AXIS Medical Education

Getting on Board With Real-World Evidence About CDK 4/6 Inhibitors for HR+/HER2- mBC:

Stay on Track with Shared Decision Making

This transcript has been edited for style and clarity and includes all slides from the presentation.

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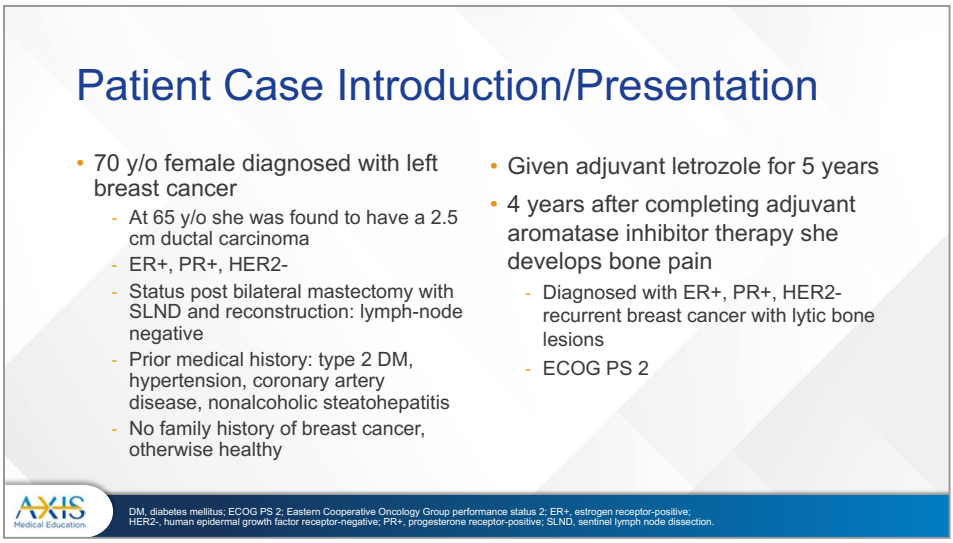
Getting on Board with Real-World Evidence About CDK 4/6 Inhibitors for HR+/HER2- mBC: Stay on Track with Shared Decision Making

Richard Finn, MD

Richard Finn, MD: Hello, I'm Dr. Richard Finn from the David Geffen School of Medicine at the University of California Los Angeles. I'd like to welcome you to our oncology clinic on CDK4/6 inhibitors in hormone-receptor positive, HER2-negative metastatic breast cancer.

There is strong clinical evidence supporting the use of CDK4/6 inhibitors combined with endocrine therapy for hormone-receptor positive, HER2-negative metastatic breast cancer. Real-world evidence shows that CDK4/6 inhibitors are safe and effective treatments for patients with hormone-receptor positive, HER2-negative metastatic breast cancer. Real-world evidence can supplement clinical-trial evidence and be more applicable to relevant community-based populations and real-world clinical practice settings. Optimal care of metastatic breast cancer involves the use of effective therapies that are supported by the latest evidence and guidelines, selected through a shared decision-making process and individualized to each patient's needs.

Today, I'll be illustrating my approach to shared decision-making and the utilization of real-world evidence that complements clinical-trial evidence through clinical vignettes with a patient who has stage IV breast cancer. Let's get started.



Paulette is a 70-year-old female diagnosed with left breast cancer. At age 65, she was found to have a 2.5-centimeter ductal carcinoma. Her tumor was ER-positive, PR-positive and HER2-negative. She had a bilateral mastectomy with sentinel lymph node dissection and breast reconstruction with a negative lymph nodes. Her past medical history includes diabetes mellitus type 2, hypertension, coronary artery disease, and nonalcoholic steatohepatitis. She has no family history of breast cancer and is otherwise healthy.

She was treated with adjuvant letrozole for 5 years. Four years after completing adjuvant aromatase inhibitor therapy, she developed bone pain and was found to have recurrent ER-positive, PR-positive, HER2-negative breast cancer with lytic lesions. Her ECOG performance status is 2. Today she is in my office to discuss her treatment options.

Patient Vignette #1: Modeling Why Real-World Evidence With CDK4/6 Inhibitors Matters

Hi, Paulette. How are you today?

Paulette: I'm doing well. But I knew something was off with the pain I am experiencing. I am feeling anxious about the cancer returning. But I'm hoping that we can find another successful treatment.

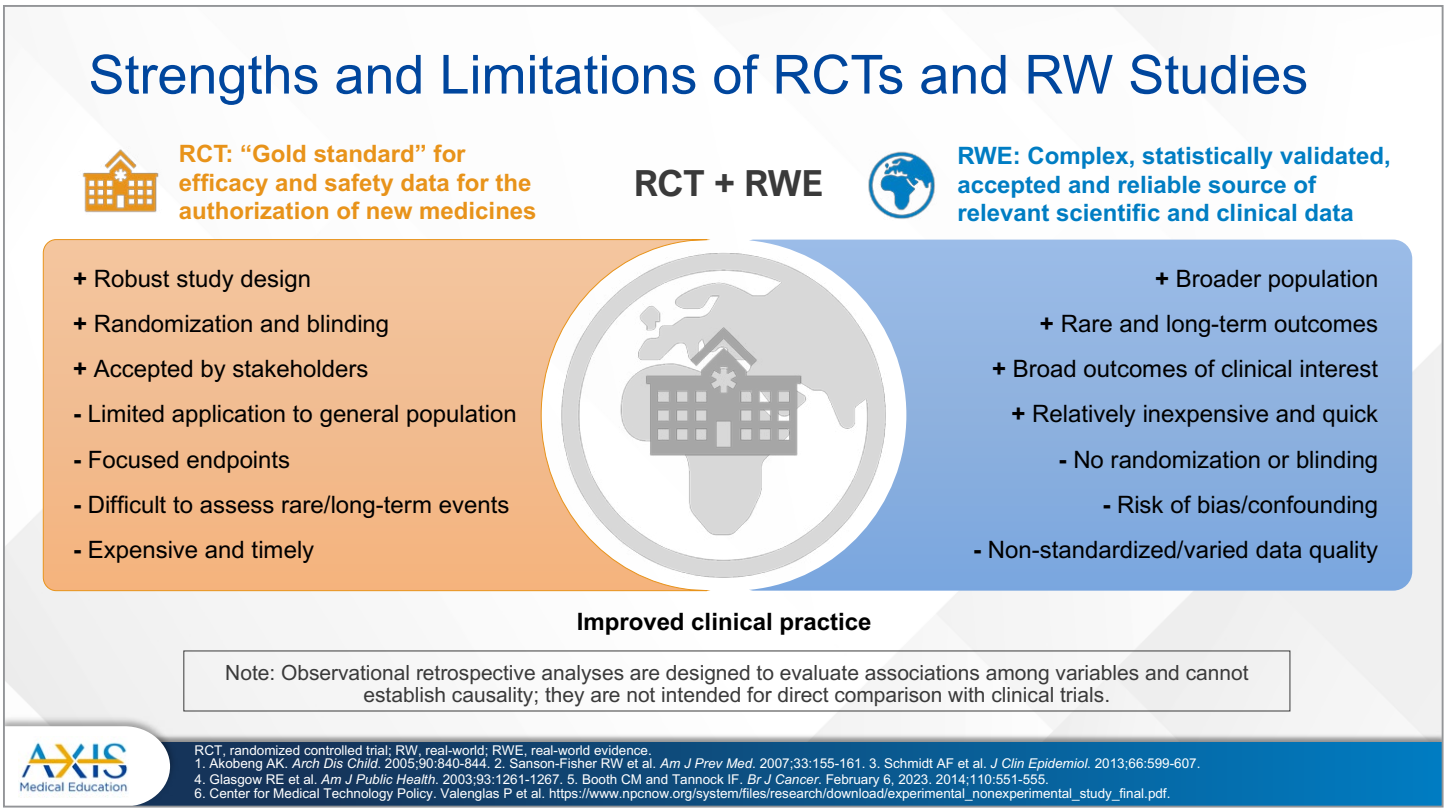
Dr. Finn: I'm glad you're doing okay. We do have a few treatment options that we can discuss today. First, tell me about your preferences and goals for treatment. What is important to you to consider for your next treatment?

Paulette: I prefer oral medication, like the letrozole that I am taking. Is that a given option or do I need chemotherapy?

Dr. Finn: We do have very effective treatment options I'd like to discuss with you today called CDK4/6 inhibitors, which are oral medications that are given with endocrine treatment. There are three CDK4/6 inhibitors that are FDA approved: abemaciclib, palbociclib, and ribociclib. The use of the CDK4/6 inhibitors is supported by clinical evidence and complemented by real-world data, which I'd like to review today to help in your decision making about treatment.

Paulette: Yes, I would like to hear more about this treatment.

Dr. Finn: Great. I want to start by telling you about the value of real-world evidence and how it differs from clinical evidence. Real-world evidence comes from data that is collected typically after a drug receives FDA approval. For FDA approval, drugs need to go through very rigorous clinical trials that have very specific endpoints and inclusion and exclusion criteria. By and large, not every patient we see in clinic will qualify for a clinical trial. Real-world evidence is looking at a broader patient population. And it's called real-world because it includes the patients we see every day in clinic. While clinical trial data is used for FDA approvals, real-world evidence can be used to complement those data.

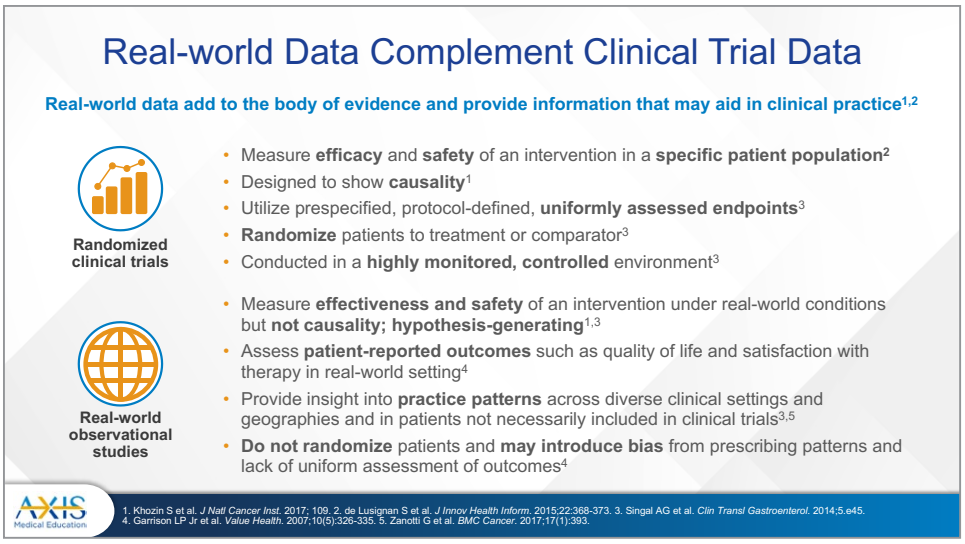


Dr. Finn:
So, our goal today will be to talk about an overview of the benefits and limitations of real-world evidence. Specifically, the value of real-world evidence picks up where randomized controlled trials lead off, meaning that randomized control trials are very strictly controlled in regards to their inclusion and exclusion criteria. And in that sense, real-world data complements the dataset for patients who are not necessarily included in those randomized controlled studies. Real-world evidence, by its name, suggests that this is a dataset derived from patients we see in the clinic that may not otherwise qualify for a clinical trial.

Still, obviously, the gold standard for FDA approvals and regulatory approvals and guidelines are randomized controlled trials. However, there is a large amount of real-world evidence that's been collected now with CDK4/6 inhibitors, and we'll discuss how this data looks and why it may be important in selecting treatments for our patients.

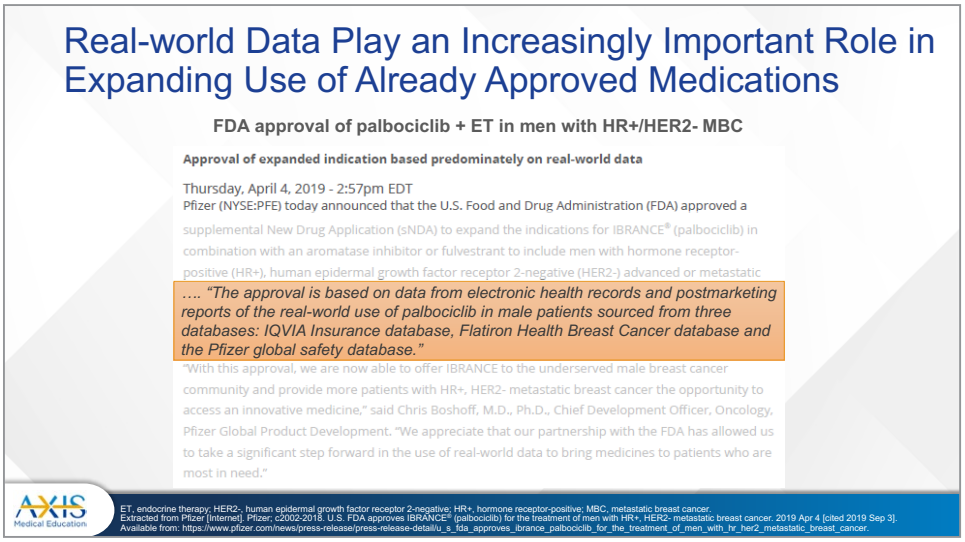
So, this slide highlights some of the differences between a randomized control trial and real-world datasets. Again, real-world data is meant to complement a randomized control trial, or RCT, it is not of the level of evidence to replace an RCT. An RCT really has very robust endpoints and is designed to answer a specific question. In the context of CDK4/6 inhibitors, the phase 3 studies were designed to show that in combination with endocrine treatments in a specific patient population, both frontline and second line, that the addition of CDK inhibitors would improve progression-free survival.

Real-world evidence really is a much broader population. Because it's broader, it can pick up subgroups of patients that are less commonly enrolled in clinical trials but have relevance to real-world data.

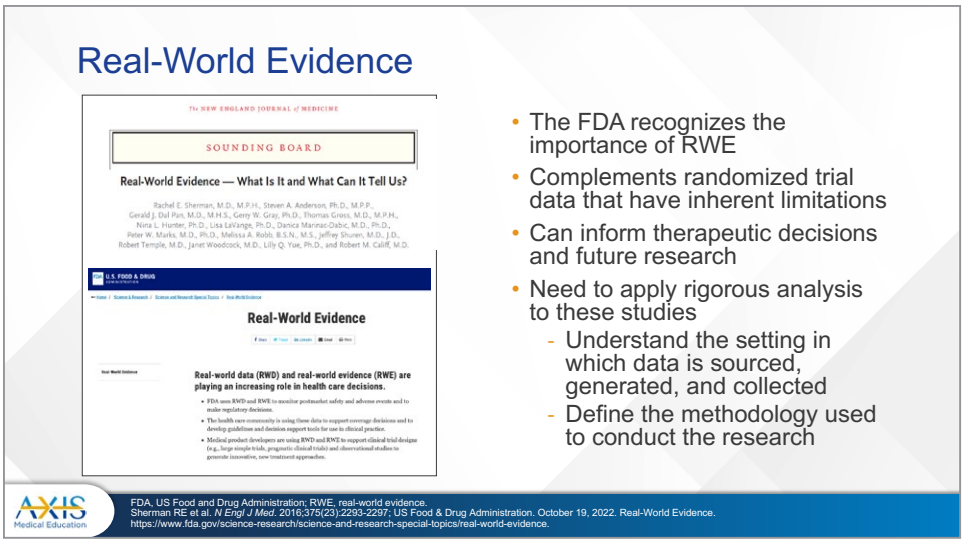


So, by doing a blinded randomized controlled study, we're looking at efficacy and safety, but it's designed to show that your intervention is responsible for the outcome. These are very highly monitored. There's a lot of oversight from both sponsor as well as regulatory bodies.

In contrast, real-world data is really observing effectiveness and safety. However, you cannot really say because of the lack of control and other limits in monitoring, that any specific intervention is responsible for these outcomes. These datasets are not controlled by when imaging is done, how physicians manage patients, how they might do dose reductions, which are otherwise very tightly controlled in randomized studies. However, having a large number of patients can capture how these drugs are used in practice across a diverse population. Also, because there is no strict protocol and physicians know what patients are getting, certainly bias can be introduced.



However, the regulatory bodies are looking at real-world data in a much more progressive way, I would say. We actually have a precedent now since the FDA has used real-world data on which to base FDA approvals. An example of that was the expanded use of palbociclib and endocrine treatment in men with hormone-receptor positive HER2-negative breast cancer. These patients were not included in the phase 3 studies done with palbociclib. However, based on real-world data, the FDA was convinced that they could extend the label to cover this group of patients.



- And there have been several commentaries now from the regulatory bodies recognizing the importance of real-world data, and how it can be used to guide further research in the future.

  Let's return to our discussion with Paulette to go over the clinical trial data and the real-world evidence we've seen with CDK4/6 inhibitors.

Patient Vignette #2: Modeling Personalizing Therapy for Patients With HR+/HER2- mBC

Dr. Finn: Do you have questions for me before we take a look at some of the data?

Paulette: That is very interesting. It is nice to know that real-world data exists. It makes me feel slightly less alone and more optimistic about treatment.

Dr. Finn: Great. Let's go ahead and review the data for CDK4/6 inhibitors to help with our decision making.

As I mentioned, there are three CDK4/6 inhibitors that have been approved by the FDA for the treatment of your type of breast cancer: abemaciclib, ribociclib, and palbociclib. All of them are approved for patients like you who have had prior endocrine treatment and then their cancer came back. The studies all combined endocrine treatments, like letrozole, which you were on, in combination with the CDK4/6 inhibitors. And all of these studies were designed to show that they delay progression of the cancer. All of them demonstrated very similar results, a very significant benefit for patients receiving these treatments, in delaying their treatment as compared to standard treatment, which was endocrine treatment or letrozole alone.

Two of the drugs, palbociclib and ribociclib, are taken 3 weeks in a row and 1 week off, whereas abemaciclib is dosed continuously, and letrozole is taken every day or whatever endocrine treatment we decide on.

When we look at real-world evidence, that is, like we said before, the data with these drugs in real-world populations, not in clinical trials, all of these drugs seem to be performing similarly to what we saw in the clinical data.

So, I think by now we have a lot of experience with these drugs. And we're confident that they can help patients with your type of breast cancer and generally are very well tolerated. We even have data now that tells us that these drugs are actually not only slowing the progression of the breast cancer, but helping women live longer and maintain a very high quality of life.

Phase 3 Endocrine Combination Studies with CDK 4/6 Inhibitors[1]

	PALOMA-2	MONALEESA-2	MONARCH-3	MONALEESA-7	PALOMA-3	MONALEESA-3	MONARCH-2
Drug	Palbociclib	Ribociclib	Abemaciclib	Ribociclib	Palbociclib	Ribociclib	Abemaciclib
Partner or control	Letrozole	Letrozole	Letrozole or anastrozole	Tamoxifen, letrozole, or anastrozole (plus goserelin)	Fulvestrant	Fulvestrant	Fulvestrant
Size, No.	666	668	493	672	521	725	669
Random assignment	2:1	1:1	2:1	1:1	2:1	2:1	2:1
Menopausal status	Post	Post	Post	Pre	Pre-or peri- and post	Post	Pre- or peri- and post
Study population	First-line advanced	First-line advanced	First-line advanced	First-line advanced	Progressed on ET on or within 1 year of adjuvant therapy or on therapy for aBC (any No. of lines)	• Newly diagnosed advanced treatment-naïve or progressed on ET • Progressed at any time during or after (neo)adjuvant ET and no treatment for metastatic disease • Progressed >12 months after adjuvant ET and then progressed after first-line ET for metastatic disease	• Progression on previous ET on or within 1 year of adjuvant therapy or on therapy for aBC • Only one prior line of ET
Prior chemotherapy	None for advanced disease	None for advanced disease	None for advanced disease	None for advanced disease	One-line for advanced disease	None for advanced disease	None for advanced disease
Response rate (measurable)	55.3% v 44%	52.7% v 37.1%	59% v 44%	50.9% v 36.45%	25% v 11%	40.9% v 28.7%	48.1% v 21.3%
PFS	27.6 v 14.5 months (HR 0.563; one-sided; $P < .0001$)	25.3 v 16.0 months (HR 0.568; 95% CI, 0.457 to 0.704; $P = 9.63 \times 10^{-8}$)	28.2 v 14.8 months (HR 0.540; 95% CI, 0.418 to 0.698; $P = .000002$)	23.8 v 13.0 months (HR 0.55; 95% CI, 0.44 to 0.69; $P < .0001$)	9.5 v 4.6 months (HR 0.46; 95% CI, 0.38 to 0.59; $P < .0001$)	20.5 v 12.8 months (HR 0.593; 95% CI, 0.480 to 0.732; $P < .0001$)	16.4 v 37.3 months (HR 0.553; 95% CI, 0.449 to 0.681; $P < .0001$)
OS (ITT)	ASCO 2022 53.9 v 51.2 months (HR 0.956; 95% CI 0.777-1.17)[2]	63.9 v 51.4 months (HR 0.76; 95% CI, 0.54 to 0.93; $P = 0.004$)	ESMO 2022 IA2 (HR 0.75; $P = .03$, NS)[3]	NE vs 40.9 months (HR 0.71; 95% CI, 0.54 to 0.95; $P = .00973$)	34.9 v 28.0 months (HR 0.81; 95% CI, 0.64 to 1.03; $P = .09$)	Not reached v 40.0 months (HR 0.72; 95% CI, 0.57 to 0.92; $P = .00455$)	46.7 v 37.3 months (HR 0.757; 95% CI, 0.606 to 0.945; $P = .01$)

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aBC, advanced breast cancer; ASCO, American Society of Clinical Oncology; ET, endocrine therapy; ESMO, European Society for Medical Oncology; IA2, second interim analysis; ITT, intent to treat; NE, not evaluable; NS, not significant; OS, overall survival; PFS, progression-free survival.
Modified from 1. McAndrew NP and Finn RS. *JCO Oncol Pract.* 2022;18(5):319-327. 2. Finn RS et al. ASCO 2022. Abstract LBA1003. 3. Goetz M et al. ESMO 2022. Abstract LBA15.

Dr. Finn: So, this slide highlights the phase 3 randomized studies done in ER-positive, HER2-negative breast cancer in both the front line and second line.

Remarkably, in these studies, when we looked at the primary endpoint—the magnitude of benefit—it was very similar. The hazard ratios were all very comparable—in the 0.5 range—and that includes those in the postmenopausal as well as in the premenopausal subsets.

With that in mind, we now have overall survival data from these studies. And it's very exciting to see that when we look at the data with abemaciclib and ribociclib, all met a secondary endpoint of improving OS. They had a significant numerical improvement in OS, as well as this being statistically significant. From the PALOMA-2 study, we did see a numerical improvement in OS, but this did not reach statistical significance.

But this is a very exciting dataset because we see now that these drugs are not just improving PFS, but also improving overall survival.

Phase 3 CDK 4/6 Studies

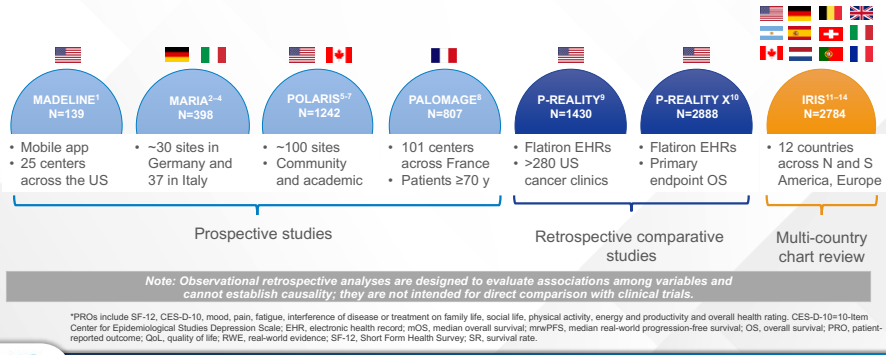
- While studies had similar designs, there were some differences in baseline characteristics and inclusion criteria
- All met PFS, the primary endpoint, with similar magnitude
- Overlapping but distinct side effects profiles
- Studies of ribociclib and abemaciclib showed improved OS, a key secondary endpoint

CDK, cyclin-dependent kinase; OS, overall survival; PFS, progression-free survival.

- So, while they all had similar designs, there were some differences in baseline characteristics and inclusion criteria. All met their primary endpoints with similar magnitude. But also, we should notice that while they had overlapping side effects, there were some distinct differences between them. And as I mentioned, ribociclib and abemaciclib showed improvement in OS that was statistically significant in combination with fulvestrant.

Palbociclib Real-world Studies

More than 8000 patients have been included in palbociclib real-world studies, providing a large base of RWE assessing multiple outcomes

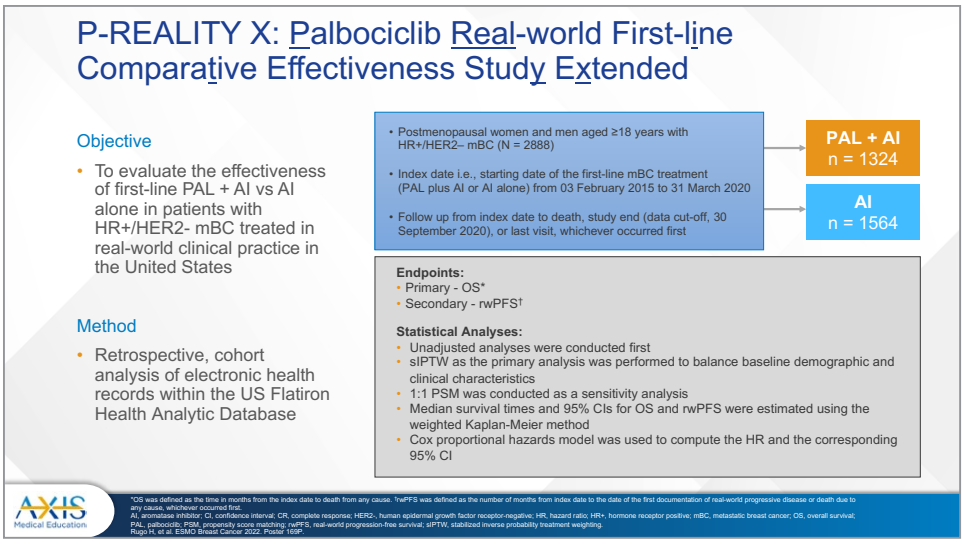


Note: Observational retrospective analyses are designed to evaluate associations among variables and cannot establish causality; they are not intended for direct comparison with clinical trials.

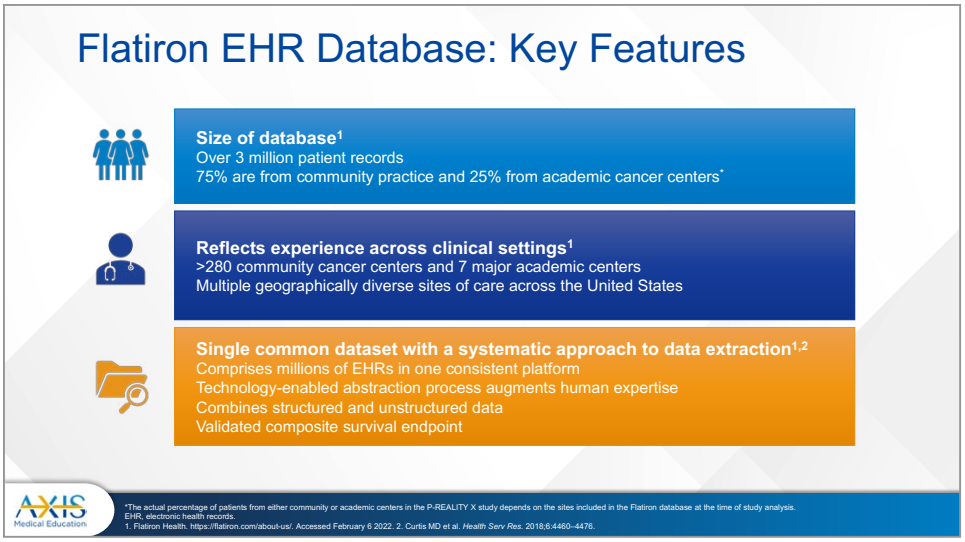
*PROs include SF-12, CES-D-10, mood, pain, fatigue, interference of disease or treatment on family life, social life, physical activity, energy and productivity and overall health rating. CES-D-10=10-Item Center for Epidemiological Studies Depression Scale; EHR, electronic health record; mOS, median overall survival; mrwPFS, median real-world progression-free survival; OS, overall survival; PRO, patient-reported outcome; QoL, quality of life; RWE, real-world evidence; SF-12, Short Form Health Survey; SR, survival rate.

1. Richardson D et al. *Breast Cancer Res Treat*. 2021;187:113-12. 2. De Laurentiis M et al. SABCS 2019. Poster P3-11-25. 3. Harbeck N et al. *Annals Oncol*. 2019; Suppl (3) III53. https://doi.org/10.1093/annonc/mdz100.016 4. de Placido S et al. ESMO Breast Cancer 2020. Poster 175P. 5. Kanduri MS et al. SABCS 2020. PS7-19. 6. Tripathy D et al. ESMO 2022. Poster 251P. 7.Rocque G et al. ESMO 2022. Poster 266P. 8. Caillet P et al. ASCO 2021. Abstract 1021. 9. DeMichele A et al. *Breast Cancer Res*. 2021;23:37. 10. Rugo HS et al. *NPJ Breast Cancer*. 2022;8(114). 11. Taylor-Stokes G et al. *Breast*. 2019;43:22-27. 12. Waller J et al. *J Glob Oncol*. 2019;5. 13. Mycock K et al. *Future Oncol*. 2021;18:349-362. 14. Mycock K, et al. *Curr Oncol*. 2021;28:678-688. *Open Access*.

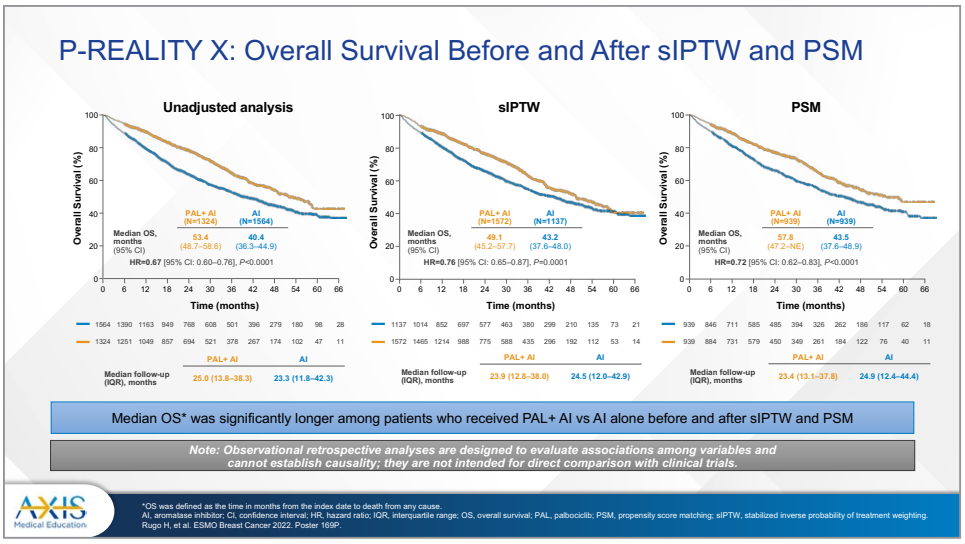
- Now turning to real-world data, you'll remember that palbociclib was the first CDK4/6 approved in the United States. It got accelerated approval in 2015. And therefore, we have a large dataset from real-world evidence from community sites as well as academic sites to look at with palbociclib. There's also real-world data evolving now with the other two CDK4/6 inhibitors as well.



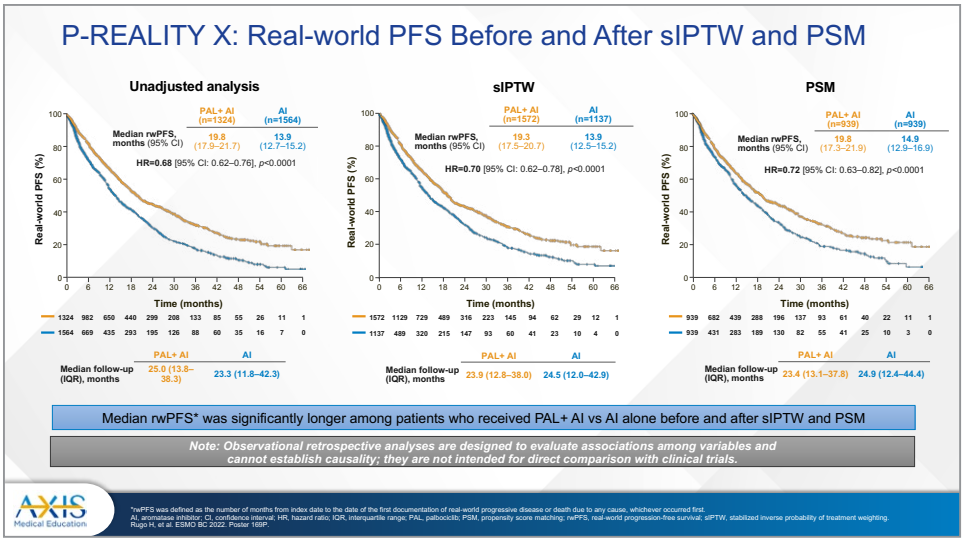
So, when we look at one of the largest datasets, which is with palbociclib, which is the P-REALITY X study, we have over 2800 patients in this dataset to evaluate the effectiveness of first-line palbociclib and an AI versus an AI alone. Now, this is retrospective, from a large electronic health record specifically the US Flatiron Health Database. And when I say over 2800 patients, this provides for 1300 patients with palbociclib and AI, versus those that got AI alone—about 1500 patients.



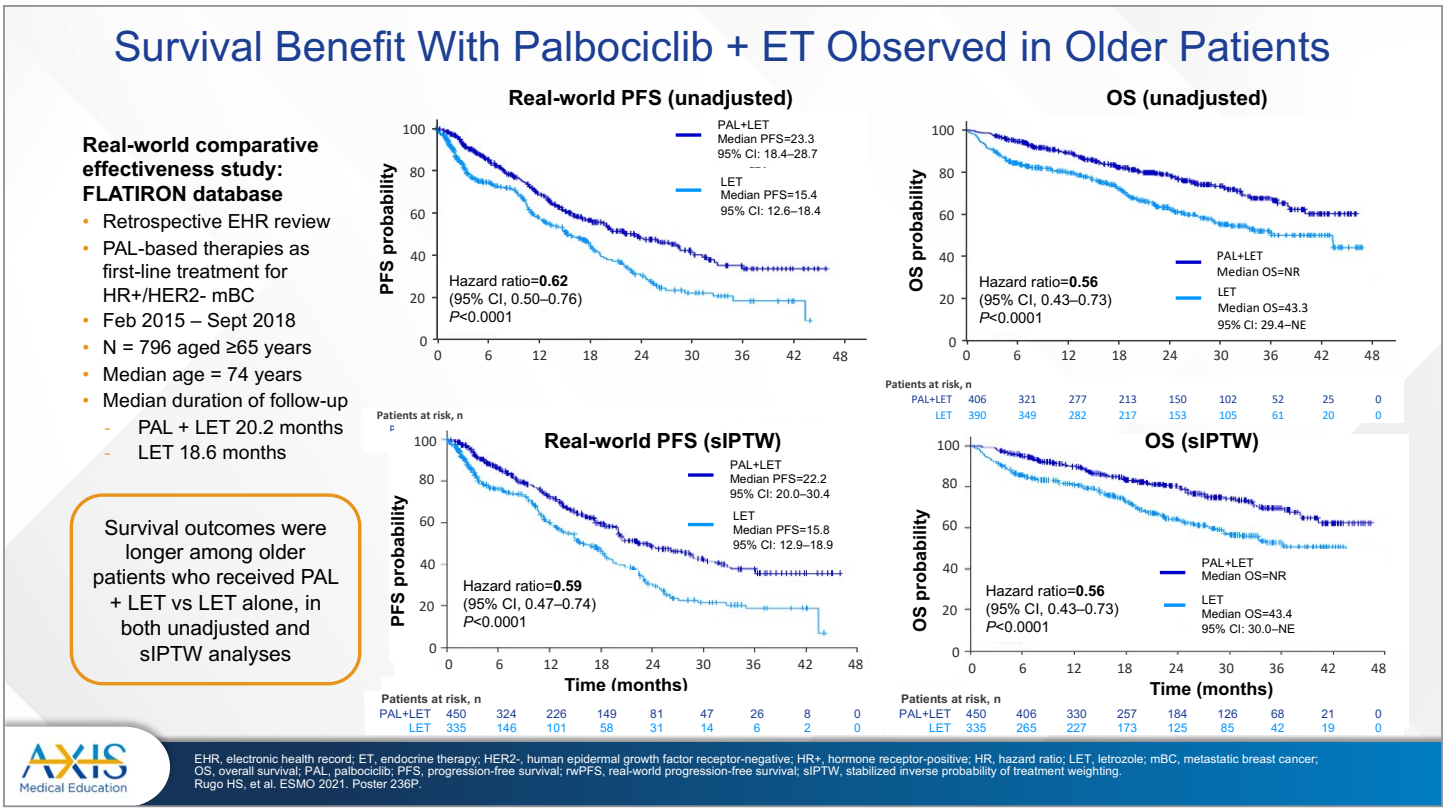
So, you know some of the strength to this dataset is that it is a very large database from electronic health records and reflects over 280 community centers, as well as a small number of academic centers from all over the United States, which really represents a diverse population. In addition, all the sites used a common electronic health record, which helps for consistent data extraction.



- Now, because this is retrospective, and there was no specific inclusion and exclusion criteria, like in a phase 3 study, there are various ways to match the populations in the treatment arm with the control arm. And what you see on this slide is the overall survival data in just an unadjusted analysis and two statistical methods that allow for matching of baseline characteristics, so the populations look a little more similar in regards to relevant clinical factors. You can see that across all these three datasets, there is a consistent improvement in overall survival with palbociclib in this real-world data set.

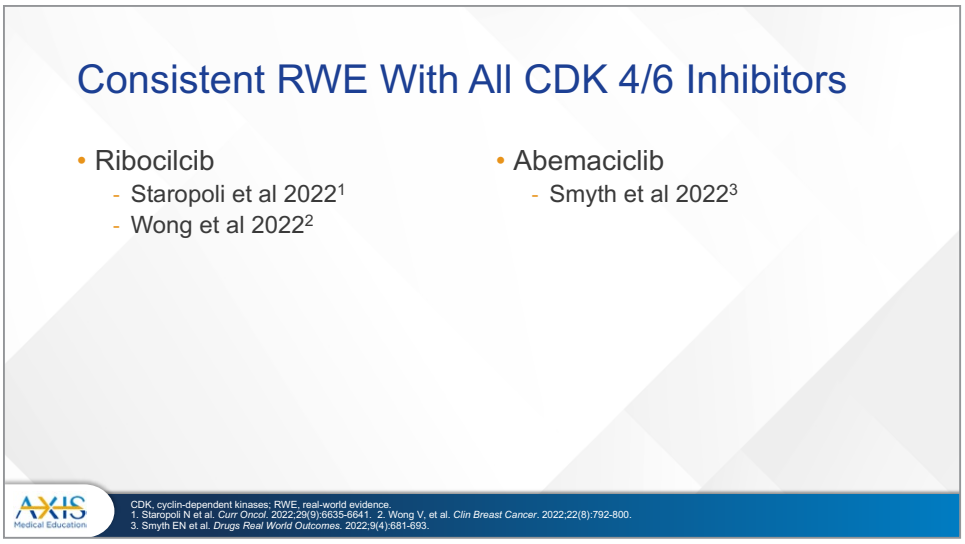


- Similarly, when we look at progression-free survival, there is a consistent benefit. Perhaps the magnitude of benefit for PFS is not as great as we saw in the randomized phase 3 study, but certainly the trend is very consistent. And we see that regardless of the statistical method used.



Here, we're looking at a population of patients which often is not expressed in high numbers in phase 3 studies and is somewhat similar to the patient we're discussing today. And here, looking at patients who are over 65, we had just under 800 patients included in the Flatiron Database for our analysis, and the median age was 74. And again, when we look at PFS or OS using various statistical analyses, this population clearly gets a benefit from the addition of palbociclib to endocrine treatment.

Having been involved in the development of these drugs for some time, initially, there were some very strong biases about who would benefit and who should get treated with CDK4/6 inhibitors. I think when we look at the phase 3 data, and now real-world data, it is clear that even older patients can get a significant benefit from the use of these doublets. And really, we need to ask ourselves, why shouldn't we offer a patient one of these doublets? And presumably, that would be driven by some comorbidity or other complication that would convince us that we shouldn't use a doublet in this patient population.



- There are also real-world data now coming from the other CDK4/6 inhibitors I mentioned. And these are very consistent with what we've seen with the palbociclib real-world data. That is to say that in the real-world setting, these drugs are recapitulating what we've seen in phase 3 studies.

  Now let's resume the discussion with our patient.

Patient Vignette #3: Modeling How Real-World Evidence Can Inform Toxicity Management

Paulette: The treatment seems very effective, but what about side effects? And how do we choose between the three therapies?

Dr. Finn: Yes, we've talked about the benefits. Now let's review some of the risks. All of these drugs have some similar side effect profiles, but they also have some differences. Very common with them is that we need to watch blood counts because they could lower your white blood cell count, which could put you at risk for infection, but generally that can be managed with dose delays or dose reductions. We do see some GI side effects more so with abemaciclib than the others. What I mean by that is some spectrum of loose stool or diarrhea. Again, generally that can be managed with dose reductions or medicines like Imodium that can help control those symptoms. And ribociclib can affect and interact with some other medications. So sometimes we need to check an EKG at the beginning to make sure that we're not having an effect on how your heart conducts.

The real-world evidence has shown us that the frequency of adverse events was lower than what we saw in the clinical trials. If you experience any side effects, we can lower the dose of your medication or take a brief treatment break.

Let's now review some of the adverse event information.

Differences Exist Across CDK4/6 Inhibitors in aBC: 1L

Adverse Events (≥20% All Grades and of special interest)	PALOMA-2[1-3] Palbociclib + Letrozole (n=444)			MONALEESA-2[3,4] Ribociclib + Letrozole (n = 334)			MONALEESA-7[5,6] Ribociclib + Tamoxifen/NSAI (n = 335)			MONARCH-3[7,8] Abemaciclib + NSAI (n = 327)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Hematological AEs												
Neutropenia	80	56	10	74	50	10	76	51	10	41	20	2
Febrile neutropenia		1.8			1.5			2			0.3	
Infections	60	6	1	50	4	<1		NR		39	4	<1
Leukopenia	39	24	1	33	20	1	31	13	1	21	7	<1
Anemia	24	5	<1	18	1	<1	21	10	0	28	6	0
Gastrointestinal AEs												
Nausea	35	<1	0	52	2	0	32	1	0	39	<1	0
Stomatitis	30	1	0	12	<1	0	10	1	0		NR	
Diarrhea	26	1	0	35	1	0	20	1	0	81	9	0
Vomiting	16	1	0	29	4	0	19	1	0	28	1	0
Constipation	19	<1	0	25	1	0	16	0	0	16	<1	0
Abdominal pain	11	1	0	11	1	0	10	1	0	28	1	0
Other												
ALT Increased	10	NR	NR	16	7	2	12	4	0	16	6	<1
AST Increased	10	NR	NR	15	5	1	13	5	0	15	3	0
Post-baseline QTcF >480/500 ms		1.6/0.2			3.3/NR			7/1			NR	
Thromboembolic events		NR			NR			NR			5	
Alopecia	33	NA	NA	33	NA	NA	19	NA	NA	27	NA	NA
Fatigue	37	2	0	37	2	<1	24	1	0	40	2	0
Discontinuation due to AEs vs PBO (%)		9.7 vs. 5.9			7.5 vs 2.1			4 vs 3			19.2 vs 2.5	
Dose Reduction due to AEs vs PBO (%)		36 vs 1.4			50.6 vs 4.2			31 vs 5			43.4 vs 6.2	
Any SAEs vs PBO (%)		19.6 vs 12.6			21.3 vs 11.8			18 vs 12			27.5 vs 14.9	

Cross-trial comparisons need to be taken with caution.
AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSAI, non-steroidal anti-inflammatory drug; PBO, placebo; QTcF, corrected QT interval by Fridericia; SAE, serious adverse events; 1L, first-line.
1. Finn et al. *N Engl J Med*. 2016;375:1925–36; 2. IBRANCE® prescribing information. Pfizer Inc; 2019; 3. Durairaj et al. *Anti-Cancer Drugs*. 2018;29:271-280; 4. Hortobagyi et al. *N Engl J Med*. 2016;375:1738-1748; 5. KISQALI® prescribing information. Novartis; 2020; 6. Tripathy et al. *Lancet Oncol*. 2018;19:904–915; 7. Goetz et al. *J Clin Oncol*. 2017;35:3638–3646; 8. VERZENIO® prescribing information. Eli Lilly; 2020.

- **Dr. Finn:** When we look at the phase 3 data, we can see that there are a lot of similarities between the drugs. A class effect of CDK4/6 inhibitors is neutropenia. However, clearly this is higher-grade and more frequent with both palbociclib and ribociclib. With that being said, febrile neutropenia is quite rare across the phase 3 studies.

  One differentiator of abemaciclib versus the other two CDK4/6 inhibitors is a higher frequency and higher grade of diarrhea. Ribociclib uniquely requires EKG monitoring, because it can affect the QT interval. And this would be something that we want to keep in mind, especially for patients who might be on multiple drugs that could interact and affect the QT. And also unique to abemaciclib is this increased risk of thromboembolic events. All of the drugs needed dose reductions or dose breaks higher than we saw in the placebo. However, the frequency was somewhat higher with abemaciclib.

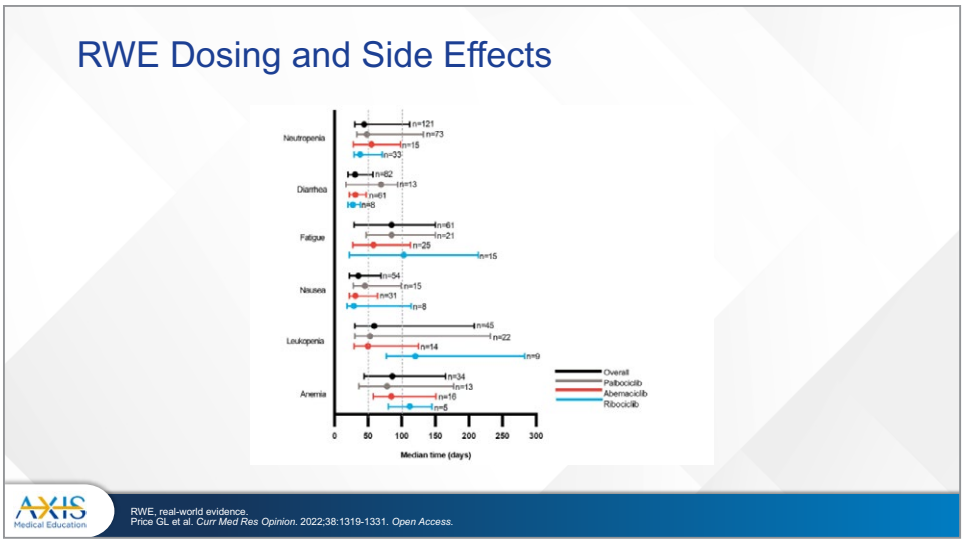
RWE Dosing and Side Effects

Table 3. Adverse events of interest (all-grade) for those AEs occurring in ≥5% of the overall cohort, and associated outcomes of female patients with HR+, HER2– MBC receiving a CDK4 and 6 inhibitor.

Variable	Overall n = 396	Palbociclib n = 163	Abemaciclib n = 142	Ribociclib n = 91
Experienced ≥ 1 protocol-defined AEs*, n (%)				
Neutropenia	121 (30.6%)	73 (44.8%)	15 (10.6%)	33 (36.3%)
Diarrhea	82 (20.7%)	13 (8.0%)	61 (43.0%)	8 (8.8%)
Fatigue	61 (15.4%)	21 (12.9%)	25 (17.6%)	15 (16.5%)
Nausea	54 (13.6%)	15 (9.2%)	31 (21.8%)	8 (8.8%)
Leukopenia	45 (11.4%)	22 (13.5%)	14 (9.9%)	9 (9.9%)
Anemia	34 (8.6%)	13 (8.0%)	16 (11.3%)	5 (5.5%)
Vomiting	30 (7.6%)	7 (4.3%)	19 (13.4%)	4 (4.4%)
Thrombocytopenia	25 (6.3%)	16 (9.8%)	3 (2.1%)	6 (6.6%)
AE incidence rate, per 100 patient years[b]				
Neutropenia	62.1	91.9	21.4	72.7
Diarrhea	35.3	10.7	132.1	12.4
Fatigue	25.4	18.7	38.4	23.8
Nausea	21.8	12.7	48.6	12.1
Leukopenia	18.3	19.8	19.9	13.8
Anemia	13.7	11.4	23.3	7.7
Vomiting	11.6	5.7	27.8	5.9
Thrombocytopenia	9.7	13.7	4.0	9.1
Potential Outcomes of AE*				
Treatment hold, n (%)				
Neutropenia	47 (38.8%)	33 (45.2%)	1 (6.7%)	13 (39.4%)
Diarrhea	24 (29.3%)	5 (38.5%)	18 (29.5%)	1 (100.0%)
Fatigue	13 (21.3%)	4 (19.0%)	5 (20.0%)	4 (26.7%)
Nausea	22 (40.7%)	5 (33.3%)	14 (45.2%)	3 (37.5%)
Leukopenia	10 (22.2%)	6 (27.3%)	2 (14.3%)	2 (22.2%)
Anemia	5 (14.7%)	1 (7.7%)	2 (12.5%)	2 (40.0%)
Vomiting	14 (46.7%)	2 (28.6%)	11 (57.9%)	1 (25.0%)
Thrombocytopenia	8 (32.0%)	5 (31.3%)	2 (66.7%)	1 (16.7%)
Dose reduction, n (%)				
Neutropenia	44 (36.4%)	25 (34.2%)	8 (53.3%)	11 (33.3%)
Diarrhea	22 (26.8%)	3 (23.1%)	18 (29.5%)	1 (12.5%)
Fatigue	18 (29.5%)	8 (38.1%)	8 (32.0%)	2 (13.3%)
Nausea	9 (16.7%)	4 (26.7%)	4 (12.9%)	1 (12.5%)
Leukopenia	9 (20.0%)	6 (27.3%)	3 (21.4%)	0
Anemia	6 (17.6%)	2 (15.4%)	3 (18.8%)	1 (20.0%)
Vomiting	6 (20.0%)	3 (42.9%)	2 (10.5%)	1 (25.0%)
Thrombocytopenia	7 (28.0%)	6 (37.5%)	0	1 (16.7%)
Permanent discontinuation, n (%)				
Neutropenia	12 (9.9%)	10 (13.7%)	0	2 (6.1%)
Diarrhea	17 (20.7%)	4 (30.8%)	11 (18.0%)	2 (25.0%)
Fatigue	11 (18.0%)	1 (4.8%)	9 (36.0%)	1 (6.7%)
Nausea	8 (14.8%)	4 (26.7%)	4 (12.9%)	0
Leukopenia	2 (20.0%)	2 (9.1%)	0	0
Anemia	2 (5.9%)	1 (7.7%)	1 (6.3%)	0
Vomiting	6 (20.0%)	3 (42.9%)	2 (10.5%)	1 (25.0%)
Thrombocytopenia	1 (4.0%)	1 (6.3%)	0	0

RWE, real-world evidence.
Price GL et al. *Curr Med Res Opinion*. 2022;38:1319-1331. *Open Access*.

- When we look at the real-world data with these drugs overall, I would say the trend is very similar to what we saw in the phase 3 data. However, it seems like the frequency of neutropenia, for example, was a little less than what was described in the phase 3 studies. Other toxicities were fairly similar between the data collected in real-world data and phase 3 data specifically in severity of the AEs and the type of AEs that are described.



- When we look at things like neutropenia, diarrhea, fatigue, nausea, anemia, these are the most common side effects that we see in the phase 3 data. These are also recapitulated in the real-world datasets. You know in this review, the numbers are somewhat small, which makes it a little hard to make conclusions. However, I think at the end of the day, the trends are always similar.

  We'll return to Paulette to see if she is ready to make a treatment decision.

Patient Vignette: Conclusion

Dr. Finn: Paulette, how are you feeling about the information we've gone over today on CDK4/6 inhibitors?

Paulette: This was a lot of information, but it was very helpful. Thank you for discussing the real-world and the clinical evidence with me and reviewing the side effects. That is my main concern about starting a new medication. I want my life to be as normal as possible.

Dr. Finn: Okay, are you ready to make a treatment decision? I'm happy to answer any further questions you may have as you make your decision.

Paulette: Yes, I would like to start treatment with palbociclib.

Dr. Finn: We'll monitor your labs for low white blood cell counts before and during treatment, but do call my office if you experience any fever or chills.

Key Takeaways

- CDK 4/6 inhibitors have changed the natural history of advanced ER+/HER2- breast cancer
- All three currently approved CDK 4/6 inhibitors met their primary endpoints in the populations studied in randomized double-blind placebo-controlled clinical trials
  - The gold standard for establishing evidence that a treatment "works"
  - All 3 have overlapping but distinct side effect profiles
- RWE has a clear established role in building on the data from phase 3 trials
  - Obtained in a different setting than phase 3 studies
  - RWE gives additional insights in broader, more variable patient populations
- In the context of CDK 4/6 inhibitors, RWE recapitulates the findings of the primary endpoints in the phase 3 studies
  - Supports the use of these agents based on efficacy and safety in a broad population of patients
- It is important to incorporate these data into discussions with patients when supporting your decision to use a specific regimen based on clinical characteristics

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CDK, cyclin-dependent kinase; ER+, estrogen receptor-positive; HER2-, human epidermal growth factor receptor-negative; RWE, real-world evidence.

- So, in conclusion, all three CDK4/6 inhibitors have demonstrated an important role for patients with ER-positive, HER2-negative breast cancer. This comes from meeting their primary endpoints of improving PFS. All of them have distinct side effect profiles. However, we can use real-world evidence to help build on this phase 3 data to give us better insight into a broader patient population and certainly larger numbers of patients.

  And in the context of these drugs, we see that real-world evidence really does recapitulate the primary endpoint in these phase 3 studies, and also supports the use of these agents building on the efficacy and safety in broad patient populations. It's important to keep in mind these data as we have discussions with patients and help support our decisions in selecting a specific recommendation for our patients.

- A shared decision-making guide, like this one, can help us form a conversation with our patients to highlight real-world evidence supporting CDK4/6 inhibitor-based treatment options and integrate shared decision-making strategies to co-create treatment plans that are reflective of patient goals, values, and perspectives.

- Thank you for joining me for Oncology Clinic vignettes on shared decision-making and real-world evidence in the management of hormone-receptor positive, HER2-negative metastatic breast cancer with CDK4/6 inhibitors. I hope you found the program useful.

REFERENCES

Akobeng AK. Understanding randomised controlled trials. *Arch Dis Child*. 2005;90:840-844.

Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. *Br J Cancer.* 2014;110:551-555.

Caillet P, Puliido M, Brain E, et al. PALOMAGE, a French real-world cohort of elderly women beyond age 70 with advanced breast cancer receiving palbociclib: Baseline characteristics and safety evaluation. *J Clin Oncol* 39, 2021 (suppl 15; abstr 1012).

Curtis MD, Griffith SD, Tucker M, et al. Development and validation of a high-quality composite real-world mortality endpoint. *Health Serv Res*. 2018;6:4460-4476.

De Laurentiis M, Harbeck N, Law E, et al. Real-world treatment patterns and clinical outcomes among women with HR+/HER2- advanced or metastatic breast cancer treated in real-world settings in Italy and Germany. Abstract presented at: San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. P3-11-25.

de Lusignan S, Crawford L, Munro N. Creating and using real-world evidence to answer questions about clinical effectiveness. *J Innov Health Inform*. 2015;22(3):368-373.

de Placido S, Brucker S, Law E, et al. Real-world patient and practice characteristics associated with use of CDK4/6 inhibitors among patients receiving first therapy for HR+/HER2- advanced or metastatic breast cancer in Italy and Germany. Abstract presented at: European Society for Medical Oncology Breast Cancer; 2020. Poster 175P.

DeMichele A, Cristofanilli M, Brufsky A, et al. Comparative effectiveness of first-line palbociclib plus letrozole versus letrozole alone for HR+/HER2- metastatic breast cancer in US real-world clinical practice. *Breast Cancer Res*. 2021;23(1):37.

Durairaj C, Ruiz-Gacia A, Gauthier ER, et al. Palbociclib has no clinically relevant effect on the QTc interval in patients with advanced breast cancer. *Anti-Cancer Drugs*. 2018;29:271-280.

Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med*. 2016;375:1925–1936.

Finn RS, Rugo HS, Dieras VC, et al. Overall survival (OS) with first-line palbociclib plus letrozole (PAL+LET) versus placebo plus letrozole (PBO+LET) in women with estrogen receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (ER+/HER2 ABC): Analyses from PALOMA-2. *J Clin Oncol* 40, 2022 (suppl 17; abstr LBA1003).

Flatiron Health. About Us. Accessed February 6, 2022. https://flatiron.com/about-us/.

Garrison LP Jr, Neumann PJ, Erickson P, et al. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. *Value Health*. 2007;10(5):326-335.

Glasgow RE, Lichtenstein E, Marcus AC, et al. Why don't we see more translation of health promotion research to practice? Rethinking the efficacy-to-effectiveness transition. *Am J Public Health*. 2003;93:1261-1267.

Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol.* 2017;35:3638-3646.

Goetz MP, Toi M, Huober J, et al. MONARCH 3: Interim overall survival (OS) results of abemaciclib plus a nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+, HER2- advanced breast cancer (ABC). *Ann Oncol* 33, 2022 (suppl 7; LBA 15). S808-S869. 10.1016/annonc/annonc1089

Harbeck N, Law EH, Ajmera M, et al. Prevalence of risk factors for QT prolongation and torsades de pointes among women with HR+/HER2– advanced or metastatic breast cancer treated in real-world settings in Italy and Germany. *Ann Oncol* 3. 2019 (suppl 3; III53). https://doi.org/10.1093/annonc/mdz100.016

Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for hr-positive, advanced breast cancer. *N Engl J Med*. 2016;375:1738-1748.

IBRANCE. Prescribing information. Pfizer, Inc. 2022. Accessed March 12, 2023. https://labeling.pfizer.com/ShowLabeling.aspx?id=2191

Karuturi MS, Garrett A, Blum JL, et al. Pre/perimenopausal (preMeno) women receiving palbociclib (PAL) for hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2) advanced breast cancer (ABC) in a real-world setting: Treatment patterns from POLARIS. Abstract presented at: San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, TX. PS7-19.

Khozin S, Blumenthal GM, Pazdur R. Real-world data for clinical evidence generation in oncology. *J Natl Cancer Inst.* 2017; 109(11).

KISQALI. Prescribing information. Novartis. 2022. Accessed March 12, 2023. https://www.novartis.com/us-en/sites/novartis_us/files/kisqali.pdf

McAndrew NP and Finn RS. Clinical review on the management of hormone receptor-positive metastatic breast cancer. *JCO Oncol Pract*. 2022;18(5):319-327.

Mycock K, Zhan L, Hart K, et al. Real-world treatment of patients with palbociclib for HR+/HER2-advanced/metastatic breast cancer: the Europe IRIS study. *Future Oncol.* 2021;18:349-362.

Mycock K, Zhan L, Taylor-Stokes G, et al. Real-world palbociclib use in HR+/HER2- advanced breast cancer in canada: The IRIS study. *Curr Oncol.* 2021;28:678-688.

Pfizer News Release. April 4, 2019. U.S. FDA approves IBRANCE® (palbociclib) for the treatment of men with HR+, HER2- metastatic breast cancer. Accessed March 12, 2023. https://www.pfizer.com/news/press-release/press-release-detail/u_s_fda_approves_ibrance_palbociclib_for_the_treatment_of_men_with_hr_her2_metastatic_breast_cancer

Price GL, Sudharshan L, Ryan P, et al. Real world incidence and management of adverse events in patients with HR+, HER2 metastatic breast cancer receiving CDK4 and 6 inhibitors in a United States community setting. *Curr Med Res Opinion* 38:1319-1331.

Richardson D, Zhan L, Mahtani R, et al. A prospective observational study of patient-reported functioning and quality of life in advanced and metastatic breast cancer utilizing a novel mobile application. *Breast Cancer Res Treat*. 2021;187:113-124.

Rocque G, Blum JL, Ji Y, et al. Real-world quality of life (QoL) in patients with HR+/HER2-advanced breast cancer (ABC) treated with palbociclib: Final clinical outcome assessment (COA) analysis from POLARIS. *Ann Oncol* 33, 2022 (suppl 7; 266P). S808-S869. 10.1016/annonc/annonc1040

Rugo HS, Brufsky A, Liu X, et al. Real-world study of overall survival with palbociclib plus aromatase inhibitor in HR+/HER2-metastatic breast cancer. *NPJ Breast Cancer.* 2022;8:114.

Rugo HS, Brufsky A, Liu X, et al. Overall survival with first-line palbociclib plus an aromatase inhibitor (AI) vs AI in metastatic breast cancer: a large real-world database analysis. Poster presented at: European Society for Medical Oncology (ESMO) Breast Cancer 2022 Congress; May 3-5, 2022; Berlin, Germany. Poster 169P.

Sanson-Fisher RW, Bonevski B, Green LW, et al. Limitations of the randomized controlled trial in evaluating population-based health interventions. *Am J Prev Med*. 2007;33:155-161.

Schmidt AF, Rovers MM, Klungel OH, et al. Differences in interaction and subgroup-specific effects were observed between randomized and nonrandomized studies in three empirical examples. *J Clin Epidemiol.* 2013;66:599-607.

Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence - what is it and what can it tell us? *N Engl J Med*. 2016;375(23):2293-2297.

REFERENCES

Singal AG, Higgins PDR, Waljee Ak. A primer on effectiveness and efficacy trials. Clin Transl Gastroenterol. 2014;5.e45.

Smyth EN, Beyrer J, Saverno KR et al. Real-world patient characteristics, utilization patterns, and outcomes of US patients with HR+, HER2- metastatic breast cancer treated with abemaciclib. *Drugs Real World Outcomes*. 2022;9(4):681-693.

Staropoli N, Geuna E, Rinaldi G, et al. Real-world clinical outcomes of ribociclib in combination with a non-steroidal aromatase inhibitor and a luteinizing hormone-releasing hormone agonist in premenopausal HR+/HER2- advanced breast cancer patients: an Italian managed access program. *Curr Oncol.* 2022;29:6635-6641.

Taylor-Stokes G, Mitra D, Waller J, et al. Treatment patterns and clinical outcomes among patients receiving palbociclib in combination with an aromatase inhibitor or fulvestrant for HR+/HER2-negative advanced/metastatic breast cancer in real-world settings in the US: Results from the IRIS study. Breast. 2019;43:22-27.

Tripathy D, Rocque G, Blum JL, et al. - Real-world clinical outcomes of palbociclib plus endocrine therapy (ET) in hormone receptor–positive advanced breast cancer: Results from the POLARIS trial. *Ann Oncol* 33, 2022 (suppl 7; 251P). S88-S121. 10.1016/annonc/annonc1040

Tripathy D, Im SA, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19:904-915.

US Food and Drug Administration. Real-World Evidence. October 19, 2022. Accessed March 12, 2023. https://www.fda.gov/science-research/science-and-research-special-topics/real-world-evidence

Valengtas P, Mohr P, Messner DA. Center for Medical Technology Policy. Making informed decisions: Assessing the strengths and weaknesses of study designs and analytic methods for comparative effectiveness research. Accessed March 12, 2023. https://www.npcnow.org/system/files/research/download/experimental_nonexperimental_study_final.pdf

VERZENIO prescribing information. Eli Lilly. 2023. Accessed March 12, 2023. https://pi.lilly.com/us/verzenio-uspi.pdf?s=pi

Waller J, Mitra D, Mycock K, et al. Real-World treatment patterns and clinical outcomes in patients receiving palbociclib for hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer in Argentina: The IRIS Study. *J Glob Oncol*. 2019;5.

Wong V, de Boer R, Baron-Hay S, et al. Real-world outcomes of ribociclib and aromatase inhibitor use in first line hormone receptor positive, HER2-negative metastatic breast cancer. *Clin Breast Cancer.* 2022;22(8):792-800.

Zanotti G, Hunger M, Perkins JJ, et al. Treatment patterns and real world clinical outcomes in ER+/HER2- post-menopausal metastatic breast cancer patients in the United States. *BMC Cancer.* 2017;17(1):393.

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