Transcript Details

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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

HR+/HER2- Metastatic Breast Cancer: Real-World Evidence in Action

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Now, here's your host, Dr. Charles Turck.

Dr. Turck:
This is ReachMD and I'm Dr. Charles Turck. Today, we'll review some real-world evidence, also called RWE. We'll look at a study of palbociclib in combination with an aromatase inhibitor, or AI, versus an AI alone for the treatment of hormone receptor-positive/human epidermal growth factor receptor two-negative metastatic breast cancer, or HR-positive/HER2-negative mBC for short. Joining me to explore RWE in action are Dr. Massimo Cristofanilli and Dr. Christos Vaklavas.

Dr. Cristofanilli is a board-certified medical oncologist specializing in breast cancer in New York City. Dr. Cristofanilli, welcome to the program.

Dr. Cristofanilli:
Thanks, Dr. Turck, for having me participate in this important educational program.

Dr. Turck:
Also with us is Dr. Vaklavas, a board-certified oncologist also specializing in breast cancer, practicing in Salt Lake City, Utah. Dr. Vaklavas, thank you for being with us today.

Dr. Vaklavas:
Well thank you, Dr. Turck, for having me as well participate in this important educational program.

Dr. Turck:
Before we dive in, let's take a moment to review the Indication and some Important Safety Information for IBRANCE®.[1]

ReachMD Announcer:
Indication
IBRANCE (palbociclib) 125 mg capsules and tablets are indicated for the treatment of adult patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer (mBC) in combination with an aromatase inhibitor as initial endocrine-based therapy.

Selected Safety Information
Neutropenia was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (55%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant. Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis

was observed in PALOMA-3. Inform patients to promptly report any fever.

Monitor complete blood count prior to starting IBRANCE, at the beginning of each cycle, on Day 15 of first 2 cycles and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Please stay on until the end of this presentation to hear the full Important Safety Information for IBRANCE.

For the full Prescribing Information, please see the links below this program on the landing page.

Dr. Turck:
Let's first take a quick look at the Phase III randomized, controlled trial for palbociclib in combination with letrozole, since this serves as the foundation for the real-world evidence study that we will be discussing today. Dr. Vaklavas— can you give us an overview of the PALOMA-2 study?

Dr. Vaklavas:
Yes, PALOMA-2 was a two-to-one randomized, double-blind Phase III trial of palbociclib plus letrozole compared with placebo plus letrozole in 666 postmenopausal women with estrogen receptor-positive/HER2-negative metastatic breast cancer with no prior treatment in the metastatic setting.[2]

The primary endpoint of progression-free survival, or PFS, was found to be a median of 24.8 months with 194 events in the palbociclib plus letrozole group versus a progression-free survival of 14.5 months with 137 events in the placebo plus letrozole group. And this difference was statistically significant with a hazard ratio of 0.58 and a p-value <0.0001.[1,3,4]

Select secondary endpoints in this study were objective response rate, or ORR, and overall survival, also called OS. The objective response rate in 338 patients with measurable disease was 55.3% with palbociclib plus letrozole compared to 44.4% in 171 patients receiving placebo plus letrozole.[1,2]

The overall survival results were not statistically significant. In a final analysis of overall survival with 435 events, which was about 65 percent of the trial population, the median overall survival with palbociclib plus letrozole was 53.8 months, versus 49.8 months with placebo plus letrozole. The hazard ratio was 0.92 and the p-value was 0.2087.[1]

ReachMD Announcer:
Safety Information
The **most common adverse reactions (≥10%)** of any grade reported in **PALOMA-2** for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (80% vs 6%), infections (60% vs 42%), leukopenia (39% vs 2%), fatigue (37% vs 28%), nausea (35% vs 26%), alopecia (33% vs 16%), stomatitis (30% vs 14%), diarrhea (26% vs 19%), anemia (24% vs 9%), rash (18% vs 12%), asthenia (17% vs 12%), thrombocytopenia (16% vs 1%), vomiting (16% vs 17%), decreased appetite (15% vs 9%), dry skin (12% vs 6%), pyrexia (12% vs 9%), and dysgeusia (10% vs 5%).

Dr. Turck:
Thank you, Dr. Vaklavas. This is helpful information as we move on to explore P-REALITY X: Palbociclib REAl-world first-LIne comparaTive effectiveness studY eXtended, an RWE study that evaluated the effectiveness of palbociclib with an aromatase inhibitor versus an aromatase inhibitor alone in HR-positive/HER2-negative mBC.[5]

Let's turn to you now, Dr. Cristofanilli. Could you give us some background on this study?

Dr. Cristofanilli:
I'd be happy to. P-REALITY X was a retrospective analysis of electronic health records that compared the real-world effectiveness of first-line palbociclib plus an aromatase inhibitor treatment, or AI, versus an aromatase inhibitor alone in patients with hormone receptor-positive/HER2-negative metastatic breast cancer.[5]

The primary endpoint was overall survival, and the secondary endpoint was real-world progression-free survival.[5]

A total of 2,859 postmenopausal women and 29 men were included in the analysis after being identified in the Flatiron Database, a longitudinal database of electronic health records from over three million actively treated cancer patients throughout the U.S.[5]

The researchers applied well-established statistical methods such as stabilized inverse probability of treatment weighting and the propensity score matching to reduce potential confounders due to the lack of prospective randomization.[5]

Dr. Turck:

Now, turning to you, Dr. Vaklavas, what are some of the limitations of the P-REALITY X study?

Dr. Vaklavas:
Limitations to P-REALITY X include the retrospective nature of the study – which can also contribute to missing data, the lack of randomization, and that safety data weren't collected as part of the study.[5,6]

Now, any data source, including Flatiron has the potential for missing or erroneous data entry. For example, we in practice know that not all visits will document every data point such as ECOG performance status or the full list of comorbidities that a patient may have. Also, there's a possibility of data entry errors.[5-7]

Also, tumor response to treatment wasn't determined by standardized criteria like RECIST, short for Response Evaluation Criteria in Solid Tumors, but instead was based on individual physician assessment.[5,6] And this is because, RECIST criteria aren't generally used outside of a clinical trial setting, so physicians' assessments of response to treatment may include some subjectivity in interpretation.[8,9] And this is different from the overall survival endpoint, which is truly objective.[5,6]

Next, although stabilized inverse probability of treatment weighting and propensity score matching are appropriate statistical approaches to balance patient characteristics between treatment arms, there is still residual confounding. This reflects confounders that weren't included, either because they weren't available in the dataset or weren't known.[5,6]

And finally, even pulling from this large database, the findings may not be generalizable to patient populations outside of the Flatiron network given different practice patterns.[5,6]

Dr. Turck:
And keeping these in mind, Dr. Cristofanilli, what were the results of the P-REALITY X study?

Dr. Cristofanilli:
The findings after applying stabilized inverse probability of treatment weighting, or sIPTW for short, showed that palbociclib plus an aromatase inhibitor was associated with a longer median overall survival of 49.1 months versus 43.2 months for patients treated with an aromatase inhibitor alone. The hazard ratio was 0.76.[5]

And then the propensity score matching was used as a sensitivity analysis, which showed consistent findings with the sIPTW analysis.[5]

The palbociclib treatment group was also associated with a prolonged real-world progression-free survival interval of 19.3 months compared to 13.9 months in the aromatase inhibitor-only treatment group.[5]

These findings were consistent across both cohorts after statistical methods were used to balance patient characteristics, as well for most subgroups analyzed.[5]

Let's keep in mind that this observational retrospective analyses aren't intended for direct comparison with clinical trials.

Dr. Turck:
Thank you both for walking us through the P-REALITY X study. As a follow-up, Dr. Cristofanilli, can you highlight the value you see with RWE studies like P-REALITY X beyond what we learn from a randomized controlled trial, or an RCT?

Dr. Cristofanilli:
Yes, real-world evidence studies can complement randomized clinical trials because real-world evidence has the ability to study how providers treat patients in routine clinical practice and how patients actually use treatments in the real world.[7]

First, let's keep in mind that observational retrospective studies aren't intended to be directly compared to clinical trials.

In essence, clinical trials are conducted in a highly monitored, controlled environment with data from prespecified endpoints which are uniformly assessed according to the trial protocol.[10] Due to these study design characteristics, along with randomization of study participants to a treatment or comparator, randomized clinical trials are designed to show causality.[10,11] And so, randomized clinical trials can provide us valuable clinical information by measuring the efficacy of an intervention because of these highly controlled conditions.[10]

With real-world evidence, a heterogeneous patient population can be evaluated.[12,13] Now, it is important to stress that real-world evidence studies are designed to assess associations and are not able to determine causality.[10,13] And because patients aren't

randomized, they can't fully address bias related to treatment selection and unobserved variables.[10,13] However, the nature of real-world observational studies allows for variability in patient assessment and adherence, as the endpoints are derived from assessments based on clinical judgement.[10] Also, these studies can result in varied outcomes, as they're based in routine clinical practice and broad patient populations.[10] So the real-world evidence can give information on the effectiveness, rather than the efficacy, of an intervention – where effectiveness describes the performance under real-world settings.[10]

Real-world evidence isn't intended to be a replacement for randomized clinical trials when it comes to assessing the safety and efficacy of therapies. Instead, they complement the randomized clinical trial data—for example, with long-term safety or real-world effectiveness information—which could help paint a fuller picture for clinical decision-making with our patients.[10,14]

Dr. Turck:
Now turning to you, Dr. Vaklavas, what aspects of an RWE study do you find necessary to evaluate before incorporating findings into your practice?

Dr. Vaklavas:
A key factor to consider when evaluating real-world evidence is that because study groups aren't randomized like randomized clinical trials, there's a potential for bias. The main types of biases seen with real-world data include:[11,15]

- information bias caused by data misclassification
- missing data from inconsistent data collection
- selection bias from different therapies being prescribed depending on patient and disease characteristics
- reporting bias caused by selective recall of events by patients or caregivers, and
- confounding due to the lack of randomization.

So, any association drawn between the treatment groups and the study outcomes could be influenced by confounding factors.[11]

So, you'd want to take a look at how potential biases were addressed in any real-world study. This is typically done using statistical methods.

Now, as we mentioned, P-REALITY X employed two standard statistical methodologies: stabilized inverse probability of treatment weighting or sIPTW, and propensity score matching or PSM, to minimize bias by reducing the effect of potential confounders.[5]

sIPTW is a statistical tool that weights patients according to their baseline characteristics using propensity scoring, which represents the probability a patient will receive a particular treatment.[16-18]

After weighting, two cohorts that have balanced characteristics are created, thereby enabling a fair comparison across treatment groups.[16-18]

Propensity score matching is another statistical matching technique that uses the propensity score—in this case to match patients from each treatment arm according to their propensity score— to create a balanced and comparable study group.[19]

The P-REALITY X study effectively employed sIPTW to balance patient baseline characteristics and to allow for better comparison between the two treatment groups in this non-randomized population.[5]

Dr. Turck:
And staying with you, Dr. Vaklavas, what other areas of an RWE study are valuable for you to review?

Dr. Vaklavas:
Another area of RWE to pay attention to is the quality and completeness of the data source. Advancements in technology have led to large volumes of real-time patient data which can be accessed and analyzed for any number of clinical questions. But with few standards guiding real-world data quality, we can see varying levels of data availability and quality.[7]

Real-world data can vary in completeness and quality depending on where, when, and how the data are being collected and recorded. For example, whether data is collected prospectively versus a retrospective review, these differences can determine the confidence in the data collected.[7]

In this respect, one strength of P-REALITY X is the use of the Flatiron data source, which is a robust dataset of U.S. cancer patients in terms of quality and validity.[5]

In fact, Flatiron data has been used in many peer-reviewed articles and within some regulatory submissions. This database of over three million electronic health records is mostly from community practices, where the majority of patients get their care, and is sourced from over 800 unique sites of care. And, to gather a more completed dataset, it uses a two-fold extraction method that combines technology with human expertise. Importantly, the death endpoint which was used in P-REALITY X for overall survival, is an objective composite datapoint of multiple confirmed death data sources—and it's been validated separately in a study. Confirming the validity of the data collected helps increase confidence in the study findings using this data source.[5,20-24]

Dr. Turck:
And coming back to you, Dr. Cristofanilli, how do the RWE findings of P-REALITY X complement prior RCT evidence for palbociclib?

Dr. Cristofanilli:
Well, let's take a look at the data, remembering that observational, retrospective analyses are not intended for direct comparison with clinical trials.

In PALOMA-2, the phase III trial of postmenopausal women with estrogen receptor-positive/HER2-negative metastatic breast cancer, patients were randomized two-to-one to receive either palbociclib plus letrozole or placebo plus letrozole. And the study had met its progression-free survival primary endpoint by showing that the palbociclib plus letrozole group had a statistically significant prolonged median progression-free survival compared to the placebo plus letrozole group.[1-4]

Now let's return to the overall survival, which we had discussed was a secondary endpoint in PALOMA-2. The patients who received palbociclib plus letrozole had a median overall survival of 53.8 months, versus 49.8 months for those who were on placebo plus letrozole, and this difference was not statistically significant in PALOMA-2.[1]

In P-REALITY X, the study met its primary endpoint of prolonging overall survival in patients receiving palbociclib plus an aromatase inhibitor, and in this retrospective analysis the overall survival increase was observed across both statistical methods used – in the sIPTW analysis, and the propensity score matching analysis.[5]

In the P-REALITY X population, the increase in survival in patients receiving palbociclib plus an aromatase inhibitor over an aromatase inhibitor alone was seen in most of the subgroups analysis examined, including patients older than 75, Black race patients, and those with visceral disease.[5]

Dr. Turck:
And as a follow-up, Dr. Cristofanilli, what do you see as the overall strengths of the trial design of P-REALITY X?

Dr. Cristofanilli:
In my opinion, this is a well-designed and conducted real world study: it used a robust dataset with a validated primary overall survival endpoint and applied strong statistical methodologies to minimize bias.[5,24]

This was a large real-world comparative effectiveness study in postmenopausal women and men with hormone receptor-positive/HER2-negative metastatic breast cancer who were mostly treated in community practices.[5,20]

Under these real-world conditions, survival outcomes from palbociclib plus an AI were compared to AI-only treatment, where the AI used for treatment varied based on the treating provider's clinical judgement. The results of this study showed that first-line palbociclib with an AI was associated with a survival benefit in the population—but as an observational retrospective analysis, we cannot draw conclusions for causality.[5,10,14]

However, the P-REALITY X real-world evidence study adds important data on the real-world effectiveness of this therapy, and complements the randomized clinical trial data[2,10] to help create a fuller understanding of the clinical impact of palbociclib plus an AI as a first-line therapy for hormone receptor-positive/HER2-negative metastatic breast cancer.

Dr. Turck:
You've given us a lot to consider in our discussion today; before we close, let's hear additional Important Safety Information.

ReachMD Announcer:
Important Safety Information
Neutropenia was the most frequently reported adverse reaction in PALOMA-2 (80%) and PALOMA-3 (83%). In PALOMA-2, Grade 3 (56%) or 4 (10%) decreased neutrophil counts were reported in patients receiving IBRANCE plus letrozole. In PALOMA-3, Grade 3 (55%) or Grade 4 (11%) decreased neutrophil counts were reported in patients receiving IBRANCE plus fulvestrant. Febrile neutropenia has been reported in 1.8% of patients exposed to IBRANCE across PALOMA-2 and PALOMA-3. One death due to neutropenic sepsis

was observed in PALOMA-3. Inform patients to promptly report any fever.

Monitor complete blood count prior to starting IBRANCE, at the beginning of each cycle, on Day 15 of first 2 cycles and as clinically indicated. Dose interruption, dose reduction, or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia.

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with CDK4/6 inhibitors, including IBRANCE when taken in combination with endocrine therapy. Across clinical trials (PALOMA-1, PALOMA-2, PALOMA-3), 1.0% of IBRANCE-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3 or 4, and no fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported. Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g., hypoxia, cough, dyspnea). In patients who have new or worsening respiratory symptoms and are suspected to have developed pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis.

Based on the mechanism of action, IBRANCE can cause fetal harm. Advise females of reproductive potential to use effective contraception during IBRANCE treatment and for at least 3 weeks after the last dose. IBRANCE may impair fertility in males and has the potential to cause genotoxicity. Advise male patients to consider sperm preservation before taking IBRANCE. Advise male patients with female partners of reproductive potential to use effective contraception during IBRANCE treatment and for 3 months after the last dose. Advise females to inform their healthcare provider of a known or suspected pregnancy. Advise women not to breastfeed during IBRANCE treatment and for 3 weeks after the last dose because of the potential for serious adverse reactions in nursing infants.

The most common adverse reactions (≥10%) of any grade reported in PALOMA-2 for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (80% vs 6%), infections (60% vs 42%), leukopenia (39% vs 2%), fatigue (37% vs 28%), nausea (35% vs 26%), alopecia (33% vs 16%), stomatitis (30% vs 14%), diarrhea (26% vs 19%), anemia (24% vs 9%), rash (18% vs 12%), asthenia (17% vs 12%), thrombocytopenia (16% vs 1%), vomiting (16% vs 17%), decreased appetite (15% vs 9%), dry skin (12% vs 6%), pyrexia (12% vs 9%), and dysgeusia (10% vs 5%).

The most frequently reported Grade ≥3 adverse reactions (≥5%) in PALOMA-2 for IBRANCE plus letrozole vs placebo plus letrozole were neutropenia (66% vs 2%), leukopenia (25% vs 0%), infections (7% vs 3%), and anemia (5% vs 2%).

Lab abnormalities of any grade occurring in PALOMA-2 for IBRANCE plus letrozole vs placebo plus letrozole were decreased WBC (97% vs 25%), decreased neutrophils (95% vs 20%), anemia (78% vs 42%), decreased platelets (63% vs 14%), increased aspartate aminotransferase (52% vs 34%), and increased alanine aminotransferase (43% vs 30%).

Avoid concurrent use of strong CYP3A inhibitors. If patients must be administered a strong CYP3A inhibitor, reduce the IBRANCE dose to 75 mg. If the strong inhibitor is discontinued, increase the IBRANCE dose (after 3-5 half-lives of the inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Grapefruit or grapefruit juice may increase plasma concentrations of IBRANCE and should be avoided. Avoid concomitant use of strong CYP3A inducers. The dose of sensitive CYP3A substrates with a narrow therapeutic index may need to be reduced as IBRANCE may increase their exposure.

For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg. The pharmacokinetics of IBRANCE have not been studied in patients requiring hemodialysis.

For the full Prescribing Information, please see the links below this program on the landing page.

Dr. Turck:
I want to thank my guests, Dr. Massimo Cristofanilli and Dr. Christos Vaklavas for sharing their insights with us. Dr. Cristofanilli, Dr. Vaklavas, it was great speaking with you today.

Dr. Cristofanilli:
Thank you for having me.

Dr. Vaklavas:
Thank you as well for having me.

ReachMD Announcer:
This program was sponsored by Pfizer Oncology Medical Affairs. If you missed any part of this series, visit *Project Oncology* on ReachMD. This is ReachMD. Be Part of the Knowledge.

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