Clinical Cancer Research

FDA Approval: Palbociclib for the Treatment of Postmenopausal Patients with Estrogen Receptor–Positive, HER2-Negative Metastatic Breast Cancer

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Abstract

On February 3, 2015, the FDA granted accelerated approval to palbociclib (IBRANCE, Pfizer Inc.), an inhibitor of cyclin-dependent kinases 4 and 6 (CDK4 and CDK6), for use in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)–positive, HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. The approval is based on a randomized, multicenter, open-label phase I/II trial (PALOMA-1) in 165 patients randomized to palbociclib (125 mg orally daily for 21 consecutive days, followed by 7 days off treatment) plus letrozole (2.5 mg orally daily) or letrozole alone. The phase II portion of the trial was divided into two cohorts: cohort 1 enrolled 66 biomarker-unselected patients and cohort 2 enrolled 99 biomarker-positive patients. The major efficacy outcome measure was investigator-assessed progression-free survival (PFS). A large magnitude of improvement in PFS was observed in patients receiving palbociclib plus letrozole compared with patients receiving letrozole alone (HR, 0.488; 95% confidence interval, 0.319–0.748). Multiple sensitivity analyses were supportive of clinical benefit. The most common adverse reaction in patients receiving palbociclib plus letrozole was neutropenia. This article summarizes the FDA thought process and data supporting accelerated approval based on PALOMA-1 that may be contingent upon verification and description of clinical benefit in the ongoing and fully accrued confirmatory trial PALOMA-2. *Clin Cancer Res; 21(21); 4760–6. ©2015 AACR.*

Introduction

Hormonal therapy is the standard of care in the first-line metastatic breast cancer (MBC) setting for estrogen receptor (ER)–positive, HER2-negative patients without rapidly progressing visceral metastases because of its ability to control disease with minimal side effects. The hormonal agents approved in first-line MBC, tamoxifen, anastrozole, and letrozole demonstrate modest improvements in response rate and time to progression but have not clearly demonstrated an improved overall survival (OS; refs. 1, 2). Unfortunately, not all patients respond to first-line hormonal therapy as they present with primary or *de novo* resistance, and some patients who initially respond subsequently have breast cancer progression (acquired resistance).

New therapeutic strategies have recently emerged in an attempt to improve the outcome of patients with ER-positive MBC. The cyclin D1–CDK4/6–retinoblastoma pathway is critical for cell proliferation and its dysregulation has been implicated in breast cancer biology (3–5). CDK4 and CDK6 are activated early in the cell cycle by cyclin D1 (CCND1) and other D-type cyclins, thus facilitating cell-cycle progression from gap 1 (G_1) to synthesis (S) phase. Activated cyclin–CDK complexes lead to phosphorylation and inactivation of the tumor suppressor retinoblastoma 1 (RB1, also known as Rb) and result in the transcription of factors involved in S-phase entry. The cyclin-dependent kinase inhibitor 2A gene (*CDKN2A*) encodes an inhibitory protein that blocks the formation of the cyclin D–CDK4/6 complexes (6). These findings support exploring therapeutic interventions that directly target the cyclin D1–CDK4/6–retinoblastoma pathway through CDK4/6 inhibition in ER-positive breast cancer. Here, we present the FDA basis for the accelerated approval of palbociclib.

Chemistry

The chemical name of palbociclib is 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one. Palbociclib is supplied as 125, 100, and 75 mg capsules for oral administration.

Nonclinical Pharmacology and Toxicology

Palbociclib is a kinase inhibitor of CDK4 and CDK6. *In vitro*, palbociclib reduced cellular proliferation of ER-positive breast cancer cell lines by blocking cell-cycle progression from G_1 to S

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phase. The most sensitive ER-positive cell lines had high levels of *RB1* and *CCND1* expression and low levels of *CDKN2A* expression (7). Palbociclib combined with antiestrogens enhanced *in vitro* inhibition of cell proliferation in ER-positive breast cancer cells, and enhanced *in vivo* antitumor activity in ER-positive breast cancer mouse models. The combination of palbociclib and letrozole increased the inhibition of RB1 phosphorylation and tumor growth compared with each drug alone in a patient-derived ER-positive breast cancer mouse xenograft model.

Adverse effects in the bone marrow, lymphoid tissues, and male reproductive organs were seen in rats and dogs after administration of oral palbociclib at clinically relevant exposures. Altered glucose metabolism with associated changes in the pancreas, and secondary effects in the eye, teeth, kidney, and adipose tissue were identified in rats at doses approximately 11 times the human exposure (AUC) at the therapeutic dose. Lens degeneration in the eye and chronic progressive nephropathy remained after the recovery period. Although hyperglycemia was not observed in clinical trials, appropriate monitoring is incorporated in the ongoing and planned palbociclib clinical trials.

Palbociclib was clastogenic in an *in vitro* micronucleus assay using Chinese Hamster Ovary cells and an *in vivo* rat bone marrow micronucleus assay through an aneugenic mechanism. Palbociclib can cause fetal harm based on its mechanism of action and findings in animals. Reports from rodent carcinogenicity studies were not submitted or required to support this application as the indication includes patients with advanced breast cancer.

Clinical Pharmacology

The palbociclib C_{max} was observed between 6 and 12 hours following oral administration. The mean ($\pm$SD) plasma elimination half-life was 29 hours ($\pm$5 hours), and the mean apparent oral clearance was 63.1 L/hour [29% Coefficient of Variation (CV)]. The mean absolute bioavailability of palbociclib after an oral 125 mg dose was 46%. Steady state was achieved within 8 days, with a median accumulation ratio of 2.4 (range, 1.5–4.2).

The palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased the palbociclib exposure in this small subset of the population, while not altering palbociclib exposure in the rest of the population. Consequently, food intake reduced the intersubject variability in palbociclib exposure, compared with the overnight fasted condition, which supports administration of palbociclib with food.

The human mass balance trial showed that palbociclib was primarily eliminated by hepatic metabolism, and renal elimination appears to play a minor role. Based on the population pharmacokinetic analysis, a dose reduction was not needed in patients with mild or moderate renal impairment, or mild hepatic impairment. Further examination of the effects of severe renal impairment or moderate and severe hepatic impairment on the palbociclib exposure will be performed as a postmarketing requirement.

An exploratory exposure–response analysis was conducted for progression-free survival (PFS). Owing to limited data at a fixed dose of 125 mg, a definitive conclusion regarding an exposure–response relationship could not be made. A greater reduction in absolute neutrophil count appears to be associated with increased palbociclib exposure.

Clinical Trial Design

The accelerated approval of palbociclib was based on a phase I/II randomized, open-label, multicenter trial (PALOMA-1) comparing palbociclib plus letrozole with letrozole alone in 165 postmenopausal women with ER-positive, HER2-negative breast cancer who had not received prior systemic treatment for advanced disease (8). Patients were randomly allocated to receive palbociclib (125 mg orally daily for 21 consecutive days, followed by 7 days off treatment) plus letrozole (2.5 mg daily continuously throughout the 28-day cycle) or letrozole alone. Treatment was continued until disease progression assessed by the investigator, unacceptable toxicity, or withdrawal of consent. The phase II portion of the trial was divided into two cohorts: cohort 1 enrolled 66 biomarker-unselected patients and cohort 2 enrolled 99 biomarker-positive (*CCND1* amplification and/or loss of *CDKN2A*) patients (Fig. 1). The randomization was stratified by disease site (visceral vs. bone only vs. other) and disease-free interval (>12 months from the end of adjuvant treatment to disease recurrence compared with ≤12 months from the end of adjuvant treatment to disease recurrence or *de novo* advanced disease). The primary efficacy outcome measure was investigator-assessed (INV) PFS evaluated according to RECIST with secondary endpoints of overall response rate (ORR), OS, and retrospective PFS analysis by the Blinded Independent Central Review (BICR).

Three amendments were incorporated while the trial was ongoing. Initially, the protocol planned to enroll 150 biomarker-unselected patients. While the study was ongoing, nonclinical data indicated the potential efficacy of palbociclib in a biomarker positive population characterized by *CCND1* amplification [*CCND1*-to-CEP11 fluorescence *in situ* hybridization (FISH) ratio ≥1.5] and/or loss of *CDKN2A* (*CDKN2A*-to-CEP9 FISH ratio <0.8]. This led to the addition of the biomarker-positive population. Cohort 1 included the unselected patient population ($N = 66$) and cohort 2 included the biomarker-selected population ($N = 99$). After an interim analysis of Cohort 1 showed a preliminary benefit, enrollment to Cohort 2 was halted and the analysis plan for the primary endpoint (PFS) was changed to include both cohorts. Initially, a total of 114 events were needed to achieve 80% power to detect an HR of 0.67 with a one-sided $\alpha = 0.10$. The plan for the final analysis was subsequently changed from 114 events to 95 events. In addition, there was a *post hoc* significance level adjustment for the two PFS interim analyses using a gate-keeping procedure for hypotheses testing in a hierarchical approach to control the family-wise error rate. Breakthrough therapy designation was granted for palbociclib based on preliminary results from PALOMA-1 reporting a substantial improvement in PFS over an existing therapy.

Demographics, Disease Characteristics, and Prior Treatment

Baseline demographics and disease characteristics were balanced between treatment groups except for misclassification of stratification factors. Site of disease was misclassified in 17 (20.2%) patients in the palbociclib plus letrozole arm and 12 (14.8%) patients in the letrozole arm, which led to an imbalance of patients with visceral disease (44%: palbociclib arm, 53%: letrozole arm) and bone-only disease (20%: palbociclib arm, 15%: letrozole arm). Patients were recruited at 50 centers in 12
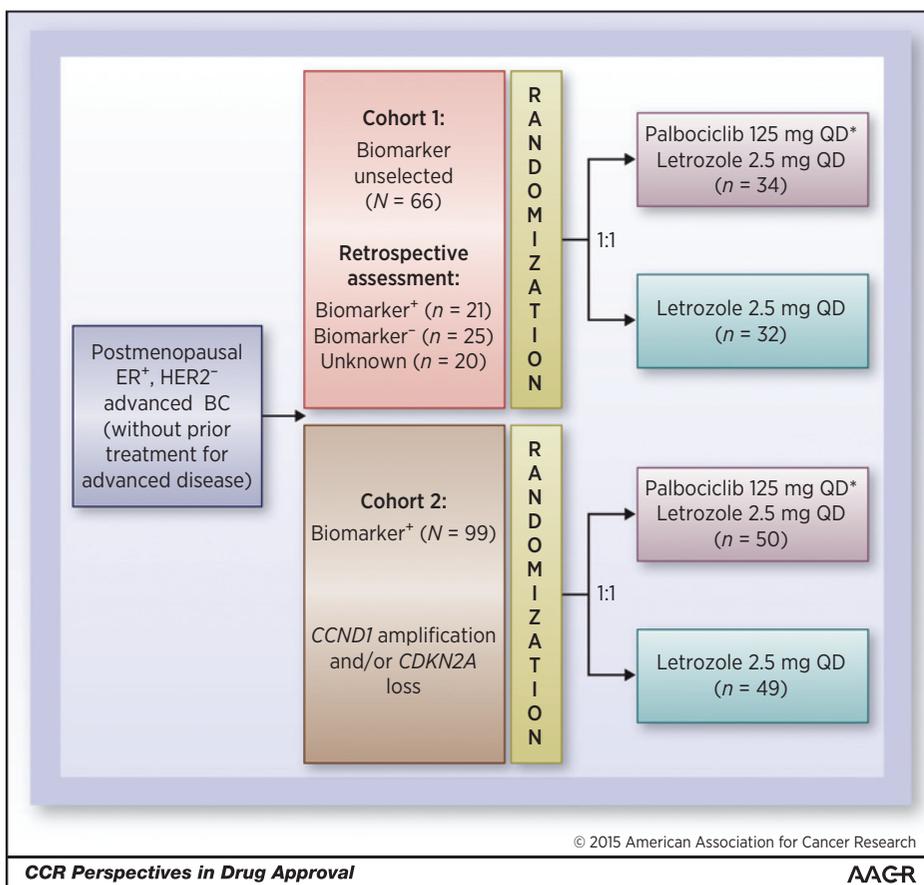
Beaver et al.

Figure 1.
PALOMA-1 study design. The asterisk indicates 21 days on, 7 days off. BC, breast cancer; QD, every day.

countries, 74% were from Europe, 22% from North America, and 4% from Asia. The median age was 63 years (range, 38–89 years), the majority were Caucasian (90%), and all patients had an ECOG PS of 0 or 1. Forty-three percent of patients had received chemotherapy and 33% had received antihormonal therapy in the neoadjuvant or adjuvant setting prior to their diagnosis of advanced breast cancer. A significant number of patients (49%) had *de novo* disease. The majority of patients (98%) had metastatic disease. Nineteen percent of patients had bone-only disease and 48% of patients had visceral disease.

Efficacy Results

At the time of the final PFS analysis, 100 INV-assessed events had occurred. An improvement in INV-assessed PFS was observed in patients receiving palbociclib plus letrozole compared with letrozole alone (HR, 0.488; 95% CI, 0.319–0.748). The estimated median PFS duration was 20.2 and 10.2 months in the palbociclib plus letrozole and letrozole-alone arm, respectively. The statistical analysis plan amendments precluded the interpretation of P values. Consistent results were observed across patient subgroups of disease-free interval, disease site, and prior therapy and did not identify a clinically defined subgroup that derived greater benefit from the addition of palbociclib. An improvement in the palbociclib plus the letrozole treatment arm was also observed when the two cohorts were analyzed separately (Table 1 and Fig. 2). However, the magnitude of PFS improvement differed between the two cohorts. PFS in the palbociclib plus letrozole treatment arm was lower in cohort 2 compared with cohort 1.

The treatment effect of palbociclib plus letrozole on PFS in the intention to treat (ITT) population was also supported by the retrospective BICR (HR, 0.621; 95% CI, 0.378–1.019). The ORR in patients with measurable disease was higher in the palbociclib plus letrozole arm than in the letrozole-alone arm (55.4%; 95% CI, 42.5–67.7 vs. 39.4%; 95% CI, 27.6–52.2). At the time of final analysis of PFS, OS data were not mature, with 37% of events (HR, 0.813; 95% CI, 0.492–1.345) in favor of palbociclib plus letrozole.

The biomarker-positive population represented 73% ($n = 120$) of the 165 patients in the phase II study. Patients in the palbociclib plus letrozole arm had a longer median PFS compared with patients in the letrozole arm, regardless of biomarker status. This PFS improvement was more pronounced in the biomarker-unselected population. Subgroup analyses based on FISH results (biomarker-positive vs. biomarker-negative) demonstrated preservation of the PFS benefit of palbociclib plus letrozole but did not identify a population that derived an improved or inferior benefit and further analysis for predictive biomarkers is warranted.

Safety Results

The safety database included 95 patients from the PALOMA-1 trial who received palbociclib at an oral daily dose of 125 mg

Table 1. Efficacy of palbociclib in ER-positive, HER2-negative advanced breast cancer

	Cohort 1 + Cohort 2		Cohort 1		Cohort 2	
	P+L N = 84	L N = 81	P+L N = 34	L N = 32	P+L N = 50	L N = 49
Number of events (%)	41 (48.8%)	59 (72.8%)	15 (44.1%)	25 (78.1%)	26 (52.0%)	34 (69.4%)
Censored (%)	43 (51.2%)	22 (27.2%)	19 (55.9%)	7 (21.9%)	24 (48.0%)	15 (30.6%)
Median PFS (mo)	20.2	10.2	26.1	5.7	18.1	11.1
95% CI	(13.8–27.5)	(5.7–12.6)	(11.2–NR)	(2.6–10.5)	(13.1–27.5)	(7.1–16.4)
HR	0.488		0.299		0.508	
95% CI	(0.319–0.748)		(0.156–0.572)		(0.303–0.853)	

Abbreviations: CI, confidence interval Kaplan–Meier estimate; L, letrozole; P, palbociclib.

supported by safety data from 700 patients participating in five industry-sponsored completed or ongoing clinical trials. In the phase II portion of PALOMA-1, 100% of patients ($n = 83$) on the palbociclib plus letrozole arm experienced a treatment-emergent adverse event (AE) and 84% of patients ($n = 65/77$) experienced a treatment-emergent AE on the letrozole arm. Sixty-four patients (77%) on the palbociclib plus letrozole arm and 16 patients (21%) on the letrozole-alone arm experienced a grade 3 or 4 AE. There was one death on study in the palbociclib plus letrozole arm, which was deemed as a result of disease progression.

The most common ($\geq 25\%$) adverse reactions were neutropenia, leukopenia, fatigue, anemia, upper respiratory infection, nausea, and stomatitis. The most common ($\geq 5\%$) grade ≥ 3 AEs in the palbociclib plus letrozole arm were neutropenia (48% grade 3, 6% grade 4), leukopenia (19% grade 3, no grade 4), and anemia (5% grade 3, 1% grade 4). Although febrile neutropenia events were reported in other palbociclib clinical programs, no cases were seen in PALOMA-1, and the majority of grade ≥ 3 neutropenia events were managed by dose reductions and/or delays and did not require permanent discontinuation or addition of supportive therapy. Dose reductions were reported in 36% of patients receiving palbociclib. Permanent discontinuation because of an AE occurred in 8% of patients receiving palbociclib plus letrozole (neutropenia 6%, asthenia 1%, and fatigue 1%). Eighteen patients (22%) on the palbociclib plus letrozole arm experienced serious adverse events (SAE) and 5 patients (7%) on the letrozole arm experienced an SAE. The most frequently reported SAEs in patients receiving palbociclib plus letrozole were pulmonary embolism (4%) and diarrhea (2%).

Discussion

The accelerated approval pathway allows for the use of surrogate endpoints and addresses added uncertainty with post-marketing trials to verify its clinical benefit (9). The accelerated approval of palbociclib was based on a large relative and absolute improvement in PFS. This magnitude of effect represents a meaningful benefit over standard therapy for first-line ER-positive, HER2-negative MBC. Consistent results were observed across subgroups of disease-free interval, disease site, and prior therapy and were supported by a higher ORR. The safety profile of palbociclib appeared to be acceptable for the patient population, and the toxicities were transient and reversible. There was an increased frequency of cytopenias (particularly neutropenia), infections, diarrhea, nausea, eye disorders, and pulmonary embolisms in palbociclib-treated patients compared with those treated with letrozole alone in PALOMA-1. However, the data provide assurance that the neutropenia can be appropriately managed using the dose modification guidance established in cohort 1 as

evidenced by a lower frequency of discontinuations due to neutropenia in the sequentially enrolled cohort 2.

These benefits were weighed against the limitations of the study that included a small sample size, open-label design, and amendments made to the statistical analysis plan. In addition, although the BICR analysis supported the primary endpoint of PFS, censoring was high. In most instances of discrepancy, the investigator determined progressive disease, although the BICR did not confirm progressive disease by imaging. Bone lesion progression according to RECIST criteria is difficult to measure and could have accounted for the difficulty of the BICR to confirm disease progression in many of these patients. FDA reviewed the narratives and case report forms from all patients and believes that the investigator assessments were appropriate. Although there was a misclassification of stratification factors resulting in an imbalance of patients with visceral disease, sensitivity analyses showed that these misclassifications did not affect the study results as the PFS analyses remained in favor of the palbociclib plus letrozole arm.

Regulatory considerations also took into account the potential for approval in a biomarker-positive population. Although 73% of the patients in the study were biomarker positive, palbociclib was approved for an unselected marker population. This decision was supported by the benefit of palbociclib, regardless of the biomarker status and the fact that approximately 40% of the population screened for cohort 2 was biomarker positive. There are many mechanisms for gene overexpression and loss of expression; PALOMA-1 only examined gene amplification and deletion. Further analysis is warranted, and a postmarketing commitment will seek to identify an optimal predictive biomarker.

Residual uncertainty in the magnitude of benefit in median PFS will be addressed in multiple ongoing and planned trials in both the adjuvant and advanced breast cancer settings (Table 2). Data from these ongoing studies did not factor into the accelerated approval decision of palbociclib as the study results were unknown. However, FDA has stated that postmarketing clinical trials to verify benefit should be well under way at the time of accelerated approval, and the fact that the confirmatory trial (PALOMA-2) was fully accrued supported the approval decision (10). If a positive benefit–risk is demonstrated in PALOMA-2, the accelerated approval requirement to verify benefit will be considered fulfilled. The recently presented results from the PALOMA-3 trial demonstrating a 5.4-month median PFS benefit of palbociclib, in combination with fulvestrant (, 0.42; 95% CI, 0.32–0.56; $P < 0.001$) in a more refractory patient population, have resolved some of the initial uncertainty regarding the efficacy of palbociclib (11). How PALOMA-3 will ultimately affect the palbociclib label or the accelerated approval conversion to regular approval is not yet known.
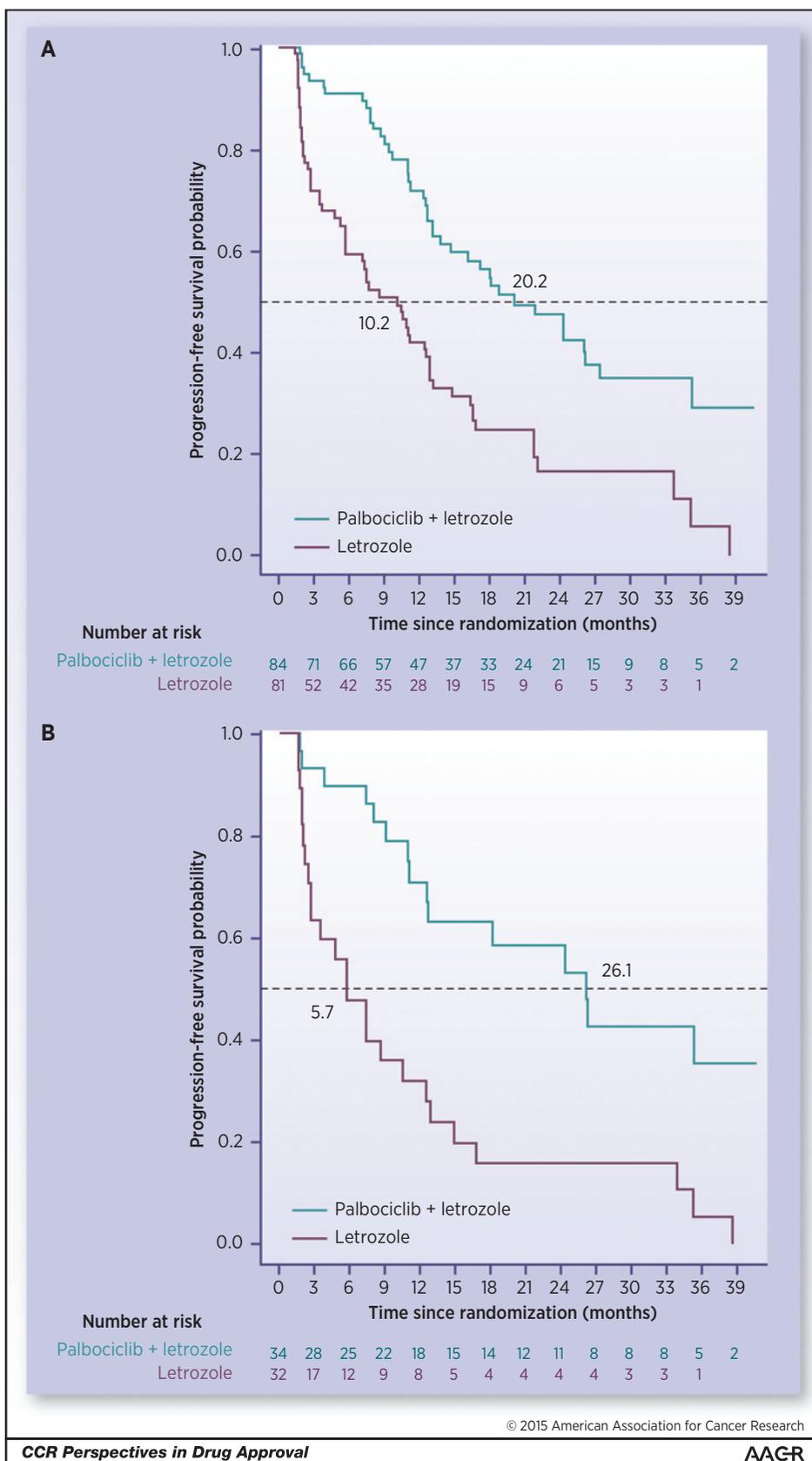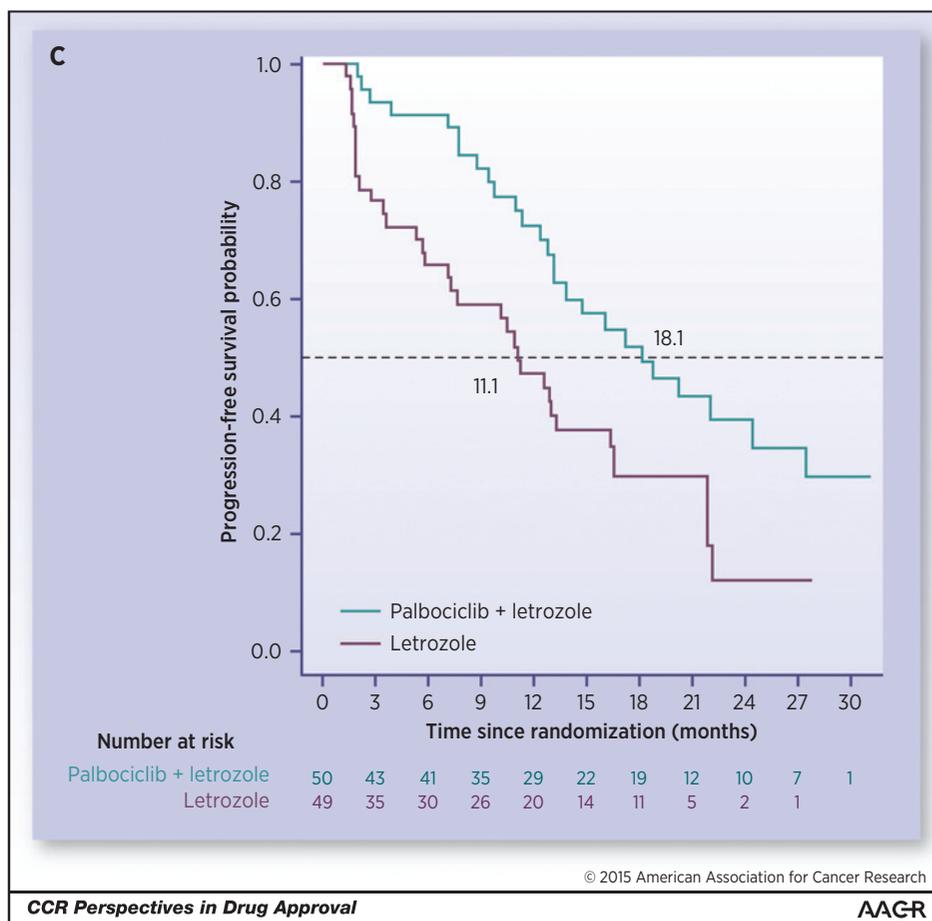
Beaver et al.

Figure 2.
Kaplan–Meier curves of PFS (investigator assessed). A, cohort 1 + cohort 2; B, cohort 1; C, cohort 2.

CCR Perspectives in Drug Approval

Figure 2
(*Continued*).

In summary, palbociclib in combination with letrozole for the first-line treatment of advanced breast cancer in postmenopausal patients with HR-positive, HER2-negative MBC has a favorable benefit–risk with sufficient evidence to support accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the fully accrued phase III trial PALOMA-2. Multiple ongoing randomized clinical trials under way at the time of the palbociclib accelerated approval strengthened the application by ensuring that FDA would receive the data necessary to verify clinical benefit in a timely fashion. The accelerated approval of palbociclib demonstrates FDA's commitment to provide earlier availability of promising anticancer agents to the patients who need them most.

Table 2. Palbociclib phase III breast cancer studies

Clinicaltrials.gov identifier/study name	Design	Arms	Setting	Primary endpoint
NCT01740427 PALOMA-2	Randomized 2:1, double-blind $N = 666$	PAL + letrozole vs. placebo + letrozole	ER⁺, HER2⁻, ABC, first-line	PFS
NCT01942135 PALOMA-3	Randomized 2:1, double-blind $N = 521$	PAL + fulvestrant vs. placebo + fulvestrant	ER⁺, HER2⁻, MBC, progression after prior hormonal therapies	PFS
NCT02297438 PALOMA-4	Randomized 1:1, double-blind $N = 330$ (target)	PAL+ letrozole vs. placebo + letrozole	ER⁺, HER2⁻, ABC, first-line Asian regional postmenopausal	PFS
NCT02028507 PEARL	Randomized 1:1, open-label $N = 348$ (target)	PAL+ exemestane vs. capecitabine	ER⁺, HER2⁻, MBC resistant to nonsteroidal aromatase inhibitors	PFS
NCT01864746 PENELOPE-B	Randomized 1:1, double-blind $N = 800$ (target)	PAL + standard endocrine therapy vs. placebo + standard endocrine therapy	HR⁺, HER2⁻, high risk, adjuvant	iDFS
Planned PALLAS	Randomized 1:1, open-label $N = 4,600$ (target)	PAL + standard endocrine therapy vs. standard endocrine therapy	HR⁺, HER2⁻, adjuvant	iDFS

Abbreviations: ABC, advanced breast cancer; HR, hormone receptor; iDFS, invasive disease-free survival; PAL, palbociclib.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P.G. Kluetz

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Other (performed the regulatory project management duties seeing the FDA approval of palbociclib from beginning to end of the review process): A. Tilley

Other (oversaw the review of the NDA for palbociclib): A. Ibrahim

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