Real-World Clinical and Economic Outcomes Associated with Palbociclib for HR-Positive/HER2 Negative Metastatic Breast Cancer: A Commentary

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SUMMARY

Despite the achieved advancement in pharmacological cancer treatments, the majority of postmenopausal women with hormone receptor-positive metastatic breast cancer (mBC) will experience disease progression. Research into alternative therapies with improved efficacy and reduced side effects has led to the development of a new class of oral anticancer medications, the cyclin-dependent kinase (CDK) 4/6 inhibitors, which include palbociclib, ribociclib, and abemaciclib. Nonetheless, there is growing evidence that the effectiveness of oral anticancer medications is sub-optimal, being influenced by low adherence, sociodemographic factors, and adverse effect profiles. In addition, there is a disconnect between the high price tags of CDK 4/6 inhibitors and their observed effectiveness, raising questions about their value. Currently, the existing knowledge base on the effectiveness and cost-effectiveness of newer oral anticancer medications in understudied populations with possible health disparities is scant. This commentary discusses what is known about palbociclib's clinical effectiveness, safety, and adherence and suggests the need for further studies of real-world effectiveness and cost-effectiveness to help establish the value of newer oncologic drugs, such as palbociclib.

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Breast cancer is the second leading cause of cancer-related death among American women.¹ Breast cancer is a heterogeneous disease composed of distinct molecular subtypes that include luminal A and B, human epidermal growth factor receptor 2 (HER2) type, and triple-negative/basal-like.² As of 2020, the average risk for a woman to develop breast cancer in her life is 13% in the United States, with an estimated 276,480 new cases of invasive breast cancer and 48,530 new cases of noninvasive breast cancer expected to be diagnosed in 2020.¹ Breast cancer accounts for approximately 25% of all cancer cases and 15% of all deaths among women and constitutes one of the most expensive malignancies to treat.^{1,3} As such, breast cancer puts a heavy burden on patients and their families, as well as health care systems across the world.⁴

Strategies to fight breast cancer are geared toward prevention, early detection, and treatment.⁵ Multiple subtypes and stages of breast cancer have been defined, which has led to the development of multiple, targeted strategies to treat the disease.² Hormone receptor-positive (HR+) and HER2 negative (HER2-) metastatic breast cancer (mBC), together, is the most common

subtype, with a highly variable prognosis that depends on the responsiveness to endocrine agents.⁶ Resistance to endocrine therapy (ET), such as aromatase inhibitors (AIs) or fulvestrant, may be the reason for the disease progression experienced by the majority of postmenopausal women with HR+ mBC. Research into alternative therapies with improved efficacy and reduced side effects has led to the development of a new class of oral anticancer medications, the cyclin-dependent kinase (CDK) 4/6 inhibitors, which include palbociclib, ribociclib, and abemaciclib. Nonetheless, there is growing evidence that the effectiveness of oral anticancer medications is suboptimal, being influenced by low adherence and adverse effect profiles.⁷ In addition, there is a disconnect between the high price tags of CDK 4/6 inhibitors and their observed effectiveness, raising questions about their value.^{8,9} Currently, the existing knowledge base regarding the effectiveness and cost-effectiveness of newer oral anticancer medications is scant.

In this U.S. market-focused opinion, we present what is known about palbociclib's clinical effectiveness, safety, adherence, and cost-effectiveness, as well as highlight the need for further studies into real-world effectiveness and cost-effectiveness with adherence in mind.

Adherence and Patient Perspective

A new weapon in the armamentarium of oral anticancer medications, the CDK 4/6 inhibitors (palbociclib, ribociclib, and abemaciclib) were approved in combination with endocrine therapy (aromatase inhibitors or fulvestrant) as first-line agents to prolong progression-free survival in this subtype.^{6,10} However, it has been shown that a significant number of patients struggle to adhere to oral anticancer medications (OAMs) as prescribed.¹¹ As noted in the systematic review by Greer et al. (2016),¹¹ nonadherence to OAMs can lead to lower survival rates,¹²⁻¹⁴ increased risk of recurrence,^{15,16} and higher health care costs.¹⁷ Also, studies looking at interventions to improve adherence have not been successful because of methodological concerns, resulting in a lack of evidence to guide practice.¹¹ For improved patient outcomes, it is essential to properly manage OAM regimens, since most of them have narrow therapeutic ranges and safety margins, making managing medication regimens essential for improved patient outcomes.¹⁸ Patient perceptions of medications influence

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TABLE 1 Description of U.S. Studies that Focus on Real-World Effectiveness and Safety

Reference	Description
Varella et al. ²⁵	In the 411 women included, the estimated overall median PFS for palbociclib plus letrozole was 8.9 months (6.16, 11.0), and the estimated median PFS was 15.1 months (12.3, not reached) for those who received palbociclib/letrozole as first-line therapy; 10.5 months (7.05, not reached) as second-line therapy; and 4.2 months (3.7, 5.6) for third-line and beyond. As for palbociclib/fulvestrant, the estimated overall PFS was 10.3 months (8.16, 12.3), with an estimated median PFS of 11.6 (8.2, not reached), 12.3 (8.66, not reached), and 6.4 months (4.23, 11), respectively, as first-, second-, or third-line and beyond therapy. The most common AEs were hematologic, with 58% of patients experiencing grade 3-4 neutropenia, but only 8% of the patients permanently discontinued palbociclib due to AEs.
Bui et al. ²⁶	This study aimed to assess the real-world effectiveness and tolerability of palbociclib combined with endocrine therapy in HR+/HER2- patients with mBC that progressed on previous endocrine therapy and to compare their results with the outcomes of the PALOMA-3 trial. The median PFS in real-world clinical practice was 10.0 months compared with 9.5 months in PALOMA-3. Most AEs were managed with palbociclib dose modifications, and only 2 patients discontinued treatment because of AEs. Neutropenia was the most frequent grade 3-4 AE, but no febrile neutropenia occurred. Overall, the effectiveness and tolerability of palbociclib in real-world clinical practice were similar to the results from PALOMA-3.
Taylor-Stokes et al. ²⁷	In the U.S. patient subgroup of the IRIS study, the authors reported that both combination of palbociclib with AI and palbociclib with fulvestrant demonstrated favorable effectiveness. For the 360 patients treated with palbociclib and AI, the progression-free rate was 84.1% and 64.3% for 12 and 24 months, respectively. For the 292 patients treated with palbociclib and fulvestrant, the 12-month progression-free rate was 79.8% overall, and the 12-month survival rate was 87.9% overall, with no progression-free and survival rates available beyond 12 months.
Watson et al. ²⁸	In a retrospective single-center analysis of HR+/HER2- mBC patients treated with palbociclib over 5 months, the authors found that 44% of the 64 patients had treatment deferrals due to neutropenia with a median time to first deferral of 4 weeks, while 23% requiring dose adjustments had no significant association with increased risk of disease progression. AEs were as expected, and only 3 patients discontinued treatment due to AEs, but 7 venous thromboembolic events were reported, which was higher than in PALOMA-3. Overall, compliance was good with existing CBC monitoring guidelines, with disease progression (n=30) as the main cause for discounting treatment.
Kish et al. ²⁹	The authors assessed the setting in which palbociclib was being initiated and examined the real-world occurrence of neutropenia and how providers monitored and managed these events. The study demonstrated a more heterogeneous line of therapy at initiation than RCTs, with 39.5% of patients receiving palbociclib as first-line, 15.7% as second-line, 13.1% as third-line, and 31.7% as fourth-line therapy or later. This study suggested good provider compliance with monitoring guidelines with a mean number of 6 CBC tests among all patients. Overall, 74.6% of patients had a neutropenic event, including 47.3% and 8.0% of patients with a grade 3 or 4 occurrence, respectively, data consistent with results in the phase 3 trials of PALOMA-2 and PALOMA-3.
Stearns et al. ³⁰	The authors showed in a real-world EAP setting and with a median treatment duration of 77 days that the combination of palbociclib and letrozole was generally well tolerated, and AEs were manageable by protocol-specified temporary treatment discontinuation, dose reductions, and/or standard medical therapy. Interestingly, most patients reported “no problem” at baseline mobility, self-care, and usual activities; however, nearly 50% reported “some problem” with respect to pain/discomfort and anxiety/depression. AEs associated with permanent discontinuation of either or both study treatments were reported for 10.2% of the patients, and permanent discontinuation of either or both study treatments were most commonly associated with disease progression (22.2%) and AEs (8.1%).
Xi et al. ³¹	In a retrospective chart review of 192 postmenopausal patients with HR+/HER2- mBC, from electronic medical records from a single-center institution, the authors analyzed treatment patterns and the effectiveness of palbociclib and subsequent regimens in mBC. They found the median PFS on palbociclib was 20.7 months (first-line setting), 12.8 months (second-line), and 4.0 months in subsequent-line settings, which was comparable to the PALOMA-2 and PALOMA-3 trials.
Gong et al. ³²	The authors conducted a single institution, retrospective study of palbociclib and ET-related AEs. Out of the 100 patients included, treatment resulted in dose modification in 38.0% of the patients due to AEs, with 18.4% requiring subsequent dose changes. Most modifications occurred during the first 2 cycles, and 54.8% of them were due to grade 3-4 neutropenia. Notably, older age (≥ 65 years) did not affect palbociclib tolerance.
Kuranz ³³	The authors investigated mBC patients with HR+/HER2- breast cancer from a health care research network to compare the occurrence of AEs in patients receiving palbociclib and letrozole with patients receiving AIs and in patients receiving palbociclib and fulvestrant with patients on second-line AIs. Compared with ET, palbociclib demonstrated an increased risk of infection and bleeding.

AE = adverse event; AI = aromatase inhibitors; CBC = complete blood count; EAP = expanded-access program; ET = endocrine therapy; HER2- = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; mBC = metastatic breast cancer; PFS = progression-free survival; RCT = randomized controlled trial.

decisions to initiate or continue cancer medications and can affect their adherence; those beliefs are multilayered with some of the most important influencing factors being the risk/benefit ratio, symptoms and side effects, and patient-provider relationships,¹⁸ as well as psychosocial factors (e.g., social support and knowledge of medication).⁷

A systematic review by Lin et al. (2017) identified psychosocial factors and barriers that may affect the adherence rate of

breast cancer patients taking OAMs.⁷ Patient-provider relationships and positive views and beliefs of medication were the most widely reported effectors. Other important motivators identified by Lin et al. included depression and emotions, perception of illness, concern of side effects, self-efficacy in medication management and decision making, knowledge of medication, and social support on OAM adherence. Contrary to demographics or clinically related factors, these interpersonal

and psychosocial factors constitute potentially modifiable effectors if the correct interventions are implemented to improve patient outcomes.

Brier et al. (2017) evaluated the relationship between health beliefs and adherence to AI in 437 postmenopausal women with HR+ breast cancer, using the Health Beliefs and Medication Adherence in Breast Cancer (HBMABC) scale and questionnaires.¹⁹ Of the participants, an estimated 21.3% were not adherent to therapy. Participants who perceived greater barriers to their AI treatments were less adherent (adjusted odds ratio [aOR] = 1.71, 95% confidence interval [CI] = 1.03-2.86). This study highlights an important connection between adherence and how it may be influenced by perceived barriers using questionnaires to ascertain patient-reported outcomes.

Harbeck et al. (2016) assessed patient-reported outcomes (PROs) from the PALOMA-3 trial.²⁰ On treatment with palbociclib plus fulvestrant (compared with fulvestrant plus placebo), overall quality-of-life (QoL) scores, assessed by the European Organisation for Research and Treatment of Cancer Quality-of-Life questionnaire (EORTC QLQ-C30), significantly favored the palbociclib plus fulvestrant group ($P=0.0313$). This patient group also had significantly greater improvement from baseline in pain, while also significantly delayed deterioration in global QoL and pain compared with fulvestrant alone.

Palbociclib Real-World Effectiveness and Safety

Palbociclib in combination with an AI or fulvestrant was the first-in-class treatment and approved as a first-line agent in this setting of HR+/HER2- mBC.¹⁰ Palbociclib has demonstrated efficacy in clinical trials,²¹⁻²⁴ but adherence issues and long-term efficacy and safety concerns are not always well captured in clinical trial settings. Several studies have attempted to demonstrate the reproducibility of evidence and external generalizability of randomized trials by assessing the real-world effectiveness and tolerability of palbociclib for advanced HR+/HER2- patients with mBC (Table 1).²⁵⁻³³

Varella et al. (2019) conducted a real-world study looking at patients with an advanced HR+ breast cancer treated with palbociclib at the Cleveland Clinical health system from February 2015 to December 2017.²⁵ In the 411 women included, the estimated overall median progression-free survival (PFS) for palbociclib/letrozole was 8.9 months. For palbociclib/fulvestrant, the estimated overall PFS was 10.3 months. The most common adverse events (AEs) were hematologic, with 8% of the patients permanently discontinuing palbociclib because of AEs. Bui et al. (2019) also aimed to assess the real-world effectiveness and tolerability of palbociclib combined with endocrine therapy in HR+/HER2- patients with mBC that progressed on previous endocrine therapy and to compare their results with the outcomes of the PALOMA-3 trial.²⁶ The median PFS in real-world clinical practice was 10.0 months compared with 9.5 months in PALOMA-3. Most AEs were managed with palbociclib dose.

Neutropenia was the most frequent grade 3-4 AE. Overall, the effectiveness and tolerability of palbociclib were similar to the results from PALOMA-3. In the U.S. patient subgroup of the IRIS study, Taylor-Stokes et al. (2019) reported that both a combination of palbociclib with AI and palbociclib with fulvestrant demonstrated favorable effectiveness.²⁷ In a retrospective single-center analysis of HR+/HER2- mBC patients treated with palbociclib over 5 months, Watson et al. (2019) found that 44% of the 64 patients had treatment deferrals due to neutropenia with a median time to first deferral of 4 weeks, while 23% requiring dose adjustments had no significant association with increased risk of disease progression.²⁸

Kish et al. (2018) assessed the setting in which palbociclib was being initiated and examined the real-world occurrence of neutropenia and how providers monitored and managed these events.²⁹ This study suggested good provider compliance with monitoring guidelines. Overall, 74.6% of patients had a neutropenic event. Stearns et al. (2018) showed in a real-world expanded-access program (EAP) setting and with a median treatment duration of 77 days that the combination of palbociclib and letrozole was generally well tolerated and AEs were manageable by protocol-specified temporary treatment discontinuation, dose reductions, and/or standard medical therapy.³⁰

In a retrospective chart review of 192 postmenopausal patients with HR+/HER2- mBC, from electronic medical records from a single-center institution, Xi et al. (2019) analyzed treatment patterns and the effectiveness of palbociclib and subsequent regimens in mBC.³¹ They found the median PFS on palbociclib was 20.7 months (first-line setting), 12.8 months (second-line), and 4.0 months in subsequent-line settings, which was comparable to the PALOMA-2 and PALOMA-3 trials. Gong et al. (2018) conducted a single institution, retrospective study of palbociclib and ET-related AEs.³² Out of the 100 patients included, treatment resulted in dose modification in 38.0% of the patients due to AEs, with 18.4% requiring subsequent dose changes. Most modifications occurred during the first 2 cycles, and 54.8% of them were due to grade 3-4 neutropenia. Kuran (2018) investigated mBC patients with HR+/HER2- breast cancer from a health care research network. Compared to ET, palbociclib demonstrated an increased risk of infection and bleeding.³³

Although informative, these were single-center/health care institution studies with small sample sizes (n varied from 30 to 411) and short follow-up time. Consequently, the generalizability of the results of these studies may be significantly reduced.

Palbociclib Real-World Cost-Effectiveness

Painful price points for payers seem to be more the rule than the exception regarding the newer add-ons for first-line therapies for HR+/HER2- breast cancer. These price points become more painful when there seem to be only marginal improvements in effectiveness over standards of care. Much of the evidence

for the cost-effectiveness of palbociclib has been conducted outside of the United States.³⁴⁻³⁷ Furthermore, no study has considered the effect of adherence on cost-effectiveness using real-world data. Mamiya et al. (2017) found that, based on the U.S. societal perspective in both previously treated patients for metastatic breast cancer and treatment naive patients, palbociclib was highly unlikely (0% probability with a willingness to pay of \$100,000 per quality-adjusted life-year [QALY]) to be cost-effective compared with usual care.³⁸ The authors used a discrete event simulation model using parameters based on published clinical trial data and other peer-reviewed studies.

A study by Mistry et al. (2018) evaluated letrozole to letrozole with palbociclib and letrozole with ribociclib, measured in life-years and QALYs, from a private third-party U.S. payer perspective.³⁹ The authors used a partitioned survival model, which simulated lifetime costs and outcomes over a 40-year lifetime horizon. The main finding was that ribociclib with letrozole was dominant versus palbociclib with letrozole, with a cost savings of \$43,037 and gain of 0.086 QALYs. Bhattacharya et al. (2016) used a Markov disease-state transition model to compare the cost-effectiveness of the combination of letrozole with palbociclib, with mainstay therapies anastrozole and letrozole, in postmenopausal women with HR+/HER2- advanced breast cancer from a third-party payer perspective.⁴⁰ Importantly, the transition state probabilities data were obtained from clinical trials and not real-world evidence, and no mention of adherence was made (only the abstract was available). The combination of palbociclib and letrozole was the least cost-effective with a cost-effectiveness value (in 2014 U.S. dollars) of \$111,791.95 compared with \$14,226.94 for anastrozole and \$14,545.26 for letrozole. Compared with anastrozole, the incremental cost-effectiveness ratio of the combination therapy was \$510,356.50, while it was \$21,824.34 for letrozole. This could be indicative of the higher acquisition cost of palbociclib.

The studies described here show that palbociclib, at its current negotiated prices in foreign universal health care systems, as well as domestically in the United States, is not cost-effective compared with other available therapies. However, these existing studies do not incorporate real-world adherence data, which may hinder an accurate estimation of the value of oral anticancer medications, including palbociclib.

Literature Gap and Future Directions

To date, the study of the real-world effectiveness of palbociclib in the treatment of women with HR+/HER2- breast cancer has been limited. What is known hinges on randomized controlled trials (RCTs) data, which does not necessarily reflect real-world use and outcomes. To address this issue, researchers have attempted to bridge the divide between RCTs and real-world evidence. One such attempt by the American Society of Clinical Oncology (ASCO) focused on the development of a framework that incorporates clinical benefit and toxicity

scores, with possible bonus points (as part of the advanced disease framework) to determine the net health benefit (NHB) score.⁴¹ The NHB score and associated costs of treatment are used to infer value gained for its degree of benefit. ASCO sought and received feedback on its conceptual value framework, leading to an update in May 2016.⁴² Within the update, a decision was made to adjust the clinical benefit component in the framework with a 20% reduction in points for RCTs that use surrogate endpoints, compared with RCTs, which use overall survival (OS). A study by Lakdawalla et al. (2017) assessed the difference between RCT efficacy and real-world effectiveness of cancer therapies and whether the type of endpoint used matters (i.e., surrogate vs. OS).⁴³ The authors found that real-world and RCTs treatment benefits based on OS were similar; however, treatment benefits based on surrogate endpoints were 16% lower in the real world. Frameworks such as that of ASCO can help prescribers make more informed decisions with their patients by taking evidence from RCTs and translating it into a patient-specific strategy to fight breast cancer in the real-world setting. The ASCO framework needs to be applied in a variety of populations with cancer and tested for validity in defined populations, such as the mBC population.

Adherence is typically assumed to be 100% in RCTs, unless otherwise stated, because of strict control over the treatment process. This level of adherence is often not replicated in the real-world setting and thus creates the opportunity to explore this matter further. Racial and geographical differences among patients with mBC may also vary regarding adherence and access to care, but clinical trials often fail to enroll enough minority patients for a complete understanding to occur. This creates another opportunity to delve into this complex subject matter further. Adherence to therapy is also important from the payer perspective (e.g., Centers for Medicare & Medicaid Services), since it is of interest for payers to know whether they, too, are dispensing funds for a therapy that will obtain desired outcomes in the real-world setting. With a more robust understanding of the real-world effectiveness of palbociclib, payers may more appropriately bargain prices of newer OAMs and, in effect, reduce the rise of oncologic drug costs while not hindering access for patients in need.

According to the willingness-to-pay thresholds from the United States, as previously discussed, the newer OAMs with AIs are not cost-effective relative to AIs alone.³⁸⁻⁴⁰ As previously mentioned, these studies were based on RCTs, which may not be reflective of real-world conditions. Therefore, it is imperative that well-designed, comprehensive studies focusing on real-world cost-effectiveness (which includes adherence to therapy), racial and geographic disparities, and patient outcomes be undertaken to fill in the knowledge gaps for women with HR+/HER2- mBC. This type of call to action has been championed by the National Institutes of Health, as stated in its Funding Opportunity Announcement Number PA-17-061.⁴⁴

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