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EPIDEMIOLOGY

Racial disparities in neutrophil counts among patients with metastatic breast cancer during treatment with CDK4/6 inhibitors

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Abstract

Purpose The three CDK4/6 inhibitors (CDK4/6i) approved for use in HR-positive/HER2-negative metastatic breast cancer (MBC), palbociclib, ribociclib, and abemaciclib, are generally well tolerated; however, neutropenia is a common toxicity. Within the general population, neutropenia has been shown to be more common in individuals of African descent. The landmark CDK4/6i trials in MBC lacked racial diversity in their patient populations. We aimed to assess the toxicity profiles of CDK4/6is in a racially diverse population.

Methods We conducted a retrospective study at Montefiore Medical Center in patients with HR-positive/HER2-negative MBC prescribed CDK4/6i as first or subsequent line therapy between January 2015 and April 2020. Baseline characteristics and laboratory data at various treatment timepoints were collected.

Results The final analysis included 182 patients, of whom 46% were Black. Baseline absolute neutrophil count (ANC) was lower in the Black vs. Non-Black cohort ($p = 0.001$) but the change in ANC from baseline (delta-ANC) was smaller in the Black cohort, and the ANC at different treatment timepoints was similar between groups. There was no difference in the rate of infection or number of dose delays/reductions between racial groups. We did not find any difference in PFS between Black and Non-Black groups, regardless of the presence of CDK4/6i-induced neutropenia.

Conclusion We analyzed toxicity profiles of 182 patients with HR-positive/HER2-negative MBC treated with CDK4/6i. Despite the lower baseline ANC seen in our Black cohort, treatment toxicities were similar between racial groups. Long-term outcomes with CDK4/6i therapy, measured by PFS, were similar between Black vs. Non-Black patients.

Keywords Metastatic breast cancer · CDK4/6 inhibitor · Benign ethnic neutropenia · Estrogen-receptor positive breast cancer

Introduction

Cyclin-dependent kinases (CDKs) play an important role in cell cycle physiology. In vitro studies of CDK4/6 inhibitors (CDK4/6i) in human breast cancer cell lines showed hormone positive cell lines to be the most sensitive; moreover, there was synergy when combined with tamoxifen [1, 2]. This work led to the phase 2 PALOMA-1 trial, where the CDK4/6i palbociclib improved progression-free survival (PFS, 20.2 vs. 10.2 months) when added to antiestrogen therapy in patients with untreated hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer (MBC). As a result, the FDA-approved palbociclib in 2015 for use in combination with antiestrogen therapy as first line treatment in HR-positive, HER2-negative MBC [3]. The three currently available CDK4/6is, palbociclib, ribociclib, and abemaciclib, are all

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FDA-approved in combination with aromatase inhibitors and with the selective estrogen receptor degrader, fulvestrant.

CDK4/6is are well tolerated and adverse events are usually managed with dose modification and supportive care measures. Neutropenia, the dose-limiting toxicity for palbociclib and ribociclib, was the most common adverse event reported in landmark trials [3–12]. In PALOMA-2, 80% of patients in the palbociclib group developed neutropenia, with 66% of events being grade 3/4 [4]. Similar results were seen in the MONALEESA trials which studied the use of ribociclib, while the MONARCH trials generally reported lower rates of neutropenia with abemaciclib [6, 8–11]. CDK4/6i-induced neutropenia is rapidly reversible, reflecting a cytostatic effect on bone marrow precursors, and is not associated with an increased risk for infection. Abemaciclib commonly exhibits gastrointestinal toxicities, whereas neutropenia is less evident due to its stronger selectivity for CDK4 compared to CDK6 [13, 14]. CDK6 regulates cytokine expression in hematopoiesis [15], contributes to the "control" of myeloid progenitor expansion, and plays many important roles in myeloid differentiation [16]. Most data about CDK4 and CDK6 are derived from total knockout mouse models. Maurer et al. generated transgenic mice that lack either CDK4 or CDK6 in adult hematopoiesis. Deletion of CDK6 affected all stem cell fractions and led to neutropenia, while deletion of CDK4 resulted in elevated numbers of myeloid progenitors without translating into numeric changes of differentiated myeloid cells [17]. Neutrophils comprise most circulating leukocytes and serve a critical antimicrobial role [18]. Asymptomatic reductions in peripheral blood neutrophil counts are observed in up to 10–30% of individuals of African descent [19]. In the USA, Blacks have lower neutrophil counts than Whites (mean difference 0.83×10^9 cells/L) and higher rates of neutropenia (4.5% vs. 0.79%) [20, 21].

Most patients enrolled in the CDK4/6i landmark trials were White, and data on the toxicity and efficacy in Black patients are limited. The number of Black patients enrolled in the PALOMA-2, PALMOMA-3, MONALEESA-3, and MONALEESA-7 trials were 11 (3.2%), 29 (6%), 5 (1.4%), and 19 (6%), respectively [4, 5, 8, 9, 12]. Given this unmet need, we aimed (1) To assess the impact of CDK4/6i on neutrophil counts in Black and Non-Black patients, and (2) To compare the efficacy measured by PFS, of CDK 4/6i between Black and Non-Black patients with MBC.

Methods

Study design and data collection

We conducted a single-center retrospective study at Montefiore Medical Center. Using the institutional clinical software, "Clinical Looking Glass", we identified patients with HR-positive, HER2-negative MBC who were prescribed a CDK4/6i as first or subsequent line therapy between January 1st, 2015 and April 28th, 2020. We excluded patients with inaccessible medical records, patients whose race was not available, patients who were lost to follow up, patients who did not take the CDK4/6i, those treated at outside institutions, and those who took the CDK4/6i for less than 14 days. Baseline characteristics including age, race, ethnicity, prior treatment lines for metastatic disease, tumor grade, visceral involvement, and menopausal status were collected through chart review. The Standard Charlson Comorbidity Index was calculated for each patient. Medication compliance and adherence were carefully tracked through diligent review of clinical notes. Patients who were not adherent to CDK4/6is as documented in clinicians' notes were excluded from the study.

Race was defined as Black, White, Asian, or Other. Complete blood count data were collected at cycle 1, day 1 (C1D1); cycle 1, day 14 (C1D14); cycle 2, day 1 (C2D1); cycle 2, day 14 (C2D14); cycle 3, day 1 (C3D1); cycle 4, day 1 (C4D1); cycle 5, day 1 (C5D1); and cycle 6, day 1 (C6D1). All relevant oncology clinic and inpatient notes were reviewed and scrutinized for information regarding treatment response and adverse events to CDK4/6i.

Statistical analysis

Baseline characteristics were summarized using descriptive statistics. To assess associations between two categorical variables, we used the Pearson's Chi-square test or Fisher's exact test. The Wilcoxon rank sum test was used to compare neutrophil counts at each time point between Black vs. Non-Black patients. Change in neutrophil count over time was compared using the Wilcoxon signed rank sum test.

Toxicities were recorded and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The number of dose reductions/delays were also recorded. The Pearson's Chi-square test was used to compare adverse event rates between Black vs. Non-Black patients.

PFS was calculated as the time in days between the CKD4/6i initiation date and the date of disease progression or death. Data was censored at the date each patient was last seen at our institution. The Kaplan–Meier method was used to estimate PFS, and the log-rank test was used to compare PFS between groups. To assess the effect of neutropenia and dose reduction on PFS, a landmark analysis was conducted excluding patients who died or had disease progression within 28 days of CDK4/6i initiation. Multivariable Cox Proportional-Hazards model, adjusting for age, visceral disease, menopausal status, prior endocrine therapy (ET) lines, prior chemotherapy lines, and neutropenia, was used to compare the PFS between Black and Non-Black patients.

Statistical analysis was conducted using STATA version 14.0 and R statistical software. This study was approved by the Albert Einstein Institutional Board Review.

When accounting for missing data, we started by excluding patients who had missing data for race, since this was our main variable of interest. We conducted detailed chart review to obtain most values for collected variables. For the evaluation of ANC over time in Black vs. Non-Black patients, we encountered 10–15% missing data for some ANC values. It was deemed that values were missing completely at random and there was no indication that any missing data were systematic. Therefore, we removed records with missing data to conduct statistical analysis of ANC at certain time points. To assess disease progression, we obtained information from imaging and clinical notes; only 1 patient had missing data for PFS analysis.

Results

Baseline characteristics

A total of 233 patients were identified. Of those, 45 were excluded for the following reasons: 11 were treated at outside institutions, 4 were lost to follow up, 13 never took the prescribed CDK4/6i, 2 had HER2 + disease, 6 had inaccessible medical records, 8 were treated with CDK4/6i for less than 14 days, and 1 patient did not have stage IV disease. Of the 188 remaining evaluable patients, an additional 6 were excluded as there were no data available on their race (Fig. 1). Our final cohort included 182 patients with a median age of 64 years [interquartile range (IQR), 54–72]. There were 61 Hispanic (34%) and 121 non-Hispanic (66%) patients. Most patients (77%) were postmenopausal and 67% had visceral metastases. Palbociclib, ribociclib, and abemaciclib were prescribed in 153 (84%), 9 (5%) and 20 (11%) patients, respectively, and this was similar between racial groups. In most circumstances, CDK4/6is were prescribed at the FDA-approved starting dose. Letrozole, fulvestrant, and anastrozole were prescribed in 88 (48%), 68 (37%), and 19 (10%) patients, respectively. The most common reason for CDK4/6i discontinuation was progression of disease (94 patients, 82%). Neutropenia was responsible for drug discontinuation in only 2 patients (2%), (Table 1).

In our cohort, 83 patients (46%) were Black, 39 (21%), 10 (5%), and 50 (27%) patients were White, Asian, and Other race, respectively. For the purpose of comparison, we consolidated all the Non-Black patients into one group. Baseline characteristics were similar between Black and Non-Black: median age (64 vs. 63 years, $p = 0.47$), postmenopausal status (75% vs. 80%, $p = 0.67$), and visceral metastases (67% vs 67%, $p > 0.99$). CDK4/6is were used in the first line for metastatic disease in 48% of patients in both groups. The endocrine therapy backbones were also similar between Black and Non-Black ($p = 0.67$), (Table 1).

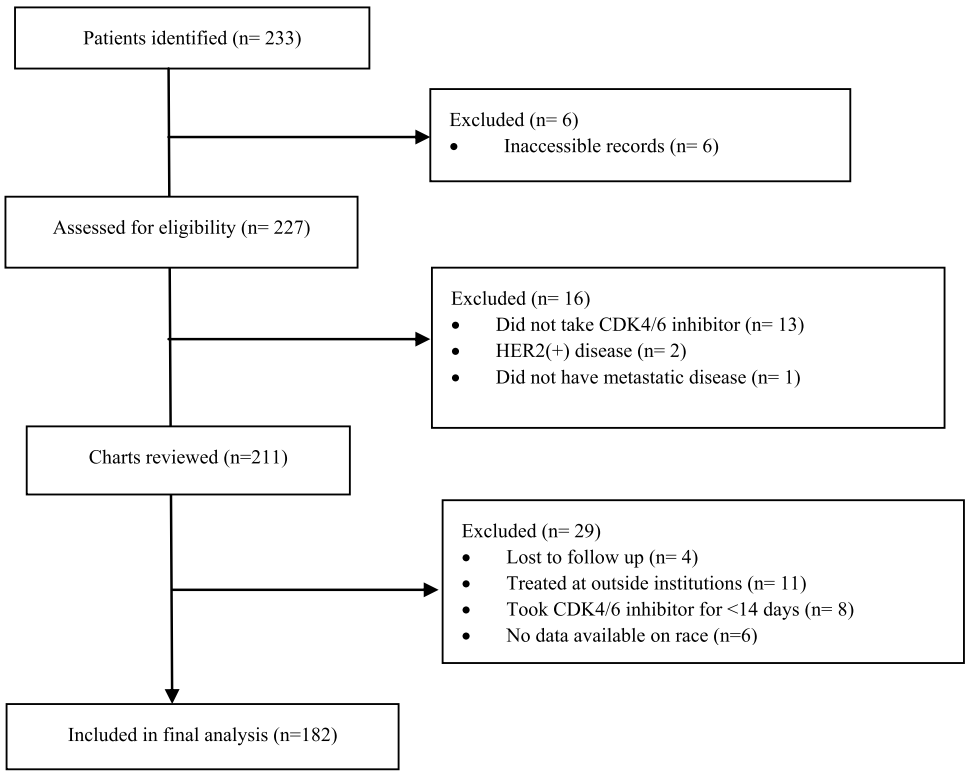

Fig. 1 Consort diagram: A total of 233 patients were initially identified and 51 patients were excluded, leaving 182 patients in the final analysis

Table 1 Baseline characteristics

	All Patients ($n=182$)	Black ($n=83$)	Non-Black ($n=99$)	P-value
Age, year, No. (%)				
Median	64	64	63	
IQR	54–72	55–73.5	53.5–72	0.47
Ethnicity, No. (%)				
Hispanic	61 (34%)	7 (8%)	54 (55%)	< 0.001
Non-Hispanic	121 (66%)	76 (92%)	45 (45%)	
Race, No. (%)				
Black	83 (46%)			
White	39 (21%)			
Asian	10 (5%)			
Other	50 (27%)			
Menopausal status, No. (%)				
Premenopausal	28 (15%)	14 (17%)	14 (14%)	
Perimenopausal	5 (3%)	3 (4%)	2 (2%)	0.67
Postmenopausal	141 (77%)	62 (75%)	79 (80%)	
Unknown	8 (4%)	4 (5%)	4 (4%)	
Charlson Comorbidity Index (CCI)				
Median	8.0	8.0	8.0	0.21
IQR	7.0–10.0	7.0–10.0	7.0–9.0	
Tumor grade, No. (%)				
Well differentiated	7 (4%)	2 (2%)	5 (5%)	
Moderately differentiated	50 (27%)	24 (29%)	26 (26%)	0.61
Poorly differentiated	55 (30%)	24 (29%)	31 (31%)	
Unknown	70 (38%)	33 (40%)	37 (37%)	
Sites of metastases, No. (%)				
Non Visceral	59(32%)	27(33%)	32(32%)	
Visceral	122(67%)	56(67%)	66(67%)	> 0.99
Unknown	1 (1%)	0 (0%)	1 (1%)	
Prior chemotherapy lines for metastatic disease, No. (%)				
0	143 (79%)	67 (81%)	76 (77%)	
1	24 (13%)	10 (12%)	14 (14%)	
2	7 (4%)	4 (5%)	3 (3%)	
3	3 (2%)	1 (1%)	2 (2%)	0.56
4	0 (0%)	0 (0%)	0 (0%)	
5	1 (1%)	0 (0%)	1 (1%)	
6	1 (1%)	0 (0%)	1 (1%)	
Unknown	3 (2%)	1 (1%)	2 (2%)	
Prior endocrine therapy lines for metastatic disease, No. (%)				
0	99 (54%)	45 (54%)	54 (55%)	
1	39 (21%)	18 (22%)	21 (21%)	
2	22 (12%)	13 (16%)	9 (9%)	
3	8 (4%)	2 (2%)	6 (6%)	
4	5 (3%)	1 (1%)	4 (4%)	0.96
5	3 (2%)	1 (1%)	2 (2%)	
6	2 (1%)	1 (1%)	1 (1%)	
7	1 (1%)	1 (1%)	0 (0%)	
Unknown	3 (2%)	1 (1%)	2 (2%)	
CDK4/6i in first line setting for metastatic disease, No. (%)				
No	91 (50%)	42 (51%)	49 (49%)	
Yes	88 (48%)	40 (48%)	48 (48%)	> 0.99

Table 1 (continued)

	All Patients ($n=182$)	Black ($n=83$)	Non-Black ($n=99$)	P-value
Unknown	3 (2%)	1 (1%)	2 (2%)	
Endocrine therapy backbone, No. (%)				
Letrozole	88 (48%)	43(52%)	45(45%)	
Anastrozole	19 (10%)	6(7%)	13(13%)	
Exemestane	5 (3%)	3(4%)	2(2%)	0.67
Fulvestrant	68 (37%)	30(36%)	38(38%)	
Tamoxifen	2 (1%)	1 (1%)	1 (1%)	
CDK 4/6i, No. (%)				
Palbociclib	153(84%)	70(84%)	83(84%)	
Abemaciclib	20(11%)	7 (8%)	13(13%)	0.28
Ribociclib	9 (5%)	6 (7%)	3 (3%)	
Reason for CDK4/6i discontinuation, No. (%)				
Progression of disease (POD)	94 (82%)	47 (82%)	47 (82%)	
Neutropenia	2 (2%)	1 (2%)	1 (2%)	
Infection	2 (2%)	1 (2%)	1 (2%)	> 0.99
Other	16 (14%)	8 (14%)	8 (14%)	
Cause of death, No. (%)				
Breast cancer	18 (10%)	11 (13%)	7 (7%)	
Other	4 (2%)	3 (4%)	1 (1%)	
Unknown	1 (1%)	1 (1%)	0 (0%)	0.65

Baseline characteristics in the total population and in Black vs. Non-Black cohorts

IQR Interquartile range, *CDK 4/6i* Cyclin Dependent Kinase 4/6 inhibitor, *No* Number

Neutrophil and white blood cell count at baseline and over time

The baseline (C1D1) median absolute neutrophil count (ANC) was lower in Black vs. Non-Black (3.0 vs. 4.0×10^9/L, $p=0.001$), with similar results at C3D1(1.40 vs. 1.75×10^9/L, $p=0.03$). However, there was no significant difference in median ANC between Black and Non-Black at C1D14 (1.15 vs. 1.30×10^9/L, $p=0.07$), C2D1 (1.2 vs. 1.3×10^9/L, $p=0.40$), and C2D14 (1.65 vs. 1.5×10^9/L, $p=0.38$) (Table 2). When the change in ANC from baseline was calculated (delta-ANC), Black patients showed a smaller decrease in median ANC over time compared to Non-Black patients. Delta-ANC at C2D1 was -1.5 vs. -2.6×10^9/L ($p=0.001$), for Black vs. Non-Black, respectively, and delta-ANC at C3D1 was -1.5 vs. -2.4×10^9/L ($p=0.007$) for Black vs. Non-Black, respectively (Table 2; Fig. 2). White blood cell count (WBC) showed a similar pattern. The baseline WBC (C1D1) was lower in Black vs. Non-Black (5.5 vs. 6.6×10^9/L, p = 0.001). Black patients also experienced a smaller decrease in WBC over time compared with Non-Black patients. Delta-WBC at C2D1 was -1.95 vs. -3.3×10^9/L ($p=0.003$) and delta-WBC at C3D1 was -1.9 vs. -2.9×10^9/L ($p=0.005$) for Black vs. Non-Black, respectively (Table 4; Figure 3 see appendix).

Neutropenia

Most patients (86%) experienced neutropenia, with grade 1, 2, 3, and 4 neutropenia reported in 10%, 24%, 43%, and 8% of patients, respectively (Table 5; see appendix). The rates of grade 1, 2, 3, and 4 neutropenia were 11%, 17%, 51%, 12% and 10%, 29%, 37%, 5%, in Black vs. Non-Black, respectively (Table 5; see appendix). There was a statistically significant difference in neutropenia rates between Black vs. Non-Black ($p=0.04$).

Infections

Infections were seen in 32 patients (18%), with no difference in the rate of infection between Black vs. Non-Black (13% vs. 21%, $p=0.22$) (Table 5; see appendix). Of note, 3 Black patients (4%) and 7 Non-Black patients (7%) experienced more than one infection. Among Black patients, there were a total of 14 infections [pneumonia ($n=4$), urinary tract infection ($n=2$), bacteremia ($n=2$), febrile neutropenia ($n=2$), and other ($n=4$)]. In Non-Black patients, there were a total of 28 infections [urinary tract infection ($n=6$), upper respiratory infection ($n=5$), pneumonia ($n=3$), osteomyelitis ($n=3$), skin infection ($n=6$), and other ($n=5$)]. Grade 3/4 infections were present in 10 Black patients and 11 Non-Black patients (Table 6; see appendix).

Table 2 Neutrophil count over time in black vs. non-black cohorts

All patients ($n=182$)	Black ($n=83$)	Non -Black ($n=99$)	P-value
ANC C1D1			
Median	3.0	4.0	0.001
IQR	2.4–4.6	3.15–5.1	
ANC C1D14			
Median	1.15	1.3	0.07
IQR	0.8–1.72	1.0–2.18	
ANC C2D1			
Median	1.2	1.3	0.40
IQR	0.9–1.72	0.9–1.9	
ANC C2D14			
Median	1.65	1.5	0.38
IQR	1.2–2.6	1.1–2.3	
ANC C3D1			
Median	1.4	1.75	0.03
IQR	1.0–2.0	1.2–2.6	
Δ ANC C1D14			
Median	−1.65	−2.45	0.03
IQR	−3.12 to -1.05	−3.4 to −1.62	
Δ ANC C2D1			
Median	−1.5	−2.6	0.001
IQR	−2.45 to −0.8	−3.3 to −1.6	
Δ ANC C2D14			
Median	−1.7	−2.25	0.15
IQR	−2.7 to −0.7	−3.02 to −1.28	
Δ ANC C3D1			
Median	−1.5	−2.4	0.007
IQR	−2.4 to −0.8	−3.18 to −1.23	

Absolute neutrophil count expressed in $\times 10^9$/L and change in neutrophil count from baseline (Δ ANC) at each treatment time point in Black vs. Non-Black cohorts during treatment with CDK 4/6i

ANC Absolute Neutrophil Count, *IQR* Interquartile range, *C1D14* Cycle 1 Day 14, *C2D1* Cycle 2 Day 1, *C2D14* Cycle 2 Day 14, *C3D1* Cycle 3 Day 1, *Δ ANC* change in ANC from baseline

Other toxicities

There were no differences in the rates of any thrombocytopenia (45% vs. 49%) or grade 3/4 thrombocytopenia (4% in each group), between racial groups ($p=0.42$; Table 5; see appendix). There was also no statistically significant difference in the rate of anemia for Black vs. Non-Black (48% vs. 56%, $p=0.25$). Grade 3 anemia was present in 11% vs. 5% in Black vs. Non-Black, (Table 5; see appendix). Commonly reported gastrointestinal toxicities were nausea, diarrhea, and decreased appetite. Grade 3 fatigue was seen in 2% of Black and 1% of Non-Black patients ($p=0.44$), and grade 3 diarrhea was seen in 1% of both cohorts ($p=0.19$) (Table 5 see appendix).

Dose reductions and delays

At least one dose reduction was required in 53 patients (29%) (Table 7; see appendix). Black patients required more dose reductions, but this difference was not statistically significant (34% vs. 25%, $p=0.27$). One dose reduction was required in 22 Black and 17 Non-Black patients, whereas more than one dose reduction was required in 6 Black and 8 Non-Black patients. Dose delay was required in 61 patients (34%); 29 patients required one dose delay, while 32 patients required more than 1 dose delay. There was no difference in the rate of dose delay between Black vs. Non-Black (36% vs. 31%, $p=0.59$). Both a dose reduction and delay were required in 26% of patients, with no difference between Black and Non-Black (33% vs. 21%, $p=0.11$). In our entire cohort, 36% of patients required either a dose reduction or dose delay, with similar rates in Black vs. Non-Black (37% vs. 35%, $p=0.90$) (Table 7; see appendix).

CDK4/6 inhibitor discontinuation

CDK4/6i was discontinued in 114 patients, and the most common reason was progression of disease ($n=94$). Among Black patients, the most common reasons for CDK 4/6i discontinuation were progression of disease ($n=47$), other ($n=8$), infection ($n=1$), and neutropenia ($n=1$). Among Non-Black patients, the most common reasons for discontinuation were progression of disease ($n=47$), other ($n=8$), infection ($n=1$), and neutropenia ($n=1$) (Table 1).

Progression-free survival

There was no difference in median PFS in Black vs. Non-Black (316 vs. 407 days, $p=0.51$) (Table 3, Figure 4; see appendix). Among patients who received CDK4/6i as first line treatment, the median PFS for Black vs. Non-Black was 390 and 518 days ($p=0.48$), respectively (Table 3, Figure 7; see appendix). We stratified breast cancer outcomes by neutropenia, to evaluate whether the drug's effects on the bone marrow could predict disease response. Among patients who developed neutropenia, the median PFS was 336 vs. 421 days ($p=0.45$) for Black and Non-Black, respectively (Table 3, Figure 5; see appendix). In patients who did not develop neutropenia, the median PFS was 141 vs. 259 days ($p=0.41$) for Black and Non-Black, respectively (Table 3, Figure 8; see appendix).

Next, we assessed the effect of dose reductions on breast cancer outcomes by racial groups. Among patients who required a dose reduction, the median PFS was 312 vs. 627 days ($p=0.26$) for Black vs. Non-Black (Table 3, Figure 6; see appendix). While in those without dose reduction, the median PFS was 346 vs. 377 days ($p=0.91$) for Black vs. Non-Black, respectively (Table 3, Figure 9; see appendix).

Table 3 Median PFS in Black vs. Non-Black Cohorts

	Number of patients analyzed	Black ($n=83$)	Non-Black ($n=99$)	*P*-value
PFS (days), [95% CI]	181	316 [205, 512]	407 [325, 598]	0.51
PFS (days), [95% CI] in the first line setting	88	390 [312, NR]	518 [401, NR]	0.48
PFS (days), [95% CI] in patients without neutropenia	23	141 [104, NR]	259 [122, NR]	0.41
PFS (days), [95% CI] in patients with neutropenia	150	336 [221, 687]	421 [325, 616]	0.45
PFS (days), [95% CI] in the first line and with neutropenia	73	390 [312, NR]	518 [401, NR]	0.45
PFS (days), [95% CI] without dose reduction	121	346 [205, 796]	377 [294, 518]	0.91
PFS (days), [95% CI] with dose reduction	52	312 [121, NR]	627 [294, NR]	0.26
PFS (days), [95% CI] with dose reduction in the first line setting	25	316 [223, NR]	627 [407, NR]	0.28

Median PFS in Black vs. Non-Black cohorts overall, in those with and without neutropenia, in those treated in the first line with CDK4/6i, and in those who required dose reductions

PFS Progression Free Survival, *CI* confidence interval, *NR* Not reached

In a univariate analysis, the use of prior endocrine therapy and prior chemotherapy for metastatic disease ($p=0.01$ for both) and presence of visceral disease ($p=0.04$) were statistically significantly associated with PFS. Black race ($p=0.51$), neutropenia ($p=0.09$), and age ($p=0.27$) were not associated with PFS (Table 8; see appendix). We then created a multivariable analysis using Cox Proportional-Hazards model including Black race, neutropenia, age, visceral status, prior endocrine therapy for metastatic disease, and prior chemotherapy for metastatic disease. In this model, the use of prior endocrine therapy for metastatic disease was inversely associated with PFS (HR 1.87, 95% CI 1.22–2.87, $p<0.01$), and the presence of visceral metastasis was inversely associated with PFS, with a trend towards statistical significance (HR 1.57, 95% CI 0.95–2.60, $p=0.08$) (Table 8; see appendix).

Discussion

Our study included 182 patients with HR-positive/HER2-negative MBC treated with CDK4/6i in a racially diverse cohort (Black = 83, Non-Black = 99). We report that Black patients have a lower baseline ANC (3.0 vs. 4.0×10^9/L, p = 0.001), and smaller decreases in ANC over time compared to Non-Black patients (delta-ANC at C2D1: − 1.5 vs. -2.6×10^9/L, $p=0.001$) while on CDK4/6is. A similar trend was observed for the total WBC count. Most patients

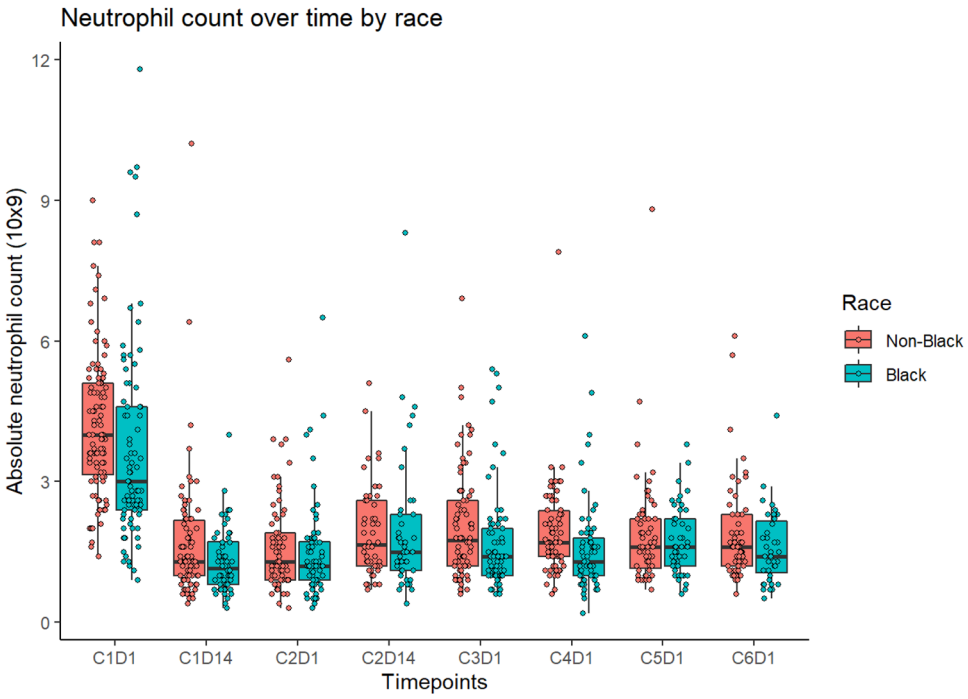

Fig. 2 Neutrophil count over time while on treatment with CDK4/6 inhibitors in Black vs. Non-Black patients. Abbreviations: C1D1: Cycle 1 Day 1; C1D14: Cycle 1 Day 14; C2D1: Cycle 2 Day 1; C2D14: Cycle 2 Day 14; C3D1: Cycle 3 Day 1; C4D1: Cycle 4 Day 1; C5D1: Cycle 5 Day 1; C6D1: Cycle 6 Day 1

did develop neutropenia while on treatment, and although there was a statistically significant difference in neutropenia rates between Black vs. Non-Black, there were no differences in the infection rates between racial groups. Further, the rates of dose reductions and delays were similar between groups. We found no difference in the median PFS between Black vs. Non-Black (316 vs. 407 days, $p=0.51$), and this was not affected by the presence or absence of neutropenia (Figure 4, Table 3; see appendix). Of note, the PFS results should be interpreted with caution, given the number of patients included in each analysis. Further, our multivariable analysis did not show an association between PFS and Black race or neutropenia. These data support the notion that the lower baseline ANC seen in Black patients does not negatively impact survival or toxicity outcomes during CDK4/6i treatment. Our results also suggest that baseline ANC alone may be a poor indicator of infection risk during CDK4/6i therapy.

Benign ethnic neutropenia (BEN), an entity where an ANC $< 1.5 \times 10^9$/L is seen in certain populations, is most common in people of African descent [22]. Although the etiology has not been elucidated, studies have identified a chromosome 1q22 polymorphism containing the Duffy antigen and receptor for chemokine (DARC) gene which strongly influences leukocyte counts in African Americans and is one potential mechanism [23]. BEN is not associated with an increased risk for infection or febrile neutropenia. Despite this, a proportion of patients with BEN may be inadvertently excluded from oncology clinical trials (which typically have an eligibility criteria of ANC $\geq 1.5 \times 10^9$/L for inclusion), or have unnecessary dose interruptions/reductions, due to their lower than normal baseline ANC [22, 24]. Our study is the first to evaluate racial disparities in toxicities and breast cancer outcomes for patients treated with CDK4/6i for MBC, and has the largest proportion of Black patients (46%; $N=83$) reported in the literature in this clinical scenario.

Prior studies have evaluated racial disparities in neutrophil counts in breast cancer patients receiving chemotherapy. Smith et al. found no racial differences in the frequency of febrile neutropenia in breast cancer patients receiving chemotherapy, despite a lower baseline ANC in Black patients [25]. A retrospective analysis by Hershman et al. found that Black patients had a lower baseline WBC prior to starting adjuvant chemotherapy but a similar mean percentage decline in WBC from baseline to treatment completion compared to White patients [26]. In another study analyzing differences in WBC counts and dose delays/discontinuations between Black and White breast cancer patients receiving adjuvant chemotherapy from two clinical trials, the rates of neutropenic fever were similar between racial groups despite a lower baseline WBC/ANC in Black patients [27]. These studies call into question the clinical relevance of a lower baseline WBC and ANC that may be seen in Black patients, and whether clinical trial inclusion criteria should more frequently be liberalized. Vastola et al. explored the ANC inclusion criteria of prostate cancer clinical trials and found that 41.4% of trials excluded patients with BEN, arguing that Black patients may be disproportionately excluded from cancer clinical trials due to benign racial laboratory variations [28]. Hsieh et al. argues that rigid eligibility criteria for WBC in cancer clinical trials may cause undue exclusion of Black patients from participation [22]. Our work provides additional evidence that clinical trial inclusion criteria for ANC should be reexamined, to provide equitable and evidence-based opportunities for participation.

Inclusion criteria for most CDK4/6i landmark trials required an ANC $\geq 1.5 \times 10^9$/L, which may have impacted the underrepresentation of Black patients in these studies [4, 7, 11, 12, 29]. The phase 2 single arm PALINA trial analyzed the hematologic safety of palbociclib in combination with letrozole or fulvestrant in self-reported African American, African, or Black women with HR-positive/HER2-negative MBC [29]. The ANC inclusion cutoff was 1.0×10^9/L. The median baseline ANC was 3.1×10^9/L, and 35 patients were enrolled. No patients experienced febrile neutropenia or required drug discontinuation due to neutropenia. Lower baseline ANC (2.4 vs 4.3×10^9/L, $p=0.006$), grade 3 neutropenia (66.7% vs. 23%, $p=0.029$), and dose reductions (55.6% vs. 7.7%, $p=0.008$) were more common in patients found to have the Duffy null polymorphism [29]. Interestingly, our study reports similar conclusions as the PALINA trial, that CDK4/6is may be safely administered in Black patients even if they have a lower baseline ANC.

Our study has certain limitations. Given its retrospective nature, information on medication compliance was limited to review of clinical notes. We encountered missing data points, which were subsequently excluded from statistical analysis and potentially limited the magnitude of the results. Despite careful attempts to reduce missing data, it is possible that systematic bias was introduced by inclusion of only those without missing data. There is also the possibility of selection bias, as perhaps only the compliant patients were included in this retrospective analysis. Our sample size is indeed smaller than those studied in landmark CDK4/6i clinical trials. However, although small, our study includes the highest proportion of Black patients for analysis of toxicities and PFS of CDK4/6i ever reported in the literature.

This is the first study to elucidate that despite lower baseline neutrophil counts seen in Black patients, there are no differences between racial groups in the frequency of infections, dose reductions, or dose delays seen with CDK4/6i use in MBC. Based on these results, the lower baseline neutrophil counts that may be seen in Black patients should not cause concern or hesitancy when initiating CDK4/6i, as they may not be clinically relevant.

Conclusion

In our cohort, Black patients had a lower baseline ANC compared to Non-Black patients, but they experienced less of a decline in ANC from baseline (delta-ANC) during treatment with CDK4/6i. Our results are the first to examine racial disparities in toxicities of patients receiving CDK4/6i. Our data suggest that CDK4/6is can be safely administered to patients who may have BEN, since their baseline ANC does not necessarily translate into increased rates of infections, dose reductions, or dose delays.

Appendix

See Tables 4, 5, 6, 7, 8
See Figs. 3, 4, 5, 6, 7, 8, 9

Table 4 White Blood Cell Count Over Time in Black vs. Non-Black Cohorts

All Patients	Black ($n=83$)	Non-Black ($n=99$)	P-value
WBC C1D1			
Median	5.5	6.6	0.001
IQR	4.25–7.1	5.1–8.1	
WBC C1D14			
Median	2.7	2.95	0.15
IQR	2.1–3.12	2.12–3.6	
WBC C2D1			
Median	3.1	3.25	0.40
IQR	2.18–4	2.6–4.1	
WBC C2D14			
Median	3.2	3.3	0.28
IQR	2.3–3.6	2.7–4.3	
WBC C3D1			
Median	3.4	3.7	0.12
IQR	2.7–4.3	2.92–4.75	
Δ WBC C1D14			
Median	− 2.3	− 3.55	0.01
IQR	− 3.95 to − 1.65	− 4.38 to − 2.2	
Δ WBC C2D1			
Median	− 1.95	− 3.3	0.003
IQR	− 3.52 to − 1.3	− 4.28 to − 2	
Δ WBC C2D14			
Median	− 2.6	− 3	0.11
IQR	− 3.6 to − 1.1	− 4.4 to − 2	
Δ WBC C3D1			
Median	− 1.9	− 2.9	0.005
IQR	− 3 to − 1.17	− 4.3 to − 1.45	

White blood cell count (WBC) expressed in $\times 10^9$/L and the change in WBC (ΔWBC) from baseline in the Black vs. Non-Black cohorts during treatment with CDK4/6 inhibitors. Abbreviations: WBC: White Blood Cell Count; IQR: Interquartile range; C1D14: Cycle 1 Day 14; C2D1: Cycle 2 Day 1; C2D14: Cycle 2 Day 14; Δ WBC: change in WBC from baseline

Table 5 All Toxicities in Black vs. Non-Black Cohorts

	All patients ($n=182$)	Black ($n=83$)	Non-Black ($n=99$)	P-value
Any Adverse Event	182 (100%)	83 (100%)	99 (100%)	0.23
Neutropenia, No. (%)				
Any grade	156 (86%)	75(90%)	81 (82%)	
Grade 1	19 (10%)	9 (11%)	10 (10%)	
Grade 2	43 (24%)	14 (17%)	29 (29%)	
Grade 3	79 (43%)	42 (51%)	37 (37%)	
Grade 4	15 (8%)	10 (12%)	5 (5%)	0.04
Fatigue, No. (%)				
Any grade	44 (24%)	17 (20%)	27 (27%)	0.44
Grade 1	36 (20%)	14 (17%)	22 (22%)	
Grade 2	5 (3%)	1 (1%)	4 (4%)	
Grade 3	3 (2%)	2 (2%)	1 (1%)	
Anemia, No. (%)				
Any grade	95 (52%)	40 (48%)	55 (56%)	0.25
Grade 1	60 (33%)	23 (28%)	37 (37%)	
Grade 2	21 (12%)	8 (10%)	13 (13%)	
Grade 3	14 (8%)	9 (11%)	5 (5%)	
Thrombocytopenia, No. (%)				
Any grade	86 (47%)	37 (45%)	49 (49%)	0.42
Grade 1	73 (40%)	32 (39%)	41 (41%)	
Grade 2	5 (3%)	1 (1%)	4 (4%)	
Grade 3	6 (3%)	2 (2%)	4 (4%)	
Grade 4	2 (1%)	2 (2%)	0 (0%)	
Nausea, No. (%)				
Any grade	22 (12%)	7 (8%)	15 (15%)	0.18
Grade 1	22 (12%)	7 (8%)	15 (15%)	
Diarrhea, No. (%)				
Any grade	19 (10%)	5 (6%)	14 (14%)	0.19
Grade 1	14 (8%)	4 (5%)	10 (10%)	
Grade 2	3 (2%)	0 (0%)	3 (3%)	
Grade 3	2 (1%)	1 (1%)	1 (1%)	
Rash, No. (%)				
Any grade	10 (5%)	6 (7%)	4 (4%)	0.51
Grade 1	10 (5%)	6 (7%)	4 (4%)	
Infections[a], No. (%)				
Number of infections	32 (18%)	11 (13%)	21 (21%)	0.22
Decreased Appetite, No. (%)				
Any grade	25 (14%)	13 (16%)	12 (12%)	0.75
Grade 1	23 (13%)	12 (14%)	11 (11%)	
Grade 2	2 (1%)	1 (1%)	1 (1%)	
Headache, No. (%)				
Any grade	10 (5%)	2 (2%)	8 (8%)	0.11
Grade 1	10 (5%)	2 (2%)	8 (8%)	
Arthralgias, No. (%)				
Any grade	13 (7%)	5 (6%)	8 (8%)	0.77
Grade 1	13 (7%)	5 (6%)	8 (8%)	
Hot flush, No. (%)				
Any grade	11 (6%)	6 (7%)	5 (5%)	0.55
Grade 1	11 (6%)	6 (7%)	5 (5%)	

All toxicities and their grade experienced in the total population and in the Black vs. Non- Black cohorts. Abbreviations: No: Number

[a]Represents the number of patients in each group who became infected while on treatment. There were 32 patients in the total population, 11 Black patients (13%) and 21 Non-Black patients (21%) who experienced infections. Of note, there were 3 Black patients and 7 Non-Black patients who experienced more than one infection; this data is shown in Table 6

Table 6 Total number of infections by grade in black vs. non-black cohorts

Race	Infection	Grade
Non-Black	Acute bronchitis	2
Non-Black	Acute diverticulitis	3
Non-Black	Acute diverticulitis	3
Non-Black	Skin infection	2
Non-Black	Skin infection	3
Non-Black	Skin infection	2
Non-Black	Colitis	3
Non-Black	Skin infection	2
Non-Black	Skin infection	2
Non-Black	Skin infection	1
Non-Black	Gingivitis/gum abscess	3
Non-Black	Osteomyelitis	3
Non-Black	Osteomyelitis	3
Non-Black	Osteomyelitis	3
Non-Black	Pneumonia	1
Non-Black	Pneumonia	4
Non-Black	Pneumonia	2
Non-Black	URI	2
Non-Black	URI	2
Non-Black	URI	2
Non-Black	URI	2
Non-Black	URI	1
Non-Black	UTI	2
Non-Black	UTI	2
Non-Black	UTI	3
Non-Black	UTI	3
Non-Black	UTI	2
Non-Black	UTI	2
Black	Bacteremia	3
Black	Bacteremia	3
Black	Skin infection	3
Black	Colitis	2
Black	Febrile neutropenia	3
Black	Febrile neutropenia	4
Black	Pneumonia	2
Black	Pneumonia	4
Black	Pneumonia	4
Black	Pneumonia	3
Black	Unclear	3
Black	URI	2
Black	UTI	2
Black	UTI	3

List of infections presented during the time the patients were treated with a CDK4/6i by grade, in the Black and Non-Black cohorts. Of note, there were 3 Black patients (3.6%) and 7 Non-Black patients (7%) who experienced more than one infection

URI Upper Respiratory Infection non specified, *UTI* Urinary Tract Infection

Table 7 Patients who required either dose reductions or dose delays

	All patients ($n=182$)	Black ($n=83$)	Non-Black ($n=99$)	*P*-value
Dose reductions, No. (%)				
Any dose reduction	53 (29%)	28 (34%)	25 (25%)	0.27
1 Dose reduction	39 (21%)	22 (27%)	17 (17%)	
2 Dose reductions	11 (6%)	5 (6%)	6 (6%)	
3 Dose reductions	3 (2%)	1 (1%)	2 (2%)	
Dose delays, No. (%)				
Any dose delay	61 (34%)	30 (36%)	31 (31%)	
1 Dose delay	29 (16%)	13 (16%)	16 (16%)	
2 Dose delays	12(7%)	6 (7%)	6 (6%)	
3 Dose delays	10 (6%)	5 (6%)	5 (5%)	
4 Dose delays	5 (3%)	3 (4%)	2 (2%)	
5 Dose delays	1 (1%)	1 (1%)	0 (0%)	0.59
> 5 Dose delays	4 (2%)	2 (2%)	2 (2%)	
Dose reduction and delay, No. (%)	48 (26%)	27 (33%)	21 (21%)	0.11
Any dose modification; reduction or delay, No. (%)	66 (36%)	31 (37%)	35 (35%)	0.90

Patients who required dose reductions or dose delays in the total population and in Black vs. Non-Black cohorts

No. Number

Table 8 Univariate and Multivariable Analysis of PFS by Cox Regression Model

Characteristic	Reference	Univariate			Multivariable[a]		
		HR	95% CI	*P* values	HR	95% CI	*P*-value
Age ≥ 60	Age < 60	0.99	(0.97–1.00)	0.27	0.75	(0.48–1.16)	0.20
Black Race	Non-Black	1.14	(0.74–1.54)	0.51	1.17	(0.77–1.77)	0.46
Visceral involvement	None	1.62	(1.15–2.09)	0.04	1.57	(0.95–2.6)	0.08
Any neutropenia	No neutropenia	0.59	(−0.02–1.19)	0.09	0.70	(0.35–1.4)	0.31
Prior ET for MBC	No prior ET for MBC	1.79	(1.38–2.2)	0.01	1.87	(1.22–2.87)	< 0.01
Prior chemo for MBC	No prior chemo for MBC	1.85	(1.36–2.34)	0.01	1.55	(0.93- 2.56)	0.09

Univariate and multivariable analysis of PFS using Cox Proportional Hazard Model, to assess the effects of age, race, visceral involvement, the development of neutropenia, and whether patients received prior endocrine therapy or prior chemotherapy for metastatic disease, on PFS

HR Hazards Ratio, *CI* Confidence Interval, *ET* endocrine therapy

[a]In our multivariable model, most patients had complete data values. For PFS there was 1 missing value, for prior endocrine therapy lines there were 2 missing values, for prior chemotherapy lines there were 2 missing values, and for visceral disease there were 2 missing values. Some patients had more than 1 missing variable. Our final multivariable model included 177 patients with complete data for variables in the model

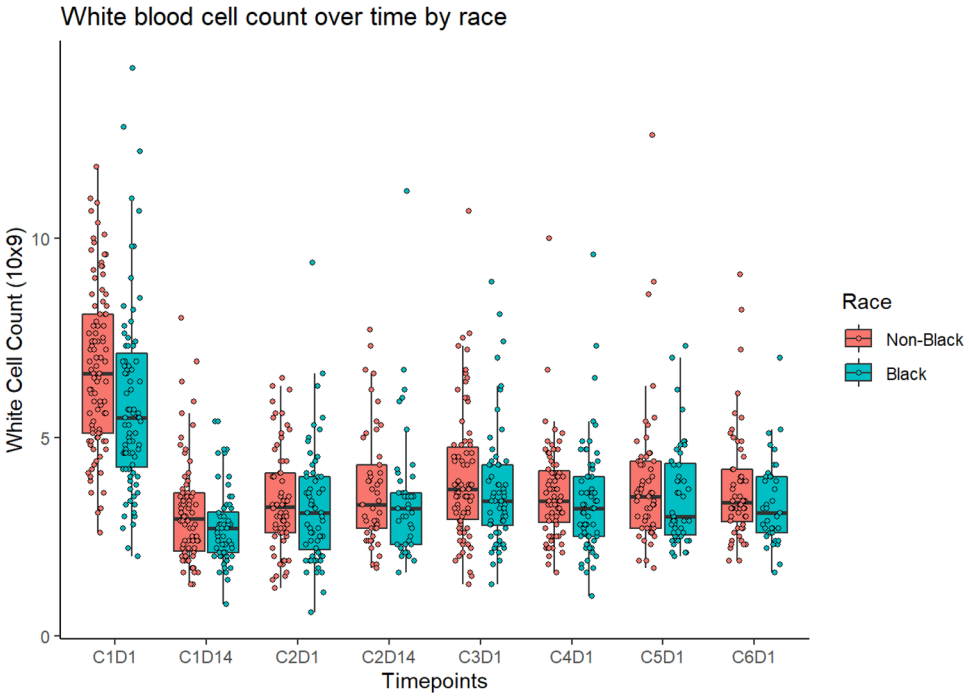

Fig. 3 White blood cell count over time while on treatment with CDK4/6 inhibitors in Black vs. Non-Black patients. Abbreviations: C1D1: Cycle 1 Day 1; C1D14: Cycle 1 Day 14; C2D1: Cycle 2 Day 1; C2D14: Cycle 2 Day 14; C3D1: Cycle 3 Day 1; C4D1: Cycle 4 Day 1; C5D1: Cycle 5 Day 1; C6D1: Cycle 6 Day 1

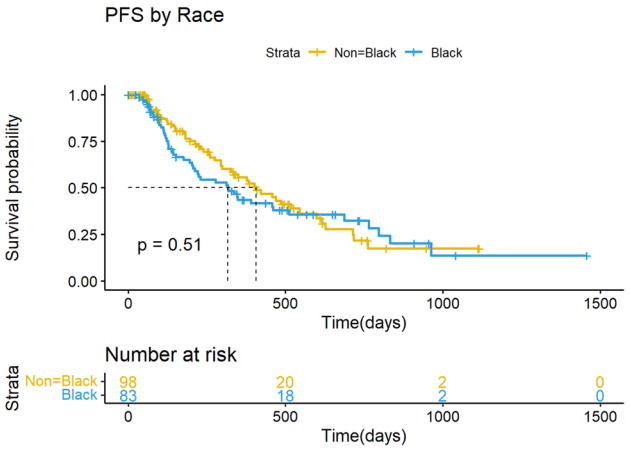

Fig. 4 PFS compared between Black vs. Non-Black cohorts expressed in days**.** The yellow line represents the Non- Black cohort and the blue line represents the Black cohort. Abbreviations: PFS: Progression Free Survival

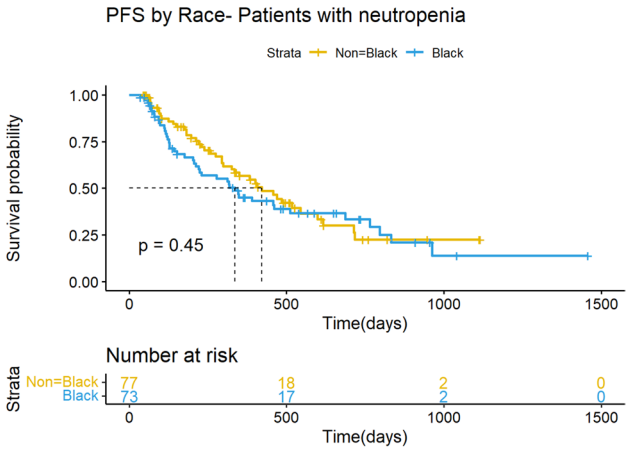

Fig. 5 PFS expressed in days in patients who experienced neutropenia while on CDK4/6 inhibitor treatment, compared between the Black vs Non-Black cohorts. The yellow line represents the Non-Black cohort and the blue line represents the Black cohort. *PFS* Progression Free Survival

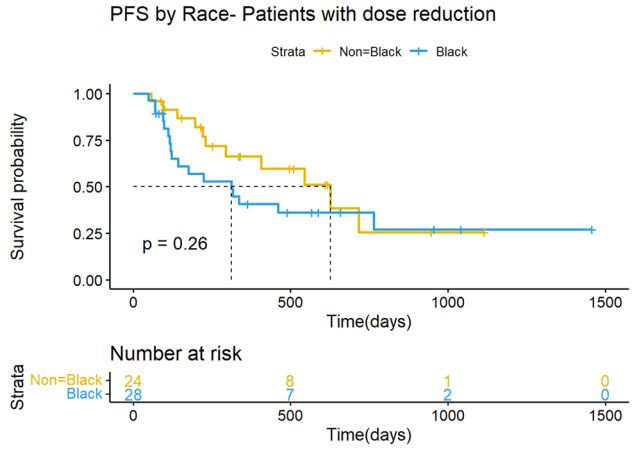

Fig. 6 PFS expressed in days in patients who required a dose reduction while on treatment with CDK4/6 inhibitors, compared between the Black vs Non-Black cohorts. The yellow line represents the Non-Black cohort and the blue line represents the Black cohort *PFS* Progression Free Survival

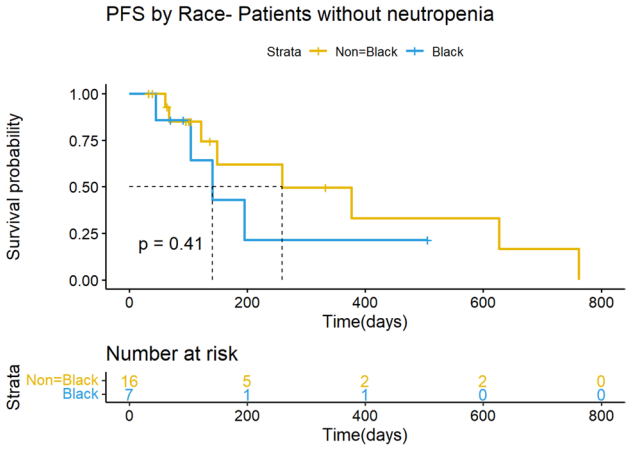

Fig. 8 PFS expressed in days in patients who did not experience neutropenia while on treatment with CDK4/6 inhibitors, compared in the Black vs. Non-Black cohorts. The yellow line represents the Non-Black cohort and the blue line represents the Black cohort. *PFS* Progression Free Survival

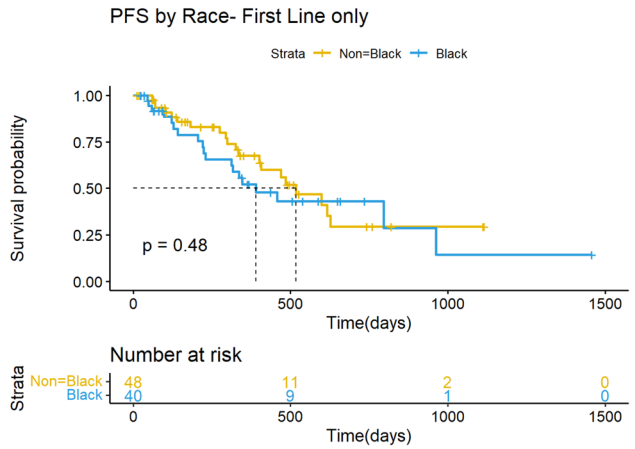

Fig. 7 PFS expressed in days in patients on first line treatment with CDK4/6 inhibitors, compared between the Black vs. Non-Black cohorts. The yellow line represents the Non-Black cohort and the blue line represents the Black cohort. *PFS* Progression Free Survival

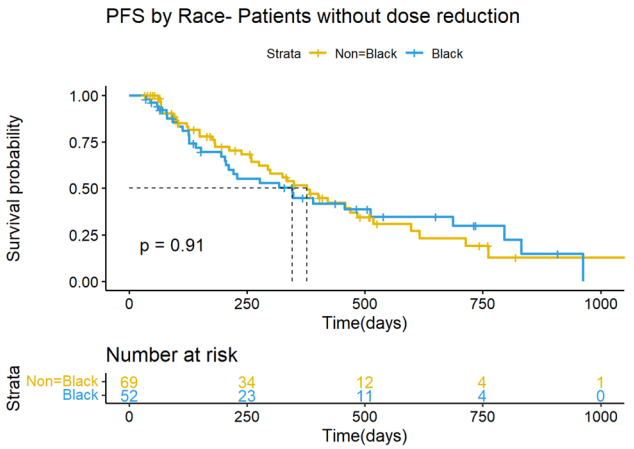

Fig. 9 PFS expressed in days in patients who did not require a dose reduction while on treatment with CDK4/6 inhibitors, compared in the Black vs. Non-Black cohorts. The yellow line represents the Non-Black cohort and the blue line represents the Black cohort. *PFS* Progression Free Survival

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest All authors declare that they have no relevant financial or non-financial interests to disclose.

Ethical approval This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Montefiore Medical Center/Einstein College of Medicine approved this study.

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