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COMMENTARY

P-REALITY X: A Real-World Analysis of Palbociclib Plus an Aromatase Inhibitor in HR+/HER2− Metastatic Breast Cancer—A Podcast

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Abstract

Stringent enrollment criteria can limit the diversity of patient populations in clinical trials and, consequently, the generalizability of clinical trial data to real-world clinical practice. In this podcast, we discuss how real-world data in heterogeneous patient populations can complement clinical trial data in informing treatment decision making for patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) metastatic breast cancer. Specifically, our focus is on P-REALITY X, an observational retrospective analysis that was recently published in *npj Breast Cancer*. P-REALITY X used real-world data from the Flatiron database to compare the effectiveness of palbociclib plus an aromatase inhibitor versus an aromatase inhibitor alone as first-line treatment for patients with HR+/HER2− metastatic breast cancer. After stabilized inverse probability treatment weighting to control for observed confounders, both overall survival and real-world progression-free survival were significantly prolonged with palbociclib plus an aromatase inhibitor versus an aromatase inhibitor alone. Furthermore, overall survival and real-world progression-free survival benefits were observed across most subgroups examined. We discuss the clinical implications of P-REALITY X data, including how these results add to data from prior randomized clinical trials and real-world studies in supporting the use of first-line palbociclib plus an aromatase inhibitor as a standard-of-care treatment for patients with HR+/HER2− metastatic breast cancer. We also provide an example of how to integrate and describe key information about the P-REALITY X study in plain language when discussing palbociclib as a therapeutic option with patients.

The podcast and transcript can be viewed below the abstract of the online version of the manuscript. Alternatively, the podcast can be downloaded here: https://doi.org/10.6084/m9.figshare.22360618.

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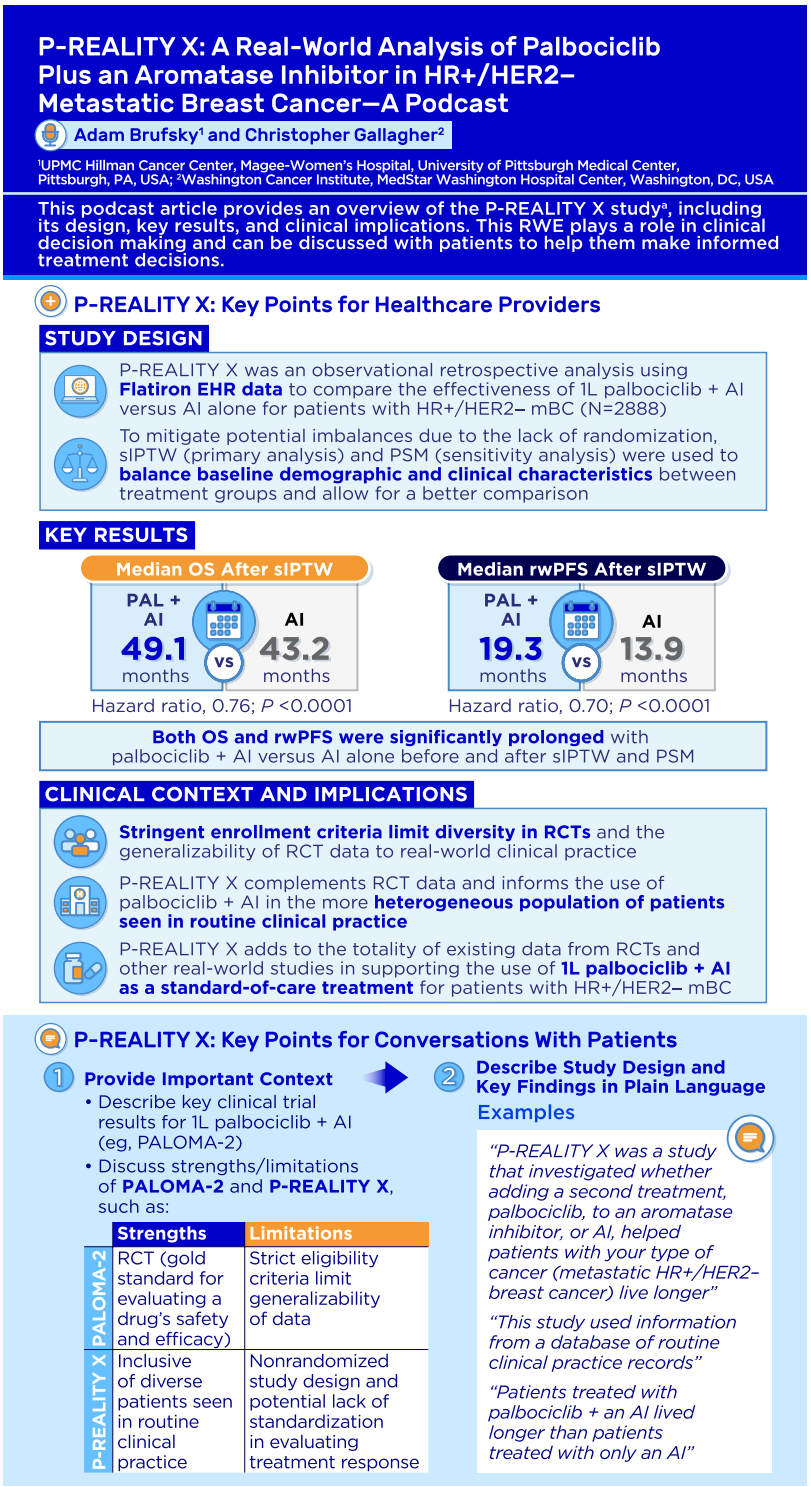
Infographic



Key Points

Real-world data in diverse patient populations can complement clinical trial data in informing routine clinical practice.

In the real-world P-REALITY X study, patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer treated with palbociclib plus an aromatase inhibitor lived longer than those treated with only an aromatase inhibitor.

This podcast provides a comprehensive overview of the P-REALITY X study, including its design, key results, and clinical implications, and how this information can be integrated into conversations with patients.

Podcast Transcript

Speakers: Adam Brufsky (AB) and Christopher Gallagher (CG).

AB: Hello, and welcome to this podcast on the P-REALITY X study for the Adis journal, *Targeted Oncology*. My name is Adam Brufsky. I'm a Professor of Medicine at the University of Pittsburgh, Medical Director of the Magee-Women's Cancer Program, and Associate Director for Strategic Initiatives at the UPMC Hillman Cancer Center in Pittsburgh, Pennsylvania. Thank you, Chris, for joining me today for this exciting discussion about the P-REALITY X study.

CG: Thank you, Adam, I'm looking forward to it. My name is Christopher Gallagher, and I'm a practicing medical oncologist and the Director of Cancer Services at MedStar Washington Hospital Center.

AB: Today, we'll be discussing the value of real-world studies in informing treatment decision making for patients with metastatic breast cancer. Specifically, we'll focus on an article that was recently published in *npj Breast Cancer* with the results of the real-world study P-REALITY X, which stands for Palbociclib REAl-world first-LIne comparaTive effectiveness studY eXtended [1]. P-REALITY X evaluated the use of palbociclib, a cyclin-dependent kinase 4/6 inhibitor, in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) metastatic breast cancer. To start, Chris, can you tell me your thoughts about real-world data? In general, how do data from real-world studies complement data from randomized clinical trials and inform your treatment decision making in the clinic?

CG: Stringent inclusion and exclusion criteria can limit the diversity of patient populations enrolled in clinical trials in terms of their demographic and clinical characteristics, such as age, performance status, and comorbidities [2]. Consequently, generalizing clinical trial data to actual clinical practice is sometimes limited. Data from real-world studies can shed light on the effectiveness of a drug in routine clinical practice in more diverse patient populations [2, 3]. But real-world studies are also subject to some limitations, including nonrandomized study design and lack of standardization in evaluating outcomes such as disease progression [3, 4]. So, I like to look at data generated from both randomized clinical trials and real-world studies when evaluating a therapy and deciding how to incorporate it into my own clinical practice, which brings us to our main topic of discussion today: the P-REALITY X study. Adam, as one of the co-authors of the recent publication, can you tell our listeners more about the study design and patient population in the P-REALITY X study?

AB: P-REALITY X was an observational retrospective analysis of electronic health records from the Flatiron database, a longitudinal database that contains de-identified patient data from over 280 cancer clinics, representing about 800 sites of care and more than 3 million actively treated patients with cancer in the United States [1]. This analysis compared the effectiveness of palbociclib and an aromatase inhibitor, or AI, versus an AI alone in postmenopausal women and men receiving first-line treatment for HR+/HER2− metastatic breast cancer. The primary outcome was overall survival, or OS, defined as the time from the start of treatment with palbociclib and an AI or an AI alone until death. Because patients in this observational study were not randomized, well-established statistical methodologies, including stabilized inverse probability treatment weighting (IPTW) and propensity score matching (PSM) were used to balance baseline demographic and clinical characteristics between the treatment groups. IPTW was the primary method used to control for observed confounders, and PSM was used as a sensitivity analysis; the combination of these methodologies confirmed the study's internal validity. Although these methods can reduce potential confounding biases, unobserved variables cannot fully be addressed by these methods. Today, we'll primarily focus our discussion on the results after IPTW, which is the primary analysis of this study.

In P-REALITY X, a total of 2888 postmenopausal women and men with HR+/HER2− metastatic breast cancer were identified in the Flatiron database [1]. These patients had started first-line treatment with palbociclib and an AI or an AI alone between February 3, 2015, and March 31, 2020. Patients had a potential follow-up time of 6–68 months from the index date to the study cut-off date of

September 30, 2020. Over 90% of the patients were treated in the community practice setting. The cohort after IPTW consisted of 2709 patients, including 1572 patients in the palbociclib + AI group and 1137 patients in the AI alone group. After IPTW, the median age was 70 years in both treatment groups. Approximately two-thirds of the patients were White, ~ 9% were Black, ~ 30% had visceral disease, and ~ 34% had de novo metastatic disease at diagnosis in both treatment groups.

CG: Thank you for that overview of the study design and patient population in P-REALITY X. I think it's a notable distinction that patients in P-REALITY X were predominantly treated in community practices, whereas patients in clinical trials are often treated in an academic setting. In your view, what are the most important results coming out of P-REALITY X that you would emphasize as an oncologist treating patients at a community practice?

AB: Focusing on the primary analysis after IPTW, I would emphasize that the adjusted OS was significantly longer with palbociclib and an AI versus an AI alone, with a median of 49.1 months versus 43.2 months, respectively [1]. An OS benefit was consistently observed across most subgroups examined, including among patients with and without visceral disease or bone-only disease. Also, patients receiving palbociclib and an AI had a significantly prolonged adjusted real-world progression-free survival (PFS) than those receiving an AI alone, with a median of 19.3 months versus 13.9 months, respectively. Like OS, this benefit in real-world PFS was observed across most subgroups examined. It's also worth noting that the significant OS and real-world PFS benefits seen with palbociclib and an AI versus an AI alone in the analysis after IPTW remained consistent in the unadjusted analysis and the analysis after PSM.

CG: I find it interesting to compare the data from P-REALITY X to the data from the PALOMA-2 study. For context, PALOMA-2 was a randomized, double blind, phase III clinical trial that compared palbociclib + letrozole versus placebo + letrozole as first-line treatment for postmenopausal women with estrogen receptor–positive/HER2− advanced breast cancer [5]. Similar to the findings from P-REALITY X, PFS was significantly prolonged in patients receiving palbociclib + letrozole versus placebo + letrozole in PALOMA-2, at a median of 27.6 versus 14.5 months, respectively. Although patients receiving palbociclib + letrozole had numerically longer OS than those receiving placebo + letrozole, at a median of 53.9 versus 51.2 months, this difference was not found to be statistically significant in PALOMA-2 [6]. Adam, what do you think might explain the discrepancy in OS findings between P-REALITY X and PALOMA-2?

AB: That's a great question. Before I respond, I want to mention that comparisons in outcomes between randomized controlled trials and real-world studies should always be interpreted with caution because of differences in study design, eligibility criteria, and other factors. There are several potential explanations for this discrepancy [1, 7]. To start, PALOMA-2 had less statistical power to detect differences in OS, which was a secondary endpoint, than in its primary endpoint of PFS. Conversely, P-REALITY X had nearly 5 times the number of patients examined compared with PALOMA-2, at a total of 2888 patients versus 666 patients, respectively, and consequently had greater statistical power to detect differences in its primary endpoint of OS.

In the P-REALITY X study, the treatment decision for palbociclib and an AI or an AI alone was made by the physician and/or the patient, whereas the treatment was randomly assigned in PALOMA-2 [1, 7]. Patient characteristics and treatment settings were rather different between the two studies. For example, the median patient age was 70 years old in P-REALITY X, but only 61–62 years old in PALOMA-2. Furthermore, the patient population in PALOMA-2 was confined to a relatively small number of patients who met rigorous inclusion and exclusion criteria. In contrast, P-REALITY X examined effectiveness in a large heterogeneous population of patients encountered in routine clinical practice. Most patients in PALOMA-2 were enrolled in academic centers, whereas over 90% of the patients in P-REALITY X were treated in community practices. It's also worth mentioning that, unlike PALOMA-2, safety data were not reported for P-REALITY X.

CG: Thank you for that important context to keep in mind when considering these real-world and clinical trial data. Thinking big picture, what are other important real-world studies beyond P-REALITY X that help inform the use of palbociclib in clinical practice?

AB: Several other studies have examined real-world effectiveness of the first-line treatment of palbociclib for patients with HR+/HER2− metastatic breast cancer, including other analyses of the Flatiron database and an analysis of the Breast Medical Oncology database at MD Anderson [8–10]. In alignment with the findings of P-REALITY X, these studies have consistently demonstrated a real-world PFS benefit of adding palbociclib to endocrine therapy in the first-line setting. Therefore, P-REALITY X adds to the growing body of literature, including clinical trial and real-world data, that supports the use of first-line palbociclib plus an AI as a standard of care for patients with HR+/HER2− metastatic breast cancer [1, 5, 8–10].

CG: I agree. I'll also point out that P-REALITY X is the largest multicenter, real-world, comparative effectiveness study to date analyzing palbociclib combination therapy in the first-line setting for patients with HR+/HER2− metastatic breast cancer [1]. Importantly, these real-world data showed an OS benefit of adding palbociclib to an AI in diverse patient populations, including in patients with

visceral or de novo metastatic disease and in Black patients or those aged 75 years or older—demographic subtypes that are often under-represented in breast cancer clinical trials. Overall, these data make me feel comfortable using palbociclib + an AI in the diverse population of patients I see in my day-to-day clinical practice.

AB: To finish our discussion, I think it's important to think about how we describe these important results to patients in the clinic to help them make informed treatment decisions. Chris, in your day-to-day practice, how would you integrate information about P-REALITY X when discussing palbociclib as a therapeutic option with a patient who has HR+/HER2− metastatic breast cancer?

CG: It can certainly be challenging to describe the implications of study data to patients in layman's terms. That said, I can provide some examples of how I would translate key information to facilitate a patient's understanding of the P-REALITY X study. Before discussing P-REALITY X data with the patient, I would first go over key results from the PALOMA-2 clinical trial. Then I would discuss the strengths and limitations of clinical trial data and the complementary value of real-world evidence when considering a therapeutic option like palbociclib. I would say, *"Clinical trial data are the gold standard for evaluating the safety and efficacy of a new therapy* [3]. *But, there are often strict rules about who can join a clinical trial, and people who have other illnesses or are taking other medicines may not be able to join* [3, 11, 12]. *In routine clinical practice, the rules about who can be treated with a medicine are less strict. Compared with people in clinical trials, people in routine clinical practices may be older, sicker, or have illnesses in addition to metastatic breast cancer."*

Thereafter, I would recommend explaining the study design and key findings from P-REALITY X in layman's terms: *"P-REALITY X was a study that investigated whether adding a second treatment, palbociclib, to an aromatase inhibitor, or AI, helped patients with your type of cancer (metastatic HR+/HER2− breast cancer) live longer* [1]. *This study used information from a database of routine clinical practice records. This information was de-identified, meaning that all personally identifiable information was removed to protect patients' privacy* [1, 13]. *The results of this study showed that, in routine clinical practice, patients treated with palbociclib plus an AI lived longer than patients treated with only an AI* [1]. *In addition, the patients who received palbociclib and an AI experienced a longer time before their cancer progressed, or got worse, than those who received an AI alone."*

Lastly, I would summarize the clinical implications of the data by saying: *"These results support the use of palbociclib plus an AI as standard first treatment for patients with metastatic HR+/HER2− breast cancer, which is why I think this combination would be a good treatment option for you"* [1].

AB: Well, I think that concludes our podcast for today. Thank you, Chris, for joining me in a robust discussion on the value of real-world evidence in informing treatment decision making for patients with metastatic breast cancer, focusing specifically on P-REALITY X. We hope our listeners have found this podcast to be a useful overview of P-REALITY X and how information about this study can be integrated into conversations with patients.

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Declarations

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Consent for Publication Not applicable.

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