

Palbociclib in Combination With Fulvestrant in Women With Hormone Receptor–Positive/HER2-Negative Advanced Metastatic Breast Cancer: Detailed Safety Analysis From a Multicenter, Randomized, Placebo-Controlled, Phase 3 Study (PALOMA-3)

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ABSTRACT

Background: Palbociclib enhances endocrine therapy and improves clinical outcomes in hormone receptor (HR)–positive/human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer (MBC). As a new target, it is clinically important to understand palbociclib’s safety profile to effectively manage toxicity and optimize clinical benefit.

Materials and Methods: Patients with endocrine-resistant, HR-positive/HER2-negative MBC ($n=521$) were randomly assigned 2:1 to receive fulvestrant (500 mg intramuscular injection) ± goserelin with either oral palbociclib (125 mg daily; 3 weeks on/1 week off) or placebo. Safety assessments at baseline and day 1 of each cycle included blood counts on day 15 for the first 2 cycles. Hematologic toxicity was assessed using laboratory data.

Results: Patients ($N=517$: palbociclib, $n=345$; placebo, $n=172$) were treated; median follow-up was 8.9 months. With palbociclib, neutropenia was the most common grade 3 (55%) and 4 (10%) AE; median time to onset and duration of grade ≥ 3 episodes was 16 and 7 days, respectively. Asian race and below median neutrophil counts at baseline were significantly associated with an increased chance of developing grade 3–4 neutropenia with palbociclib. Dose modifications for grade 3–4 neutropenia had no adverse affect on progression-free survival. In the palbociclib arm, febrile neutropenia occurred in 3 (<1%) patients. The percentage of grade 1–2 infections was higher compared with the placebo arm. Grade 1 stomatitis occurred in 8% of patients.

Conclusion: Palbociclib plus fulvestrant treatment was well tolerated and the primary toxicity of asymptomatic neutropenia was effectively managed by dose modification without apparent loss of efficacy.

Implications for Practice: Treatment with palbociclib in combination with fulvestrant was generally safe and well tolerated in patients with hormone receptor (HR)–positive metastatic breast cancer. Consistent with its proposed mechanism of action, palbociclib-related neutropenia differs in its clinical time course, patterns, and consequences from that seen with chemotherapy. Neutropenia can be effectively managed by a dose reduction, interruption, or cycle delay without compromising efficacy. A significant efficacy gain and a favorable safety profile support the consideration of palbociclib into the routine management of HR-positive/human epidermal growth factor receptor 2–negative metastatic breast cancer.

INTRODUCTION

Endocrine therapy is the preferred first-line treatment option for hormone receptor (HR)–positive and human epidermal growth factor receptor 2 (HER2)–negative metastatic breast cancer (MBC) [1].

However, the fundamental clinical challenge associated with this treatment option is the development of resistance to endocrine therapy [2]. The mechanisms of resistance have yet to be fully elucidated [2].

Among women with disease progression following prior endocrine therapy, treatment options include sequential endocrine-based therapies, as monotherapy or in combination with a targeted therapy (eg, everolimus for some postmenopausal women), before switching to chemotherapy [1]. Clinical research has focused on enhancing and improving outcomes of endocrine-based therapy to augment disease control, delay the use of chemotherapy, and optimize the length and quality of life [1].

Palbociclib is a first-in-class potent oral inhibitor of cyclin-dependent kinases (CDK) 4/6 and a novel therapeutic option for the treatment of HR-positive/HER2-negative MBC [3]. In the endocrine-resistant setting, the recent global PALOMA-3 trial demonstrated the improved efficacy of palbociclib in combination with fulvestrant over fulvestrant plus placebo in pre-, peri- and postmenopausal women whose disease had progressed on prior endocrine therapy (median progression-free survival [PFS], 9.5 vs 4.6 months; hazard ratio, 0.46 (95% CI, 0.36–0.59); $p = .0001$) [4]. The current data therefore suggest that palbociclib enhances endocrine therapy and improves clinical outcomes in both treatment-naive and endocrine-resistant patients with HR-positive/HER2-negative MBC [3,5].

Because palbociclib is incorporated into treatment paradigms for patients with HR-positive MBC, it is clinically important to understand its safety profile, both to effectively manage toxicity and to balance risk and benefit. With these goals in mind, a comprehensive safety analysis of patients enrolled in the PALOMA-3 study was undertaken, with particular emphasis given to neutropenia as the most frequently reported adverse event (AE) associated with palbociclib treatment.

MATERIALS and METHODS

Patients

Eligible patients had breast cancer and histologic or cytologic confirmation of recurrent local or distant disease progression during or within 12 months of completion of adjuvant endocrine therapy or while receiving or within 1 month after receiving endocrine therapy for MBC. Premenopausal and postmenopausal patients who had an Eastern Cooperative Oncology Group (ECOG) performance status 0–1 and measurable disease as defined by the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1 [6]) or bone-only disease with a lytic lesion were eligible. One prior line of chemotherapy in the advanced setting was allowed, but there was no limit on the number of prior lines of endocrine therapy in the MBC setting. Eligibility criteria and study design details are documented elsewhere [5]. The protocol was approved by an institutional review board/independent ethics committee, and the study was conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent before the start of any study procedures.

Study Design

The PALOMA-3 study (NCT01942135), a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial, was designed to assess the superiority of palbociclib in combination with fulvestrant compared with placebo plus fulvestrant in prolonging PFS in women with HR-positive/HER2-negative MBC and disease progression after prior endocrine therapy. The primary endpoint is PFS and the secondary endpoints include a comparison of safety between treatment arms [5].

Treatment

Patients were randomized (2:1) to receive palbociclib (125 mg per day, orally, 3 weeks on and 1 week off) plus fulvestrant (500 mg per month, intramuscularly, on days 1 and 15 of the first 28-day cycle and day 1 of subsequent cycles, ± goserelin per menopausal status; palbociclib arm) or placebo plus fulvestrant (placebo arm). If patients experienced a hematologic toxicity, such as grade 3–4 neutropenia, a specific dose modification schema consisting of dose interruption, dose delay, or dose reduction was

followed (**Fig. 1**). Dose modification for fulvestrant was not allowed. Primary prophylactic use of granulocyte-colony stimulating factors (G-CSFs) was not permitted [5]. If neutropenic complications were observed in a cycle in which primary prophylaxis with G-CSFs was not received, secondary prophylaxis was given at the discretion of the investigator, but only if dose modification was not considered a reasonable alternative.

Safety Assessment

Adverse events were assessed based on type, incidence, severity, timing, seriousness, and relatedness to study treatment. Severity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 [7]. Laboratory safety assessments were performed at baseline and on day 1 of each cycle and included blood counts on day 15 for the first 2 cycles and at end of treatment/withdrawal. Additional blood tests were permitted at the investigator's discretion as clinically indicated for the purpose of planning treatment, dose modification, or following AEs.

Analysis

Descriptive analysis was used to summarize the maximum grade AEs on treatment, using the Medical Dictionary for Regulatory Activities version 18.0 (MedDRA) terms. For hematologic toxicities, descriptive analyses of laboratory data were also performed when possible, because not all hematologic events may have been reported. The risk difference between the 2 treatment arms for hematologic events and nonhematologic events of interest was calculated, and the respective 95% CIs were also provided without adjustment for multiplicity. The AE incidence was based on the maximum toxicity grade during the treatment, as reported by investigators. Because many patients can have multiple episodes of an adverse hematologic event, and to further delineate the patterns of neutropenia, some of the analysis was per episode using the laboratory data in aggregate whereas the risk difference for hematologic events in both arms was considered using the proportion of patients with hematologic events in both arms. Exploratory analyses of PFS were conducted for different subgroups among the patients who received

palbociclib plus fulvestrant. The Kaplan-Meier (KM) method was used to estimate the median PFS and the 2-sided log-rank test was performed for the PFS comparisons. Hazard ratios and 2-sided 95% confidence intervals were estimated using Cox proportional hazards model. The KM method was also used to estimate the cumulative probability (ie, cumulative incidence function) of neutropenia and fatigue, separately.

The relationship between baseline characteristics and grade 3–4 neutropenia was examined individually among patients in the palbociclib arm. Univariate analysis was used to assess the individual associations of these risk factors, which are presented as odds ratios with 95% CIs. A multivariate logistic model was run to evaluate the relationship between grade 3 and/or 4 neutropenia versus infection status, treatment, and key baseline factors (simultaneously considered in the model).

RESULTS

Patient Population

Between October 7, 2013, and August 26, 2014, 521 patients were enrolled [5]. Two randomized patients per arm did not receive study treatment. The safety populations (as-treated) comprised 345 patients for the palbociclib arm and 172 patients for the placebo arm (**Fig. S1**). The safety data presented are from the March 16, 2015, cutoff with a median follow-up of 8.9 (interquartile range, 8.7–9.2) months for the intent-to-treat population. More than half (67%) of all patients had ≥ 2 disease sites, 35% of patients had ≥ 2 lines of prior therapy in the MBC setting, and 34% of patients had undergone 1 line of prior chemotherapy in MBC setting.

Overall Safety Profile

For all cycles, the reported incidence of any grade and grade 3–4 AEs was 99% and 73%, respectively, in the palbociclib arm and 90% and 22% in the placebo arm. The risk difference for toxicities was higher for hematologic than for nonhematologic toxicities during the study (**Fig. 2A**). A significant difference

(>10%) in the incidence of the following treatment-emergent AEs of any cause (all grade) was reported in the palbociclib arm compared with the placebo arm: neutropenia, leukopenia, anemia, thrombocytopenia, stomatitis, alopecia, rash (all $p < .005$), infection, and fatigue (both $p < .02$). AEs of interest are shown in **Fig. 2B**. Most reported infections were upper respiratory tract infections of likely viral etiology. Fatigue in the palbociclib arm was commonly experienced (all grade, 39%), with 13% and 2% of patients experiencing grade 2 and 3 fatigue, respectively. The cumulative incidence of fatigue over time in the palbociclib arm is shown in **Fig. S2**. Among patients who had stomatitis or alopecia in the palbociclib arm, the severity was predominantly grade 1. Discontinuations due to AEs were similarly low in the palbociclib (4%) and the placebo (2%) arms (**Fig. S1**). In the palbociclib arm, treatment was discontinued for 1 patient each because of the following AEs: grade 4 neutropenia, grade 2 anemia, and grade 2 and 3 thrombocytopenia. Four (1.2%) patients in the palbociclib arm and 3 (1.7%) patients in the placebo arm had grade 5 events (mainly related to disease progression) and after the data cutoff, one case of neutropenic sepsis and multiorgan failure in the context of disease progression was reported.

The incidence of all-causality serious AEs (SAEs) was 44 (12.8%) of 345 patients in the palbociclib arm and 30 (17.4%) of 172 patients in the placebo arm. The most frequently reported type of SAE in the palbociclib arm was infections (2.0% vs 4.1% in the placebo arm), defined as any event that is part of the corresponding MedDRA System Organ Class. Besides infections, no other SAE occurring on study up to 28 days after the last dose of study drug reached an incidence of 2.0% in both arms: in the palbociclib arm, neutropenia and pyrexia were reported in 4 patients each and pulmonary embolism and pleural effusion were reported in 3 patients each; in the placebo arm, pleural effusion and ascites were reported in 3 patients each. Results for SAEs occurring in >1 patient are shown in the supplement (**Table S1**).

Thromboembolic events occurred in 2% of patients in the palbociclib arm (4 cases reported as SAEs and 2 cases as AEs) and in no patients in the placebo arm. These events were not considered related to study drug by the investigator; however, the causal role of palbociclib cannot be completely excluded.

Clinical Patterns of Neutropenia, Anemia, and Thrombocytopenia

In the palbociclib arm, grade 3 and 4 hematologic toxicities occurred for neutropenia (55.3% and 9.7%, respectively), leukopenia (41.5% and 1.2%), anemia (2.9% and 0%), and thrombocytopenia (2.1% and 0.9%) per laboratory data. Among the patients who had grade 3–4 neutropenia, only 3.2% had concurrent grade 3–4 anemia and 3.2% had concurrent grade 3–4 thrombocytopenia (**Fig. S3**).

Median time from the first dose of palbociclib plus fulvestrant to the first appearance of a neutropenia episode of any grade was 15 (range, 13–140) days, and the onset of the first episode of grade ≥ 3 neutropenia was 16 (range, 13–293) days (**Fig. 3A**). The median time from the first dose to the lowest absolute neutrophil count (ANC) on study was 29 (range, 13–334) days. The median time from the first dose to the first occurrence of grade ≥ 3 anemia or thrombocytopenia was 39.5 and 26.5 days, respectively. The median duration of grade ≥ 3 episodes of neutropenia, anemia, and thrombocytopenia was 7.0 days for each event, with ranges of 1–98, 1–141, and 1–27 days, respectively (**Fig. 3B**).

Among the 144 patients with a maximum of grade ≤ 2 (ie, grade 0, 1, and 2) neutropenia in the first 2 cycles, 25 (17.4%) experienced grade 3 neutropenia beyond cycle 2, whereas 13 (9.8%) of 132 patients with a maximum of grade ≤ 2 neutropenia in the first 4 cycles experienced grade 3 neutropenia beyond cycle 4, and only 8 (6.3%) of 127 patients with a maximum of grade ≤ 2 neutropenia in the first 6 cycles experienced grade 3 neutropenia beyond cycle 6. None of the 132 or 127 patients in the palbociclib arm who experienced maximum grade ≤ 2 neutropenia within the first 4 or 6 cycles, respectively, developed grade 4 neutropenia in subsequent cycles.

Univariate analysis revealed that Asian ethnicity and a below median value for ANC at baseline were patient characteristics that conferred a significantly increased risk for developing grade 3–4 neutropenia in the palbociclib arm. The percentage of Asian patients that developed grade 3–4 neutropenia was higher than for non-Asians (92% vs 57%; data not shown). Prior chemotherapy, age, ECOG performance status, and number of disease sites did not significantly increase the risk for developing grade 3–4 neutropenia (**Table 1**).

Clinical Outcomes of Neutropenia Associated With Palbociclib Treatment

Although grade 3–4 neutropenia occurred in 221 (65%) of 340 patients in the palbociclib arm, febrile neutropenia was reported in only 3 (0.9%) of 345 patients in the palbociclib arm and 2 (0.6%) of 172 patients in the placebo arm. During study treatment, 39 (11%) patients in the palbociclib arm received G-CSF based on the investigator's judgment.

There was a higher incidence of all-grade infections in the palbociclib arm (42%) than in the placebo arm (30%); however, infections were mainly grade 1–2 in severity; **Fig. 2B**. The frequency of grade 3–4 events was similar between treatment arms (2% and 3%, respectively). Fewer than 2% of patients in the palbociclib arm had concurrent grade 3–4 neutropenia and grade 3–4 infections. The multivariate analysis performed to assess the association between grade 3–4 neutropenia and infection showed that infection status was not significantly related to the presence of grade 3–4 neutropenia ($p = .17$; **Table S2**) when treatment arm and important baseline characteristics were simultaneously considered in the analysis. Asian ethnicity and a lower median ANC at baseline were also found to be significantly associated with grade 3–4 neutropenia in multivariate analysis, which is consistent with the results from the univariate analysis.

Assessment of Dose Modification Strategy and Effect on Efficacy

The overall mean relative dose intensity was 86% for palbociclib plus fulvestrant and 100% for placebo plus fulvestrant (**Fig. S4**). For the palbociclib arm, 28% of patients had 1 dose reduction (from 125 to 100 mg or from 125 mg directly to 75 mg) and 6% of patients had 2 dose reductions (**Fig. 4**). The median time to the first dose reduction was 57.0 days (125 to 100 mg) and 36.0 days (125 to 75 mg and 125 mg directly to 75 mg [$n = 8$]), whereas for the second dose reduction the median time was 33.5 days (125 to 100 mg for patients who had a dosing schedule change as a first dose reduction) and 119.5 days (100 to 75 mg). Of the 117 (34%) patients in the palbociclib arm who received at least 1 dose reduction, 108 (31%) were treated at the 100-mg dose level and 31 (9%) were treated at the 75-mg dose level. The

median duration of a dose interruption or dose delay in the palbociclib arm was 6.0 or 2.5 days, respectively. Among palbociclib-treated patients who had at least 1 dose reduction because of an AE versus those patients who had no dose reduction because of an AE, there was no effect on PFS (10.2 vs 9.5 months, respectively; HR=0.74 [95% CI, 0.52–1.05]); 2-sided log-rank test, $p = .09$; **Fig. S5**)

Dose modification appeared to be effective at reducing the risk of subsequent grade 3–4 neutropenia. Among the 21 (6%) patients who had a dose reduction owing to grade 4 neutropenia in cycles 1 and 2, only 1 patient developed subsequent grade 4 neutropenia. Among the patients (215 [62%] of 345) who developed grade 3–4 neutropenia in cycles 1 through 6, 56 (26%) had grade 3 neutropenia and 2 (0.9%) had grade 4 neutropenia subsequent to cycle 6. Although the number of repeated grade 3 events was reduced by half, it remained high because there was no mandated dose reduction for repeated grade 3 neutropenia. A dose reduction due to uncomplicated grade 3 neutropenia was implemented if recovery to grade 2 neutropenia was protracted, or at the discretion of the investigator if uncomplicated grade 3 neutropenia recurred in 2 consecutive cycles (**Fig. 1**). The KM plot estimates show that the cumulative incidence of grade 3–4 neutropenia after receiving palbociclib plus fulvestrant increased early, predominantly in the first month, and subsequently plateaued (**Fig. 5A**). For patients who had mild to moderate neutropenia (grade ≤ 2) within the first 4 cycles of treatment, the risk of grade 3–4 neutropenia was not substantially increased thereafter; it marginally increased over time up to 9 to 10 months, at which time it plateaued (**Fig. 5B**).

Neutropenia and dose modifications due to neutropenia did not have a detrimental effect on efficacy among patients who had been treated with palbociclib plus fulvestrant for more than 3 cycles. There was no difference in PFS among patients who had grade ≥ 3 neutropenia versus grade ≤ 2 neutropenia (median PFS of 11.1 vs 11.0 months, respectively; HR=0.98 [95% CI, 0.64–1.51]; 2-sided log-rank test, $p = .93$; **Fig. 6A**). PFS was not different among patients in the palbociclib arm who had at least 1 dose reduction because of neutropenia versus patients who had no dose reductions because of neutropenia (median PFS of 9.5 months each; HR=0.87 [95% CI, 0.61–1.25]; 2-sided log-rank test, $p = .45$; **Fig. 6B**). Among

palbociclib-treated patients who had a dose reduction, dose interruption, or cycle delay owing to neutropenia versus those who did not, there was no effect on PFS (median PFS of 9.5 vs 9.4 months; HR=0.85 [95% CI, 0.61–1.18]; 2-sided log-rank test, $p = .33$; **Fig. 6C**).

DISCUSSION

The results of this global, randomized, placebo-controlled, phase 3 study in which palbociclib was combined with fulvestrant to treat patients whose HR-positive HER2-negative breast cancer had progressed on prior endocrine therapy confirmed the generally favorable safety profile that was also observed when palbociclib was combined with letrozole as first-line treatment for HR-positive/HER2-negative MBC in a phase 2 study [3]. The AE incidence was similarly low for nonhematologic events across both treatment arms, and these AEs were mostly mild to moderate in severity. Although low grade stomatitis (aphthous type ulcers which can bother patients) occurred more often in the palbociclib arm than the placebo arm, it can be effectively managed using steroid dental paste. The rate of thromboembolic events in the palbociclib and placebo arms was 2% and 0%, respectively. The 0.9% rate of pulmonary embolism in the palbociclib arm was consistent with recent data reported for pulmonary emboli in a similar patient population [8]. The overall SAE incidence was also low across both treatment arms. The hematologic AEs identified in the PALOMA-3 study were considered manageable and reversible and were not commonly associated with complications. The treatment discontinuation rate due to AEs was low (4%). This discontinuation rate is much lower than for other treatment options in this setting (ie, for inhibitors of the PI3K/mTOR pathways) that reached 19% in the BOLERO-2 trial[9] and 13% in the Belle-2 study[10]). The improved efficacy, coupled with the favorable safety profile of palbociclib plus fulvestrant, was also reflected in patient reported outcome data, which demonstrate patients were able to maintain quality of life during treatment whereas patients treated with placebo plus fulvestrant experienced a deterioration of their quality of life [11].

Although the most commonly observed grade 3–4 AE, neutropenia, occurred in more than 50% of patients, there was a low rate of associated febrile neutropenia. This observation confirms prior reports showing that the consequences of myelosuppression experienced during palbociclib treatment are different from those associated with chemotherapy-induced myeloablation [12], which is characterized by a more acute onset of neutropenia (observed clinically within 3 to 5 days) [13], and a prolonged suppression of all cell lines. This comprehensive safety analysis confirms that clinical time course, severity, and pattern of neutropenia are specific to the mechanism of action of palbociclib and do not appear to pose a significant safety risk for patients. In contrast to chemotherapy-induced neutropenia, the median time from first dose of palbociclib plus fulvestrant to first occurrence of grade ≥ 3 neutropenia, anemia, and thrombocytopenia was 16.0, 39.5, and 26.5 days, respectively. The median time from the first dose to the lowest ANC count was 29 days in the palbociclib arm. Reports in the literature show ANC nadirs postchemotherapy can range from 7 to 14 days[14]. Most importantly, the neutropenia associated with palbociclib treatment was effectively managed within days by dose delay, interruption, or reduction, without primary use of G-CSF, suggesting that mature white blood cells are present in the bone marrow, and can rapidly demarginate when drug levels fall.

The clinical patterns of hematologic toxicities associated with palbociclib treatment are the mechanistic result of selective inhibition of CDK 4/6, which has been described in numerous other detailed reports of in vitro and preclinical in vivo experiments [12,15-17]. This mechanism of action is characterized by a blockage of the G1/S cell cycle transition to induce G1 arrest. Recent published data showed that palbociclib-induced bone marrow suppression follows cell cycle arrest in hematopoietic precursor cells, resulting in quiescence without apoptosis [12,15,16], whereas treatment with chemotherapy caused DNA damage and apoptotic cell death in human bone marrow mononuclear cells at clinically relevant concentrations [12,15,16]. Moreover, the short-term production of well-differentiated or mature peripheral blood effector cells (ie, mature neutrophils) was relatively resistant to CDK 4/6 inhibition. Myelosuppressive effects of CDK 4/6 inhibition were rapidly reversible in vivo. The destruction of

progenitor cells with subsequent development of neutropenia [18] is a major dose-limiting toxicity of chemotherapy [19]. Not only can it delay neutrophil recovery for several weeks, but it often leads to suboptimal treatment because of reduced dose intensity [20]. In contrast, the median duration of grade ≥ 3 hematologic episodes in the current study was 7 days, suggesting that patients were generally able to resume treatment after 1 additional week off palbociclib treatment, and, as such, maintain the relative mean dose intensity. Chemotherapy-induced neutropenia is a well-known cause of complications, such as febrile neutropenia and infections, which may be life threatening [20,21]. In the PALOMA-3 study, febrile neutropenia occurred in 3 (0.9%) patients who received palbociclib plus fulvestrant treatment, a rate that was not markedly different from that observed in the PALOMA-1 study [3]. This confirms that febrile neutropenia is not commonly associated with palbociclib, likely owing to the shorter duration and lesser severity of neutropenia compared with chemotherapy [3].

Preclinical data shows the cell cycle arrest caused by palbociclib plus fulvestrant is transient and reversible in hematopoietic cells [12]. However, cell cycle arrest was shown to minimally recover in the presence of fulvestrant alone during a palbociclib-free phase in breast cancer cells (MCF-7) [12]. The mechanistic difference between the effect of palbociclib on bone marrow versus MCF-7 breast cancer cells supports the current clinical dosing schedule and dose modification strategy by introducing short palbociclib-free periods to enable neutrophil recovery without affecting efficacy. This could also partially explain our finding that PFS was not affected by dose modification among patients who experienced grade ≥ 3 neutropenia compared with those who experienced grade ≤ 2 neutropenia.

The data presented in this manuscript have important implications for clinical practice. There was no decrease in efficacy despite dose reductions, suggesting that patients maintained drug levels that were therapeutic during the study. Although many patients can be more susceptible to the myelosuppressive effects of palbociclib, our data suggest that the susceptibility to develop higher grade neutropenia during treatment can generally be recognized within the first several months of treatment and appropriately tailored dose modifications can be implemented to reduce the likelihood of recurrent episodes of severe

neutropenia and/or febrile neutropenia. Therefore, it is important to closely monitor ANC early during treatment with palbociclib so that dose adjustments can be made promptly in patients experiencing grade 4 or prolonged and recurrent grade 3 neutropenia. This is particularly important for patients of Asian ethnicity and patients with a low baseline ANC. In PALOMA-3, patients had a complete blood count on day 15 for the first 2 cycles, and it is reasonable to consider this approach in clinical practice.

The study showed that the incidence of all-grade infections was greater in the palbociclib arm than the placebo arm. Although the rate of grade ≥ 3 infections was similar between the palbociclib and placebo arms (2.0% and 2.9%, respectively), it is advisable to alert patients of the potential increased risk of infection.

As with any targeted therapy, adherence to the recommended dose is critical to ensure treatment efficacy as well as safety in individual patients. Patients should be made aware of the palbociclib schedule, (3 weeks on/1 week off). With close monitoring of the complete blood count, particularly early on during treatment, dosing can be optimized and ongoing treatment can be administered while minimizing the risk of clinically significant AEs.

CONCLUSION

Palbociclib has now been shown to be clinically effective in combination with 2 different endocrine agents in previously untreated and treated patients with HR-positive/HER2-negative MBC. A thorough understanding of the safety profile of this agent is a high priority consideration as clinicians incorporate this class of drug into their routine clinical practice. Treatment with palbociclib in combination with fulvestrant in the PALOMA-3 study was generally safe and well tolerated, with neutropenia representing the most common AE associated with its use. Clinical trial experience to date indicates a consistent and therefore predictable safety profile for palbociclib, with neutropenia being predominantly uncomplicated, and with a low associated risk of febrile neutropenia. Palbociclib-induced neutropenia is reversible and can be readily managed by dose delay, dose interruption, or dose modification without affecting efficacy.

The data presented here may also be informative for guiding ongoing trials including adjuvant and neo-adjuvant treatment settings.

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Figure Legends

Figure 1. Palbociclib/placebo dose modification schema for managing treatment-related toxicities. ^aIf patients still have not returned to grade 2 on day 1 of next cycle. ^bReduce by 2 dose levels. ^cIf uncomplicated grade 3 neutropenia recurs in 2 consecutive cycles, after recovery as per retreatment criteria ($ANC \geq 1000/mm^3$ and no fever), treatment may restart at the next lower dose level at investigator's discretion. ^dIf no further dose reduction is possible (ie, patient is already receiving 75 mg/d according to schedule 3/1), consider changing the schedule to 75 mg per day, 2 weeks on/2 weeks off, or discontinue palbociclib/placebo and continue with fulvestrant alone.

Abbreviation: ANC, absolute neutrophil count.

Figure 2. (A) Risk difference for AEs (hematologic lab and nonhematologic – all cycles, as treated) and (B) additional information on AEs of note. Percentages were calculated with respect to the total number of evaluable patients in a group (n), for which the denominators varied for laboratory measures.

Hematology and chemistry laboratory results were graded according to the CTCAE severity grade. P values and CIs have not been adjusted for multiplicity. Palbociclib plus fulvestrant arm ($n = 345$); placebo plus fulvestrant arm ($n = 172$). ^aInfections includes any reported PTs that are part of the System Organ Class infections and infestations. ^bRash includes the following PTs: rash, rash maculo-papular, rash pruritic, rash erythematous, rash papular, dermatitis, dermatitis acneiform. ^cPulmonary embolism includes the following PTs: pulmonary embolism, pulmonary artery thrombosis.

Abbreviations: AE, adverse events; CTCAE, Common Terminology Criteria for Adverse Events version 4.0; Gr, grade(s); PT, preferred term.

Figure 3. (A) Time to onset of hematologic toxicity in the palbociclib plus fulvestrant arm only and (B) duration of each episode by grade analysis based on laboratory data. Includes patients with postbaseline CTCAEs grade >0 and greater than baseline CTCAE grade. Percentages are based on number of episodes

in each subgroup. For multiple time to recovery periods within a patient, an average was calculated prior to summarizing among patients.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events.

Figure 4. Exposure to palbociclib plus fulvestrant, time to onset for first and second dose reductions, time to dose interruption, and time to dose delay. ^aDue to adverse event.

Figure 5. Kaplan-Meier curves showing cumulative incidence of grade 3–4 neutropenia.^{a,b} (A) Patients treated with palbociclib plus fulvestrant. (B) Patients treated with palbociclib plus fulvestrant who had grade ≤ 2 neutropenia within the first 4 cycles and grade 3–4 neutropenia after cycle 4.

^aNeutropenia includes the following preferred terms: neutropenia, neutrophil count decreased. ^bThe Kaplan-Meier estimator was used to estimate the cumulative incidence in the plot.

Abbreviation: Gr, Grade.

Figure 6. Kaplan-Meier curves of progression-free survival in patients treated with palbociclib plus fulvestrant. (A) Patients treated for more than 3 cycles who had maximum grade ≥ 3 ($n = 186$) vs maximum grade ≤ 2 neutropenia^a ($n = 93$), per investigator assessment. (B) Patients who had at least 1 dose reduction because of neutropenia ($n = 100$)^a versus no dose reduction ($n = 245$). (C) Patients who had a dose reduction, dose interruption or cycle delay due to neutropenia ($n = 218$)^a versus the remaining patients ($n = 127$). ^aNeutropenia was any event having a preferred term equal to neutropenia or neutrophil decreased.

Abbreviations: HR, hazard ratio; Gr, grade; max, maximum; NE, not estimable; PFS, progression-free survival.

TABLES

Table 1. Risk of developing grade 3 or 4 neutropenia by clinical characteristics (odds ratio): as-treated

Patient characteristics	Palbociclib + fulvestrant (N = 345)		Odds ratio	p value
	Grade 3–4 neutropenia ^a			
	With, n (%) (n = 223)	Without, n (%) (n = 122)		
Received prior chemotherapy, mo				
<12	50 (22.4)	24 (19.7)		
≥12	113 (50.7)	63 (51.6)	1.162	.61
Immediately prior chemotherapy				
Yes	24 (10.8)	7 (5.7)		
No	199 (89.2)	115 (94.3)	1.981	.12
Age, y				
<50	64 (28.7)	28 (23.0)		
50–70	128 (57.4)	75 (61.5)	1.339	.28
≥70	31 (13.9)	19 (15.6)	1.401	.36
ECOG performance status				
0	133 (59.6)	71 (58.2)		
1	90 (40.4)	51 (41.8)	1.062	.79
Number of disease sites				
1	70 (31.4)	41 (33.6)		
2	62 (27.8)	33 (27.0)	0.909	.74
≥3	91 (40.8)	48 (39.3)	0.901	.69
Ethnicity				
Asian	67 (30.0)	6 (4.9)		
Non-Asian	156 (70.0)	116 (95.1)	8.303	<.0001
Bone metastasis				
Yes	175 (78.5)	89 (73.0)		
No	48 (21.5)	33 (27.0)	1.352	.25
Baseline ANC ^b				
≥ median value	86 (38.6)	94 (77.0)		
< median value	135 (60.5)	27 (22.1)	0.183	<.0001

^aNeutropenia included the following preferred terms: neutropenia, neutrophil count decreased.

^bANC median value in palbociclib + fulvestrant treatment arm was 3.6.

Abbreviations: ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group.

Supplemental Figures and Tables for:

Palbociclib in Combination With Fulvestrant in Women With Hormone Receptor–Positive/HER2-Negative Advanced Metastatic Breast Cancer: Detailed Safety Analysis From a Multicenter, Randomized, Placebo-Controlled, Phase 3 Study (PALOMA-3)

Sunil Verma et al.

Figure S1. CONSORT diagram for the PALOMA-3 trial.

(a) For reasons other than an adverse event.

Figure S2. Kaplan-Meier failure plot of the cumulative incidence of all grades of fatigue for patients treated with palbociclib plus fulvestrant.

Figure S3. Concurrent grade 3–4 hematologic events. Based on laboratory data. Neutropenia included laboratory tests of neutrophils (absolute/percentage). A neutropenia event was defined when the CTCAE grade for postbaseline tests of neutrophils (absolute) is >0 and >baseline CTCAE grade. Overlap percentages are based on the subgroup of patients in the palbociclib plus fulvestrant arm with grade 3–4 neutropenia, $n = 221$. Neutropenia included the following preferred terms: neutropenia, neutrophil count decreased.

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events version 4.0.

Figure S4. Mean relative dose intensities for treatment arms by cycle number. Dose intensity was defined as the actual dose intensity divided by the intended dose intensity multiplied by 100%.

Figure S5. Kaplan-Meier plot of patients in the palbociclib plus fulvestrant arm who had at least 1 dose reduction because of adverse events ($n = 114$) vs no dose reduction ($n = 231$).

Abbreviation: NE, not estimable.

Study | Cycle Delay Allowance

PALOMA-3

3 weeks on

1 week off

2 weeks off (additional)*

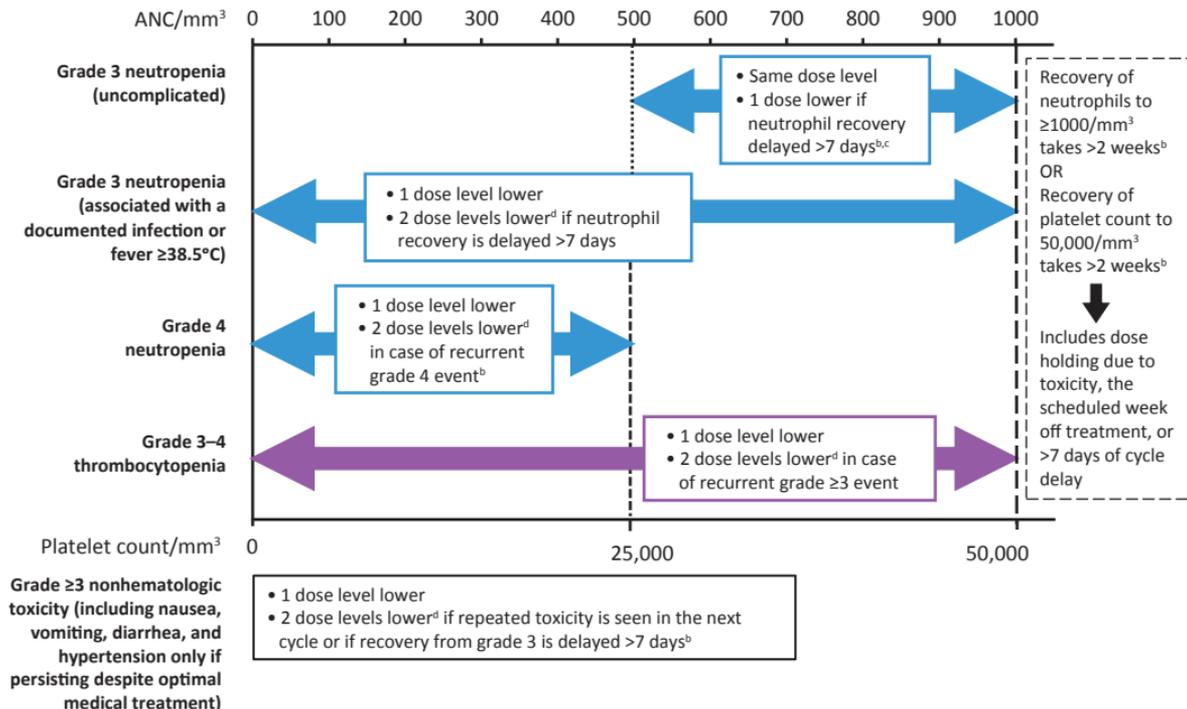
| Allowed before discontinuation

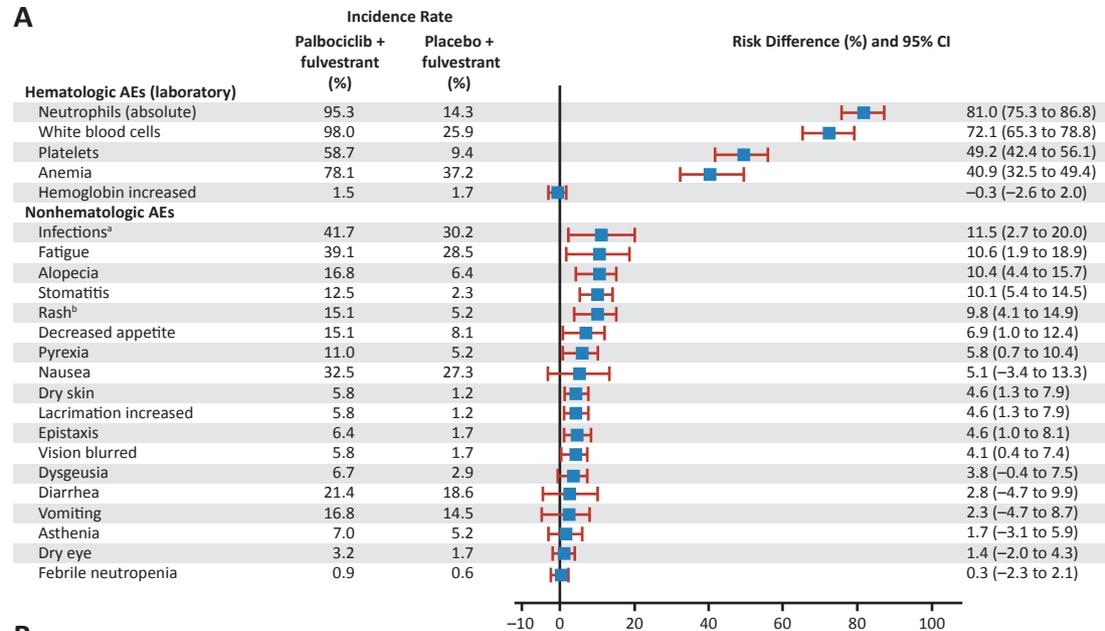
2 weeks on 75 mg

2 weeks off

due to neutropenia |

Toxicity | Palbociclib/Placebo Treatment

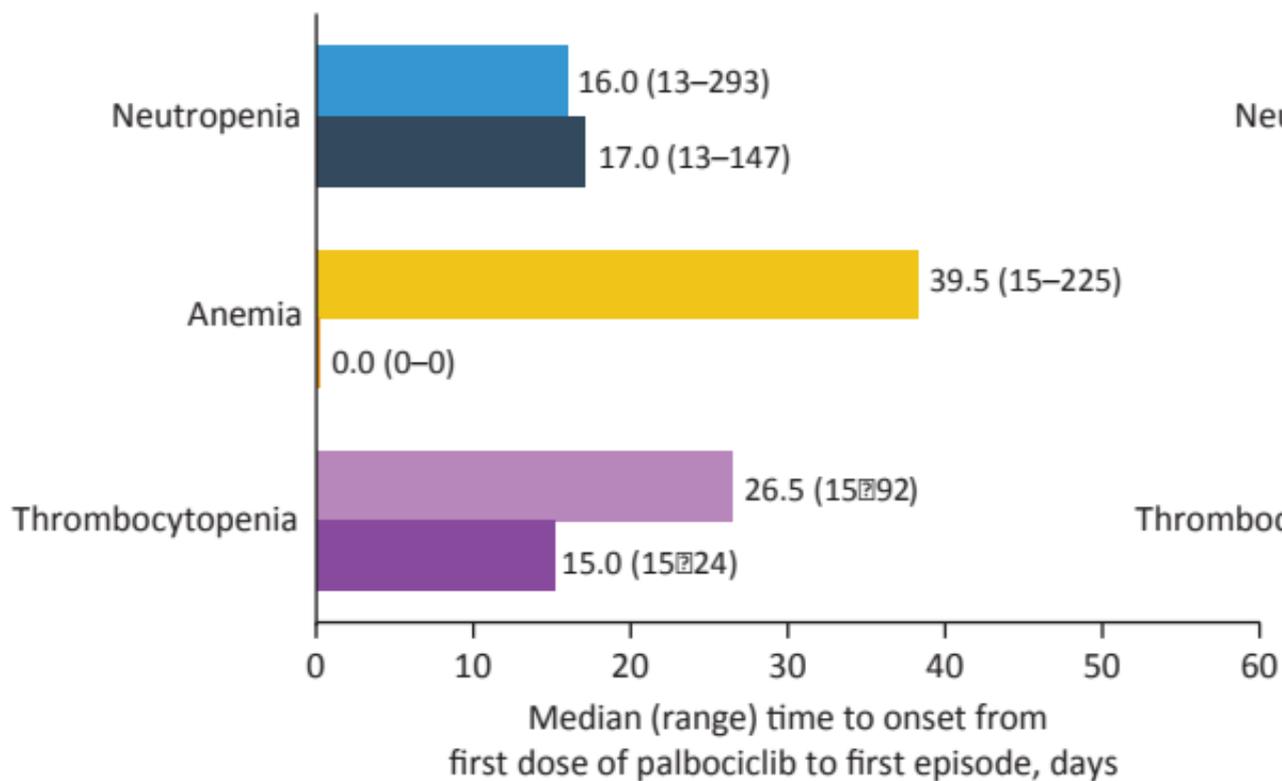
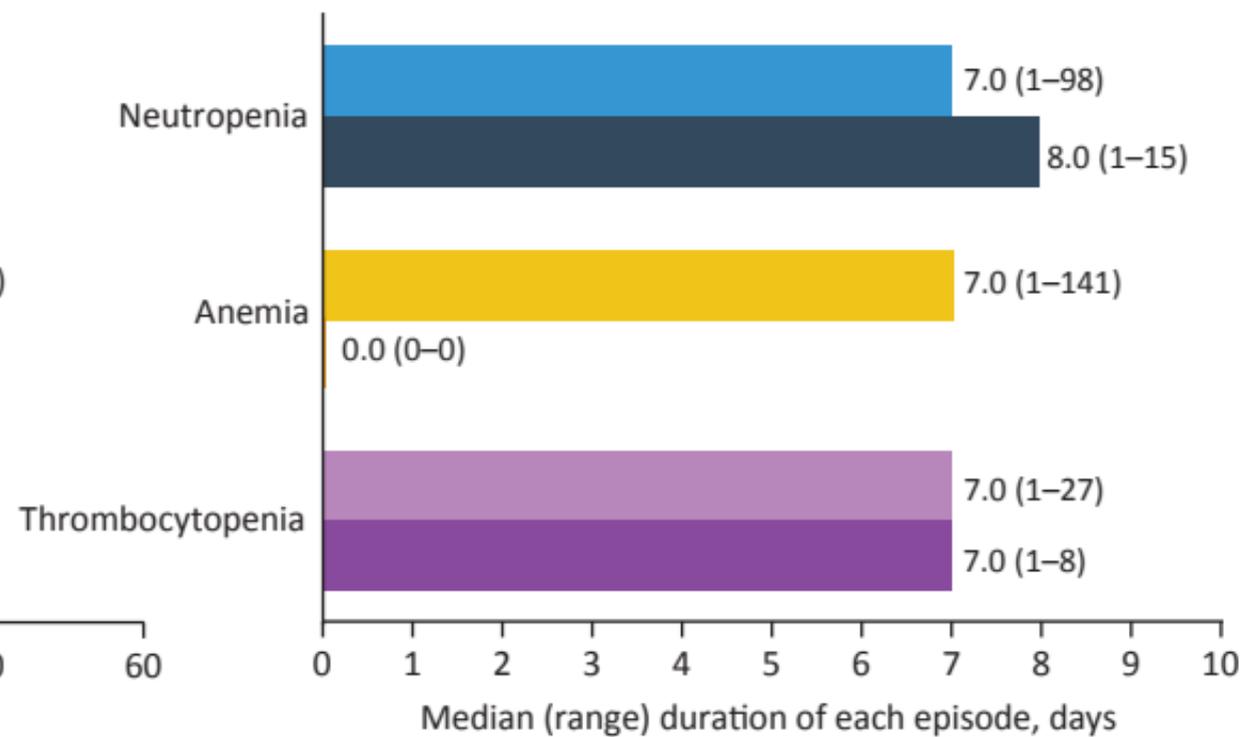




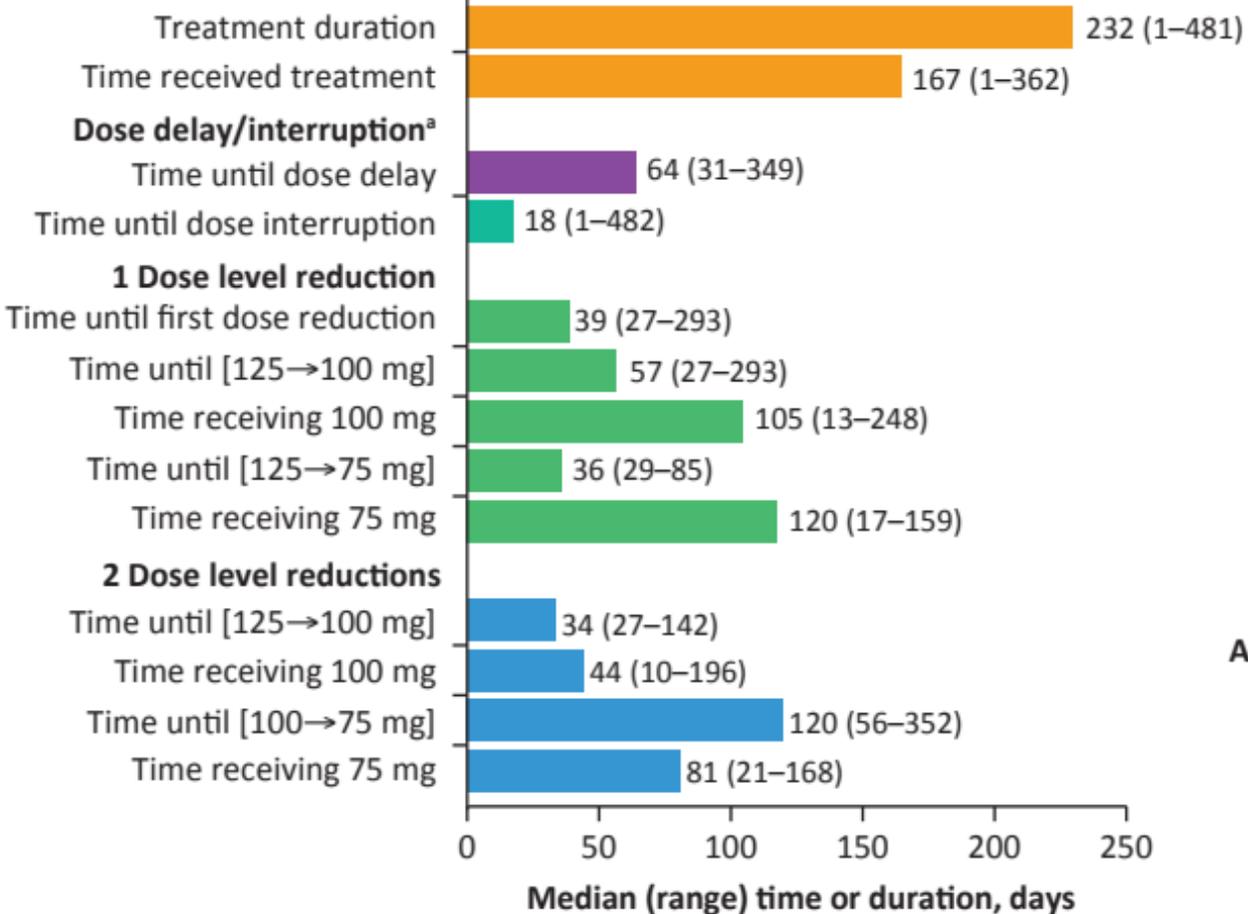
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Other adverse events of note

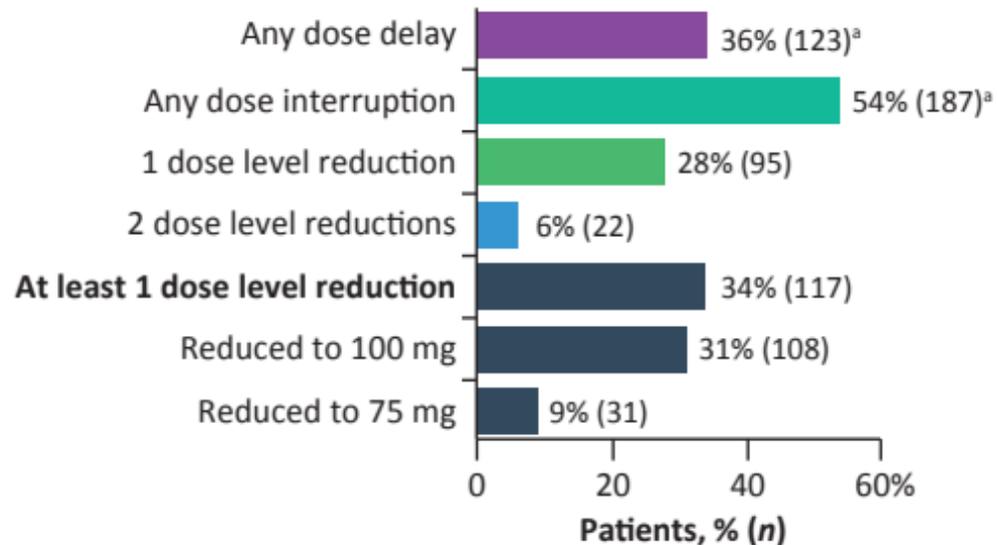
Infection^a	<p>↑ rate for all Gr infections: - 144 (42%) patients (palbociclib); 52 (30%) patients (placebo)</p> <p>Majority of all Gr events were Gr ≤2 infections: - 137 (40%) patients (palbociclib); 47 (27%) patients (placebo)</p> <p>5 (1%) patients (palbociclib) had a Gr 3–4 infection AND any Gr neutropenia</p>
Fatigue	<p>↑ rate for all Gr fatigue: 135 (39%) patients (palbociclib); 49 (28%) patients (placebo): - All Gr fatigue risk increased over time (palbociclib) (Fig. S2)</p> <p>Majority of the all Gr events were Gr 1–2 (palbociclib): - Gr 1: 81 (23%) patients; Gr 2: 46 (13%) patients</p>
Alopecia	<p>↑ rate for all Gr alopecia: - 58 (17%) patients (palbociclib); 11 (6%) patients (placebo)</p> <p>Majority of all the events were Gr 1: 53 (15%) patients (palbociclib): - Gr 1 hair loss, considered only noticeable on close inspection - 5 (1%) patients had Gr 2 alopecia or ≥50% hair loss (ie, maximum Gr per CTCAE v4.0)</p>
Stomatitis	<p>↑ rate for all Gr stomatitis: - 43 (12%) patients (palbociclib); 4 (2%) patients (placebo) - Gr 1: 28 (8%) patients; Gr 2: 13 (4%) patients; Gr 3: 2 (<1%) patients (palbociclib)</p>
Rash^b	<p>↑ rate for all Gr rash: 52 (15%) patients (palbociclib); 9 (5%) patients (placebo)</p> <p>Majority of all the events were Gr 1: 48 (14%) patients (palbociclib)</p>
Thromboembolic events	<p>↑ rate for thromboembolic events: 5 (2%) patients (palbociclib); 0% patients (placebo): - 4 serious AEs (Gr 3: 3 pulmonary emboli; Gr 2: 1 deep vein thrombosis) - 2 nonserious AEs (Gr 1: 1 subclavian vein thrombosis; Gr 2: 1 vena cava thrombosis)</p>

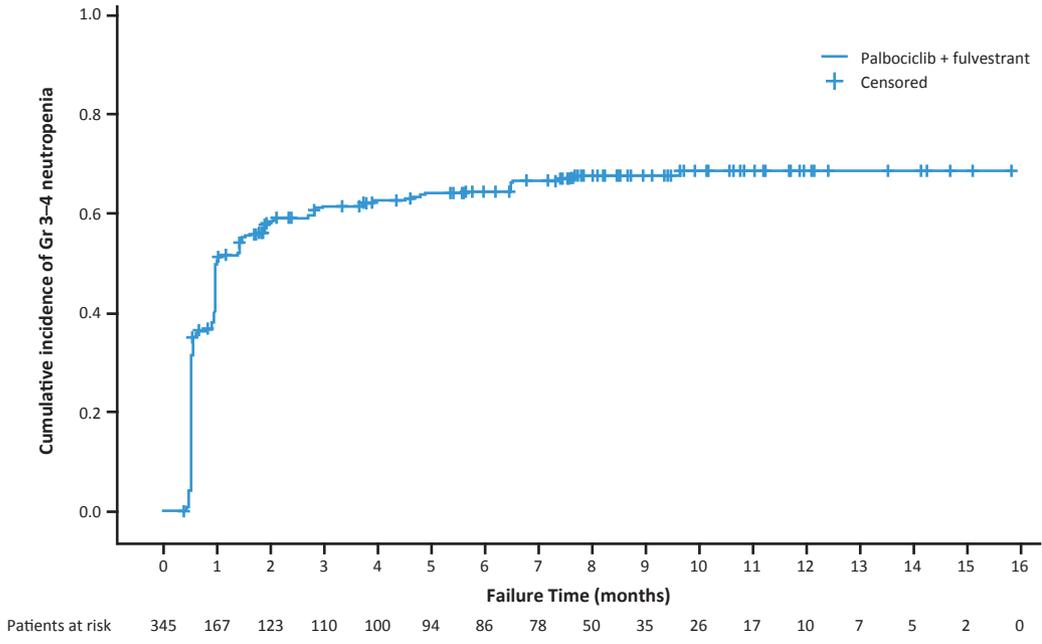
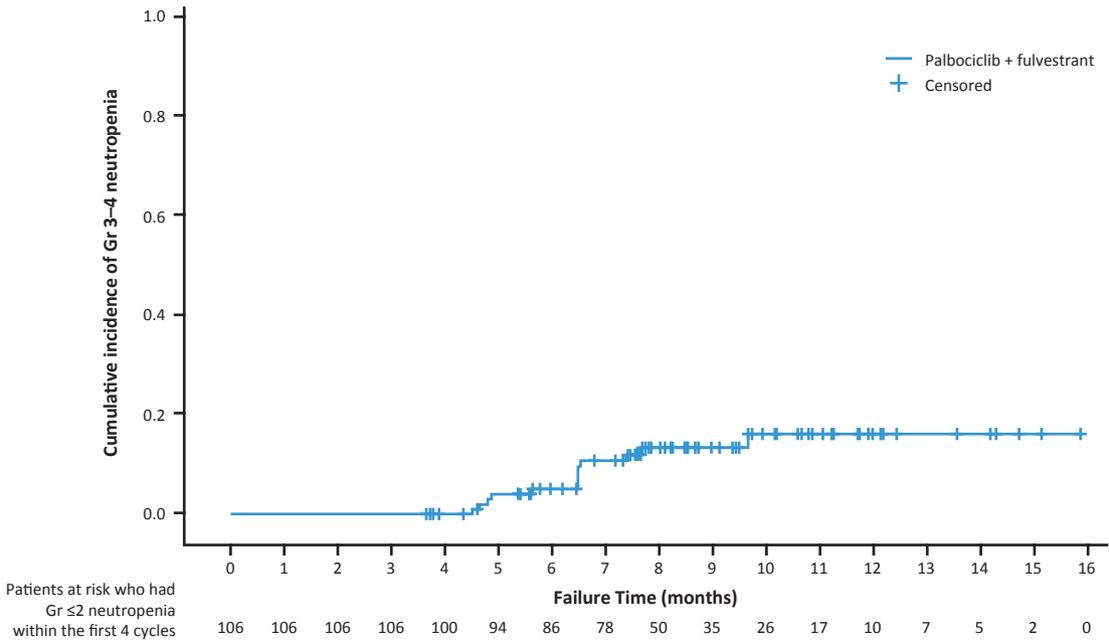
A**B**

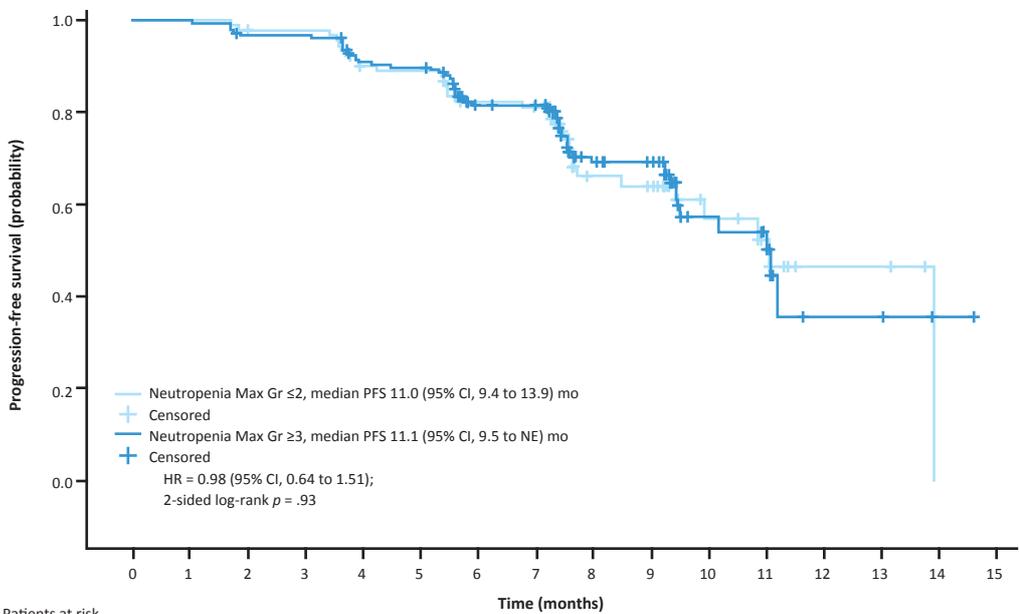
■ ■ ■ Grade ≥3
 ■ ■ ■ Grade 4

Treatment or Modification**Exposure: palbociclib plus fulvestrant**

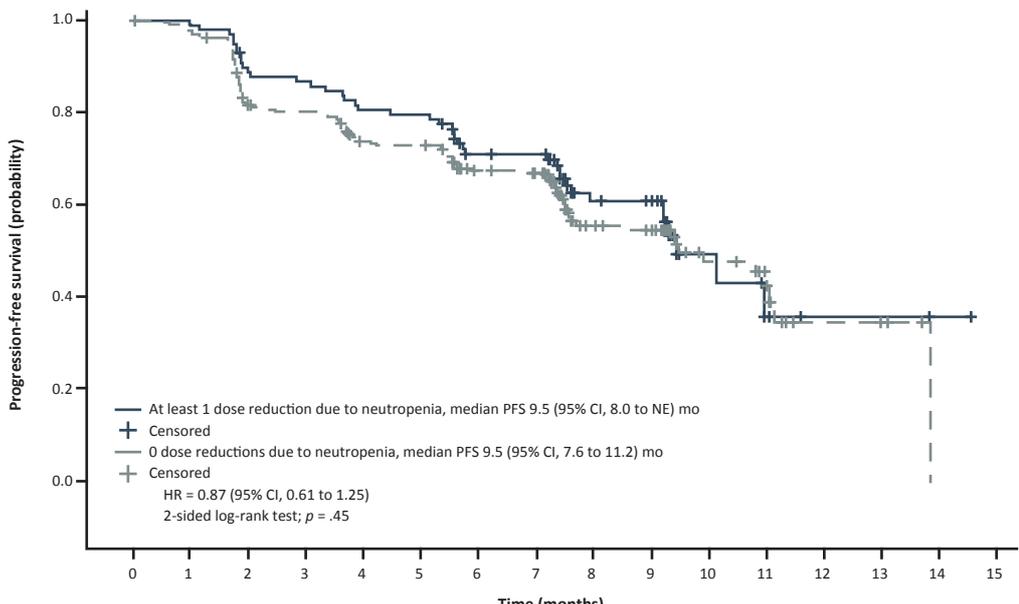
Safety population, <i>n</i>	345
Relative dose intensity, mean (\pm SD)	86 \pm 15%
Daily dose administered, mean (\pm SD)	118 \pm 12mg
Median (range) average duration in days:	
Dose delay	3 (2–16)
Dose interruption	6 (1–20)



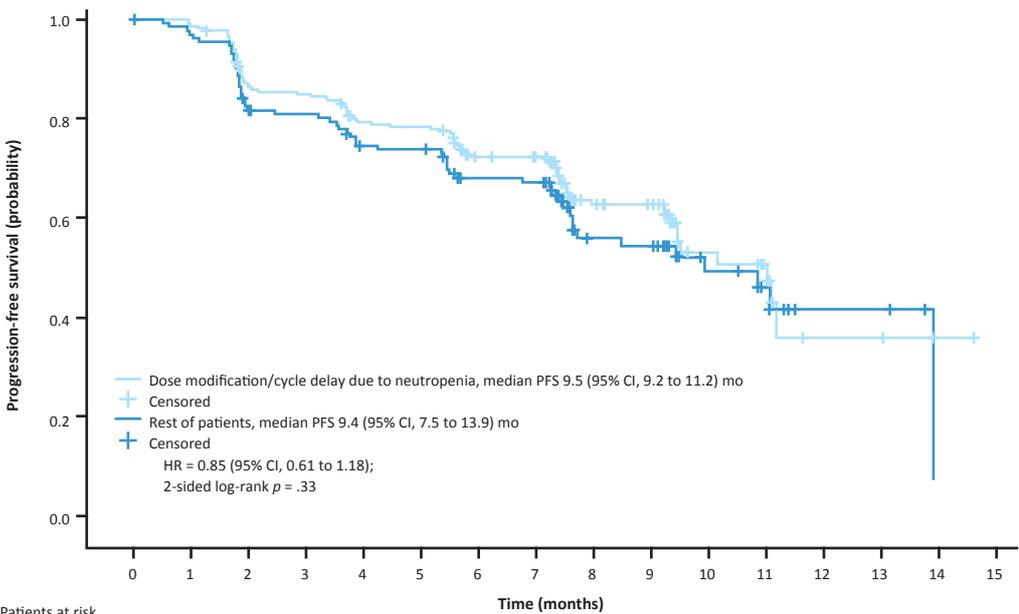
A**B**

A

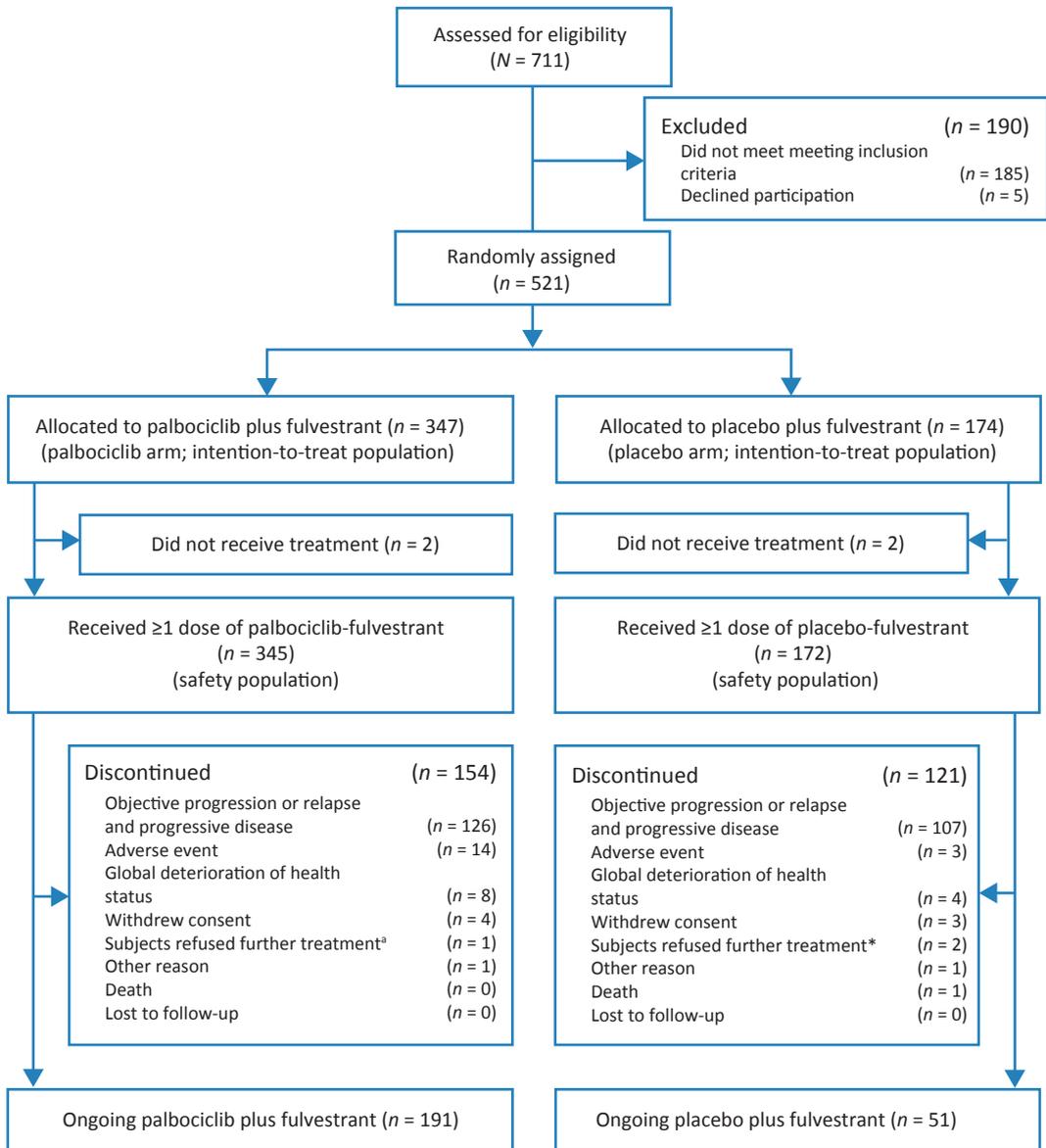
Patients at risk		Time (months)														
Neutropenia Max Gr ≤ 2	93	93	91	90	81	80	71	69	31	29	14	9	4	4	0	
Neutropenia Max Gr ≥ 3	186	186	179	179	166	164	131	128	60	56	18	14	3	3	1	0

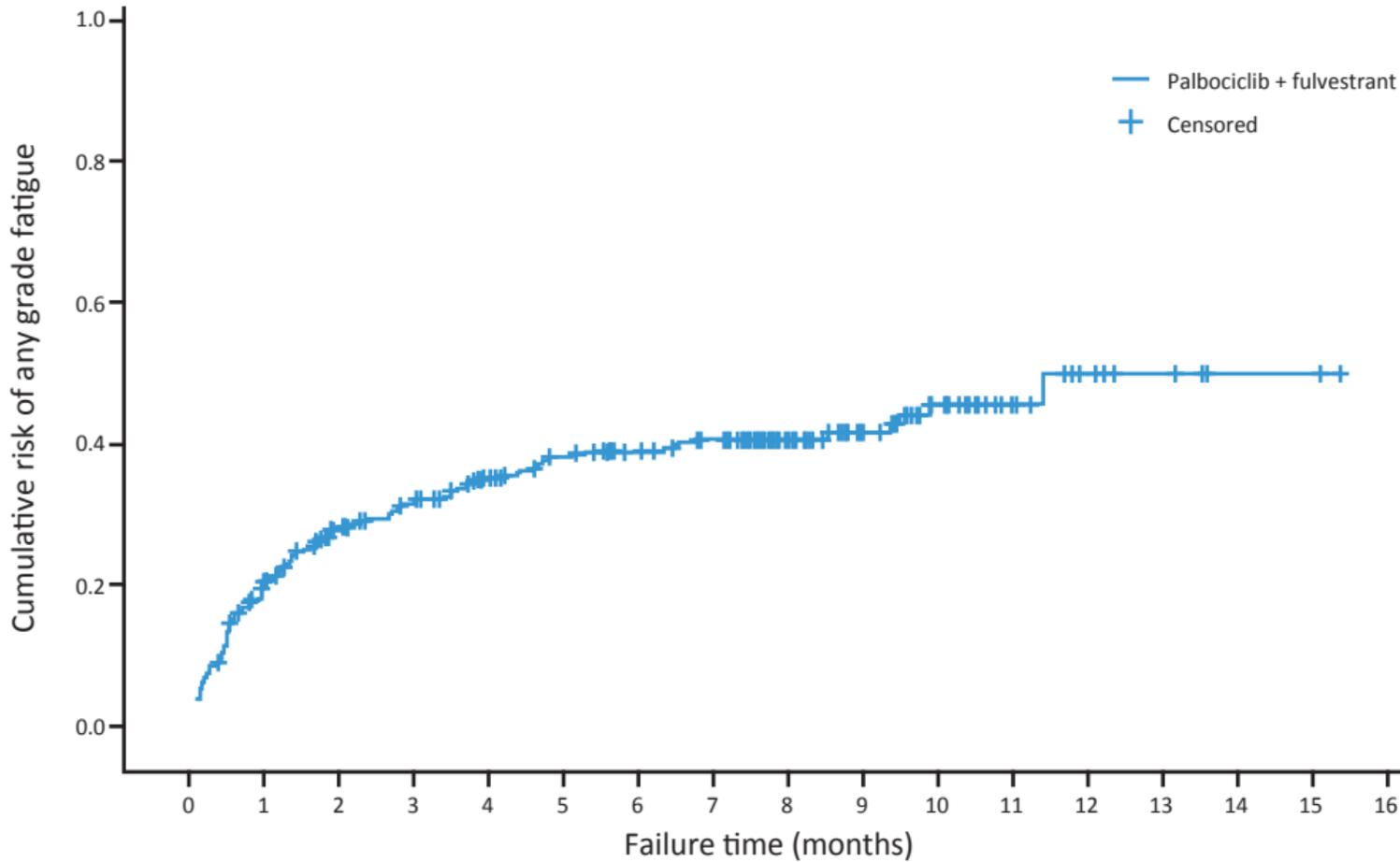
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Patients at risk		Time (months)														
At least 1 dose reduction	100	98	88	85	79	78	63	62	33	31	8	6	2	2	1	0
0 dose reduction	245	235	193	188	168	166	139	135	58	54	24	17	5	5	0	

C

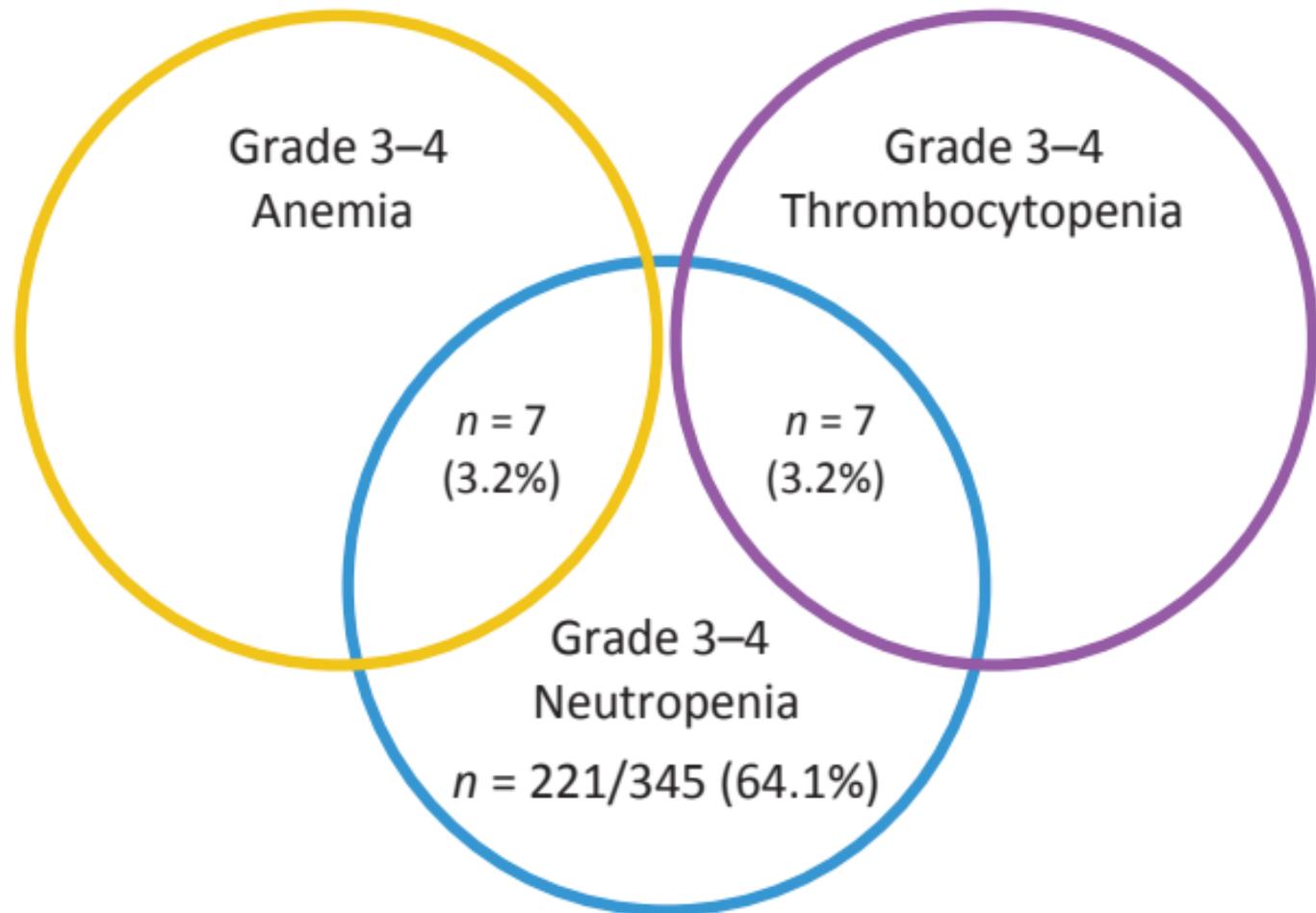
Patients at risk		Time (months)														
Dose reduction/interruption or cycle delay	218	215	184	179	163	161	131	127	61	56	18	14	3	3	1	0
Rest of patients	127	118	97	94	84	83	71	70	30	29	14	9	4	4	0	

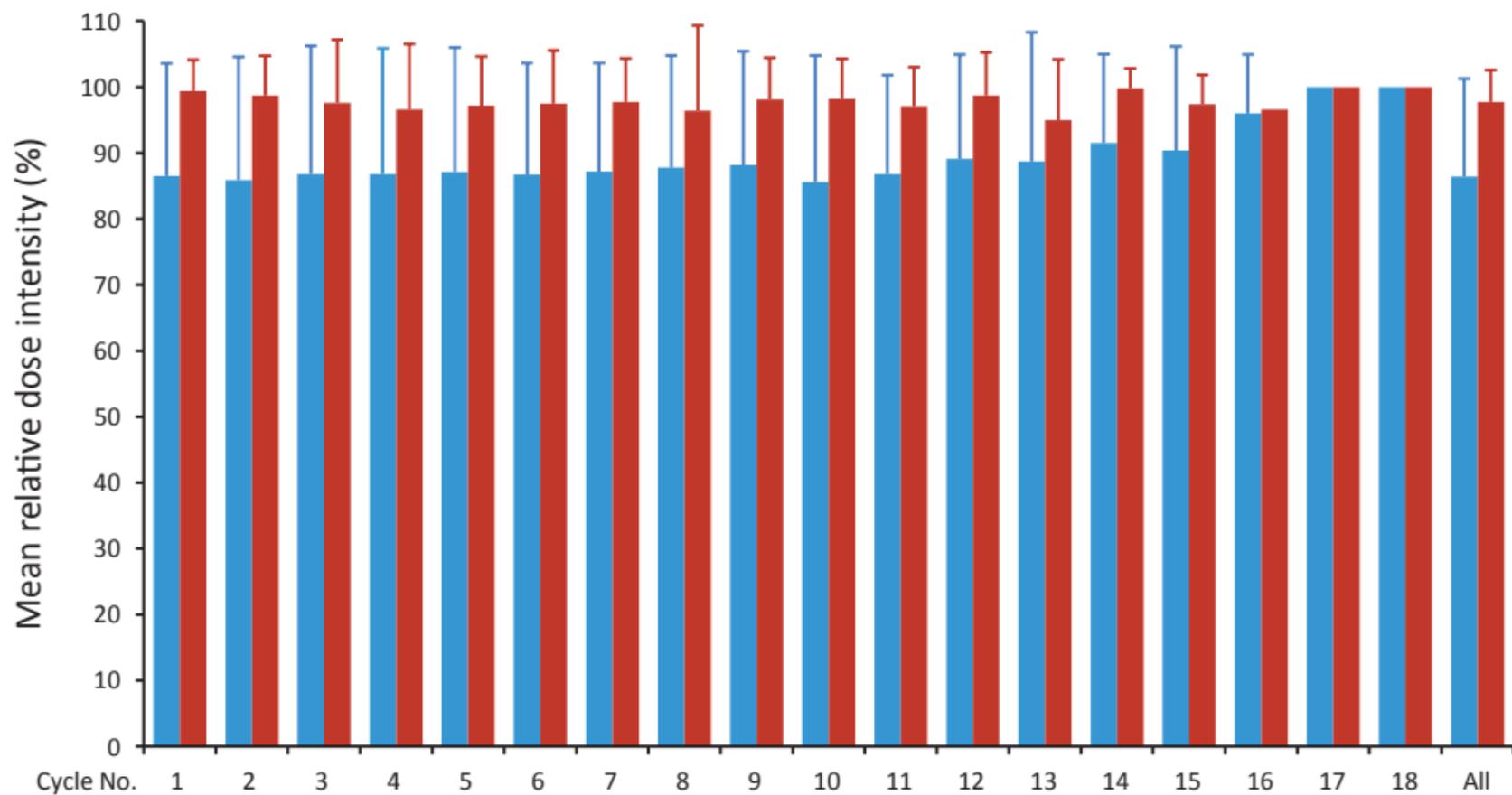




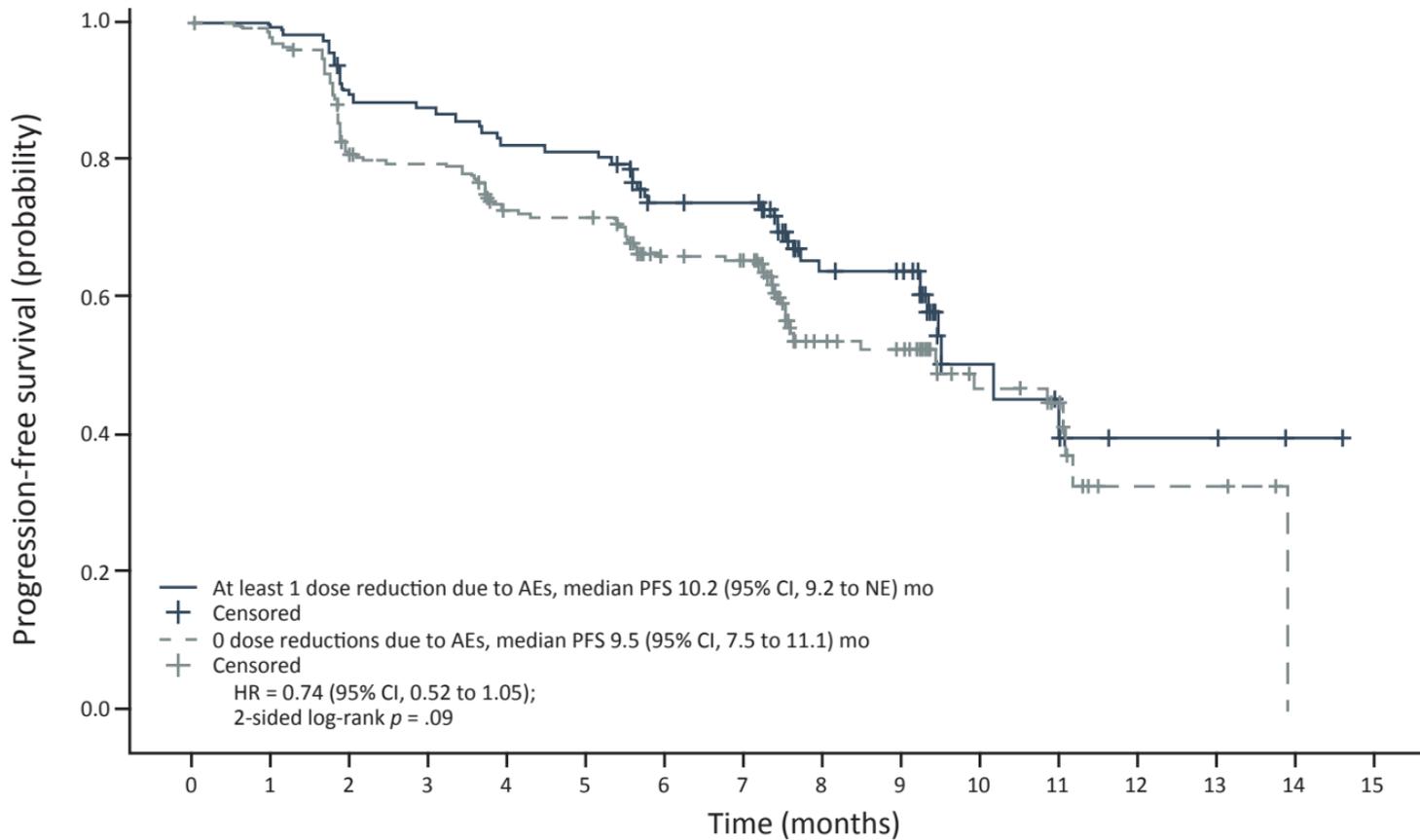
Patients at risk

345 266 216 195 173 159 147 137 84 49 33 14 8 5 2 2 0





■ Palbociclib + fulvestrant, n:	345	332	289	277	257	250	231	221	172	114	78	55	28	16	10	5	1	1	345
■ Placebo + fulvestrant, n:	172	162	123	109	91	85	70	67	54	30	20	18	11	5	3	1	1	1	172



Patients at risk

At least 1 dose reduction	114	112	101	98	92	91	76	75	42	40	10	8	3	3	1	0
0 dose reduction	231	221	180	175	155	153	126	122	49	45	22	15	4	4	0	