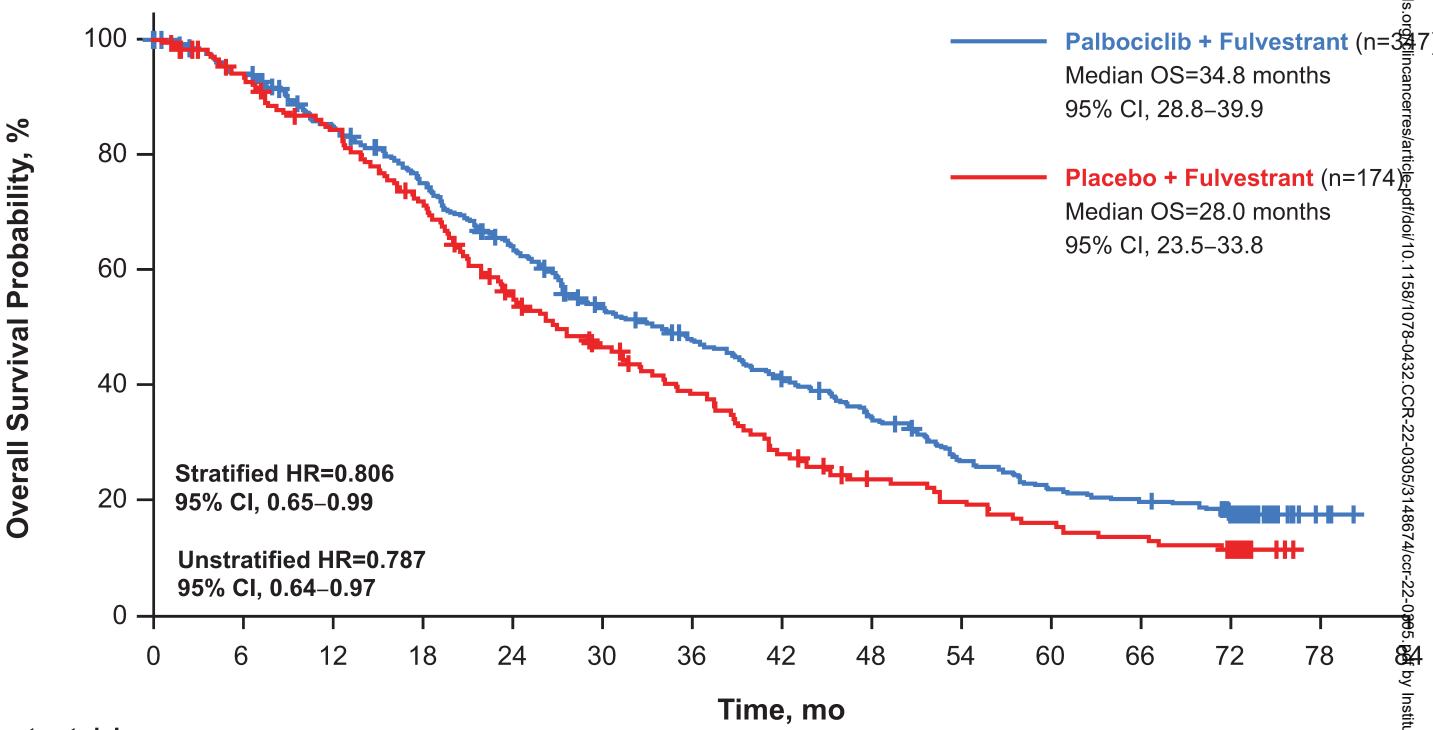
ctDNA=circulating tumor DNA; FUL=fulvestrant; HR=hazard ratio; mut=mutation; OS=overall survival; PAL=palbociclib; PBO=placebo; PFS=progression-free survival; *PIK3CA*=phosphatidylinositol 3-kinase catalytic alpha polypeptide; WT=wild type.

Figure 5. Outcomes by *TP53* mutation status in ctDNA at Day 1 or end of treatment.

A) progression-free survival by treatment, **B)** overall survival regardless of treatment, and **C)** overall survival by treatment.

ctDNA=circulating tumor DNA; FUL=fulvestrant; HR=hazard ratio; mut=mutation; OS=overall survival; PAL=palbociclib; PBO=placebo; PFS=progression-free survival; *TP53*=tumor protein 53; WT=wild type.

Fig. 1

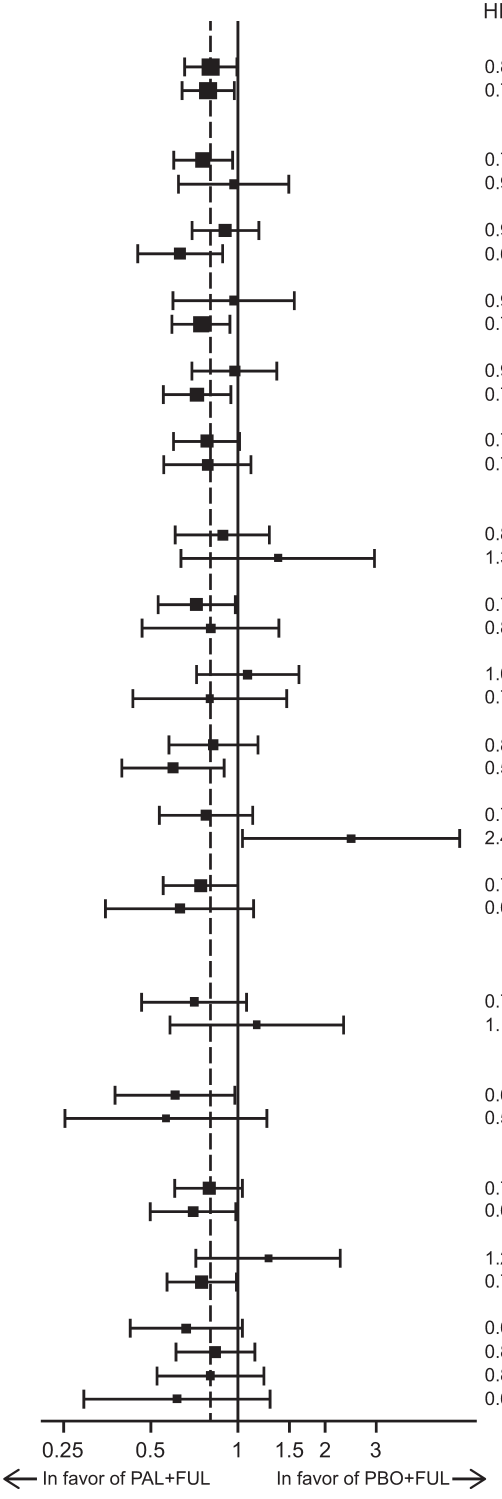


Patients at risk, n

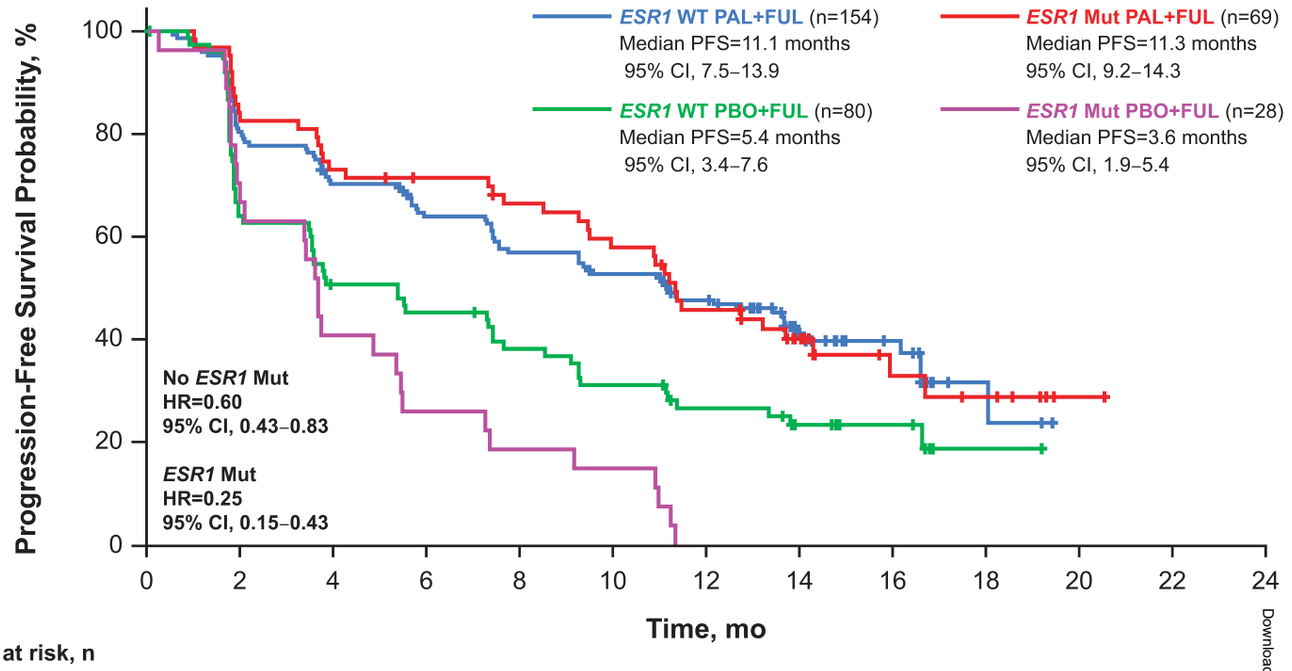
PAL+FUL	347	322	288	250	211	167	149	128	109	84	68	60	54	4
PBO+FUL	174	156	138	117	89	71	58	43	33	27	22	19	17	0

Fig. 2

ITT and Subgroup	PAL+FUL Events/N	(%)	PBO+FUL Events/N	(%)	HR (95% CI)	Interaction *P* Value
All randomized patients (ITT, stratified)	258/347	(74.4)	135/174	(77.6)	0.806 (0.654, 0.994)	
All randomized patients (ITT, unstratified)	258/347	(74.4)	135/174	(77.6)	0.787 (0.639, 0.970)	
Sensitivity to previous hormonal therapy						
Yes	202/274	(73.7)	104/136	(76.5)	0.757 (0.597, 0.960)	0.513
No	56/73	(76.7)	31/38	(81.6)	0.966 (0.622, 1.499)	
Site of metastatic disease						
Visceral	166/206	(80.6)	81/105	(77.1)	0.904 (0.693, 1.179)	0.141
Non-visceral	92/141	(65.2)	54/69	(78.3)	0.631 (0.450, 0.886)	
Menopausal status at study entry						
Pre/Peri	53/72	(73.6)	24/36	(66.7)	0.966 (0.596, 1.568)	0.328
Post	205/275	(74.5)	111/138	(80.4)	0.744 (0.590, 0.938)	
Prior chemotherapy in ABC						
Yes	94/113	(83.2)	53/64	(82.8)	0.971 (0.693, 1.360)	0.193
No	164/234	(70.1)	82/110	(74.5)	0.720 (0.552, 0.940)	
Number of prior regimens						
≤2	154/208	(74.0)	88/111	(79.3)	0.779 (0.599, 1.013)	0.915
>2	104/139	(74.8)	47/63	(74.6)	0.784 (0.555, 1.107)	
Wtih prior chemotherapy in ABC						
Endocrine sensitive	71/86	(82.6)	44/54	(81.5)	0.883 (0.606, 1.287)	0.314
Endocrine resistant	23/27	(85.2)	9/10	(90.0)	1.374 (0.634, 2.979)	
Without prior chemotherapy in ABC						
Endocrine sensitive	131/188	(69.7)	60/82	(73.2)	0.719 (0.529, 0.977)	0.988
Endocrine resistant	33/46	(71.7)	22/28	(78.6)	0.803 (0.467, 1.381)	
Wtih prior chemotherapy in ABC						
Visceral disease	67/77	(87.0)	36/43	(83.7)	1.079 (0.719, 1.619)	0.401
Nonvisceral disease	27/36	(75.0)	17/21	(81.0)	0.798 (0.433, 1.471)	
Without prior chemotherapy in ABC						
Visceral disease	99/129	(76.7)	45/62	(72.6)	0.821 (0.577, 1.169)	0.323
Nonvisceral disease	65/105	(61.9)	37/48	(77.1)	0.596 (0.397, 0.894)	
Wtih prior chemotherapy in ABC						
Postmenopausal	73/90	(81.1)	46/52	(88.5)	0.775 (0.535, 1.122)	0.008
Pre/perimenopausal	21/23	(91.3)	7/12	(58.3)	2.455 (1.036, 5.818)	
Without prior chemotherapy in ABC						
Postmenopausal	132/185	(71.4)	65/86	(75.6)	0.743 (0.552, 1.001)	0.707
Pre/perimenopausal	32/49	(65.3)	17/24	(70.8)	0.628 (0.348, 1.134)	
Without prior chemotherapy & with visceral disease						
≤2 prior regimens	68/87	(78.2)	34/44	(77.3)	0.705 (0.465, 1.069)	0.210
>2 prior regimens	31/42	(73.8)	11/18	(61.1)	1.160 (0.582, 2.314)	
Without prior chemotherapy & with nonvisceral disease						
≤2 prior regimens	49/78	(62.8)	27/33	(81.8)	0.605 (0.377, 0.971)	0.805
>2 prior regimens	16/27	(59.3)	10/15	(66.7)	0.564 (0.253, 1.258)	
ECOG Performance Status						
0	144/206	(69.9)	86/115	(74.8)	0.793 (0.607, 1.037)	0.545
1	114/141	(80.9)	49/59	(83.1)	0.699 (0.498, 0.980)	
Disease-free interval						
≤24 months	33/40	(82.5)	19/22	(86.4)	1.272 (0.717, 2.255)	0.102
>24 months	138/191	(72.3)	77/101	(76.2)	0.749 (0.566, 0.990)	
Prior lines of therapy in ABC setting						
0	50/74	(67.6)	32/40	(80.0)	0.664 (0.425, 1.036)	0.818
1	104/141	(73.8)	63/84	(75.0)	0.835 (0.610, 1.142)	
2	74/94	(78.7)	30/37	(81.1)	0.802 (0.524, 1.227)	
≥3	30/38	(78.9)	10/13	(76.9)	0.616 (0.294, 1.291)	



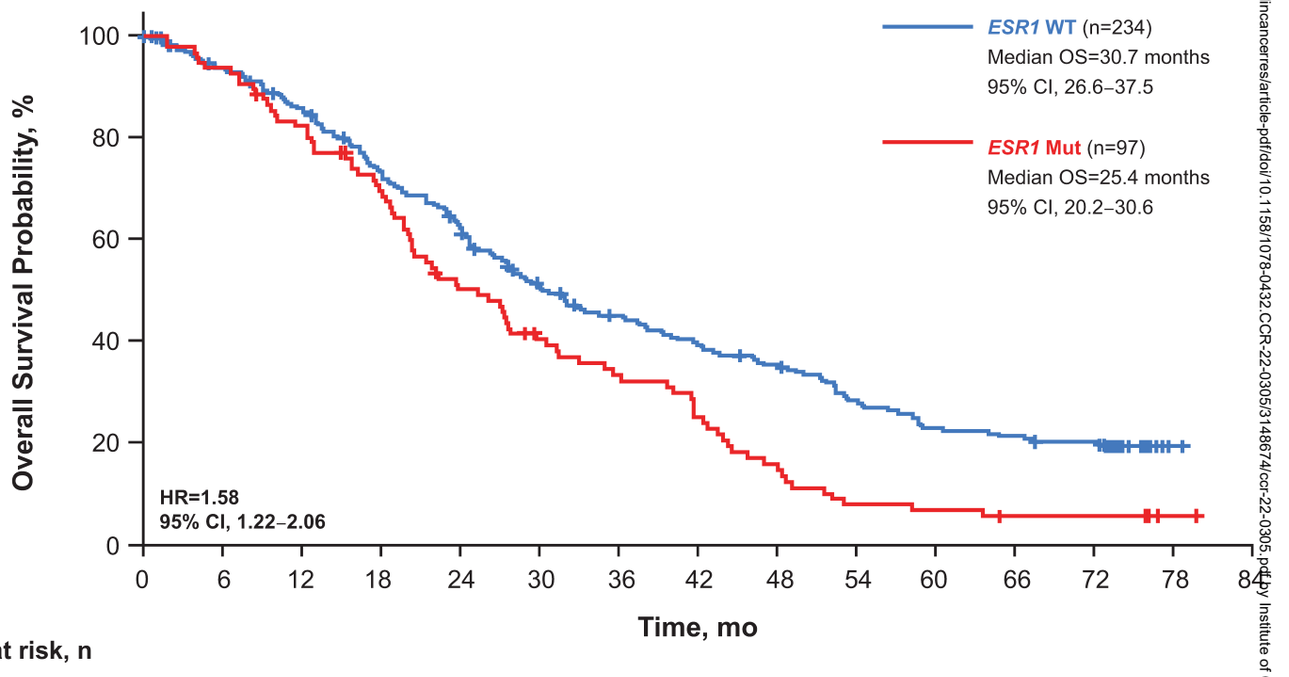
A. PFS By Treatment



Patients at risk, n

ESR1 Mut PAL+FUL	69	52	46	43	39	34	26	16	8	6	1	0
ESR1 Mut PBO+FUL	28	18	11	7	5	4	0					
ESR1 Wt PAL+FUL	154	119	102	91	81	74	64	28	17	4	0	
ESR1 Wt PBO+FUL	80	48	37	33	27	22	17	10	7	1	0	

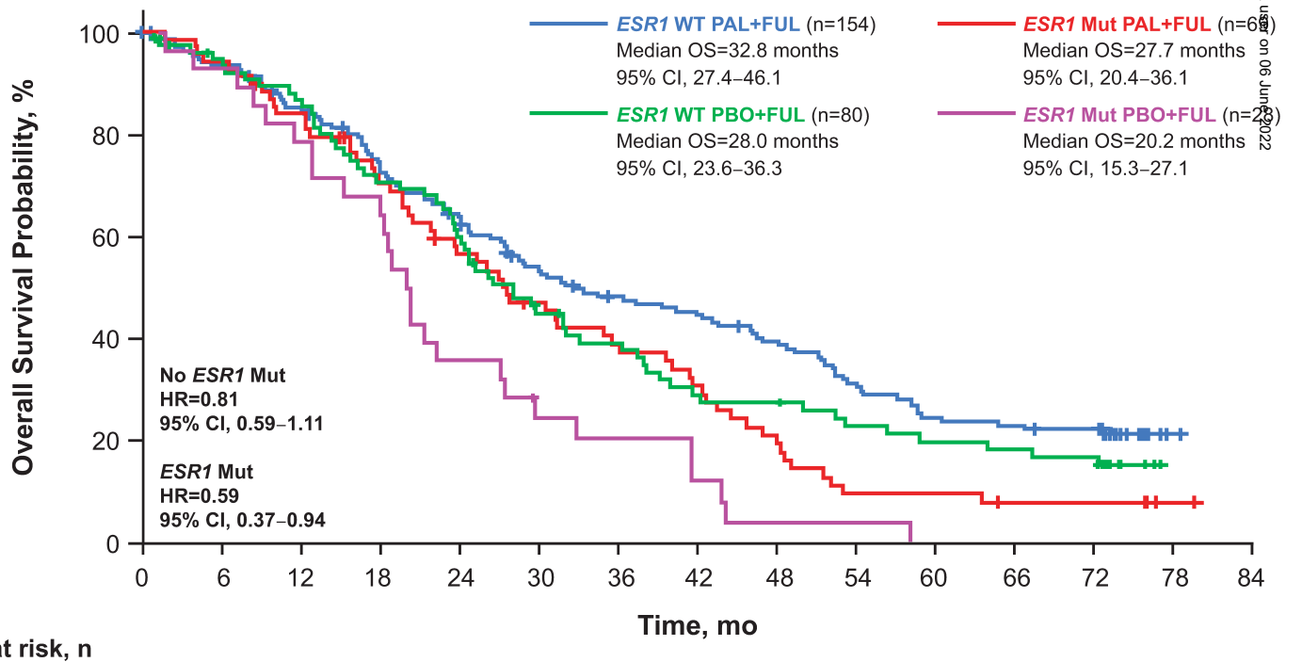
B. OS Regardless of Treatment



Patients at risk, n

ESR1 Mut	97	91	79	64	46	35	29	22	14	7	6	4	4	1	0
ESR1 WT	234	213	192	162	138	107	93	81	72	57	46	43	40	1	0

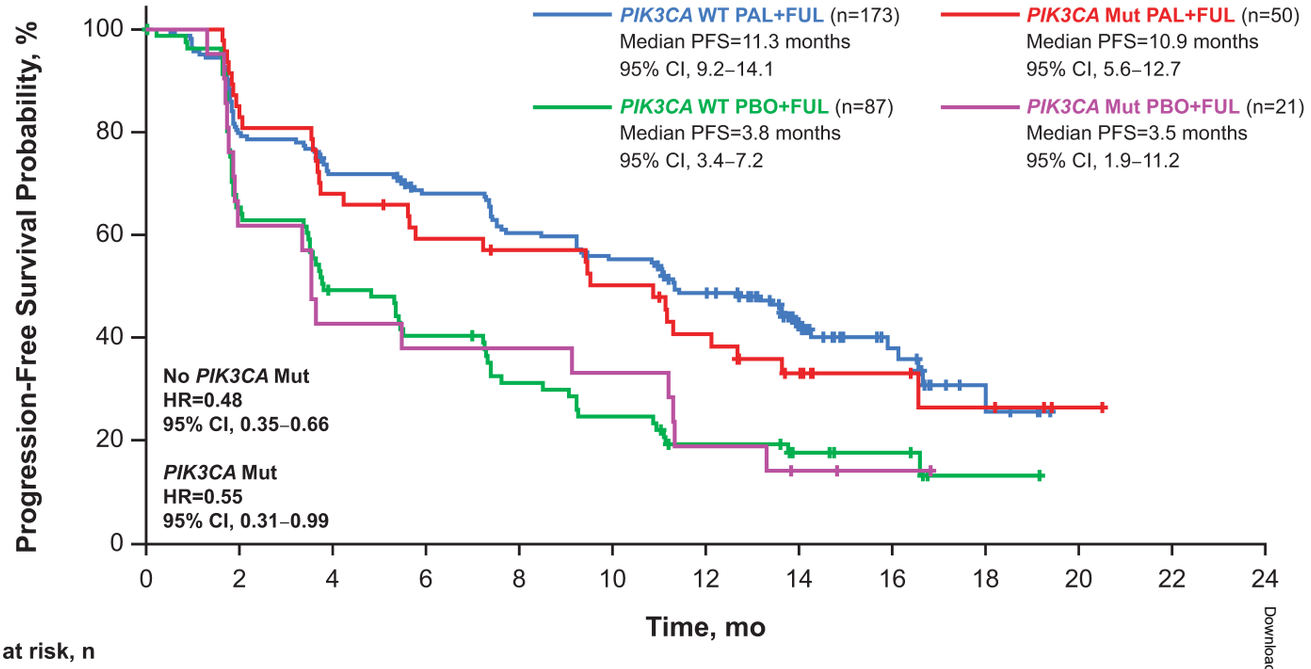
C. OS By Treatment



Patients at risk, n

ESR1 Mut PAL+FUL	69	65	57	46	36	29	24	19	13	6	6	4	4	1	0
ESR1 Mut PBO+FUL	28	26	22	18	10	6	5	3	1	1	0				
ESR1 Wt PAL+FUL	154	142	128	109	93	75	66	61	53	42	33	31	29	1	0
ESR1 Wt PBO+FUL	80	71	64	53	45	32	27	20	19	15	13	12	11	0	

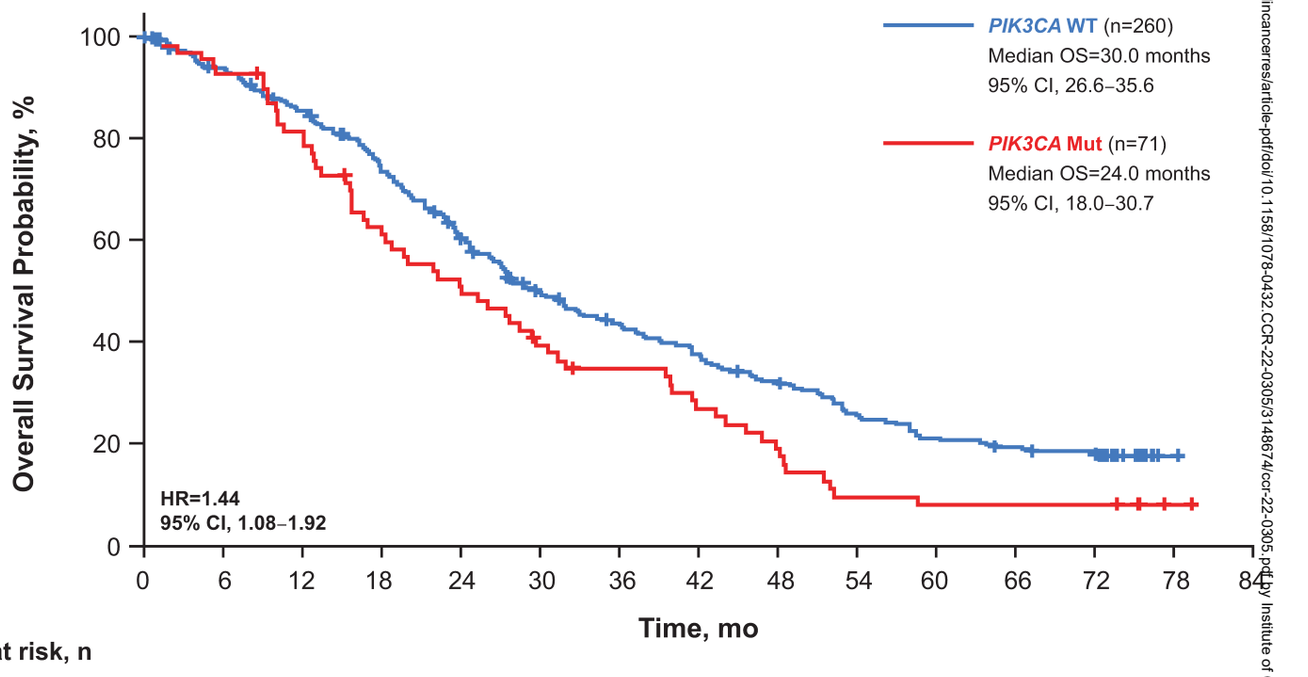
A. PFS By Treatment



Patients at risk, n

PIK3CA Mut PAL+FUL	50	40	32	27	25	22	17	11	7	4	1	0
PIK3CA Mut PBO+FUL	21	13	9	8	8	7	4	2	1	0		
PIK3CA Wt PAL+FUL	173	131	116	107	95	86	73	33	18	6	0	
PIK3CA Wt PBO+FUL	87	53	39	32	24	19	13	8	6	1	0	

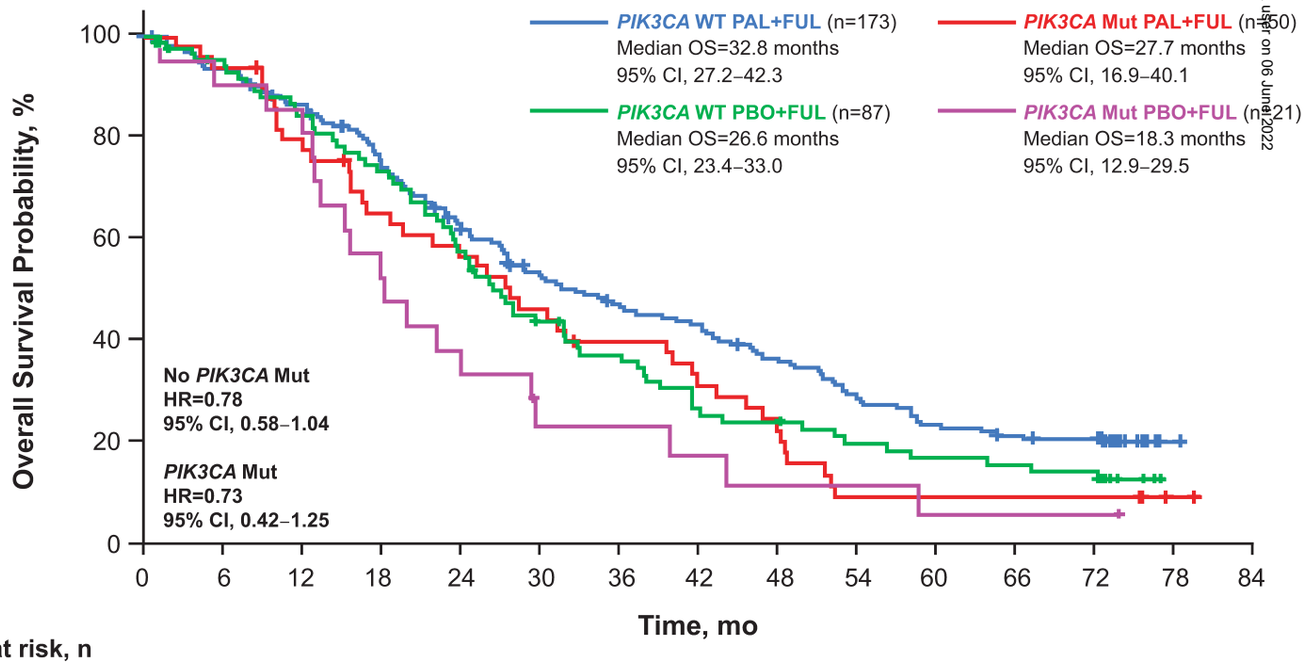
B. OS Regardless of Treatment



Patients at risk, n

PIK3CA Mut	71	66	56	42	35	26	22	17	13	6	5	5	5	1	0
PIK3CA WT	260	238	215	184	149	116	100	86	73	58	47	42	39	1	0

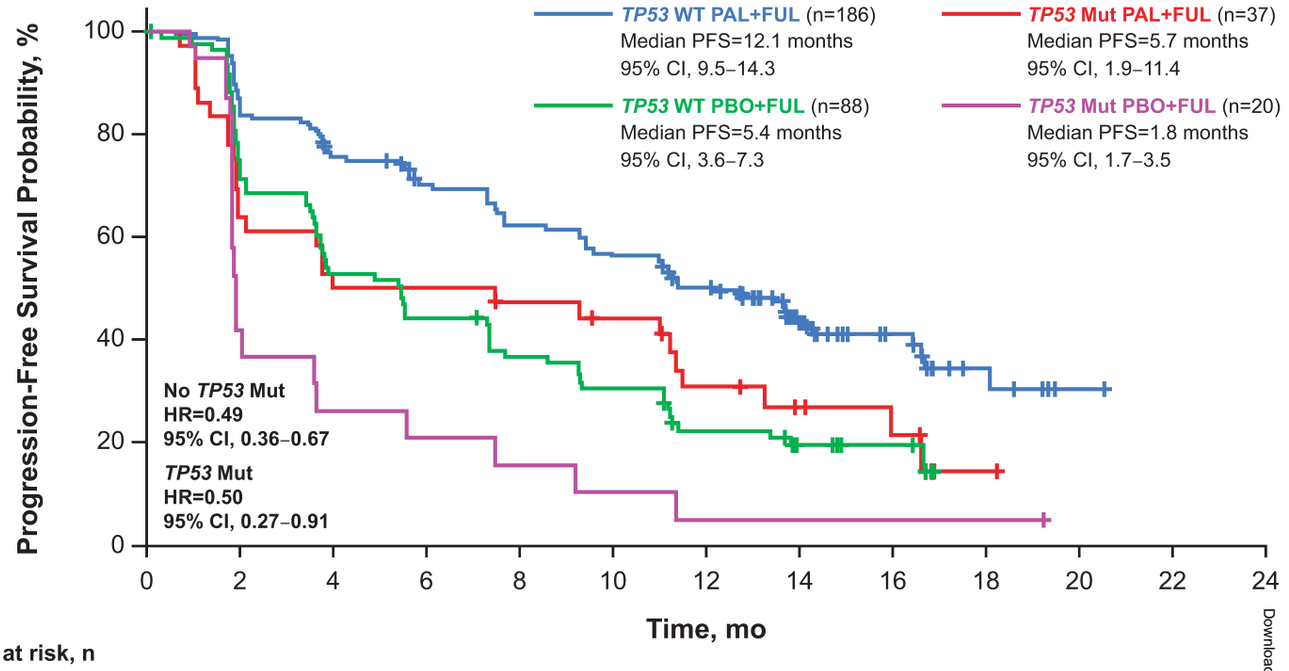
C. OS By Treatment



Patients at risk, n

PIK3CA Mut PAL+FUL	50	47	39	31	27	22	18	14	11	4	4	4	4	1	0
PIK3CA Mut PBO+FUL	21	19	17	11	8	4	4	3	2	2	1	1	1	0	
PIK3CA Wt PAL+FUL	173	160	146	124	102	82	72	66	55	44	35	31	29	1	0
PIK3CA Wt PBO+FUL	87	78	69	60	47	34	28	20	18	14	12	11	10	0	

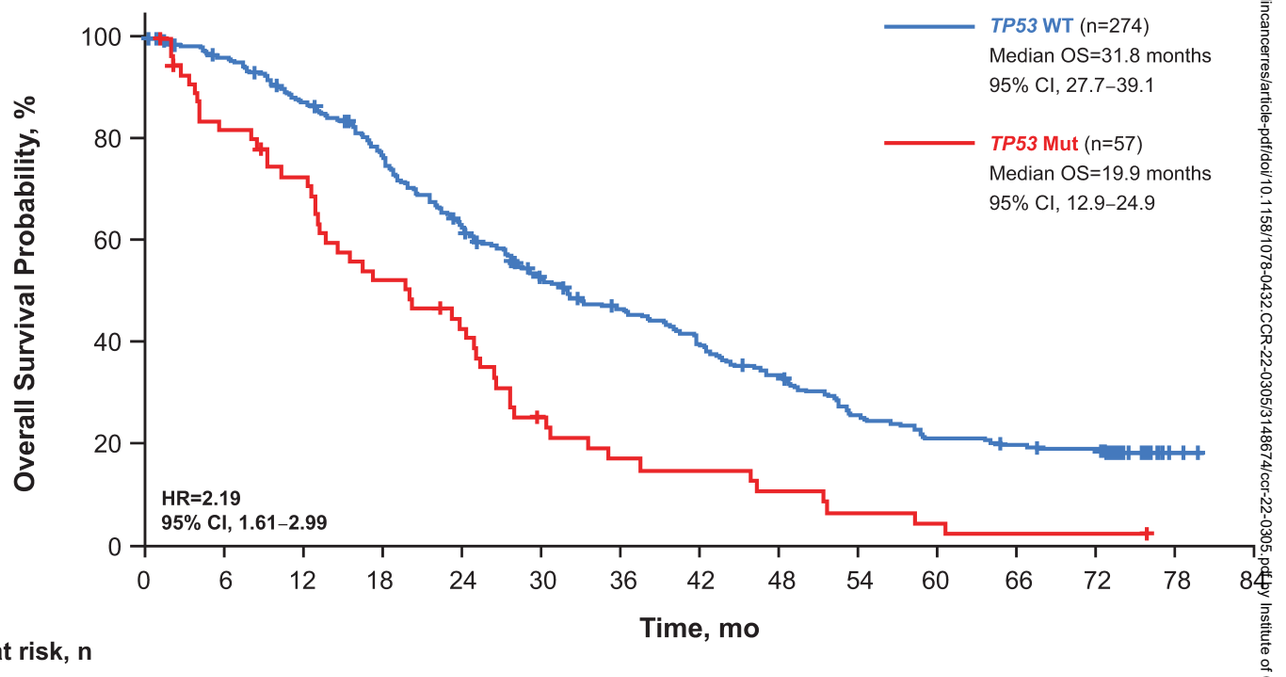
A. PFS By Treatment



Patients at risk, n

TP53 Mut PAL+FUL	37	23	18	18	16	14	9	6	4	1	0	
TP53 Mut PBO+FUL	20	7	5	4	3	2	1	1	1	1	0	
TP53 Wt PAL+FUL	186	148	130	116	104	94	81	38	21	9	1	0
TP53 Wt PBO+FUL	88	59	43	36	29	24	16	9	6	0		

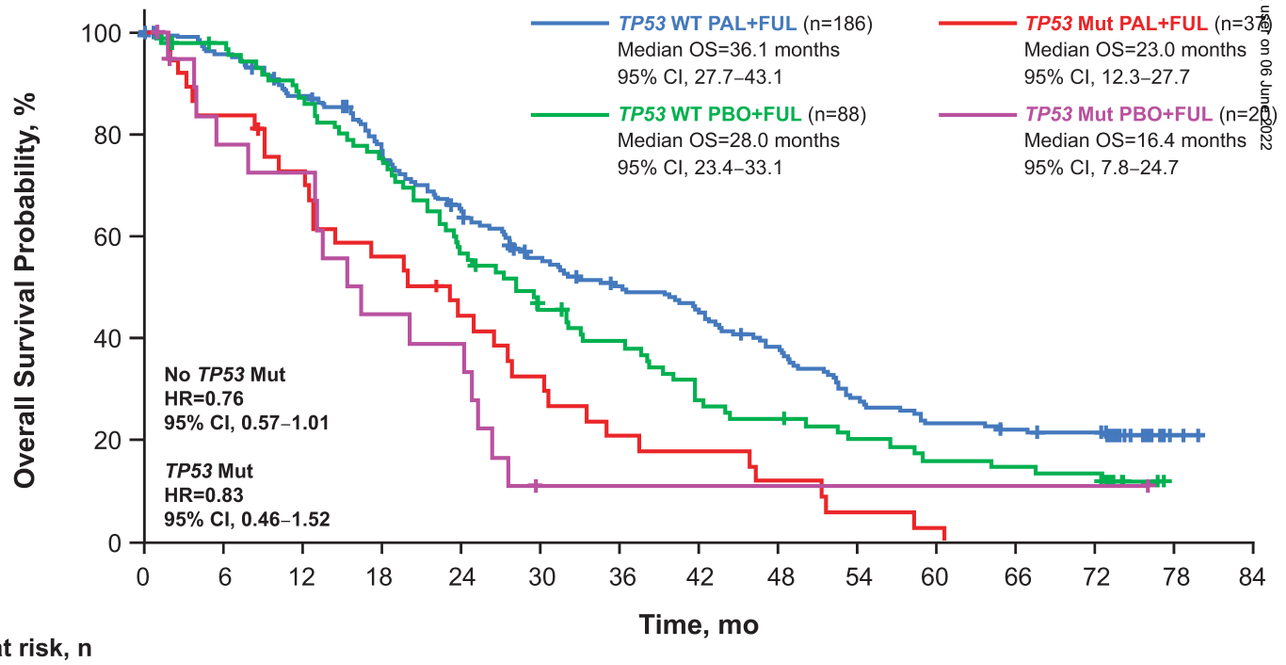
B. OS Regardless of Treatment



Patients at risk, n

TP53 Mut	57	45	39	28	22	12	8	7	5	3	2	1	1	0
TP53 WT	274	259	232	198	162	130	114	96	81	61	50	46	43	2	0

C. OS By Treatment



Patients at risk, n

TP53 Mut PAL+FUL	37	31	26	20	15	11	7	6	4	2	1	0		
TP53 Mut PBO+FUL	20	14	13	8	7	1	1	1	1	1	1	1	1	0
TP53 Wt PAL+FUL	186	176	159	135	114	93	83	74	62	46	38	35	33	2	0
TP53 Wt PBO+FUL	88	83	73	63	48	37	31	22	19	15	12	11	10	0	