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Hematological Safety of Palbociclib in Combination With Endocrine Therapy in Patients with Benign Ethnic Neutropenia and Advanced Breast Cancer

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Abstract

Background—Cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, including palbociclib, are approved to treat hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (HR+/HER2– ABC) and are associated with hematological toxicity. African American women, underrepresented in CDK4/6 inhibitor clinical trials, may experience worse neutropenia owing to benign ethnic neutropenia. This study specifically investigated the hematologic safety of palbociclib in African American women with HR+/HER2– ABC.

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*At the time of the study.

Author contribution statement: FL, MJB, RZ, CG, OH, MA-K, MM, TW, PRP, AD, SRT, AC, RW, MT, ANS-H, and CI participated in study design, and data collection and interpretation. TW and MT performed statistical analyses. All authors participated in manuscript development, and have read and approved the manuscript for submission.

Conflict of interest statement: **OMH** reports consulting/advisory roles for Pfizer Inc. **MJB, RZ, CG, MA-K, MM, RW, TW, SRT, AC, MT** and **ANS-H** have no conflicts of interest to report.

Methods—PALINA was a single-arm, open-label, investigator-initiated study of palbociclib (125 mg/d; 21 days on/7 days off) plus endocrine therapy (ET) in African American women with HR+/HER2– ABC and baseline absolute neutrophil count ≥1000/mm^3. Primary outcome was the proportion of patients completing 12 months of therapy without experiencing febrile neutropenia (FN) or treatment discontinuation due to neutropenia. Single nucleotide polymorphism analysis was used to assess Duffy polymorphism status.

Results—Thirty-five patients received ≥1 dose of palbociclib plus ET; 19 had Duffy null polymorphism (C/C). There were no reports of FN or permanent study discontinuation due to neutropenia. Significantly more patients with Duffy null versus wild-type polymorphism had grade 3/4 neutropenia (72.2% vs 23.1%; *P*=0.029 and required palbociclib dose reduction (55.6% vs 7.7%; *P*=0.008). Patients with Duffy null versus wild-type had lower overall relative dose intensity (mean [SD], 81.89 [15.87] and 95.67 [5.89]; *P*=0.0026) and lower clinical benefit rate (66.7% and 84.6%).

Conclusions—These findings suggest that palbociclib is well tolerated in African American women with HR+/HER2– ABC. Duffy null status may affect incidence of grade 3 neutropenia, dose intensity, and possibly clinical benefit.

ClinicalTrials.gov NCT02692755

Precis for use in Table of Contents:

Palbociclib is well tolerated in African American patients with HR+/HER2– ABC who do not have Duffy null genotype. Duffy null status appeared to impact the incidence of grade 3 neutropenia, dose intensity, and clinical response.

Keywords

Palbociclib; African Americans; safety; CDK4/6 inhibitor; neutropenia; endocrine therapy; benign ethnic neutropenia; Duffy null; DARC

INTRODUCTION

The introduction of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors in combination with endocrine therapy (ET) has led to a profound shift in the treatment guidelines for women with hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer (HR+/HER2– ABC).[1,2] Although these agents are generally safe and efficacious, their use is associated with higher rates of hematologic adverse events (AEs), particularly neutropenia, compared with ET alone.[3] Palbociclib is a first-in-class CDK4/6 inhibitor that is approved in combination with ET as treatment for adults with HR+/HER2– ABC.[4] The efficacy and safety of palbociclib in combination with an aromatase inhibitor as first-line treatment or with fulvestrant in patients with disease progression following ET was demonstrated in the PALOMA-2 and PALOMA-3 clinical trials, respectively.[5,6]

The most common AE with palbociclib treatment in the clinical trial setting was neutropenia.[5,6] In a pooled analysis of the PALOMA trials, 80.6% of patients in the palbociclib arm experienced all-grade neutropenia with palbociclib plus ET treatment; the rate of grade 3/4 neutropenia was 65.4%.[7] Despite this relatively high incidence, febrile

neutropenia was reported in only 1.6% of palbociclib-treated patients.[7] However real world data suggest that the use of palbociclib in later lines of therapy may be associated with higher rates of febrile neutropenia.[8] Post hoc analyses suggest that the incidence of hematologic AEs in the PALOMA trials is influenced by ethnicity. Both all-grade and grade 3/4 neutropenia were higher in Asian compared with non-Asian patients in the palbociclib arm of PALOMA-2 (all grade, 95.4% vs 76.8%; grade 3/4, 89.2% vs 62.5%) and PALOMA-3 (all grade, 91.8% vs 77.9%; grade 3/4, 91.8% vs 57.4%).[9,10] Baseline absolute neutrophil counts (ANCs) also differed by ethnicity. Asian patients in PALOMA-2 and PALOMA-3 had median baseline ANC values that were respectively 18% and 19% lower than those of the non-Asian patients.[9,10] These findings suggest that certain patient populations may have a greater risk of developing hematologic side effects during CDK4/6 inhibitor therapy.

Although African American women have slightly lower rates of breast cancer than white women (126.7 vs 130.8 per 100,000, respectively), their mortality rates are 40% higher (28.4 vs 20.3 per 100,000).[11] African American patients are typically underrepresented in clinical trials, including in the PALOMA clinical trial program and in clinical trials of other CDK4/6 inhibitors.[5,6,12–14] This lack of diversity can influence the generalizability of clinical trial results to the population at large. Ultimately, the dearth of information regarding the efficacy and safety of CDK4/6 inhibitors in the African American population can have major public health consequences.

The estimated prevalence of benign ethnic neutropenia (BEN), defined as ANC $\leq 1.5\times10^9$ cells/L, among individuals of African descent ranges between 4% and 40%.[15–17] Polymorphisms in the Duffy Antigen Receptor for Chemokines (DARC) gene have been linked to the pathophysiology of BEN.[18,19] Population studies suggest that between 60% and 70% of African Americans have the Duffy null polymorphism, which results from a homozygous point mutation in the SNP at position −30 of the *DARC* promoter region in which thymine (T) is replaced by cytosine (C), resulting in C/C genotype and a Duffy null phenotype.[20] The ANC levels that characterize BEN are potentially below the minimum threshold for clinical study inclusion, which may contribute to the underrepresentation of African Americans enrolled in clinical trials.[15] Given the importance of understanding the safety of palbociclib in African American women, the PALINA trial was conducted to investigate the hematologic safety of palbociclib in this group of patients, allowing women with lower baseline ANCs to enroll.

METHODS

A detailed methodology for the PALINA trial (NCT02692755) has been previously published.[21] This trial conforms to the principles of the Declaration of Helsinki and was approved by Georgetown University Medical Center's institutional review board. All participants provided written informed consent before inclusion in the study.

Study Design and Treatment

In brief, PALINA (NCT02692755) was a phase 2, multicenter, single-arm, open-label, investigator-initiated study of palbociclib plus ET in self-reported African American,

African, or Black women with HR+/HER2– ABC.[21] Additional key inclusion criteria were age ≥18 years, adequate bone marrow function (ie, ANC ≥1000/mm^3, platelets ≥100,000/mm^3, and hemoglobin ≥9 g/dL), and Eastern Cooperative Oncology Group performance status 0 to 2. Key exclusion criteria included previous use of a CDK4/6 inhibitor. Patients with baseline ANC ≥1500/mm^3 received palbociclib 125 mg/day for 21 days, followed by 7 days off treatment; those with baseline ANC <1500/mm^3 received an initial palbociclib dose of 100 mg/day. All patients received palbociclib in combination with ET (either letrozole 2.5 mg/day, anastrozole 1 mg/day, exemestane 25 mg/day, tamoxifen 20 mg/day, or fulvestrant 500 mg intramuscular injection days 1, 15, and 29 of cycle 1, and then every 4 weeks for all additional cycles). Palbociclib dose modifications due to neutropenia were permitted per the palbociclib prescribing information.[4] Dose modifications occurred in response to grade 3 (ANC 500–<1000/mm^3) or grade 4 (ANC <500/mm^3) neutropenia; with grade 3 neutropenia without fever/infection, the next cycle of palbociclib treatment was allowed to resume at the same dose when ANC recovered to ≥1000 mm^3. In response to grade 4 neutropenia (or grade 3 with fever and/or infection), palbociclib was withheld until ANC recovered to ≥1000 mm^3 and then the next cycle of palbociclib treatment was allowed to resume at the next lower dose.

Outcomes and Assessments

The primary outcome measure was the proportion of patients who completed planned oncologic therapy without the development of a hematologic event within 12 months.[21] Hematologic events were defined as episodes of febrile neutropenia or treatment discontinuation due to neutropenia. Planned oncology therapy was defined as completion of 1 year of therapy for ABC in the absence of disease progression or cessation of study drug due to progressive disease or nonhematologic toxicity. Febrile neutropenia was defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. Secondary outcome measures were palbociclib dose delays and reductions attributable to neutropenia and clinical benefit rate (CBR). For patients with evaluable disease, CBR was defined as the percentage of patients who achieved complete response, partial response, or stable disease ≥24 weeks. Patients could continue treatment as standard of care after participation in PALINA.

Single Nucleotide Polymorphism (SNP) Analysis

Blood samples were obtained from each patient, and DNA was isolated and purified from blood using QIAamp DNA Blood Mini Kits (Qiagen, Germantown, MD, USA). Purified DNA samples were genotyped using TaqMan SNP Genotyping Assay (ID: C__15769614_10) for rs2814778, designed and synthesized by Applied Biosystems (Waltham, MA, USA) for real-time PCR-based SNP genotyping.

Statistical Analyses

A completion rate of 80% was considered clinically relevant to benefit breast cancer patients who are at a higher risk of having BEN; a completion rate of 60% was not considered to be clinically meaningful. A two-stage design with 35 patients was used to test if the completion rate was ≥80% versus <60%, with 80% power at a significance level of 5%. An exact confidence interval of the completion rate was calculated. Secondary outcome

measures were analyzed descriptively. Relative dose (RD; [actual total dose/intended total dose]*100) and relative dose intensity (RDI; [actual overall dose intensity/intended overall dose intensity]*100 were analyzed post hoc. The percentage of patients with RD <85% and RDI <85% were calculated. Means and standard errors were calculated. Welch's 2-sample *t* test was performed; Fisher's exact test was performed for RD <85% and RDI <85%. All computations were performed using R 3.6.2.

RESULTS

Patients

In total, 35 patients were enrolled. Twenty patients (57.1%) had known bone metastases at time of study enrollment. Nineteen patients (54.3%) had the Duffy null polymorphism (C/C; Figure 1); 14 patients (40.0%) had wild-type polymorphism at the Duffy locus (C/T, n=11 or T/T, n=3; Figure 1). Two patients did not have Duffy polymorphism status reported. Thirty-three patients received ≥1 dose of palbociclib plus ET. Thirty-one patients had both Duffy polymorphism status and completed at least one cycle of palbociclib and were included in the primary outcome analysis. Patient baseline demographic and disease characteristics were generally similar between patients with Duffy null and wild-type polymorphisms; however, those with wild-type (T alleles) had higher median baseline ANC (Table 1). Only one patient had ANC <1500/mm^3 at enrollment. Approximately 63% of patients with Duffy null and 50% of patients with wild-type polymorphisms received aromatase inhibitor therapy, with the remainder receiving either fulvestrant or tamoxifen. Although more patients with Duffy null than wild-type polymorphisms had received previous chemotherapy in any setting (adjuvant or metastatic; 47% and 29%, respectively), this difference was not statistically significant.

Safety and Dose Modifications

Absolute neutrophil count levels decreased at cycle 1 day 14 (C1D14) for patients with Duffy null and wild-type polymorphisms (median ANC baseline and C1D14 for Duffy Null 2350/mm^3 and 1200/mm^3; and for wild-type 4460/mm^3 and 1900/mm^3 respectively), but these levels stabilized by the end of study treatment (median ANC for Duffy Null and wild-type 1400/mm^3 and 1700/mm^3, respectively) (Figure 2). Approximately 55% of patients experienced grade 3/4 neutropenia (Table 2). There was no difference in the incidence of grade 3/4 neutropenia according to the presence of bone metastases (P=0.88). Significantly more patients with Duffy null versus wild-type polymorphisms had grade 3/4 neutropenia (67% vs 23%; P=0.029). Although grade 3/4 neutropenia was relatively common in these patients, there were no reports of febrile neutropenia. Approximately 40% of patients required ≥1 palbociclib dose reduction owing to neutropenia (Table 2).

Dose reduction due to neutropenia was more frequent in patients with Duffy null versus wild-type polymorphisms (55.6% vs 7.7%; P=0.008). The mean (range) time to first palbociclib dose reduction due to neutropenia was 82.6 (38–273) days for the 10 patients with Duffy null polymorphisms and 63 days for the 1 patient with wild-type who received palbociclib dose reduction. Approximately 39% of those with Duffy null polymorphisms had their palbociclib dose further reduced to 75 mg/day; no patients with wild-type required

a similar dose reduction (*P*=0.025). No patients permanently discontinued from the study owing to neutropenia.

Approximately half of the patients in the study required ≥1 palbociclib dose delay due to neutropenia (Table 2). Significantly more patients with Duffy null polymorphisms had ≥1 palbociclib dose delay due to neutropenia compared with patients with wild-type (67% vs 23%; *P*=0.029). The mean time to the first dose delay due to neutropenia was longer in those with Duffy null rather than wild-type polymorphisms (46 vs 28 days). Those with Duffy null polymorphisms also experienced more dose delays than those with wild-type (mean, 4.0 and 1.7).

The most common grade 3 or 4 non-hematological toxicities reported were gastrointestinal (diarrhea and colitis), occurring in 5.7% of patients, followed by dehydration, anorexia, hyperglycemia and urinary tract infection occurring each in 2.9% of patients. There were no grade 5 toxicities attributed to palbociclib.

Post Hoc Analysis of Treatment Exposure and Dose Intensity

Median duration of palbociclib treatment was similar for patients with Duffy null and wild-type polymorphisms (Table 3). Previous reports have suggested that a cutoff RDI of 85% resulted in improved outcomes in patients with breast cancer who received first-line chemotherapy.[22] Therefore, we calculated the RD and RDI for patients with Duffy null and wild-type polymorphisms. Mean (SD) overall RD was 87.7% (12.99) and 99.1% (3.23) in patients with Duffy null and wild-type polymorphisms, respectively (t=3.57, *P*=0.0019). The number of patients with RD <85% and RD ≥85% was 8 and 10, respectively, with Duffy null and 0 and 13 with wild-type; this association was significant (*P*=0.009). Mean (SD) overall RDI was significantly lower for patients with Duffy null (81.9% [15.87]) than for those with wild-type (95.7% [5.89]; *P*=0.0026). There was a significant association between Duffy polymorphism and RDI reduction (*P*=0.02). Eighteen patients (58.1%) who did not have disease progression remained on commercial palbociclib after study completion.

Clinical Response

Best clinical response was assessed in the 31 patients with available Duffy polymorphism status (Table 4). CBR was lower in patients with the Duffy null compared with the wild-type polymorphism (66.7% and 84.6%, respectively), and more than twice as many patients with the Duffy null polymorphism had progressive disease (33.3% and 15.4%). The objective response rate was 22.2% and 38.5% in the Duffy null and wild-type groups, respectively. The rate of stable disease was similar between patients with the Duffy null and the wild-type polymorphism (44.4% and 46.2%, respectively).

DISCUSSION

This was the first clinical trial designed to investigate the hematologic safety of a CDK4/6 inhibitor in African American women. These results suggest that palbociclib was generally safe in African American women with baseline ANC ≥1000/mm^3. Although a statistically significantly increased incidence of grade 3 neutropenia was observed in those patients with Duffy null mutations (unadjusted *P*=0.029), there were no reports of febrile neutropenia,

and no patient discontinued the study owing to neutropenia, suggesting that subclinical BEN in African American women does not lead directly to neutropenic fever or treatment discontinuation due to hematologic toxicity. Based on our data we would not recommend screening for polymorphism in the DARC gene prior to initiation of palbociclib, as our findings suggest that even for patients with Duffy null polymorphism, palbociclib begun at standard dose is safe.

We also reported that patients with the Duffy null polymorphism experienced more dose reductions/delays due to neutropenia than those with wild-type. Furthermore, the median and mean RDIs were lower for patients with Duffy null than for those with wild-type polymorphisms. Dose modifications could have hampered the clinical response to palbociclib in patients with Duffy null, who had a lower CBR than those with wild-type. However, interpretation of efficacy results needs to be made with caution given the heterogeneity of patients enrolled in this trial in terms of previous lines of therapy in the metastatic setting or treatment free interval since completion of adjuvant therapy as well as lack of predefined schedule of staging scans that were left to physician's description. In fact, PFS results of two large randomized phase 3 trials found that dose modifications due to neutropenia do not appear to negatively impact the efficacy of palbociclib. A landmark analysis of PALOMA-2 revealed that PFS was similar in patients treated with palbociclib plus letrozole who experienced dose reductions and those who did not.[23] In PALOMA-3, PFS of patients receiving palbociclib plus fulvestrant was similar between those who had one or more dose reductions due to neutropenia and those without any dose reduction.[24]

Interestingly, only 1 patient with Duffy null genotype in this study had baseline ANC <1500/mm^3; thus, the prevalence of BEN based on ANC alone may be underestimated. However, up to two-thirds of African Americans, and 54% of patients in this study, have the Duffy null phenotype; baseline ANC alone may greatly underestimate the number of African American women who will have grade 3 neutropenia requiring dose modifications. Overall, these findings support the hypothesis that African American patients with BEN and the Duffy null phenotype may receive a lower palbociclib exposure than planned; this reduction in exposure could lead to a negative effect on clinical benefit in African American women.

Low baseline ANC is also observed in Asian participants in clinical trials. Previous subgroup analyses from the pivotal PALOMA clinical trials found that Asian patients had lower baseline ANC than non-Asian patients.[9,10] Asian patients in PALOMA-2 and −3 also had higher rates of grade 3/4 neutropenia than the overall patient population.[9,10] Similar to our observations regarding African American patients in this study, Asian patients who received palbociclib in the PALOMA trials experienced differences in treatment exposure compared with non-Asian patients, including higher rates of dose modifications and cycle delays.[9,10] However, subgroup analysis of participants of PALOMA-2 and PALOMA-3 demonstrated that Asian and non-Asian patients had similar PFS outcomes, despite the fact that Asian patients experienced more dose reductions.[9] Importantly, few Asian patients in the PALOMA trials and no African American patients in the present study discontinued study treatment due to an AE.[9,10]

These findings may have broader implications for other myelosuppressive therapies. Two additional CDK4/6 inhibitors, ribociclib and abemaciclib, are approved in combination with ET for the treatment of patients with HR+/HER2– ABC. These agents have mechanisms of action similar to palbociclib and have also been reported to result in a high incidence of hematologic AEs.[13,14] To date, the specific hematologic safety of ribociclib and abemaciclib in African American women has not been reported. Although it is biologically plausible that Duffy status also impacts the hematologic toxicity associated with other CDK inhibitors, it would be important to report results of the use of these agents in a patient population likely to have BEN. Of note, the myelosuppressive effect of CDK4/6 inhibitors is reversible[25]; thus, frequent dose modifications of this class of drugs, beyond palbociclib, may help in managing hematologic AEs in African American patients.

This study is subject to several limitations, including its small sample size and open-label design with multiple factors and subgroups analyzed. The analysis was not adjusted to differences in median age and previous receipt of chemotherapy between the two groups, given the low numbers. Despite these limitations, this report provides important evidence regarding the safety of palbociclib in a patient population, African American women, that is traditionally underrepresented in clinical trials. Our findings suggest that palbociclib is well tolerated in African American patients with HR+/HER2– ABC. Duffy null status appeared to affect the incidence of grade 3 neutropenia and dose intensity. The absence of infectious complications, regardless of degree of neutropenia triggering dose modifications with consequent decreased drug exposure and possible increased incidence of PD in Duffy null patients treated with palbociclib, raise the question of whether the current dose modification recommendations based on neutrophil counts should be revisited in patients with BEN.

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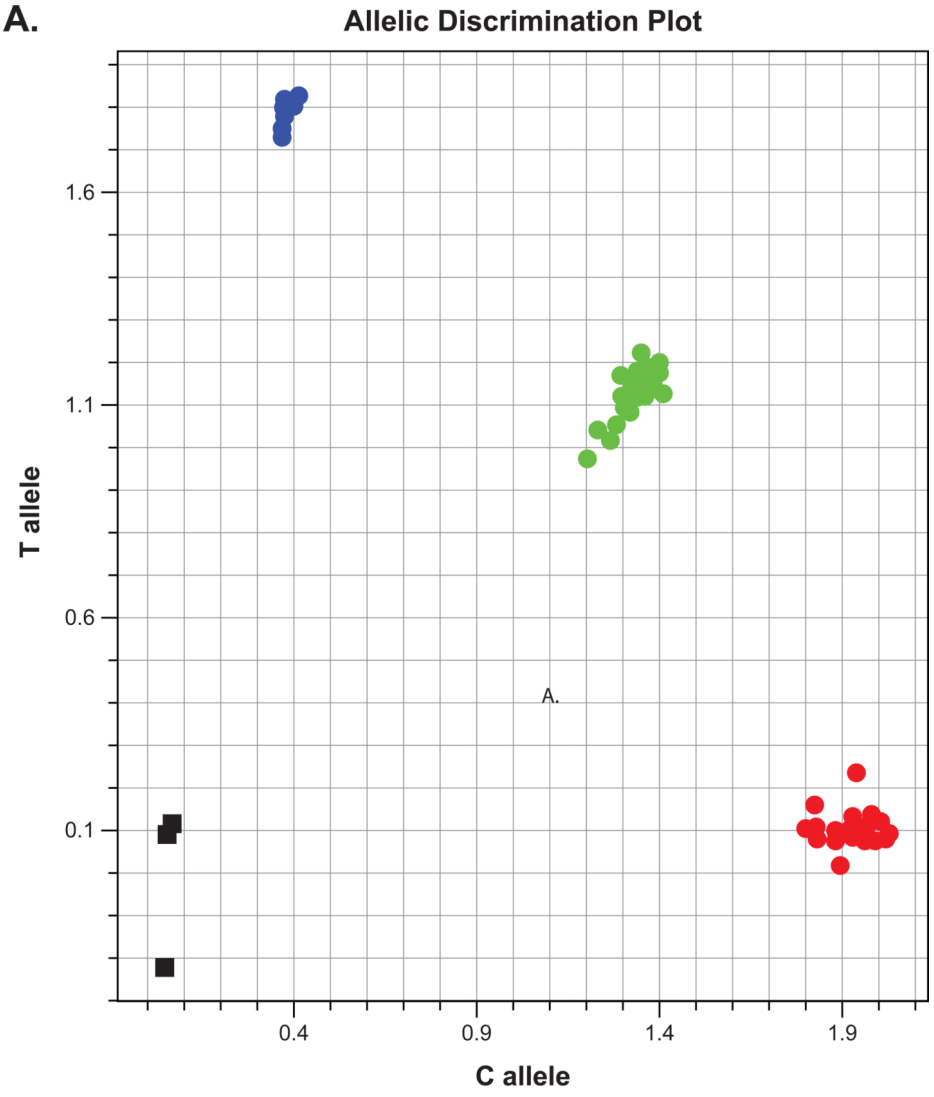
A.



B.

Duffy Genotype	Patients, n (n=33)	Total Patients Tested, %
C/C	19	57.6
C/T	11	33.3
T/T	3	9.1

Figure 1.

Assessment of Duffy null genotype status. (A) Allelic discrimination (cluster) plot for SNP (rs2814778) genotyping. Duffy expression is interrupted by a T to C substitution (at nucleotide −33) preventing transcription and resulting in the null phenotype. T to C polymorphism on both alleles indicates a homozygous C/C state (FY^{a-b-}), which results in the absence of Duffy antigen expression (Duffy null phenotype). Blue, T/T homozygote cluster; green, C/T heterozygote cluster; red, C/C homozygote cluster; black, no-template

control. (B) Table summarizing Duffy null status for 33 patients; 2 patients did not have Duffy null status reported. SNP=single nucleotide polymorphism.

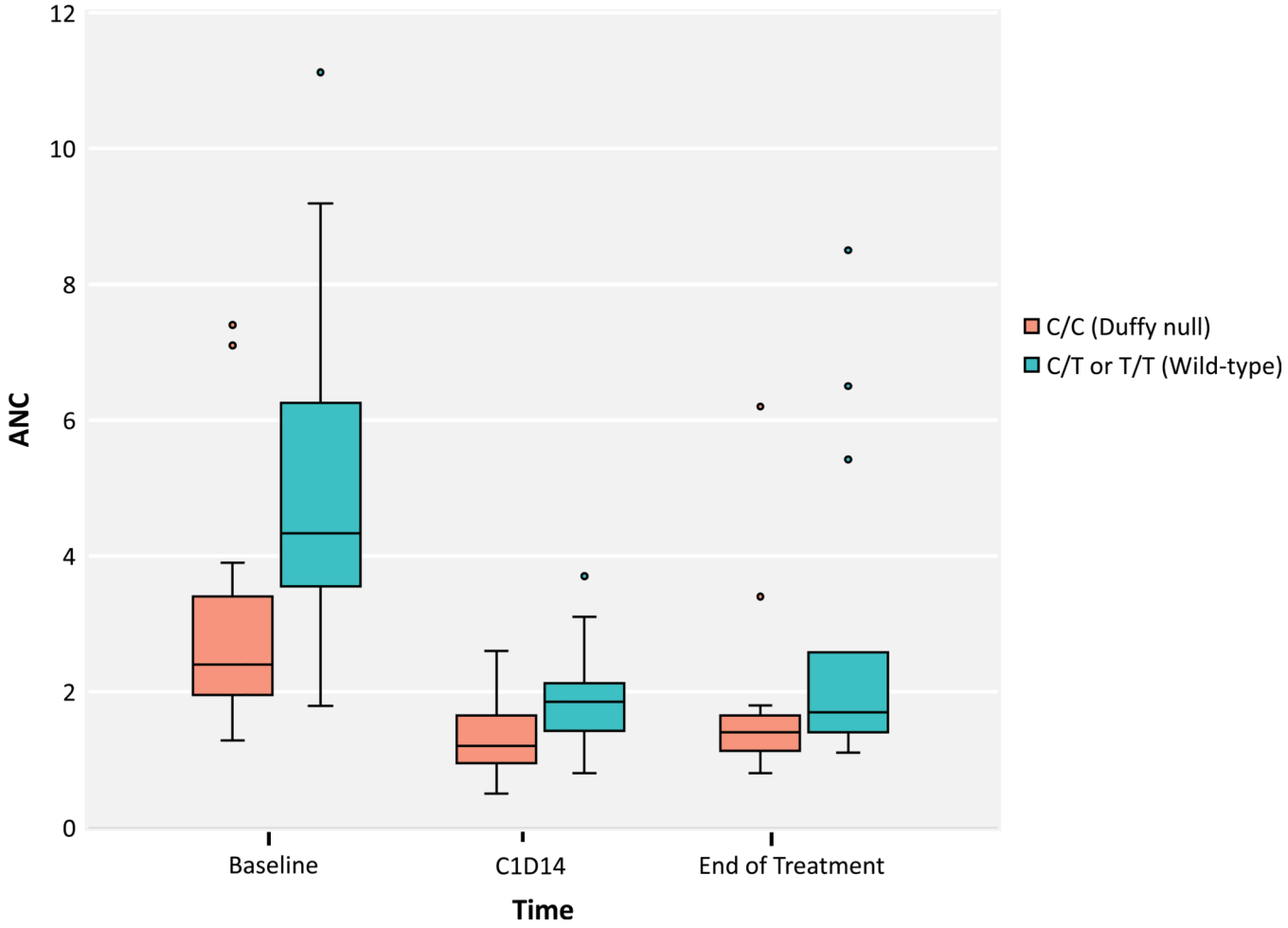


Figure 2.

ANC levels over time. Box-and-whisker plot of ANC levels in patients with ANC and Duffy null status data at baseline (total, n=31; Duffy null, n=18; wild-type, n=13), cycle 1 day 14 (Duffy null, n=18; wild-type; n=13), and end of treatment (Duffy null, n=17; wild-type, n=13). Horizontal lines represent the median value; boxes include the upper and lower quartiles. Vertical lines and dots indicate maxima and minima. ANC=absolute neutrophil count.

Table 1.

Baseline Demographic and Disease Characteristics

Characteristic	Total N=35	Duffy Null n=19*	Duffy WT n=14
Age, median (range), y	63.56 (30–90)	62.5 (30–90)	68 (44–82)
<65, n (%)	19 (54.3)	12 (63.2)	7 (50.0)
≥65, n (%)	16 (45.7)	6 (31.6)	7 (50.0)
ECOG PS, n (%)			
0	14 (40.0)	8 (42.1)	6 (42.9)
1	18 (51.4)	9 (47.4)	7 (50.0)
2	3 (8.6)	2 (10.5)	1 (7.1)
Disease site, n (%)			
Visceral	18 (51.4)	10 (52.6)	7 (50.0)
Nonvisceral	17 (48.6)	9 (47.4)	7 (50.0)
Number of metastatic sites, median (range)	1 (0–5)	1 (1–3)	1 (0–5)
Previous chemotherapy, n (%)†	14 (40.0)	9 (47.4)	4 (28.6)
Current hormonal therapy, n (%)			
Fulvestrant/tamoxifen	14 (40.0)	7 (36.8)	7 (50.0)
Aromatase inhibitors	21 (60.0)	12 (63.2)	7 (50.0)
Baseline ANC, median (range), $\times 10^9$/L	3.1 (1.3–11.1)	2.4 (1.3–7.4)	4.33 (1.8–11.1)

ANC=absolute neutrophil count; ECOG PS=Eastern Cooperative Oncology Group performance status; WT=wild-type.

*Two patients did not have Duffy polymorphism status reported.

†Chemotherapy in any setting (adjuvant or metastatic).

Table 2.

Neutropenia Incidence and Palbociclib Dose Modifications

Safety	Total n=33*	Duffy Null n=18**	Duffy WT n=13	*P* Value
Neutropenia, n (%)				
Grade 3	17 (51.5)	12 (66.7)	3 (23.1)	**0.029**
Grade 4	1 (3.0)	1 (5.6)	0 (0.0)	1
Febrile neutropenia, n (%)	0 (0)	0 (0)	0 (0)	
≥1 dose reduction due to neutropenia, n (%)	13 (39.4)	10 (55.6)	1 (7.7)	**0.008**
Mean (range) time to first dose reduction, d	75.3 (36–273)	82.6 (38–273)	63.0 (63)	
1 reduction, 100 mg, n (%)	5 (15.2)	3 (16.7)	1 (7.7)	0.63
2 reductions, 75 mg, n (%)	8 (24.2)	7 (38.9)	0 (0)	**0.025**
Permanent discontinuation, n (%)	0 (0)	0 (0)	0 (0)	
≥1 dose delay due to neutropenia, n (%)	17 (51.5)	12 (66.7)	3 (23.1)	**0.029**
Mean (range) time to first delay, d	40.9 (14–111)	46.3 (14–111)	28.0 (28)	
Mean (range) number of delays/patient	3.1 (1–9)	4 (2–9)	1.7 (1–2)	

WT=wild-type.

*Including all patients who completed ≥1 treatment cycle.

**Duffy polymorphism information was unavailable for 2 patients and 2 patients didn’t complete at least one cycle of palbociclib.

Table 3.

Palbociclib Treatment Exposure

Treatment Exposure	Duffy Null n=18*	Duffy WT n=13
Median (range) duration of treatment, wk	48.7 (10.42–52.0)	48.4 (17.0–52.0)
Median (range) overall relative dose, mg	90.7 (68.1–100.0)	100 (88.3–125.0)
Median (range) relative dose intensity, %	82.1 (49.49–100.0)	97.95 (80.0–100.0)
Patients continuing on commercial palbociclib after EOS, n (%)	9 (50.0)	9 (69.2)

EOS=end of study; RD=relative dose; RDI=relative dose intensity; WT=wild-type.

*31 patients had both Duffy polymorphism status and RD/RDI data and were included in the analysis.

Table 4.

Clinical Response

Response, n (%)	All n=33*	Duffy Null n=18	Duffy WT n=13
CR	1 (3.0)	1 (5.6)	0 (0)
PR	8 (24.2)	3 (16.7)	5 (38.5)
PD	10 (30.3)	6 (33.3)	2 (15.4)
SD	14 (42.4)	8 (44.4)	6 (46.2)
CBR	23 (69.7)	12 (66.7)	11 (84.6)

CBR=clinical benefit rate; CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; WT=wild-type

*Two patients did not have Duffy polymorphism status reported.