Evaluation of the Association of Polymorphisms With Palbociclib-Induced Neutropenia: Pharmacogenetic Analysis of PALOMA-2/-3

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Implications for Practice

Palbociclib plus endocrine therapy improves HR+/HER2– advanced breast cancer (ABC) outcomes, but is commonly associated with neutropenia. Genetic variants in *ABCB1* may influence palbociclib exposure, and in *ERCC1* are associated with chemotherapy-induced severe neutropenia. Here, the associations of single nucleotide polymorphisms in these genes and baseline characteristics with neutropenia were assessed. Low baseline absolute neutrophil count was a strong risk factor ($P<0.0001$) for grade 3/4 neutropenia. There was a trend indicating that *ABCB1*_rs1128503 and *ERCC1*_rs11615 were potential risk factors ($P<0.10$) for grade 3/4 neutropenia in non-Asian patients. Pharmacogenetic testing could inform clinicians about the likelihood of severe neutropenia with palbociclib.

Abstract

Background: The most frequently reported treatment-related adverse event in clinical trials with the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor palbociclib is neutropenia. Allelic variants in *ABCB1* and *ERCC1* might be associated with early occurrence (ie, end of Week 2 treatment) of grade 3/4 neutropenia. Pharmacogenetic analyses were performed to uncover associations between single nucleotide polymorphisms (SNPs) in these genes, patient baseline characteristics, and early occurrence of grade 3/4 neutropenia.

Materials and Methods: *ABCB1* (rs1045642, rs1128503) and *ERCC1* (rs3212986, rs11615) were analyzed in germline DNA from palbociclib-treated patients from PALOMA-2 (n=584) and PALOMA-3 (n=442). SNP, race, and Cycle 1 Day 15 (C1D15) absolute neutrophil count (ANC) data were available for 652 patients. Univariate and multivariable analyses evaluated associations between SNPs, patient baseline characteristics, and early occurrence of grade 3/4 neutropenia. Analyses were stratified by Asian (n=122) and non-Asian (n=530) ethnicity. Median progression-free survival (mPFS) was estimated using the Kaplan-Meier method. The effect of genetic variants on palbociclib pharmacokinetics was analyzed.

Results: *ABCB1* and *ERCC1*_rs11615 SNP frequencies differed between Asian and non-Asian patients. Multivariable analysis showed that low baseline ANC was a strong independent risk factor for C1D15 grade 3/4 neutropenia regardless of race (Asians: odds ratio [OR]=6.033, 95% CI=2.615−13.922, *P*<0.0001; Non-Asians: OR=6.884, 95% CI=4.138−11.451, *P*<0.0001). *ABCB1*_rs1128503 (C/C vs T/T: OR=0.57, 95% CI=0.311−1.047, P=0.070) and *ERCC1*_rs11615 (A/A vs G/G: OR=1.75, 95% CI=0.901−3.397, *P*=0.098) were potential independent risk factors for C1D15 grade 3/4 neutropenia in non-Asian patients. Palbociclib mPFS was consistent across genetic variants; exposure was not associated with *ABCB1* genotype.

Conclusion: This is the first comprehensive assessment of pharmacogenetic data in relationship to exposure to a CDK4/6 inhibitor. Pharmacogenetic testing may inform about potentially increased likelihood of patients developing severe neutropenia (NCT01740427, NCT01942135).

Introduction

The cyclin-dependent kinase 4/6 (CDK4/6) inhibitor palbociclib in combination with endocrine therapy (ET) is the current standard of care for patients with previously untreated or treated hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (HR+/HER2– ABC) [1,2]. The most frequently reported palbociclib treatment-related adverse event (AE) in the PALOMA trials is neutropenia [3-8]. Unlike chemotherapy, which causes apoptotic cell death, the mechanism of action underlying palbociclib-induced neutropenia involves potent cell cycle arrest of progenitor cells at the G1/S phase and thus is reversible [9].

Palbociclib is metabolized primarily by cytochrome P450 isozyme (CYP)3A and sulfotransferase (SULT) enzyme SULT2A1 [10]. The genetic variants of adenosine triphosphate–binding cassette subfamily B member 1 (*ABCB1)* (P-glycoprotein) may be associated with palbociclib exposure, as it is generally known that the substrates and/or inhibitors of CYP3A and *ABCB1* overlap with each other [11,12]. The *CYP3A7*1C* allele may be associated with less drug exposure, which may lead to worse clinical outcomes, and reduced grade 3/4 neutropenia occurrence [13].

Previous reports suggest that genetic variants of *ABCB1* and excision repair cross-complementing 1 (*ERCC1*) are associated with increased exposure to a number of chemotherapy agents and reduced DNA repair capability of normal cells damaged by chemotherapy, respectively [11,14,15]. *ABCB1*, expressed in cell plasma membrane, plays a role in the first-pass elimination of drugs administered orally, limiting their bioavailability [11], and *ERCC1* plays a role in repairing DNA damage [16]. Previous reports have also shown a strong association between *ERCC1* genotype and developing grade 4 neutropenia among Asian patients treated with anthracycline-based chemotherapy regimens [14]. Thus, these genes are potentially linked to the increased occurrence of grade 3/4 neutropenia during treatment for breast cancer and may not be limited to cytotoxic agents.

In the PALOMA-2 (ClinicalTrials.gov Identifier: NCT01740427) and PALOMA-3 (ClinicalTrials.gov Identifier: NCT01942135) clinical trials, Asian patients who received palbociclib combination therapy tended to have higher incidence rates of grade 4 neutropenia (18%–34% in Asians vs 8% in non-Asians) and dose reduction associated with AEs compared with non-Asian patients [17-19]. Lower body mass index (BMI) and lower pretreatment white blood cell (WBC) count have been identified as risk factors for higher rates of grade 4 neutropenia in patients treated with anthracycline-based chemotherapy [14] and therefore may be linked to high-grade neutropenia in response to palbociclib treatment as well. Germline polymorphisms are attractive candidates that may potentially explain these differences and can be easily assessed in available samples.

Because neutropenia is a mechanism-based, treatment-related AE, we hypothesized that the presence of any pharmacogenetic differences between subgroups of patients would manifest in the rapid (within 2 weeks) appearance of high-grade neutropenia compared with the overall population, where the median time of first onset of grade 3 or higher neutropenia is 4 weeks [20]. In addition, the median time of first onset of grade 3 or higher neutropenia was 15.0 to 15.5 days in Japanese patients treated with palbociclib plus letrozole or fulvestrant [21]. Therefore, pharmacogenetic analyses of these variants in patients from the phase 3 PALOMA-2 and PALOMA-3 clinical trials were performed to evaluate potential associations between single nucleotide polymorphisms (SNPs) and early occurrence (defined as Day 15±1 day of treatment) of grade 3/4 neutropenia. The association between patient baseline characteristics and early occurrence of grade 3/4 neutropenia was also investigated. In addition, the association between SNP variants and clinical outcome (progression-free survival [PFS]) in patients receiving palbociclib or placebo in combination with ET from PALOMA-2 and PALOMA-3 was explored.

Materials and Methods

Study Design

The study designs of both PALOMA-2 and PALOMA-3 have been previously described in detail [4,5]. In PALOMA-2, 666 patients were randomized 2:1 to receive either palbociclib (125 mg/d, oral, 3/1 schedule) plus letrozole (2.5 mg/d, oral, continuous) or matching placebo plus letrozole [4]. In PALOMA-3, 521 patients were randomized 2:1 to receive either palbociclib (125 mg/d, oral, 3/1 schedule) plus fulvestrant (500 mg, intramuscular injection, on Days 1 and 15 of Cycle 1, and then Day 1 of every cycle thereafter) or matching placebo plus fulvestrant [5]. Absolute neutrophil count (ANC) was collected from laboratory data for hematology (not from reported AEs) on Days 1 and 15 for the first 2 cycles, on Day 1 of subsequent cycles, and at end of treatment or study withdrawal. Neutropenia based on ANC was graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.0 and counted once by maximum grade. Both studies were approved by an institutional review board, or equivalent, at each site, and all patients gave written informed consent before enrollment. Both studies were conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki [4,5].

Genomic Analyses

Genomic DNA was extracted from blood samples (n=1026) of patients in PALOMA-2 (n=584) and PALOMA-3 (n=442) using a QIAsymphony (QIAGEN, Hilden, Germany) automated platform running a DSP DNA Mini Kit. DNA was quantified by NanoDrop (ThermoFisher, Waltham, MA, USA). DNA was genotyped using commercially available TaqMan assays (Applied Biosystems, Waltham, MA, USA) for 2 variants for *ABCB1*, rs1045642 (C___7586657_20) and rs1128503 (C_7586662_10); 2 variants for *ERCC1*, rs3212986 (C___2532948_10) and rs11615 (C___2532959_20); and 1 variant that tags the *CYP3A7*1C* allele (rs45446698; C_30634320_10). Analyses were performed utilizing a QuantStudio (ThermoFisher) 12K Flex Real-Time PCR system.

Pharmacokinetics

Data from the palbociclib pharmacokinetics (PK) analysis sets from PALOMA-2 (ie, patients under fed conditions [after eating a meal] at the time of PK sampling; n=180) and PALOMA-3 (n=218) were pooled to investigate the association between palbociclib exposure and *ABCB1* genotypes. Of the 398 patients, 344 had available genotype data. Individual plasma palbociclib concentration was calculated as within-patient mean steady-state trough concentrations across Cycles 1 and 2 (ie, the arithmetic mean of predose concentration of Day 14 [PALOMA-2] or Day 15 [PALOMA-3] of Cycles 1 and 2). Distribution of plasma palbociclib concentration across *ABCB1* genotypes and race was evaluated.

Statistical Analysis

Associations of SNP variants and patient baseline characteristics with early occurrence of grade 3/4 neutropenia at Cycle 1 Day 15 (C1D15) of palbociclib treatment were assessed in a pooled analysis from PALOMA-2 and PALOMA-3 studies. Patient baseline characteristics such as age, body weight, BMI, Eastern Cooperative Oncology Group performance status, prior radiotherapy or chemotherapy, ANC, WBC, and platelet counts were included. Cutoff values for laboratory data were based on the medians. Univariate and multivariable logistic regression analyses were performed to identify independent risk factors for C1D15 grade 3/4 neutropenia. Odds ratios (ORs) were estimated with corresponding 95% CIs. Risk factors of C1D15 grade 3/4 neutropenia with P values <0.10 by univariate analysis were considered in the multivariable analysis. This variable selection criterion was applied to the overall population only. Collinearity among potential risk factors was further examined so that highly correlated covariates were not simultaneously included in the multivariable models. Analyses stratified by Asian (n=122) and non-Asian (n=530) ethnicity were also conducted, considering that allelic variation is race specific (Asian or non-Asian) and that the multivariable analysis in the overall population is potentially confounded by race. Limited by small sample sizes, especially for Asian patients, variables included in the multivariable model for Asian and non-Asian patients were driven by biological and/or clinical relevance. SNPs were tested for Hardy-Weinberg equilibrium in the Asian and non-Asian populations using a permutation-based exact test. The median PFS (mPFS) and associated 95% CIs of patients with each variant were estimated separately in PALOMA-2 and PALOMA-3 using the Kaplan-Meier method. *P* values were calculated using the 2-sided log-rank test and not adjusted for multiplicity. Hazard ratios and corresponding 95% CIs were estimated using Cox proportional hazards models. All statistical tests were 2-sided, with *P* values <0.05 considered statistically significant. All statistical analyses were performed using SAS v.9.4 (SAS Institute, Cary, NC).

Results

In total, 652 patients receiving palbociclib in PALOMA-2 and PALOMA-3 had available SNP, race, and C1D15 ANC data. Of these 652 patients, 122 were Asian and 530 were non-Asian; the category "non-Asian" comprised predominantly self-reported white patients (94%). C1D15 grade 3/4 neutropenia was reported in 67 Asian patients (54.9%) and 123 non-Asian patients (23.2%). Alleles for the 4 SNPs (*ABCB1*_rs1128503, *ABCB1*_rs1045642, *ERCC1*_rs11615, *ERCC1*_rs3212986) were in Hardy-Weinberg equilibrium in both Asian patients (P>0.999, P>0.999, P=0.6638, and P=0.8205, respectively) and non-Asian patients (P=0.4329, P=0.3870, P=0.7903, and P=0.5723, respectively). Allele frequencies for *ABCB1*_rs1128503, *ABCB1*_rs1045642, and *ERCC1*_rs11615 differed between Asians and non-Asian patients, whereas allele frequencies for *ERCC1*_rs3212986 were relatively similar between non-Asian and Asian patients (**Figure 1**). The *CYP3A7*1C* allele was found only in non-Asian patients, consistent with the dbSNP database. Due to the low frequency, it was not possible to assess the impact of this polymorphism on clinical outcomes.

To investigate the associations between early occurrence of neutropenia and *ABCB1* and *ERCC1* genotypes, and between early occurrence of neutropenia and patient baseline characteristics in the palbociclib arms of the overall populations of PALOMA-2 and PALOMA-3, univariate analyses were initially performed (**Table 1**). For *ABCB1*_rs1128503, the frequency of early occurrence of grade 3/4 neutropenia was higher for patients with the T/T allele than for those with C/T or C/C (38.2% vs 28.5% or 23.1%; OR=0.647 and 0.486; *P*=0.038 and 0.003, respectively). For *ERCC1*_rs11615, the frequency of early occurrence of grade 3/4 neutropenia was higher in patients with G/G than in those with A/G (36.1% vs 26.6%; OR=0.641; *P*=0.039). In the univariate analysis (**Table 1**), early occurrence of grade 3/4 neutropenia was more likely to develop in Asian versus non-Asian patients (OR=0.248; P<0.0001), patients aged <50 years versus 50 to 69 or ≥70 years (OR=0.616 and 0.518; *P*=0.024 and 0.017, respectively), patients with weight <55 versus ≥65 kg (OR=0.463; *P*=0.0009), patients with BMI <18.5 versus ≥30 kg/m^2 (OR=0.358; *P*=0.029), as well as patients with low baseline ANC (ie, counts less than the median value vs greater than or equal to the median value; OR=7.628; P<0.0001), WBC count (OR=6.183; P<0.0001), or platelet count (OR=2.073; *P*<0.0001).

After identifying individual genotypes and baseline characteristics that may influence the likelihood of developing early occurrence of neutropenia, multivariable analyses were performed adjusting for the covariates to uncover potential independent associations among clinical variables and early occurrence of neutropenia in the palbociclib arms of the overall populations of PALOMA-2 and PALOMA-3 (**Table 1**). High multicollinearity existed among the significant risk factors identified in the univariate analysis. For example, race was highly correlated with *ABCB1*_rs1128503 (*P*<0.0001), *ERCC1*_rs11615 (*P*<0.0001), baseline BMI (*P*<0.0001), baseline ANC (*P*<0.0001), baseline WBC count (*P*=0.0006), and baseline platelet count (*P*=0.006). Thus, race and the other collinear variables could not be simultaneously included in the multivariable logistic regression model. Ultimately, the variables included in the multivariable model were *ABCB1*_rs1128503, *ERCC1*_rs11615, age, baseline BMI, and baseline ANC. No significant correlation was observed between *ABCB1*_rs1128503 and

*ERCC1*_rs11615. Risk factors for *ABCB1*_rs1128503 (C/C vs T/T: OR=0.560; 95% CI=0.334–0.937; *P*=0.027) and baseline ANC (low vs high by median: OR=7.251; 95% CI=4.788–10.982; *P*<0.0001) remained statistically significant in the multivariable analysis. The observed association of *ABCB1*_rs1128503 is likely attributable to populations of different genetic ancestry.

The multivariable analysis in the overall population was potentially confounded by race due to the high multicollinearity of Asian ethnicity with the risk factors in the multivariable risk model. Therefore, analyses stratified by Asian (n=122) and non-Asian (n=530) ethnicity were performed next. Univariate analyses were performed to investigate the association between genotypes, patient baseline characteristics, and early occurrence of neutropenia in Asian patients in the palbociclib arms of PALOMA-2 and -3 (**Table 2**). For *ABCB1*_rs1128503, among the 67 Asian patients with grade 3/4 neutropenia, 26 were T/T, 31 were C/T, and 10 were C/C. The frequency of early occurrence of grade 3/4 neutropenia was not significantly different with any genotype in Asian patients. Early occurrence of grade 3/4 neutropenia was more likely in Asian patients with low compared with high baseline ANC or WBC count (OR=4.986; *P*<0.0001 and OR=2.759; *P*=0.007, respectively). Based on these findings from the univariate analysis, a multivariable analysis was performed to investigate the independent association among the clinical variables and early occurrence of neutropenia in Asian patients in the palbociclib arms of PALOMA-2 and PALOMA-3 (**Table 2**). Due to multicollinearity issues among the risk factors, the variables included in the model were *ABCB1*_rs1128503, *ERCC1*_rs11615, and baseline ANC. Baseline WBC count was highly correlated with ANC and thus not co-presented in the model. No significant correlation was observed between *ABCB1*_rs1128503 and *ERCC1*_rs11615. Baseline ANC was the only variable with a statistically significant association with early occurrence of grade 3/4 neutropenia (low vs high by median: OR=6.033; 95% CI=2.615–13.922; *P*<0.0001).

The association between *ABCB1* and *ERCC1* genotypes and early occurrence of neutropenia, as well as patient baseline characteristics and early occurrence of neutropenia, in non-Asian patients in the palbociclib arms of PALOMA-2 and -3 using univariate analysis was investigated (**Table 3**). For *ABCB1*_rs1128503, of the 123 non-Asian patients with early occurrence of grade 3/4 neutropenia, 32 were T/T, 56 were C/T, and 35 were the C/C genotype. The frequency of early occurrence of grade 3/4 neutropenia was higher in patients with T/T than in those with C/C (32.0% vs 19.4%; OR=0.513; *P*=0.019). Early occurrence of grade 3/4 neutropenia was more likely for patients aged <50 years versus those aged 50 to 69 or ≥70 years (OR=0.564 and 0.474; *P*=0.025 and 0.021, respectively) and in patients with low baseline ANC, WBC count, or platelet count by median (OR=7.161, 7.143, and 2.155; *P*<0.0001, <0.0001, and =0.0003, respectively). Multivariable analyses were used to determine the independent associations among the clinical variables identified from the univariate analysis and early occurrence of neutropenia in non-Asian palbociclib-treated patients (**Table 3**). Due to multicollinearity among the risk factors, the variables included in the model were *ABCB1*_rs1128503, *ERCC1*_rs11615, age, and baseline ANC. No significant correlation between *ABCB1*_rs1128503 and *ERCC1*_rs11615 was observed. Baseline ANC remained significant (low vs high by median: OR=6.884; 95% CI=4.138–11.451; *P*<0.0001). *ABCB1*_rs1128503 (C/C vs T/T: OR=0.570; 95% CI=0.311–1.047; *P*=0.070) and *ERCC1*_rs11615 (A/A vs G/G: OR=1.750; 95% CI=0.901–3.397; *P*=0.098) were potential independent risk factors for C1D15 grade 3/4 neutropenia in non-Asians, albeit not statistically significant.

Because genetic variants in *ABCB1* may be associated with palbociclib exposure, the association between palbociclib exposure and *ABCB1* genotypes was assessed in the palbociclib arms of the overall populations of PALOMA-2 and -3. No associations between *ABCB1* genotypes and palbociclib exposure were observed (**Figure 2A**). Geometric mean plasma palbociclib concentrations were 70.7, 72.5, and 70.3 ng/mL, respectively, in patients with the C/C, C/T, and T/T variants of *ABCB1*_rs1128503, and 76.8, 69.6, and 69.6 ng/mL in patients with the C/C, T/C, and T/T variants of

*ABCB1*_rs1045642. Exposure was higher in Asian compared with non-Asian patients, with geometric mean plasma palbociclib concentrations of 89.6 and 68.6 ng/mL, respectively **(Figure 2B)**; however, individual values in Asian patients were within the ranges reported in non-Asian patients.

The influence of genotype on the clinical efficacy of palbociclib was assessed. Patients showed a consistent treatment effect, as measured by mPFS of the 2 treatment arms as well as hazard ratios, across the gene variants. The mPFS was significantly prolonged with palbociclib plus ET versus placebo plus ET for all genetic variants in both PALOMA-2 and -3, except for *ABCB1*_rs1045642 T/T and *ERCC1*_rs3212986 A/A, although this was not statistically significant due to the limited numbers of events (**Table 4**).

Discussion

This is the first comprehensive assessment of pharmacogenetic data in relationship to a CDK4/6 inhibitor. This analysis suggested that allele and genotype frequencies were in Hardy-Weinberg equilibrium for the studied population. *ABCB1* and *ERCC1*_rs11615 SNP allele frequencies differed between Asian and non-Asian patients. The *ABCB1*_rs1128503 T/T and *ERCC1*_rs11615 G/G SNP allele frequencies were higher in Asian than non-Asian patients, whereas the *ABCB1*_rs1128503 C/C and *ERCC1*_rs11615 A/A SNP allele frequencies were lower in Asian than non-Asian patients; although the magnitude of difference was smaller, the allele frequencies for *ABCB1*_rs1045642 C/C and T/T also differed between Asian and non-Asian patients. The early occurrence of grade 3/4 neutropenia was significantly higher in patients with *ABCB1*_rs1128503 T/T versus C/C and numerically higher in patients with *ERCC1*_rs11615 G/G versus A/A, whereas the frequency of early occurrence of grade 3/4 neutropenia was similar regardless of *ABCB1*_rs1045642 and *ERCC1*_rs3212986 genotype in the overall population **(Table 1)**. It was hypothesized that the differences in *ABCB1*_rs1128503 and *ERCC1*_rs11615 SNP allele frequencies in Asian and non-Asian patients might explain the higher frequency of neutropenia in Asian patients. Based on these findings, the associations between genotypes, patient baseline characteristics, and risk of early occurrence of neutropenia were further evaluated. In the overall population, *ABCB1*_rs1128503 and baseline ANC were independent risk factors for early occurrence of grade 3/4 neutropenia; however, the results are probably confounded by race. Thus, analyses stratified by Asian and non-Asian ethnicity were also conducted. In both Asian and non-Asian patients, low baseline ANC was a strong independent risk factor for early occurrence of grade 3/4 neutropenia. These findings support those of previous reports, which also found low baseline ANC to be a predictor of increased neutropenia with palbociclib treatment in both Asian and non-Asian patients [17-20]. *ABCB1*_rs1128503 and *ERCC1*_rs11615 were also identified as potential independent risk factors ($P<0.10$) for grade 3/4 neutropenia in non-Asian patients but not in Asian patients in this analysis ($P>0.10$). However, as the number of Asian patients in these clinical trials was small, these data should be interpreted with caution. Together, given the limited number of Asian patients and the finding that *ABCB1*_rs1128503 and *ERCC1*_rs11615 were identified as potential independent risk factors for grade 3/4 neutropenia in non-Asian patients, the differences in *ABCB1*_rs1128503 and *ERCC1*_rs11615 SNP allele frequencies between Asian and non-Asian patients could be a potential factor that causes a higher incidence of neutropenia in Asian patients.

Notably, age and weight/BMI were not associated with early occurrence of grade 3/4 neutropenia in Asian patients in the univariate analysis, whereas younger age was associated with early occurrence of grade 3/4 neutropenia in non-Asian patients in the univariate analysis, but was not an independent factor for the early occurrence of grade 3/4 neutropenia in the multivariable analysis. These findings were consistent with previous reports that showed no apparent correlation between palbociclib posttreatment ANC and age, weight, or body surface area (BSA)/BMI [17,18].

Palbociclib is metabolized primarily by CYP3A and the SULT enzyme SULT2A1 [10]. The substrates and/or inhibitors of CYP3A and *ABCB1* are thought to overlap with each other. Therefore, the association between *ABCB1*_rs1128503 or *ABCB1*_rs1045642 and palbociclib exposure was investigated in the current analyses. Our data suggest that differences in *ABCB1*_rs1128503 and *ABCB1*_rs1045642 genotyping did not affect palbociclib exposure. Previous findings showed no apparent correlation between palbociclib posttreatment ANC and steady state C_{trough} [17,18]. Taking into account our findings in the current analysis that *ABCB1* rs1128503 was identified as a potential independent risk factor for grade 3/4 neutropenia, the difference in the incidence of neutropenia between Asian and non-Asian patients might in part be due to the differences in *ABCB1* activity that are correlated with *ABCB1*_rs1128503 and which differ between Asian and non-Asian patients, and was not associated with palbociclib exposure.

The geometric mean plasma palbociclib concentration was lower in non-Asian patients than in Asian patients; however, individual values overlapped between Asian and non-Asian patients. In addition, it was reported that no apparent correlation was observed between palbociclib posttreatment ANC and steady state C_{trough}, body weight, or BSA/BMI, which suggested that the higher incidence of neutropenia observed in Japanese patients was not related to higher palbociclib exposure or lower body weight/BSA/BMI [17,18].

Palbociclib treatment effect, as measured by mPFS and hazard ratios, was generally consistent across genetic variants and between studies. PFS was significantly prolonged with palbociclib plus ET compared with placebo plus ET in almost all genetic variants, although not statistically significant with *ABCB1*_rs1045642 T/T and *ERCC1*_rs3212986 A/A. Of note, the numbers of patients in each genetic variant subgroup were relatively small, and thus these findings should be interpreted cautiously. Overall, these findings support palbociclib plus ET as treatment for patients with HR+/HER2– ABC, regardless of which alleles of *ABCB1* and *ERCC1* they carry.

In the current analysis, *ABCB1*_rs1128503 alleles were not associated with palbociclib exposure or efficacy. Additionally, a previous analysis reported that palbociclib dose reduction does not affect treatment efficacy [20]. One hypothesis is that in patients with neutropenia who require dose reduction, palbociclib pharmacokinetic and pharmacodynamic properties result in adequate exposure levels, leading to consistent efficacy. However, findings from previous studies suggest that the higher incidence of neutropenia was not due to higher palbociclib exposure, but rather lower baseline ANC levels [17,18]. The reason palbociclib dose reduction does not affect treatment efficacy is unclear and further investigations are warranted.

A limitation of the current analysis is that high multicollinearity existed among significant risk factors for the early occurrence of grade 3/4 neutropenia identified in the univariate analysis. Therefore, it may be challenging to draw a definitive conclusion from this analysis with the exclusion of covariates with high multicollinearity in the multivariable analysis models. In addition, large studies including populations with various ancestries are necessary to determine the impact of racial differences on SNP frequencies and to determine whether these differences are associated with variances in the incidences of neutropenia between racial subgroups [22]. The potential findings from this study warrant further investigation.

Conclusion

The current pharmacogenetic analyses potentially identified predictive risk factors that could help clinicians understand expectations associated with palbociclib treatment in patients with HR+/HER2–

ABC with specific genetic variants; differences in *ABCB1* and *ERCC1* activity that are correlated with the common variants *ABCB1*_rs1128503 and *ERCC1*_rs11615 and that differ between the Asian and non-Asian patients might have been a contributing factor to the higher incidence of neutropenia in Asian versus non-Asian patients. Pharmacogenetic testing may inform, to some degree, about a potentially increased likelihood of a patient developing severe neutropenia that, in the future, could be used for monitoring or individualized dosing. However, such testing is not currently warranted due to the relatively tenuous relationship between test outcome and the event in question (neutropenia), as well as the limited impact on actual patient management, which would still be dictated by ANC counts observed under treatment.

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Conflict of Interest Statement

This study was sponsored by Pfizer Inc. **H. Iwata** has served in an advisory/consulting role for Chugai and Daiichi-Sankyo; and has received personal fees from Pfizer, AstraZeneca, Chugai, Daiichi-Sankyo, Novartis, and Eli Lilly. **O. Fletcher** has no conflicts of interest to report. **M. Toi** has received honoraria from Novartis, MSD, Takeda, AstraZeneca, Taiho, Chugai, Pfizer, Eisai, Eli Lilly, Kyowa-Hakko Kirin, and Genomic Health Institute; research funding from Novartis, AstraZeneca, Taiho, Chugai, Pfizer, and Eli Lilly; and served as a consultant/independent contractor for Kyowa-Hakko Kirin and on an advisory board for Genomic Health Institute. **R.S. Finn** has received consulting fees from Pfizer, Bayer, Novartis, Bristol-Myers Squibb, and Merck, as well as other research funding from Pfizer; and honoraria from Bayer, Pfizer, Bristol-Myers Squibb, Novartis, Eisai, and Eli Lilly. **N.C. Turner** has received consulting fees from Pfizer; researching funding from Pfizer, Eli Lilly, and Novartis; and honoraria from Pfizer. **M. Cristofanilli** has received consulting fees from Pfizer, Eli Lilly, Novartis, Sermonix, G1 Therapeutics, CytoDyn, and Foundation Medicine. **Y. Umeyama, Y. Liu, Z. Zhang, P. Schnell, Y. Mori, J.-C. Marshall, J.G. Johnson,** and **L.S. Wood** are employees of Pfizer. **Y. Umeyama** and **Y. Mori** own stock in Pfizer Inc. **C. Huang Bartlett** was an employee of Pfizer at the time of the study.

Data Availability Statement

Upon request, and subject to certain criteria, conditions and exceptions (see https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information), Pfizer will provide access to individual de-identified participant data from Pfizer-sponsored global interventional clinical studies conducted for medicines, vaccines and medical devices (1) for indications that have been approved in the US and/or EU or (2) in programs that have been terminated (i.e., development for all indications has been discontinued). Pfizer will also consider requests for the protocol, data dictionary, and statistical analysis plan. Data may be requested from Pfizer trials 24 months after study completion. The de-identified participant data will be made available to researchers whose proposals meet the research criteria and other conditions, and for which an exception does not apply, via a secure portal. To gain access, data requestors must enter into a data access agreement with Pfizer.

Author Contributions

H. Iwata, Y. Umeyama, Y. Liu, P. Schnell, Y. Mori, O. Fletcher, M. Toi, R.S. Finn, N.C. Turner, C. Huang Bartlett, Z. Zhang, and M. Cristofanilli participated in the study conception and design. Y. Umeyama, Y. Liu, P. Schnell, Y. Mori, J.-C. Marshall, J.G. Johnson, and L.S. Wood participated in data acquisition and analysis. Z. Zhang performed statistical analyses. All authors participated in the analysis and interpretation of the data and the writing, review, and revision of the manuscript.

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Figure Legends

Figure 1. Allele frequencies by population. *ABCB1*=adenosine triphosphate–binding cassette subfamily B member 1. *ERCC1*=excision repair cross-complementing 1.

Figure 2. Association between *ABCB1* genotype, race, and palbociclib exposure. Plasma palbociclib concentration for (A) *ABCB1* genotypes and (B) Asian and non-Asian patients. Box plots depict the median (horizontal bar) and 25% and 75% quartiles, including values within the 1.5 times interquartile range. Diamonds represent the geometric mean, and green dots represent individual within-patient mean concentration values. *ABCB1*=adenosine triphosphate–binding cassette subfamily B member 1.

Table 1. Association between genotypes, patient baseline characteristics, and neutropenia in the overall population (palbociclib arm) in PALOMA-2 and PALOMA-3

Univariate Analysis					
	N (%)	C1D15 Neutropenia, n (%)		Odds Ratio (95% CI)	*P* Value
		Grade 0–2	Grade 3–4		
Genotypes					
***ABCB1*_rs1128503**	**652**				
T/T	152 (23.3)	94 (61.8)	58 (38.2)		
C/T	305 (46.8)	218 (71.5)	87 (28.5)	0.647 (0.429–0.975)	0.038
C/C	195 (29.9)	150 (76.9)	45 (23.1)	0.486 (0.305–0.776)	0.003
***ABCB1*_rs1045642**	**652**				
C/C	166 (25.5)	115 (69.3)	51 (30.7)		
T/C	333 (51.1)	238 (71.5)	95 (28.5)	0.900 (0.599–1.352)	0.612
T/T	153 (23.5)	109 (71.2)	44 (28.8)	0.910 (0.563–1.472)	0.702
***ERCC1*_rs11615**	**652**				
G/G	147 (22.5)	94 (63.9)	53 (36.1)		
A/G	305 (46.8)	224 (73.4)	81 (26.6)	0.641 (0.421–0.978)	0.039
A/A	200 (30.7)	144 (72.0)	56 (28.0)	0.690 (0.437–1.089)	0.111
***ERCC1*_rs3212986**	**652**				
C/C	355 (54.4)	253 (71.3)	102 (28.7)		
A/C	250 (38.3)	175 (70.0)	75 (30.0)	1.063 (0.745–1.516)	0.736
A/A	47 (7.2)	34 (72.3)	13 (27.7)	0.948 (0.481–1.871)	0.879
Patient Baseline Characteristics					
Race	**652**				
Asian	122 (18.7)	55 (45.1)	67 (54.9)		
Non-Asian	530 (81.3)	407 (76.8)	123 (23.2)	0.248 (0.165–0.374)	<0.0001
Age (years)	**652**				
<50	125 (19.2)	77 (61.6)	48 (38.4)		

50–69	400 (61.3)	289 (72.3)	111 (27.8)	0.616 (0.404–0.939)	0.024
≥70	127 (19.5)	96 (75.6)	31 (24.4)	0.518 (0.301–0.891)	0.017
Weight (kg)	**652**				
<55	106 (16.3)	63 (59.4)	43 (40.6)		
55–<65	167 (25.6)	111 (66.5)	56 (33.5)	0.739 (0.447–1.223)	0.239
≥65	379 (58.1)	288 (76.0)	91 (24.0)	0.463 (0.294–0.729)	0.0009
BMI (kg/m^2)	**651**				
<18.5	21 (3.2)	11 (52.4)	10 (47.6)		
18.5–<30	455 (69.9)	318 (69.9)	137 (30.1)	0.474 (0.197–1.142)	0.096
≥30	175 (26.9)	132 (75.4)	43 (24.6)	0.358 (0.142–0.902)	0.029
ECOG PS	**652**				
0	373 (57.2)	256 (68.6)	117 (31.4)		
1 or 2	279 (42.8)	206 (73.8)	73 (26.2)	0.775 (0.549–1.095)	0.149
Received prior chemotherapy	**652**				
No	265 (40.6)	191 (72.1)	74 (27.9)		
Yes	387 (59.4)	271 (70.0)	116 (30.0)	1.105 (0.782–1.561)	0.572
Received prior radiotherapy	**650**				
No	256 (39.4)	180 (70.3)	76 (29.7)		
Yes	394 (60.6)	280 (71.1)	114 (28.9)	0.964 (0.683–1.362)	0.836
Baseline ANC (x10^3/mm^3)	**652**				
≥Median value[a]`	332 (50.9)	296 (89.2)	36 (10.8)		
<Median value[a]	320 (49.1)	166 (51.9)	154 (48.1)	7.628 (5.064–11.489)	<0.0001
Baseline WBC count (x10^3/mm^3)	**652**				
≥Median value[b]	332 (50.9)	291 (87.7)	41 (12.3)		
<Median value[b]	320 (49.1)	171 (53.4)	149 (46.6)	6.183 (4.170–9.168)	<0.0001
Baseline PLT count (x10^3/mm^3)	**652**				
≥Median value[c]	330 (50.6)	258 (78.2)	72 (21.8)		
<Median value[c]	322 (49.4)	204 (63.4)	118 (36.6)	2.073 (1.467–2.929)	<0.0001
Multivariable Analysis					
Risk factor				**Odds Ratio (95% CI)**	***P* Value**

***ABCB1*_rs1128503**			
	C/T vs T/T	0.765 (0.484–1.207)	0.249
	C/C vs T/T	0.560 (0.334–0.937)	0.027
***ERCC1*_rs11615**			
	A/G vs G/G	0.726 (0.454–1.163)	0.183
	A/A vs G/G	0.838 (0.504–1.395)	0.497
Age (years)			
	50–69 vs <50	0.804 (0.504–1.284)	0.361
	≥70 vs <50	0.725 (0.398–1.322)	0.295
BMI (kg/m^2)			
	18.5–<30 vs <18.5	0.586 (0.218–1.575)	0.289
	≥30 vs <18.5	0.451 (0.159–1.274)	0.133
Baseline ANC (x10^3/mm^3)			
	<Median vs ≥median value[a]	7.251 (4.788–10.982)	<0.0001

ABCB1=adenosine triphosphate–binding cassette subfamily B member 1; ANC=absolute neutrophil count; BMI=body mass index; C1D15=Cycle 1 Day 15; ECOG PS=Eastern Cooperative Oncology Group performance status; *ERCC1*=excision repair cross-complementing 1; PLT=platelet; WBC=white blood cell.

[a]Baseline ANC median value was 3.60 (x10^3/mm^3). [b]Baseline WBC median value was 5.80 (x10^3/mm^3). [c]Baseline PLT median value was 241.0 (x10^3/mm^3).

Table 2. Association between genotypes, patient baseline characteristics, and neutropenia in the Asian population (palbociclib arm) in PALOMA-2 and PALOMA-3

Univariate Analysis					
	N (%)	**C1D15 Neutropenia, n (%)**		**Odds Ratio (95% CI)**	***P* Value**
		Grade 0–2	**Grade 3–4**		
Genotypes					
***ABCB1*_rs1128503**	**122**				
T/T	52 (42.6)	26 (50.0)	26 (50.0)		
C/T	55 (45.1)	24 (43.6)	31 (56.4)	1.292 (0.603–2.765)	0.510
C/C	15 (12.3)	5 (33.3)	10 (66.7)	2.000 (0.600–6.662)	0.259
***ABCB1*_rs1045642**	**122**				
C/C	47 (38.5)	18 (38.3)	29 (61.7)		
T/C	57 (46.7)	29 (50.9)	28 (49.1)	0.599 (0.273–1.313)	0.201
T/T	18 (14.8)	8 (44.4)	10 (55.6)	0.776 (0.258–2.331)	0.651
***ERCC1*_rs11615**	**122**				
G/G	60 (49.2)	24 (40.0)	36 (60.0)		
A/G	53 (43.4)	25 (47.2)	28 (52.8)	0.747 (0.354–1.576)	0.443
A/A	9 (7.4)	6 (66.7)	3 (33.3)	0.333 (0.076–1.463)	0.145
***ERCC1*_rs3212986**	**122**				
C/C	64 (52.5)	33 (51.6)	31 (48.4)		
A/C	50 (41.0)	20 (40.0)	30 (60.0)	1.597 (0.755–3.376)	0.221
A/A	8 (6.6)	2 (25.0)	6 (75.0)	3.194 (0.599–17.028)	0.174
Patient Baseline Characteristics					
Age (years)	**122**				
<50	28 (23.0)	12 (42.9)	16 (57.1)		
50–69	78 (63.9)	37 (47.4)	41 (52.6)	0.831 (0.348–1.985)	0.677
≥70	16 (13.1)	6 (37.5)	10 (62.5)	1.250 (0.355–4.402)	0.728

Weight (kg)	**122**				
<55	53 (43.4)	23 (43.4)	30 (56.6)		
55–<65	43 (35.2)	16 (37.2)	27 (62.8)	1.294 (0.568–2.946)	0.540
≥65	26 (21.3)	16 (61.5)	10 (38.5)	0.479 (0.184–1.250)	0.133
BMI (kg/m^2)	**122**				
<18.5	12 (9.8)	4 (33.3)	8 (66.7)		
18.5–<30	101 (82.8)	48 (47.5)	53 (52.5)	0.552 (0.156–1.951)	0.356
≥30	9 (7.4)	3 (33.3)	6 (66.7)	1.000 (0.160–6.255)	1.000
ECOG PS	**122**				
0	80 (65.6)	34 (42.5)	46 (57.5)		
1 or 2	42 (34.4)	21 (50.0)	21 (50.0)	0.739 (0.349–1.565)	0.430
Received prior chemotherapy	**122**				
No	49 (40.2)	25 (51.0)	24 (49.0)		
Yes	73 (59.8)	30 (41.1)	43 (58.9)	1.493 (0.720–3.094)	0.281
Received prior radiotherapy	**122**				
No	50 (41.0)	22 (44.0)	28 (56.0)		
Yes	72 (59.0)	33 (45.8)	39 (54.2)	0.929 (0.449–1.919)	0.842
Baseline ANC (x10^3/mm^3)	**122**				
≥Median value[a]	61 (50.0)	39 (63.9)	22 (36.1)		
<Median value[a]	61 (50.0)	16 (26.2)	45 (73.8)	4.986 (2.300–10.808)	<0.0001
Baseline WBC count (x10^3/mm^3)	**122**				
≥Median value[b]	61 (50.0)	35 (57.4)	26 (42.6)		
<Median value[b]	61 (50.0)	20 (32.8)	41 (67.2)	2.759 (1.320–5.766)	0.007
Baseline PLT count (x10^3/mm^3)	**122**				
≥Median value[c]	63 (51.6)	30 (47.6)	33 (52.4)		
<Median value[c]	59 (48.4)	25 (42.4)	34 (57.6)	1.236 (0.605–2.527)	0.561
Multivariable Analysis					
Risk factor				**Odds Ratio (95% CI)**	***P* Value**
***ABCB1*_rs1128503**					

	C/T vs T/T	1.575 (0.670–3.701)	0.297
	C/C vs T/T	2.417 (0.650–8.987)	0.188
***ERCC1*_rs11615**			
	A/G vs G/G	0.509 (0.217–1.196)	0.122
	A/A vs G/G	0.339 (0.062–1.857)	0.212
Baseline ANC ($x10^3/mm^3$)			
	<Median vs ≥median value[a]	6.033 (2.615–13.922)	<0.0001

ABCB1=adenosine triphosphate–binding cassette subfamily B member 1; ANC=absolute neutrophil count; BMI=body mass index; C1D15=Cycle 1 Day 15; ECOG PS=Eastern Cooperative Oncology Group performance status; *ERCC1*=excision repair cross-complementing 1; PLT=platelet; WBC=white blood cell.

[a]Baseline ANC median value was 3.094 ($x10^3/mm^3$). [b]Baseline WBC median value was 5.22 ($x10^3/mm^3$).

[c]Baseline PLT median value was 225.0 ($x10^3/mm^3$).

Table 3. Association between genotypes, patient baseline characteristics, and neutropenia in the non-Asian population (palbociclib arm) in PALOMA-2 and PALOMA-3

Univariate Analysis					
	N (%)	**C1D15 Neutropenia, n (%)**		**Odds Ratio (95% CI)**	***P* Value**
		Grade 0–2	**Grade 3–4**		
Genotypes					
***ABCB1*_rs1128503**	**530**				
T/T	100 (18.9)	68 (68.0)	32 (32.0)		
C/T	250 (47.2)	194 (77.6)	56 (22.4)	0.613 (0.367–1.026)	0.063
C/C	180 (34.0)	145 (80.6)	35 (19.4)	0.513 (0.293–0.897)	0.019
***ABCB1*_rs1045642**	**530**				
C/C	119 (22.5)	97 (81.5)	22 (18.5)		
T/C	276 (52.1)	209 (75.7)	67 (24.3)	1.413 (0.825–2.421)	0.208
T/T	135 (25.5)	101 (74.8)	34 (25.2)	1.484 (0.811–2.716)	0.200
***ERCC1*_rs11615**	**530**				
G/G	87 (16.4)	70 (80.5)	17 (19.5)		
A/G	252 (47.5)	199 (79.0)	53 (21.0)	1.097 (0.596–2.019)	0.767
A/A	191 (36.0)	138 (72.3)	53 (27.7)	1.581 (0.853–2.932)	0.146
***ERCC1*_rs3212986**	**530**				
C/C	291 (54.9)	220 (75.6)	71 (24.4)		
A/C	200 (37.7)	155 (77.5)	45 (22.5)	0.900 (0.587–1.378)	0.627
A/A	39 (7.4)	32 (82.1)	7 (17.9)	0.678 (0.287–1.603)	0.376
Patient Baseline Characteristics					
Age (years)	**530**				
<50	97 (18.3)	65 (67.0)	32 (33.0)		
50–69	322 (60.8)	252 (78.3)	70 (21.7)	0.564 (0.342–0.930)	0.025
≥70	111 (20.9)	90 (81.1)	21 (18.9)	0.474 (0.251–0.895)	0.021
Weight (kg)	**530**				

<55	53 (10.0)	40 (75.5)	13 (24.5)		
55–<65	124 (23.4)	95 (76.6)	29 (23.4)	0.939 (0.443–1.991)	0.870
≥65	353 (66.6)	272 (77.1)	81 (22.9)	0.916 (0.467–1.796)	0.799
BMI (kg/m^2)	**529**				
<18.5	9 (1.7)	7 (77.8)	2 (22.2)		
18.5–<30	354 (66.9)	270 (76.3)	84 (23.7)	1.089 (0.222–5.342)	0.916
≥30	166 (31.4)	129 (77.7)	37 (22.3)	1.004 (0.200–5.039)	0.996
ECOG PS	**530**				
0	293 (55.3)	222 (75.8)	71 (24.2)		
1 or 2	237 (44.7)	185 (78.1)	52 (21.9)	0.879 (0.585–1.321)	0.535
Received prior chemotherapy	**530**				
No	216 (40.8)	166 (76.9)	50 (23.1)		
Yes	314 (59.2)	241 (76.8)	73 (23.2)	1.006 (0.667–1.516)	0.979
Received prior radiotherapy	**528**				
No	206 (39.0)	158 (76.7)	48 (23.3)		
Yes	322 (61.0)	247 (76.7)	75 (23.3)	0.999 (0.661–1.512)	0.998
Baseline ANC (x10^3/mm^3)	**530**				
≥Median value[a]	270 (50.9)	248 (91.9)	22 (8.1)		
<Median value[a]	260 (49.1)	159 (61.2)	101 (38.8)	7.161 (4.333–11.833)	<0.0001
Baseline WBC count (x10^3/mm^3)	**530**				
≥Median value[b]	276 (52.1)	253 (91.7)	23 (8.3)		
<Median value[b]	254 (47.9)	154 (60.6)	100 (39.4)	7.143 (4.352–11.724)	<0.0001
Baseline PLT count (x10^3/mm^3)	**530**				
≥Median value[c]	266 (50.2)	222 (83.5)	44 (16.5)		
<Median value[c]	264 (49.8)	185 (70.1)	79 (29.9)	2.155 (1.420–3.270)	0.0003

Multivariable Analysis

Risk factor		**Odds Ratio (95% CI)**	***P* Value**
***ABCB1*_rs1128503**			
	C/T vs T/T	0.734 (0.420–1.283)	0.278
	C/C vs T/T	0.570 (0.311–1.047)	0.070

***ERCC1*_rs11615**			
	A/G vs G/G	1.165 (0.605–2.243)	0.647
	A/A vs G/G	1.750 (0.901–3.397)	0.098
Age (years)			
	50–69 vs <50	0.696 (0.405–1.195)	0.189
	≥70 vs <50	0.615 (0.310–1.219)	0.164
Baseline ANC ($x10^3/mm^3$)			
	<Median vs ≥median value[a]	6.884 (4.138–11.451)	<0.0001

ABCB1=adenosine triphosphate–binding cassette subfamily B member 1; ANC=absolute neutrophil count; BMI=body mass index; C1D15=Cycle 1 Day 15; ECOG PS=Eastern Cooperative Oncology Group performance status; *ERCC1*=excision repair cross-complementing 1; PLT=platelet; WBC=white blood cell.

[a]Baseline ANC median value was 3.70 ($x10^3/mm^3$). [b]Baseline WBC median value was 5.90 ($x10^3/mm^3$). [c]Baseline PLT median value was 244.0 ($x10^3/mm^3$).

Table 4. Progression-free survival by genetic variants in PALOMA-2 and PALOMA-3

	PALOMA-2			PALOMA-3		
	PAL+LET	**PBO+LET**	***P* Value**	**PAL+FUL**	**PBO+FUL**	***P* Value**
***ABCB1*_rs1128503**						
C/C, n	112	43		90	45	
mPFS (95% CI), months	28.1 (21.4–37.2)	14.5 (10.9–23.3)	0.003	13.4 (9.4–16.6)	4.8 (1.9–5.6)	<0.0001
Hazard ratio (95% CI)	0.53 (0.34–0.82)			0.42 (0.27–0.65)		
C/T, n	180	102		137	74	
mPFS (95% CI), months	27.4 (20.2–30.6)	16.8 (13.6–22.2)	0.008	11.1 (9.2–12.7)	7.2 (3.4–9.2)	0.004
Hazard ratio (95% CI)	0.66 (0.49–0.90)			0.61 (0.43–0.86)		
T/T, n	95	52		63	32	
mPFS (95% CI), months	23.9 (13.9–27.9)	13.9 (5.4–19.3)	0.005	16.7 (9.9–NE)	4.6 (2.1–9.2)	0.0009
Hazard ratio (95% CI)	0.57 (0.38–0.85)			0.40 (0.23–0.70)		
***ABCB1*_rs1045642**						
C/C, n	97	36		74	42	
mPFS (95% CI), months	28.1 (22.4–NE)	12.9 (7.4–18.2)	<0.0001	11.3 (7.5–16.6)	5.4 (3.4–7.3)	0.002
Hazard ratio (95% CI)	0.39 (0.24–0.62)			0.49 (0.31–0.78)		
T/C, n	184	104		162	74	
mPFS (95% CI), months	27.6 (20.2–33.1)	17.1 (13.7–24.8)	0.0005	12.1 (10.9–13.7)	3.7 (2.8–7.4)	<0.0001
Hazard ratio (95% CI)	0.59 (0.44–0.80)			0.43 (0.31–0.60)		
T/T, n	106	57		54	35	
mPFS (95% CI), months	21.9 (12.9–27.6)	15.9 (8.3–22.2)	0.302	11.2 (7.5–18.0)	7.2 (2.1–10.9)	0.155
Hazard ratio (95% CI)	0.81 (0.55–1.22)			0.67 (0.38–1.17)		
***ERCC1*_rs11615**						
A/A, n	123	72		86	48	
mPFS (95% CI), months	24.2 (19.2–30.6)	16.8 (12.3–38.9)	0.004	11.1 (9.4–NE)	5.5 (2.8–10.9)	0.006
Hazard ratio (95% CI)	0.60 (0.42–0.86)			0.54 (0.34–0.85)		
A/G, n	181	85		134	70	
mPFS (95% CI), months	27.6 (19.4–30.7)	13.8 (11.0–21.9)	0.002	12.1 (11.0–13.9)	3.8 (2.1–5.6)	<0.0001

Hazard ratio (95% CI)	0.60 (0.43–0.83)			0.44 (0.31–0.63)		
G/G, n	83	40		70	33	
mPFS (95% CI), months	27.4 (19.2–35.9)	15.2 (7.4–24.8)	0.015	11.3 (9.2–16.1)	5.7 (3.4–8.5)	0.012
Hazard ratio (95% CI)	0.57 (0.36–0.91)			0.54 (0.34–0.85)		
***ERCC1*_rs3212986**						
A/A, n	30	9		20	10	
mPFS (95% CI), months	27.4 (13.6–NE)	16.6 (1.6–38.9)	0.589	5.6 (1.8–11.3)	6.3 (1.8–13.8)	0.921
Hazard ratio (95% CI)	0.77 (0.31–2.17)			0.95 (0.42–2.37)		
A/C, n	147	66		111	61	
mPFS (95% CI), months	27.6 (19.3–35.9)	14.5 (10.3–22.2)	0.005	13.4 (11.1–15.5)	3.7 (2.1–5.6)	<0.0001
Hazard ratio (95% CI)	0.60 (0.42–0.87)			0.45 (0.31–0.67)		
C/C, n	210	122		159	80	
mPFS (95% CI), months	25.1 (19.6–29.3)	16.4 (12.9–21.9)	<0.0001	12.7 (9.9–NE)	5.6 (3.6–9.2)	<0.0001
Hazard ratio (95% CI)	0.58 (0.44–0.77)			0.47 (0.34–0.66)		

ABCB1=adenosine triphosphate–binding cassette subfamily B member 1; *ERCC1*=excision repair cross-complementing 1; FUL=fulvestrant; LET=letrozole; mPFS=median progression-free survival; NE=not estimable; PAL=palbociclib; PBO=placebo.

Figure 1. Allele frequencies by population.

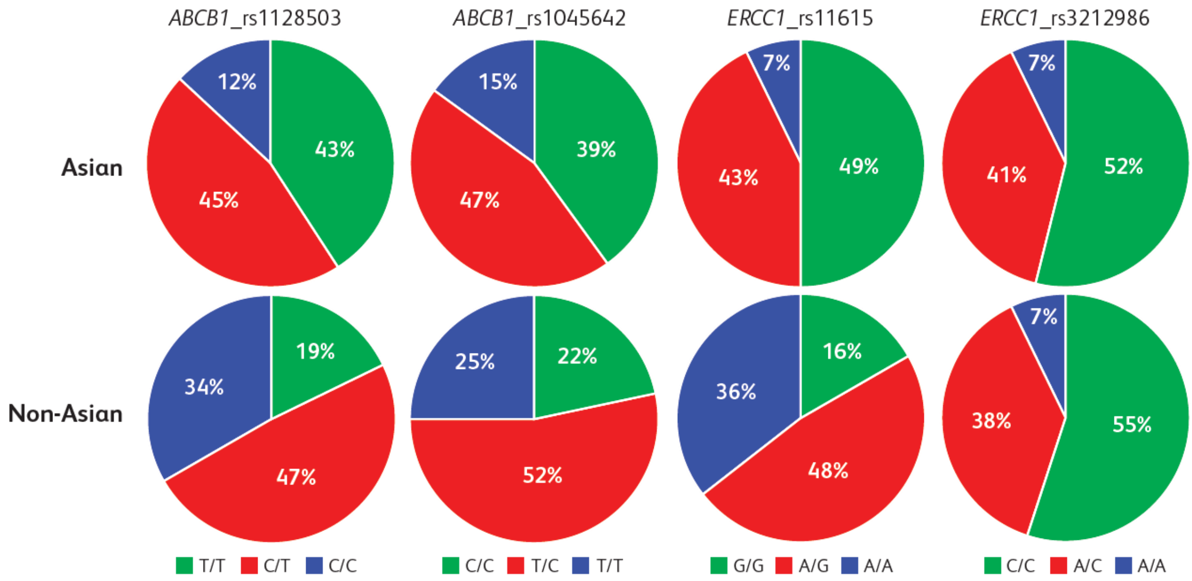

Figure 2. Association between *ABCB1* genotype, race, and palbociclib exposure.