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Advanced Practice Perspectives on CDK 4/6 Inhibitors:

Paving the Way for HR+, HER2-Negative Early Breast Cancer

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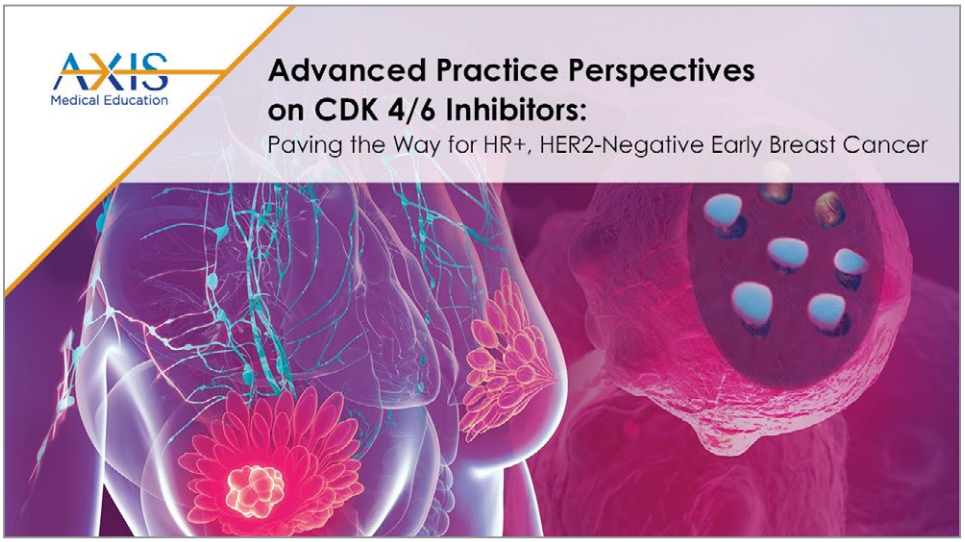
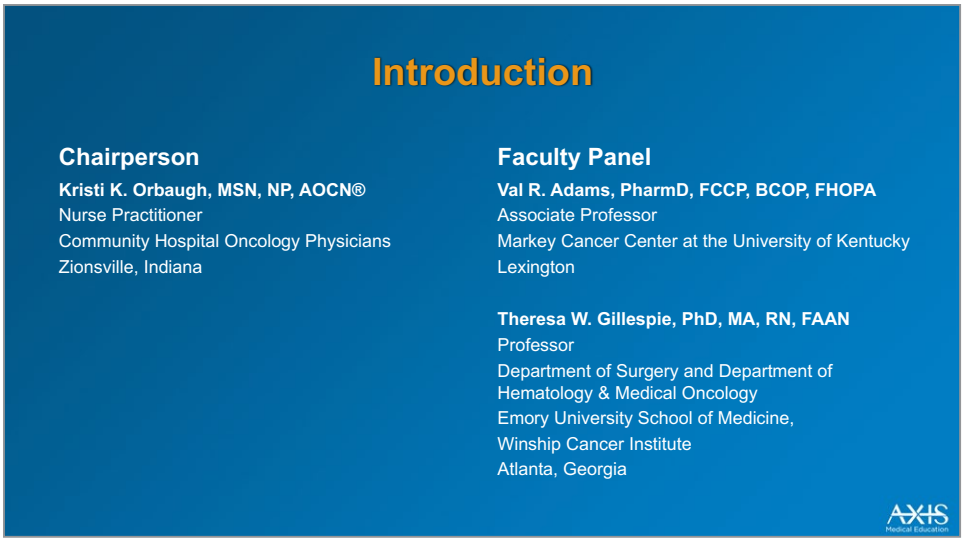
Advanced Practice Perspectives on CDK4/6 Inhibitors: Paving the Way for Hormone Receptor–Positive/HER2-Negative Early Breast Cancer

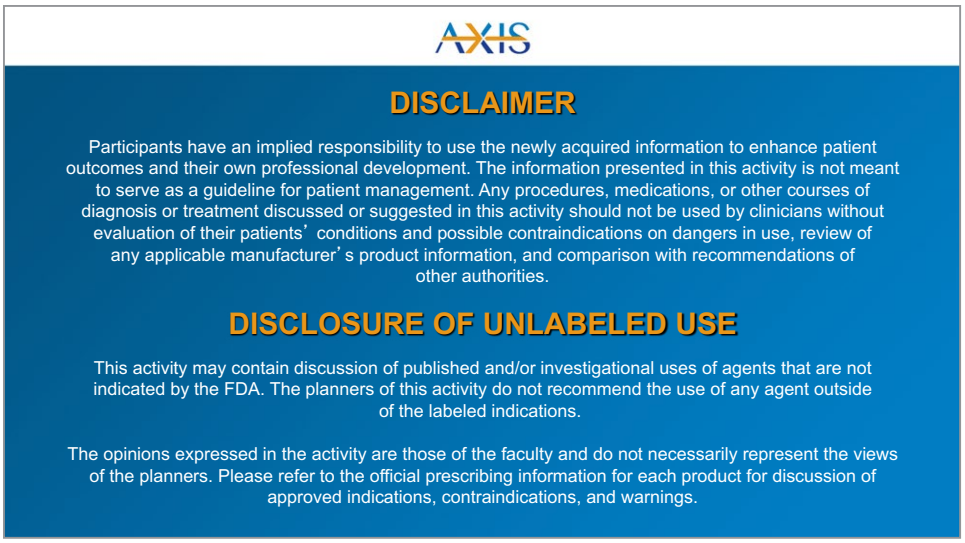
Kristi K. Orbaugh, MSN, NP, AOCN, Theresa W. Gillespie, PhD, MA, RN, FAAN and Val R. Adams, PharmD, FCCP, BCOP, FHOPA



Kristi K. Orbaugh, MSN, NP, AOCN
Hello, and welcome to the educational activity entitled *Advanced Practice Perspectives on CDK4/6 Inhibitors: Paving the Way for Hormone Receptor–Positive/HER2-Negative Early Breast Cancer*.



I'm Kristi Orbaugh. I'm a nurse practitioner at Community Hospital Oncology Physicians. Today I'm joined by Val Adams, an associate professor at Markey Cancer Center at the University of Kentucky. I'm also joined by Theresa Gillespie, a professor at the department of surgery and department of hematology and medical oncology at Emory University School of Medicine and Winship Cancer Institute.



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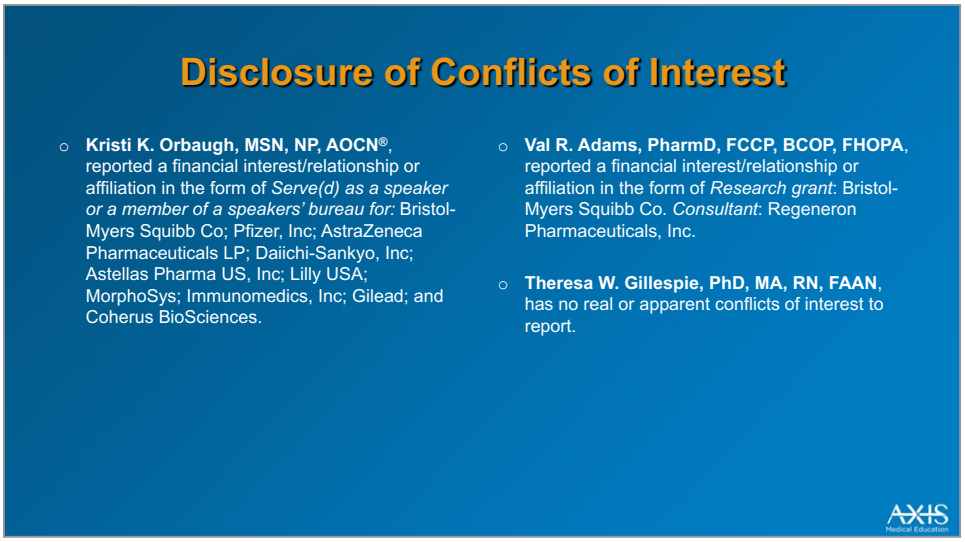
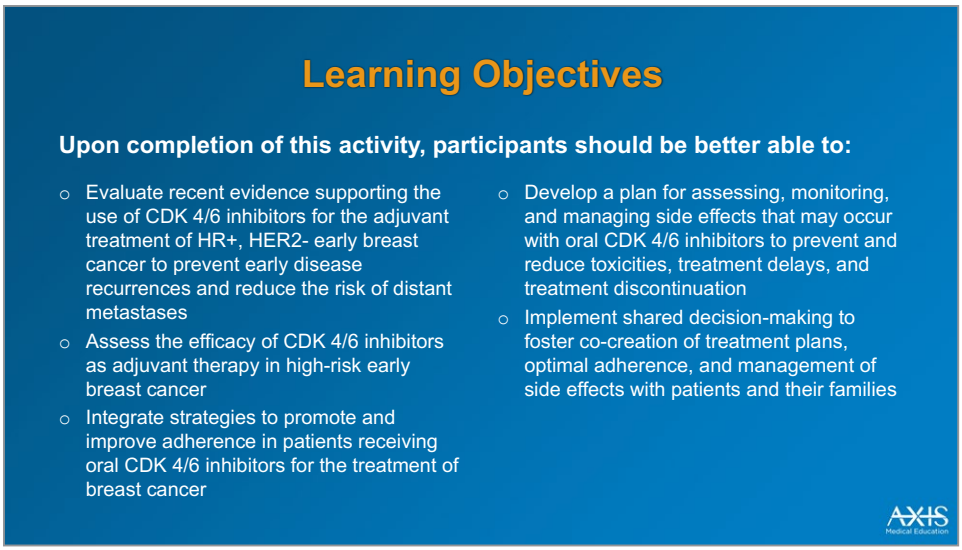
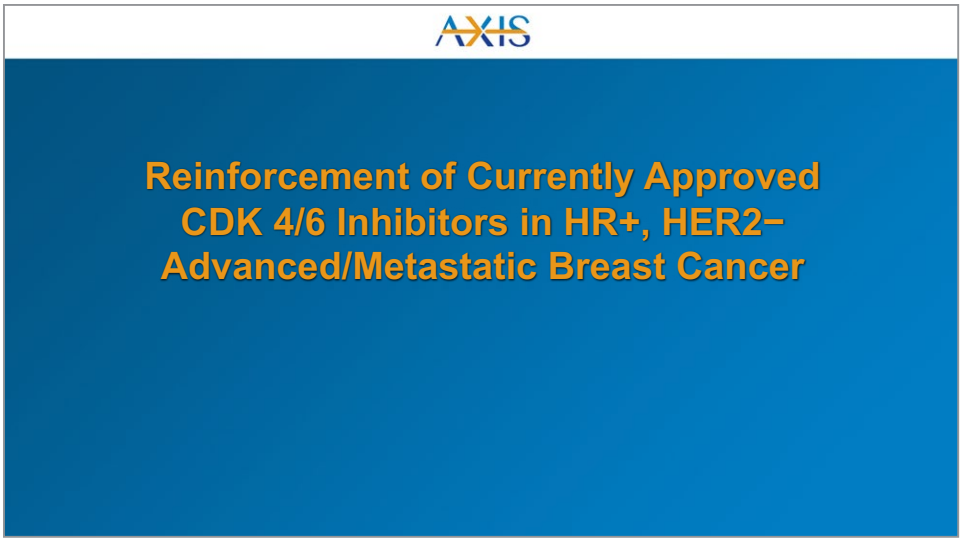


- Here are the disclosures of conflicts of interest.



- And here are the learning objectives.



- So we'll start today's activity by briefly reviewing three oral CDK4/6 inhibitors that are approved for hormone receptor–positive/HER2-negative metastatic breast cancer, and then move on to our main focus of our activity with a discussion on these agents in early breast cancer as adjuvant treatment.

FDA Approvals: CDK 4/6 Inhibitors in HR+/HER2− Advanced/Metastatic Breast Cancer

CDK 4/6 Inhibitor	FDA Approval Date	Initial Endocrine-based Therapy	FDA Approval Date	After Disease Progression Following Endocrine Therapy
Palbociclib	2/3/15	with letrozole first-line postmenopausal women	2/19/16	with fulvestrant
	3/31/17	with an AI in postmenopausal women		
	4/4/19	with an AI in postmenopausal women or in men		
Ribociclib	3/13/17	with an AI for postmenopausal women	7/18/18	with fulvestrant for postmenopausal women
	7/18/18	with an AI for pre/perimenopausal women		
		with fulvestrant for postmenopausal women		
Abemaciclib	2/26/18	with an AI for postmenopausal women	9/28/17	with fulvestrant
				as monotherapy for adult patients with prior chemotherapy in metastatic setting

AI, aromatase inhibitor; CDK, cyclin-dependent kinase; FDA, Food and Drug Administration; HER2−, human epidermal growth factor receptor 2 negative; HR+, hormone receptor positive.
FDA 2015, 2016, 2017, 2018, 2019.

- Endocrine therapy has been the backbone, historically, for people with hormone receptor–positive metastatic breast cancer. Unfortunately, endocrine resistance or progression in the midst of endocrine therapy develops in a large number of people who do have metastatic hormone receptor–positive breast cancer. So this has been a population that has needed hope, that has needed a new class of drugs.

  In 2015, a new class of drugs was approved called CDK4/6 inhibitors. And this was a very important addition to our armamentarium that we use to treat metastatic breast cancer. CDK4/6 inhibitors are important in one of the signaling pathways that is used in patients who have endocrine resistance. There are currently three CDK4/6 inhibitors on the market. The first to market was palbociclib, the second is ribociclib, the third is abemaciclib. Each of these drugs has an indication both in initial endocrine-based therapy as well as use after disease progression following endocrine therapy.

Overview of CDK 4/6 Inhibitors: First-Line Treatment

Study/Arms	Phase	N	Median PFS (mo)		HR	*P*	Median OS (mo)		HR	*P*
			Placebo	CDK 4/6i			Placebo	CDK 4/6i		
PALOMA-1[1,8] Letrozole ± Palbociclib	2	165	10.2	20.2	0.488	.0004	34.5	37.5	0/897	.281
PALOMA-2[2] Letrozole ± Palbociclib	3	666	14.5	24.8	0.58	.000001	-	-	-	-
MONALEESA-2[3] Letrozole ± Ribociclib	3	668	16.0	25.3	0.568	9.63×10^{-8}	-	-	-	-
MONALEESA-7[4,7] Tamoxifen/NSAI + goserelin ± Ribociclib	3	672	13.0	23.8	0.553	.0000000983	40.9	Not reached	0.712	.00973
MONARCH 3[5,6] NSAIs ± Abemaciclib	3	493	14.76	28.18	0.540	.000002	-	-	-	-

CDK 4/6i, cyclin-dependent kinase 4/6 inhibitor; NR, not reached; NSAIs, nonsteroidal aromatase inhibitors; PFS, progression-free survival.
[1]Finn et al. *Lancet Oncol*. 2015;16:25-35; [2]Finn et al. *N Engl J Med*. 2016;375:1925-1936; [3]Hortobagyi et al. *N Engl J Med*. 2016;375:1738-1748; [4]Tripathy et al. *Lancet Oncol*. 2018;19:904-915; [5]Goetz et al. *J Clin Oncol*. 2017;35:3638-3646; [6]Johnston et al. *npj Breast Cancer* 2019;5:5; [7]Im et al. *N Engl J Med* 2019;381:307-316. [8]Finn et al. *Breast Cancer Res Treat*. 2020; 183(2): 419–428.

- When you look at the overview of the use of CDK4/6s in first-line therapy, regardless of whether we use palbociclib, ribociclib, or abemaciclib, we have an improvement in the median progression-free survival in patients who have that addition of the CDK4/6 inhibitors. We also highlighted a difference in median overall survival that we saw in MONALEESA-7.

Overview of CDK 4/6 Inhibitors: After Disease Progression Following Endocrine Therapy

Study/Arms	Phase	N	Median PFS (mo)		HR	*P*	Median OS (mo)		HR	*P*
			Placebo	CDK 4/6i			Placebo	CDK 4/6i		
PALOMA-3[1,2,8] Fulvestrant ± palbociclib	3	521	4.6	9.5	0.46	.0001	28.0	34.8	0.806	.0221
MONALEESA-3[3,6,9] Fulvestrant ± ribociclib	3	726	12.8	20.5	0.593	.00000041	41.5	53.7	0.726	.0045
MONARCH 2[4,7] Fulvestrant ± abemaciclib	3	669	9.3	16.4	0.553	.000001	37.3	46.7	0.757	.0137

Study/Arms	Phase	N	Investigator-assessed ORR
			CDK 4/6i
MONARCH1[5] Single-agent abemaciclib	2	132	19.7%

CDK 4/6i, cyclin-dependent kinase 4/6 inhibitor; ORR, objective response rate; PFS, progression-free survival.
[1]Cristofanilli et al. *Lancet Oncol*. 2016;17:425-439; [2]Turner et al. *N Engl J Med*. 2015; 373:209-219; [3]Slamon et al. *J Clin Oncol*. 2018;36:2465-2472; [4]Sledge et al. *J Clin Oncol*. 2017;35:2875; [5]Dickler et al. *Clin Cancer Res*. 2017;23:5218-5224; [6]Slamon et al. *N Engl J Med*. 2020;382:514-524; [7]Sledge et al. *JAMA Oncol*. 2020;6:115-124; [8]Cristofanilli et al. *J Clin Oncol*. 2021;39(suppl 15):1000. [9]Slamon et al. *J Clin Oncol*. 2021;39(suppl 15):1001.

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- Here are the updated overall survival data. What we see consistently across first line as well as after disease progression is the addition of that CDK4/6 inhibitor, regardless of which one we choose, increases the median progression-free survival. We also see that in certain situations, we see improvement in median overall survival.

How Do the CDK 4/6 Inhibitors Differ?

HR+/HER2– Advanced or Metastatic Breast Cancer	Palbociclib	Ribociclib	Abemaciclib
Initial endocrine-based therapy in postmenopausal women	with AI	with fulvestrant or AI	with AI
Initial endocrine-based therapy in pre-/perimenopausal women	-	with AI	-
With disease progression following endocrine therapy	with fulvestrant	with fulvestrant	with fulvestrant
			as monotherapy*
Administration	Oral (tablets or capsules)	Oral (tablets)	Oral (tablets)
Recommended starting dose	125 mg	600 mg (three 200 mg tablets)	with AI or fulvestrant:150 mg
			monotherapy: 200 mg
Dose frequency	Once daily	Once daily	Twice daily
Schedule	21 days on, 7 days off (28 day cycle)	21 days on, 7 days off (28 day cycle)	Continuously until disease progression or unacceptable toxicity
With/without food	With (capsules) With or without (tablets)	With or without	With or without

*In patients with prior chemotherapy in the metastatic setting.
See full prescribing information.
AI, aromatase inhibitor; CDK, cyclin-dependent kinase; HER2, human epidermal growth factor receptor; HR, hormone receptor.
Verzenio prescribing information; Ibrance prescribing information; Kisqali prescribing information.

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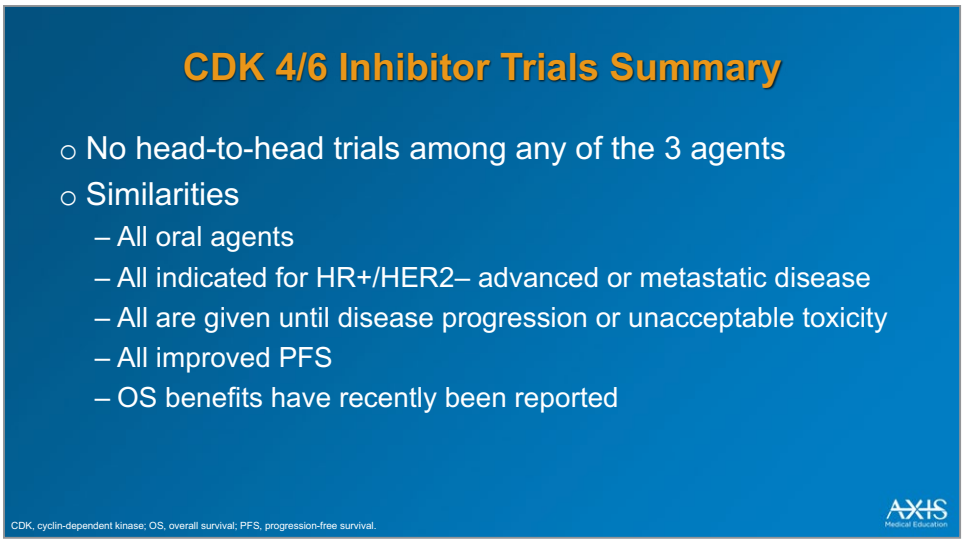
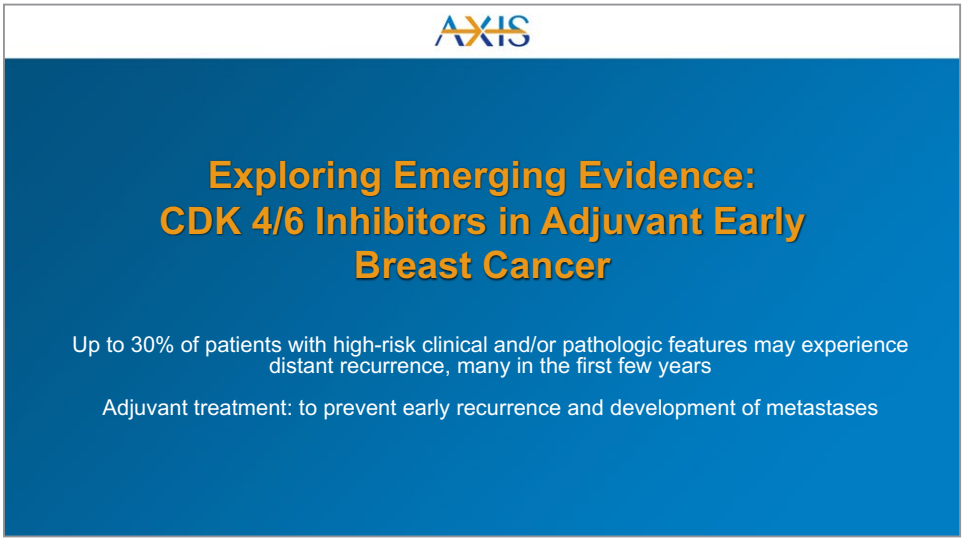
- Now there are some differences. Palbociclib has tablets as well as capsule. The dosing difference is palbociclib 125 mg daily, it's only given once; ribociclib is given 600 mg once a day. Both of those drugs are given 21 days on/7 days off. Then you move to abemaciclib, it's given 150 mg BID when it's used in conjunction or in partnership with fulvestrant or an aromatase inhibitor. As monotherapy, it's given 200 mg BID. This is the one that's dosed continuously.



- So to pull that together, there's been no head-to-head trial among the three agents. The similarities are that they're all oral agents, they're all indicated for hormone receptor–positive/HER2-negative advanced or metastatic breast cancer, they're given until disease progression or unacceptable toxicity, and all improved progression-free survival. We do know that ribociclib and abemaciclib have shown improved overall survival compared to the standard of care arm in advanced breast cancer. In the PALOMA-3 trial, the new updated data that we just received from ASCO demonstrated a survival benefit in certain subsets.



- Let's move on to the adjuvant setting.

  When we have drugs that are useful and beneficial in the metastatic setting, we try to move them into earlier stages of the disease to see if we can decrease recurrence rates.

CDK 4/6 Inhibitors in the Adjuvant Setting

CDK 4/6 Inhibitor	Trial	Setting	Study Arms	Results/Status
Abemaciclib	monarchE NCT03155997	High-risk, node-positive HR+, HER2- EBC	Abemaciclib + standard adjuvant ET vs standard adjuvant ET alone	2-year iDFS: 92.3% vs 89.3% (HR 0.75)[1]
				Ki-67 ≥20% 2-year iDFS: 91.6% vs 87.1%
	ADAPTlate NCT04565054	High-risk HR+, HER2- EBC	Adjuvant dynamic marker-adjusted personalized therapy comparing abemaciclib + standard adjuvant ET vs standard adjuvant ET	Trial recruiting
Palbociclib	PALLAS NCT02513394	HR+, HER2- EBC	Palbociclib + standard adjuvant ET vs standard adjuvant ET alone	Did not improve iDFS 3-year IDFS: 88.2% vs 88.5% (HR 0.93)[2]
	PENELOPE-B NCT01864746	HR+, HER2- EBC at high risk of recurrence	Palbociclib + standard adjuvant ET vs placebo + standard adjuvant ET	Did not improve iDFS 3-year IDFS: 81.2% vs 77.7% (HR 0.93) 4 year IDFS: 73% vs 72.4%[3]
Ribociclib	NATALEE NCT03701334	HR+, HER2- EBC	Ribociclib + ET vs ET	Recently completed enrollment
	ADAPTcycle NCT04055493	Intermediate-risk HR+, HER2- EBC	Adjuvant dynamic marker-adjusted personalized therapy comparing ET + ribociclib vs chemotherapy	Trial recruiting

CDK, cyclin-dependent kinase; EBC, early breast cancer; ET, endocrine therapy; iDFS, invasive disease free survival.
[1]O'Shaughnessyet al. *Cancer Res*. 2021;81:GS1-01; [2]Mayer et al. *Ann Oncol*. 2020;31:S1145 ; [3]Loibl et al. *J Clin Oncol*. 2021;39:1518-1530.

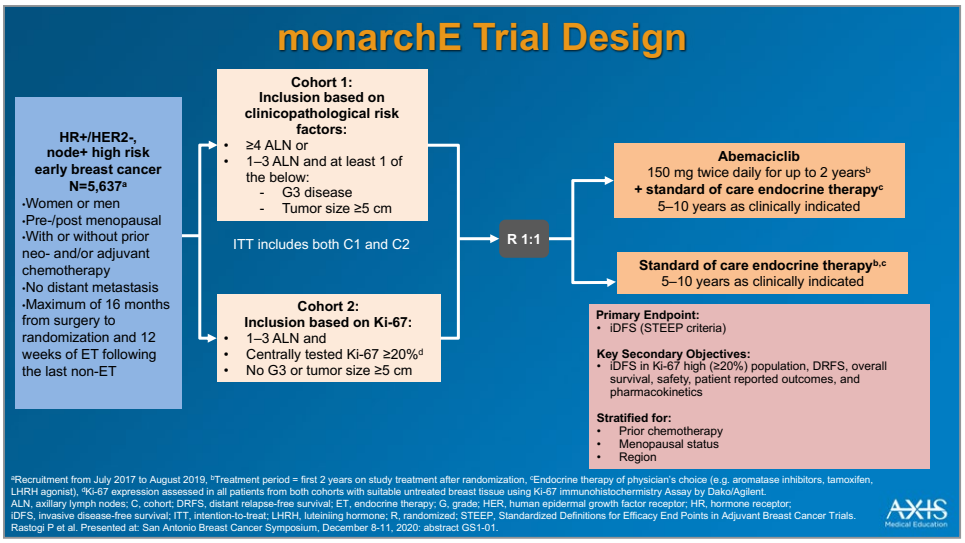
- Here you'll see the CDK4/6 inhibitors that have been studied in the adjuvant setting.

CDK 4/6 Inhibitors in the Neoadjuvant Setting

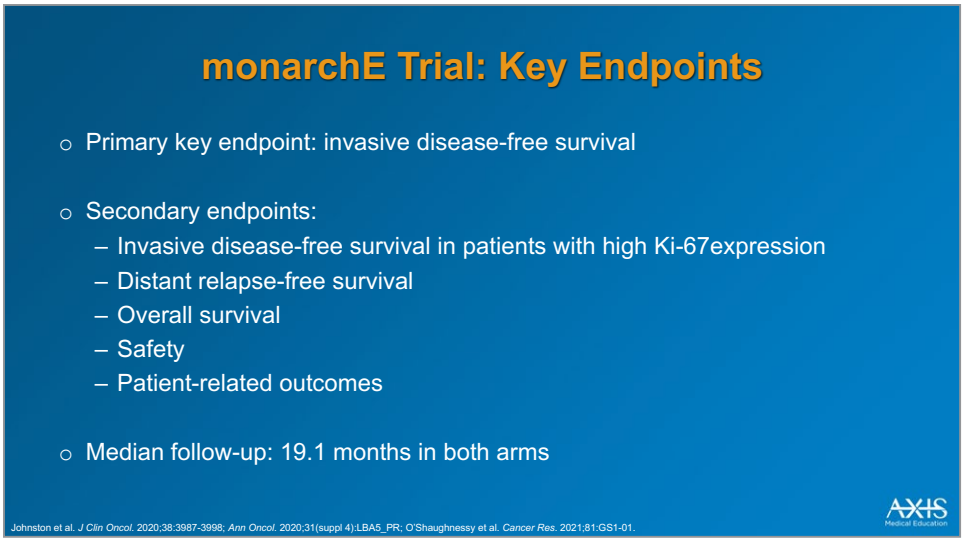
CDK 4/6 Inhibitor	Trial	Setting	Study Arms	Results/Status
Abemaciclib	CARABELA NCT04293393	HR+, HER2- high/intermediate risk breast cancer	Chemotherapy vs letrozole + abemaciclib	Trial recruiting
	neoMONARCH NCT02441946	HR+, HER2- EBC	Abemaciclib + anastrozole vs abemaciclib vs anastrozole	Abemaciclib + anastrozole induced complete cell cycle arrest, the primary end point, as measured by Ki67 for 67.8% of patients[1]
Palbociclib	PALLET NCT02296801	ER+, HER2- EBC	Letrozole + palbociclib vs letrozole alone	Palbociclib + letrozole increased rates of complete cell-cycle arrest, reduced apoptosis, and did not significantly improve clinical response rate[2]
Ribociclib	FELINE NCT02712723	ER+, HER2- EBC	Letrozole + ribociclib vs letrozole + placebo	Trial active, not recruiting

CDK, cyclin-dependent kinase; EBC, early breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.
[1]Hurvitz et al. *J Clin Oncol*. 2019;37:178-189; [2]Johnston et al, *J Clin Oncol*. 2019;37:178-189.

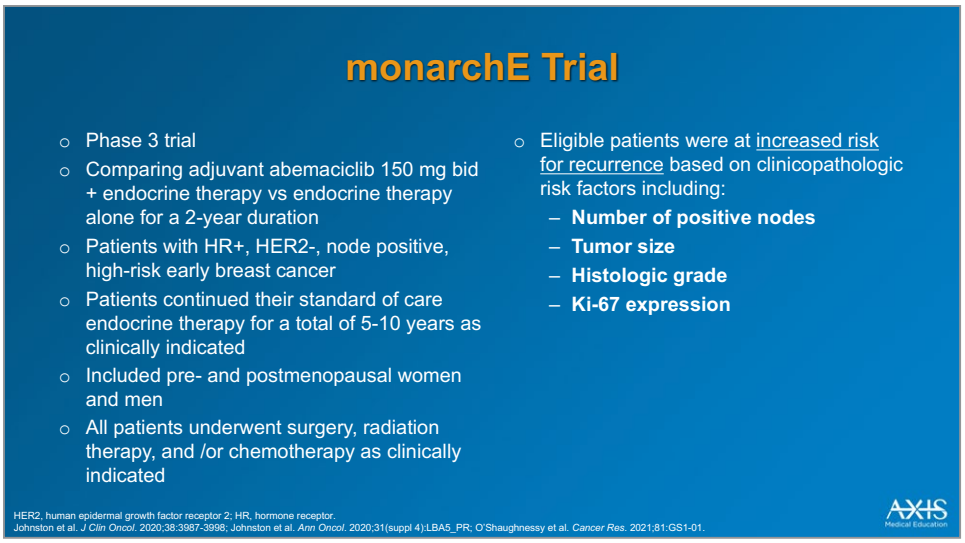
- Studies have also been ongoing, and some are still recruiting looking at can we give these drugs, these CDK4/6s, in the neoadjuvant setting to improve benefit and decrease recurrence.



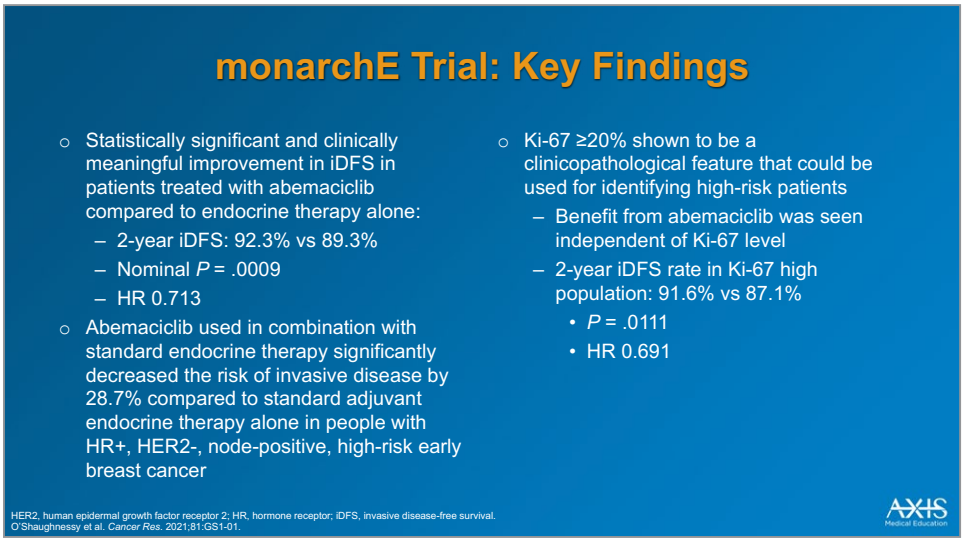
- Let's review the monarchE trial. Here's how the trial design looked specifically looking at patients with high-risk breast cancer. And then they were randomized to abemaciclib 150 mg BID for 2 years plus standard of care endocrine therapy. The control arm was standard of care endocrine therapy, and that was given for somewhere between 5 and 10 years, whatever was appropriate. The primary objective was invasive disease-free survival.



- Here, you'll see the primary endpoints that we discussed. The median follow-up is 19.1 months. That's a relatively short follow-up. It's going to be really important that we continue to watch these data.

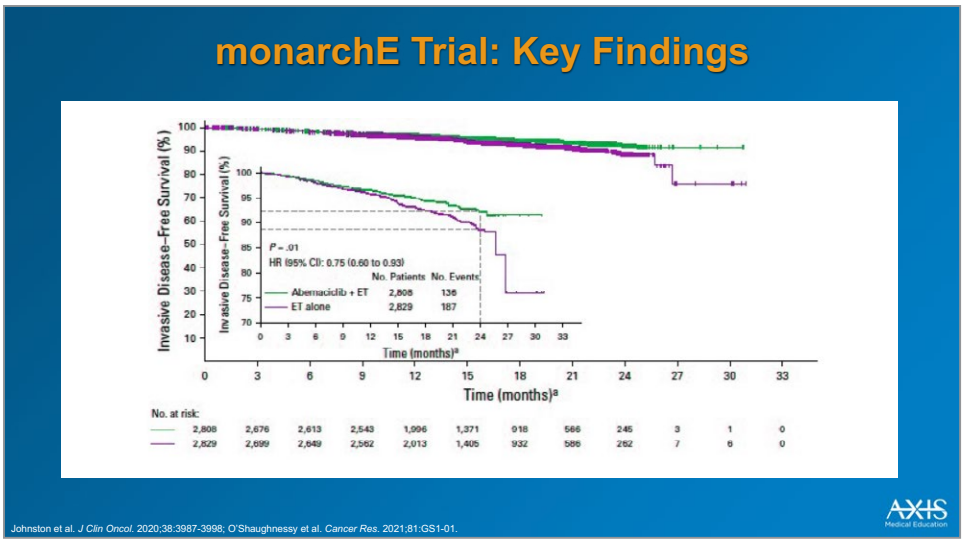


- monarchE was a phase 3 trial looking at adjuvant abemaciclib BID plus endocrine therapy versus endocrine therapy alone for a 2-year duration in patients that were deemed high risk. Now, high risk included clinicopathologic risk factors, including positive nodes, tumor size, histologic grade, and Ki-67 expression. To qualify for this study, the patient had to have at least 4 positive lymph nodes at the time of surgery. If they did not have 4 positive lymph nodes—if they had 1 to 3 positive lymph nodes—they had to have one of the following: either a very high-grade tumor; a large tumor, which was considered 5 cm or greater; or they had to have an elevated Ki-67. And they considered a high Ki-67 to be ≥20%.

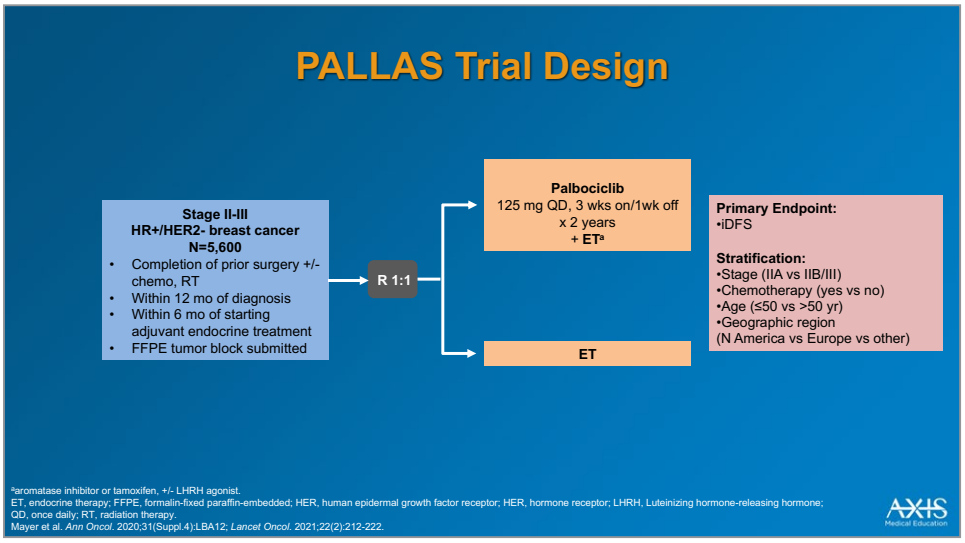


- The results showed a statistically significant and clinically meaningful improvement in invasive disease-free survival in patients who were treated with abemaciclib. The 2-year invasive disease-free survival was 92.3% in the abemaciclib arm compared to 89.3% in the control arm.

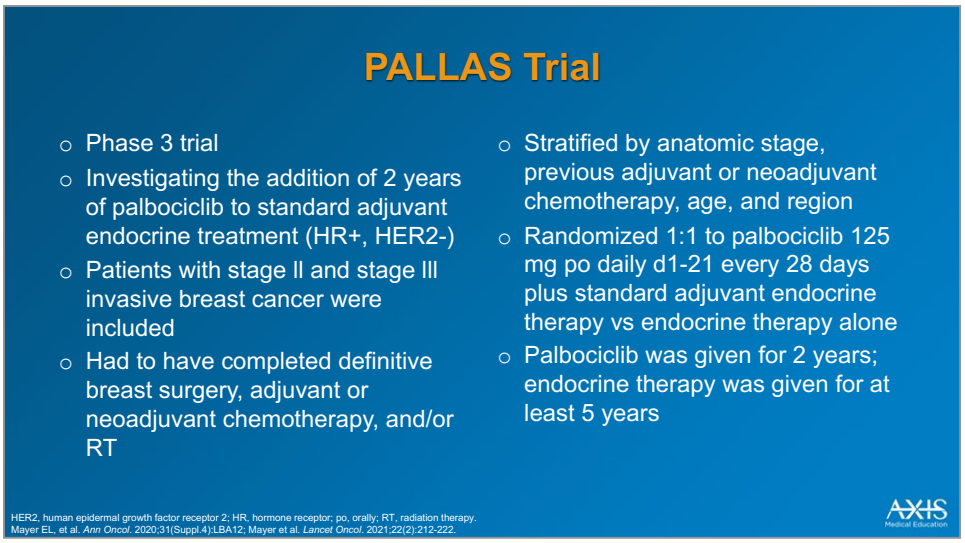
  Abemaciclib used in combination with standard endocrine therapy significantly decreased the risk for invasive disease by 28.7% compared to standard adjuvant endocrine therapy alone in patients with hormone-positive, HER2-negative, node-positive, high-risk early breast cancer patients. You will see that in the patients who had high Ki-67 scores, the 2-year invasive disease-free survival rate was 91.6% compared to 87.1% with a hazard ratio of 0.691.



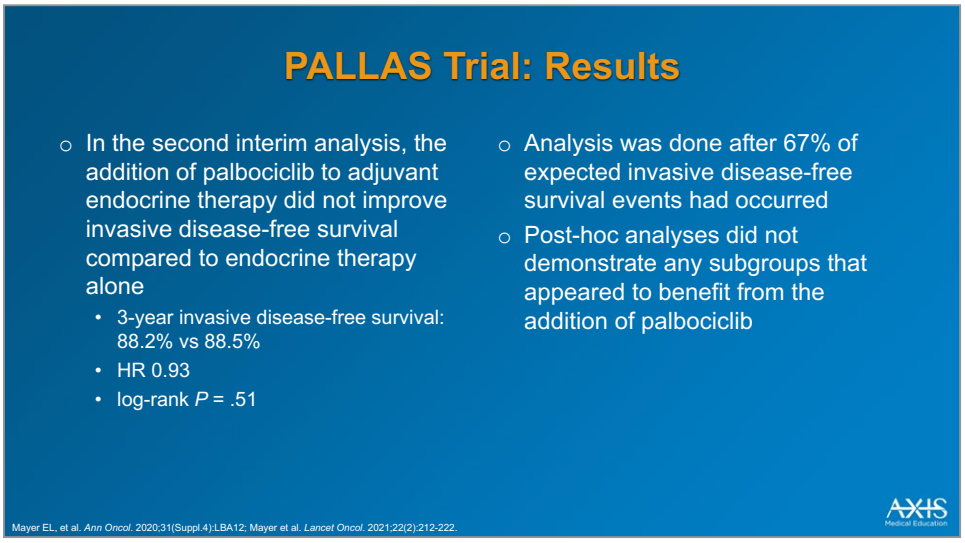
- Here's what the Kaplan-Meier curve looked like, and you'll see that the curves actually started separating at 9 to 12 months.



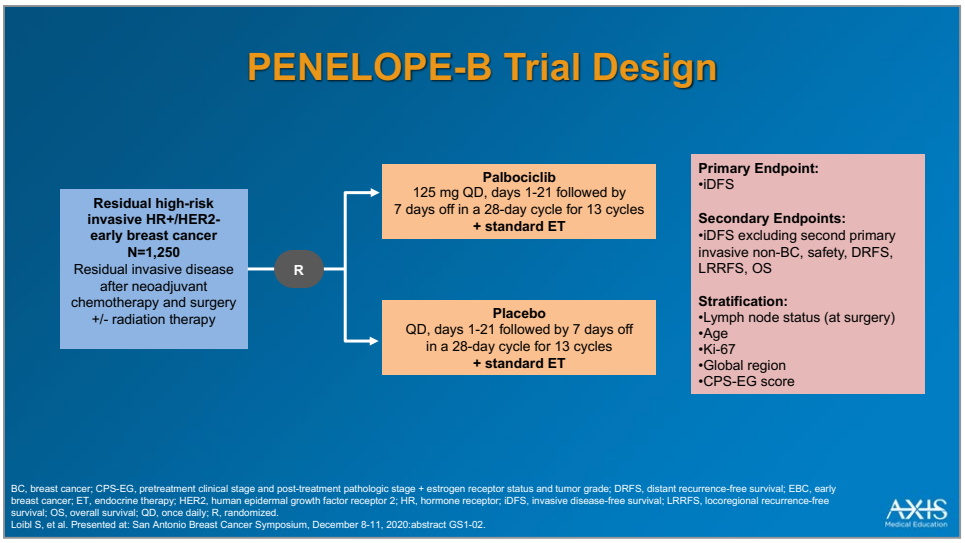
- The PALLAS study was a randomized phase 3 trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for hormone receptor–positive/HER2-negative early breast cancer. This study included patients with Stage II and Stage III disease and then randomized between palbociclib given for 2 years at 125 mg every day for 3 weeks plus the endocrine therapy given per the appropriate endocrine therapy regimen, and then the other arm was endocrine therapy alone.



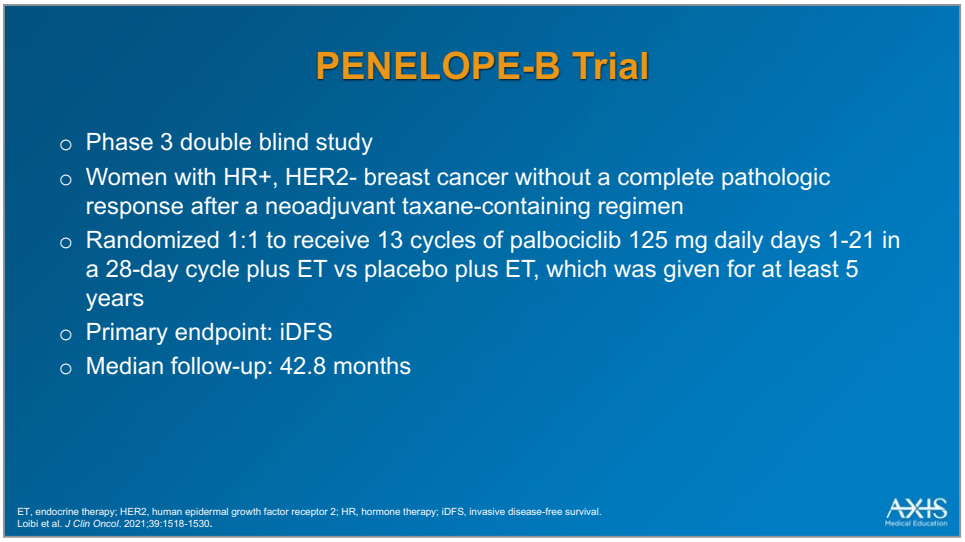
- So in the PALLAS trial, patients with Stage II disease were allowed, and in fact, 13% on each arm were node negative.



- In the second interim analysis, the addition of palbociclib to adjuvant endocrine therapy did not show improved invasive disease-free survival compared to endocrine therapy alone. The 3-year invasive disease-free survival was 88.2% with palbociclib plus endocrine therapy and 88.5% for endocrine therapy alone with a hazard ratio of 0.93. Analysis was done after 67% of expected invasive disease-free survival events had occurred. And unfortunately, on post hoc analysis, no specific subgroup appeared to benefit from the addition of the palbociclib.



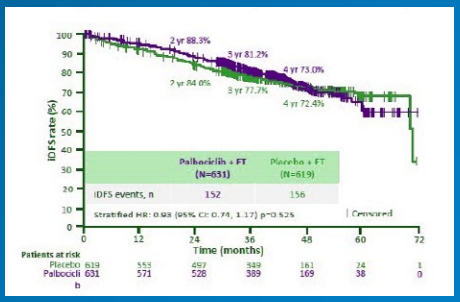
- The PENELOPE-B trial looked at patients who had received neoadjuvant chemotherapy and had residual invasive disease after that neoadjuvant therapy. They were randomized to palbociclib 125 mg every day, day 1 through 21, followed by 7 days off for 13 cycles, and then the endocrine therapy was given, as appropriate, for the appropriate time for the endocrine therapy.



- In this phase 3 double-blind study, they were specifically looking for patients who had not had that complete pathologic response. And the primary endpoint in this study was invasive disease-free survival.

PENELOPE-B Trial: Results

- Palbociclib for 1 year in addition to standard of care ET did not improve iDFS in women with residual invasive disease after neoadjuvant chemotherapy
  - Estimated 3-year iDFS: 81.2% vs 77.7%
  - HR 0.93



ET, endocrine therapy; iDFS, invasive disease-free survival.
Loibl S, et al. Persented at: San Antonio Breast Cancer Symposium, December 8-11, 2020: abstract GS1-02; Loibi et al. *J Clin Oncol*. 2021;39:1518-1530.

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The palbociclib for 1 year, in addition to standard of care in endocrine therapy, did not improve invasive disease-free survival in women with residual invasive disease after neoadjuvant chemotherapy. The estimated 3-year invasive disease-free survival was 81.2% with palbociclib and 77.7% with placebo. But as you'll see as we proceed, unfortunately, after year 4, those curves crossed, and we no longer saw the benefit.

NATALEE Trial Design

HR+, HER2- EBC
N= ~4,000
- Pre- and postmenopausal women, men
- Anatomic Stage II[a]
- Anatomic Stage III

R
1:1

Ribociclib[b]
400 mg/d PO (36 months)
+ ET[c] (60 months)
+ LHRH agonist[d]

ET[c] only (60 months)
+ LHRH agonist[d]

Primary Endpoint:
- iDFS

Secondary Endpoints:
- Recurrence-free survival
- Distant disease-free survival
- Overall survival
- Patient-reported outcomes
- PK parameters
- Safety and tolerability

[a]Stage II: N1 or N0 (T2-3, N0) with G2-3 and/or Ki67 ≥ 20% (testing for Ki67 not mandatory), excluding G1.
[b]3 weeks on/1 week off, 36 months (-39 cycles).
[c]Letrozole or anastrozole; treatment with NSAI may start up to 12 months before study treatment start date.
[d]Goserelin in premenopausal women and men.
EBC, early breast cancer; ET, endocrine therapy; HER2-, human epidermal growth factor receptor-2-negative; HR+, hormone receptor-positive; LHRH, luteinizing hormone-releasing hormone; NSAI, nonsteroidal aromatase inhibitor; PK, pharmacokinetic; PO, orally; R, randomization.
Slamon et al. *J Clin Oncol*. 2019;37(15):TPS597.

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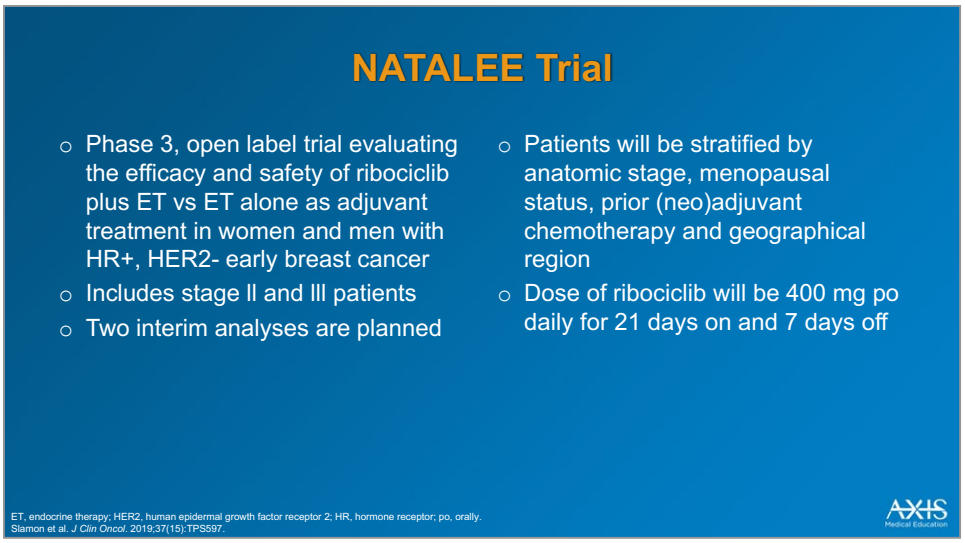
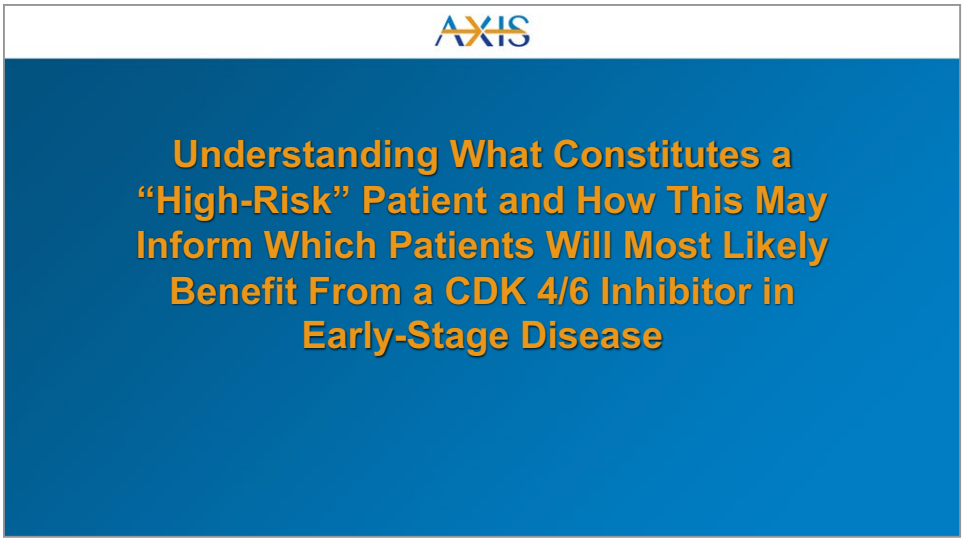
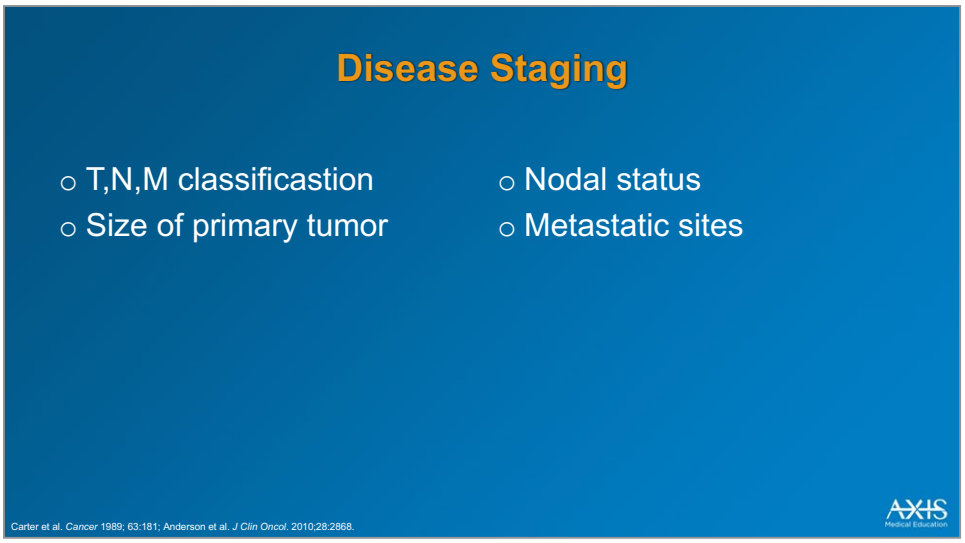
The NATALEE trial has just recently ended its recruitment phase. This was the ribociclib trial, which included Stage II and Stage III. It looked at ribociclib given 400 mg daily on an intermittent dosing of days 1 through 21 followed by 7 days rest plus endocrine therapy. If the patient was premenopausal, they received an LHRH agonist. The ribociclib dose in the metastatic setting was 600 mg daily. In the NATALEE trial, it was 400 mg daily. And I believe that that was probably in hopes of being able to minimize toxicity but maximize efficacy and hopefully keep patients on longer.



- There are two interim analysis that are planned.



- It looks as if patients who may benefit most from the potential addition of a CDK4/6 inhibitor in early-stage therapy are patients with truly high-risk disease. But what exactly does that mean, and what are things we need to look at when we're evaluating high risk in determining who exactly has high-risk disease?



- We know that the size of the primary tumor is very important. The larger the tumor, the more concern we have for patients who might have developed microscopic distant metastasis. Nodal status is also important. We know that the more nodes a patient has, the more concern we have for potential for recurrence down the line or micrometastasis.

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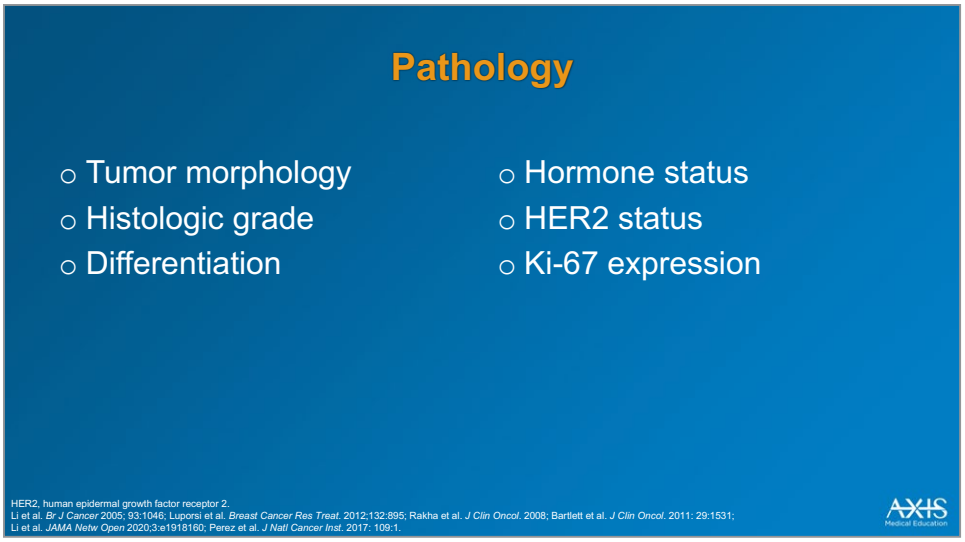

- Regarding pathology—what does that tumor look like under the microscope? Does it look a lot like its cell of origin, or does it look very different? Is it high grade, is it rapidly dividing? Is it poorly differentiated or very well differentiated? What's the hormone status? Are they estrogen positive? Are they progesterone positive? What about that HER2 status? All of those are very important. And then as we begin to look at and explore the Ki-67 expression, we find that that can be important as well.

Ki-67

- Ki-67 is a protein that is associated with cellular proliferation
- As cells are dividing more rapidly, eg, cancer cells, the expression of Ki-67 increases; thus, a higher Ki-67 score represents a higher grade or more aggressive cancer
- Ki-67 protein level is determined based on staining of pathologic tissue from breast cancer samples
  - <10% staining = low, 10%-20% = borderline, >20% = high
- Ki-67 biomarker can be used to predict response as well as provide a prognosis for likelihood of survival

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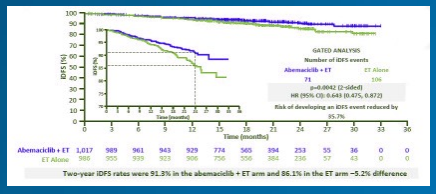
- Ki-67 is a protein, and it's associated with cellular proliferation. As cells are dividing more rapidly, the expression of Ki-67 increases. Thus, a higher Ki-67 score represents a higher grade or more aggressive cancer. A Ki-67 protein level is determined based on staining of pathologic tissue from breast cancer samples. Less than 10% staining demonstrates a low Ki-67, 10% to 20% demonstrates a borderline Ki-67 score, and those that have greater than 20% staining have a high Ki-67 score.

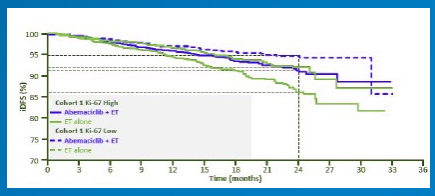
monarchE: High Ki-67 as a Biomarker for Identifying Patients With High-Risk EBC

Significant and clinically meaningful improvement in iDFS in patients with high Ki-67 tumors



Among patients with high clinicopathological risk factors, patients with high Ki-67 tumours had a greater risk of disease recurrence

- Patients with high Ki-67 tumors had an even greater risk of disease recurrence than those with low Ki-67 tumors – confirming the prognostic value of Ki-67



EBC, early breast cancer; ET, endocrine therapy, HR, hazard ratio; iDFS, invasive disease-free survival
Adapted from Johnston et al. *J Clin Oncol*. 2020;38:3987-3998.

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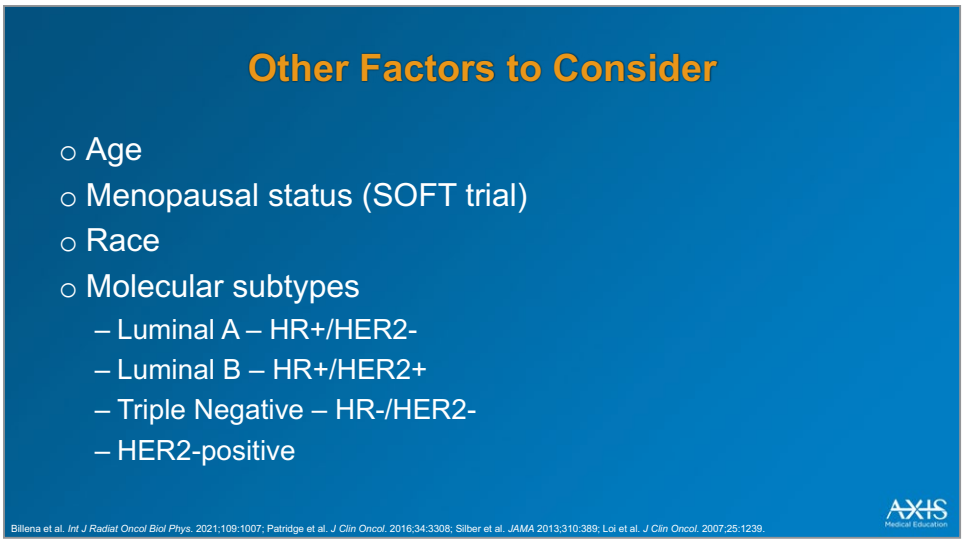
- You'll see here the monarchE study. And you'll see how the high Ki-67 staining was used as a potential biomarker for identifying patients with that high-risk early breast cancer.



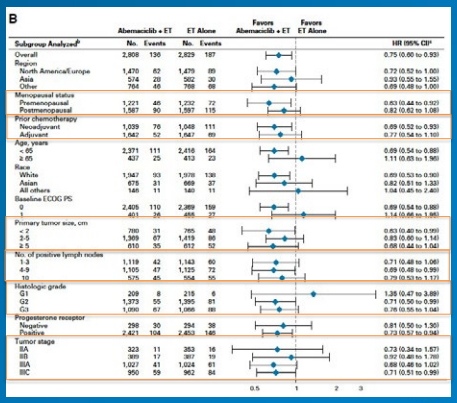
- Other factors that we need to consider are the age of the patient menopausal status, and race. Then we need to think about those molecular subtypes.

monarchE: High-Risk Disease and Subgroup Analysis

- High risk defined as:
  - ≥4 positive pathologic axillary lymph nodes

  OR
  - 1-3 positive axillary lymph nodes **and** at least 1 of the following:
    - Tumor size ≥5 cm
    - Histologic grade 3
    - Centrally assessed Ki-67 ≥20%

iDFS of Patient Subgroups



iDFS, invasive disease-free survival.
Johnston et al. *J Clin Oncol*. 2020;38:3987-3998

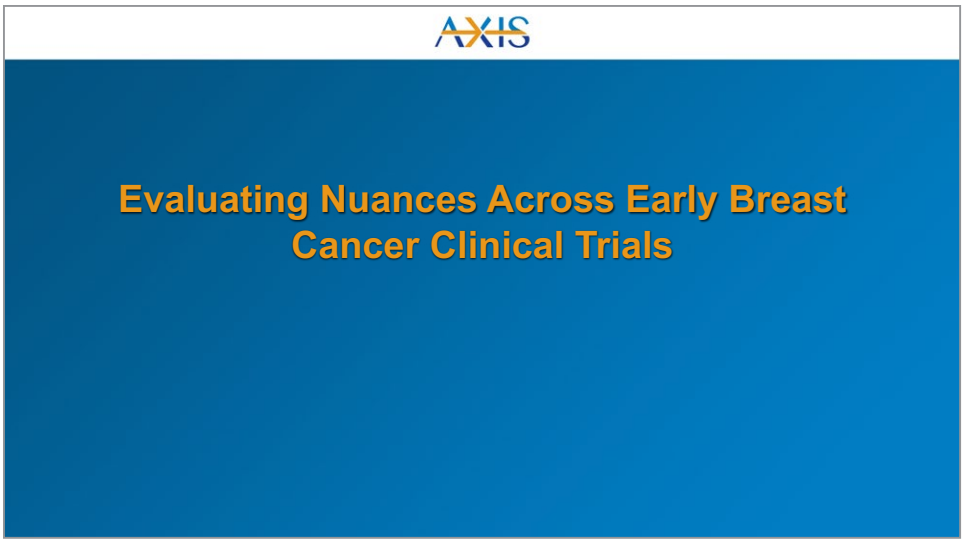
- In this particular slide what we're looking at is the invasive disease-free survival from the monarchE study in various subgroups. You'll see that basically most of the subgroups benefited from the addition of the abemaciclib.

monarchE trial: Patients Who Received Neoadjuvant Chemotherapy

- Patients with HR+, HER2- EBC who received neoadjuvant chemotherapy were noted to be at a higher risk of recurrence
- Abemaciclib + ET demonstrated treatment benefit in iDFS vs ET alone
  - HR: 0.614
  - 2-year iDFS rates: 87.2% vs 80.6%
- Addition of abemaciclib to ET resulted in an improvement in distant relapse-free survival
  - HR: 0.609
  - 2-year distant relapse-free survival rates: 89.5% and 82.8%

EBC, early breast cancer; ET, estrogen therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival.
Martin et al. *J Clin Oncol*. 2021;39(15):517.

- You'll also see that in patients who had received neoadjuvant chemotherapy, the 2-year invasive disease-free survival rate was 87.2% versus 80.6%.



- I think it was probably obvious that there were some differences in those studies. And so let's talk about that and highlight some of the differences that we saw across the clinical trials.

Nuances Across Early Breast Cancer Clinical Trials

	monarchE: abemaciclib	PALLAS: palbociclib	PENELOPE-B: palbociclib	NATALEE: ribociclib

Patients	High-risk disease:
	• ≥4 positive nodes
	Or
	• 1-3 positive nodes with one of the following risk factors:
	  ○ Ki-67 expression ≥20%
	  ○ Grade 3
	  ○ Tumor size ≥5 cm
		• Initially designed with broad eligibility criteria
		  ○ Stage II included
		• Approx. 13% of patients in each arm were node negative
		• Enrolled within 6 months of adjuvant therapy and 12 months of diagnosis
		• Many patients discontinued due to protocol requirements
			• Chemotherapy given neoadjuvantly
			• Included patients without a pCR after a taxane-containing regimen
			• Most patients had tumors with low Ki-67 expression at surgery; 25% had tumors with high Ki-67 expression
			• Palbociclib given for 1 year; ET given for 5 years
				• Treatment with ribociclib expected to last up to 36 months; treatment with ET will last up to 60 months
				• Tumor tissue samples will be collected to identify biomarkers that might predict benefit
				• Ribociclib dosing: 400 mg daily in the adjuvant trial; 600 mg daily in metastatic

Efficacy	• Statistically significant & clinically meaningful improvement in iDFS for abemaciclib vs ET alone • Curves separated at 9 to 12 months • Duration of follow-up: 19.1 months • Most frequent AEs in abemaciclib arm: diarrhea, neutropenia, fatigue • Dose adjustments due to AEs: 68.1% • Discontinuation due to AEs: 16.6% • Discontinued both treatments: 6.2%	• Addition of palbociclib to adjuvant ET did not improve iDFS compared to ET alone • Post-hoc analyses: no subgroup appeared to benefit from addition of palbociclib • Median follow-up: 23.7 months	• No statistical evidence of improvement with the addition of palbociclib plus ET • At year 4, curves came together • None of the prespecified subgroups benefited from palbociclib • Median follow-up: 42.8 months	Trial recently completed enrollment
	2-year iDFS: 92.3% vs 89.3%	3-year iDFS: 88.2% vs 88.5%	3 year iDFS: 81.2% vs 77.7%	
	2-year iDFS in Ki-67 ≥20%: 91.6% vs 87.1%			

AE, adverse events, ET, endocrine therapy; iDFS, invasive disease-free survival; pCR, pathologic complete response.
Johnston et al. J Clin Oncol. 2020;38:3987-3998; O'Shaughnessy et al. *Cancer Res*. 2021;81:GS1-01; Mayer et al. *Ann Oncol*. 2020:-31(supp 4):LBA12; Mayer et al. *Lancet Oncol*. 2021 Feb;22(2):212-222; Loibl et al. *J Clin Oncol*. 2021;39:1518-1530; Slamon et al. *J Clin Oncol*. 2019;37(15):TPS597.

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First, in the monarchE trial it appears they really sought out those patients who had truly high-risk disease. Remember, the patients in the study all had ≥4 positive nodes. If they didn't have ≥4 positive nodes, then they had to have 1 to 3 positive nodes with one of the following risk factors: a high Ki-67 expression of 20% or greater, a Grade 3 tumor, or a tumor that was larger; ≥5 cm. We know that that invasive disease-free survival curve we saw that started to spread as early as 9 months. However, we also have to keep in mind that the duration of follow-up is really relatively short in this study, it's 19.1 months. So we need to be diligent and watch these data.

In the PALLAS study, as I alluded to earlier, they included Stage II patients. And in fact, some patients were actually node negative. 13% of patients in each arm were node negative. And so was that an important piece to think about. Because perhaps these were very low-risk patients, and they weren't going to have recurrence. And so, if they weren't going to have recurrence, you really wouldn't see the benefit of the addition of a CDK4/6. That's one hypothesis, of course.

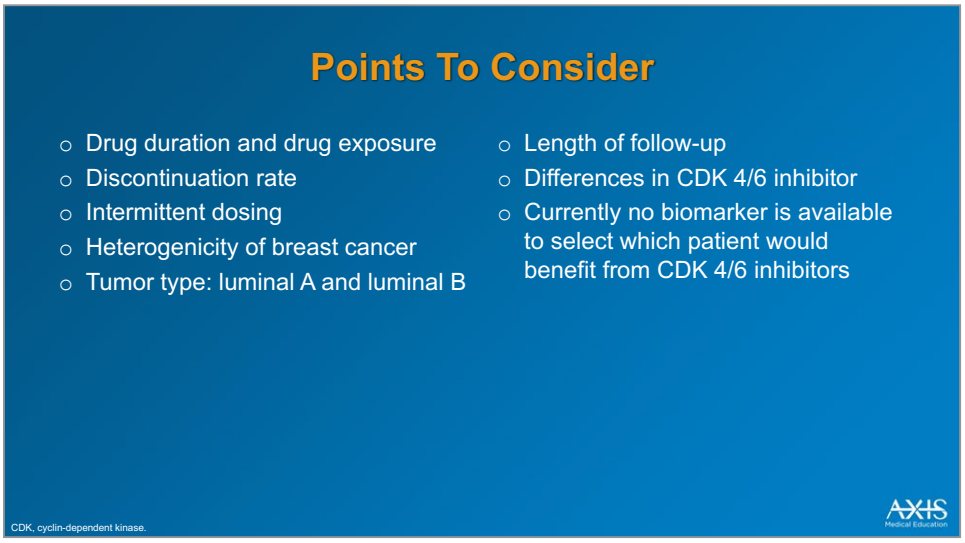
The other thing about the PALLAS trial is it had very strict toxicity criteria and dose reduction requirements per protocol. And so 42% of the patients actually discontinued palbociclib and did not continue it for the entire 2 years. Now, we all know that if a patient doesn't take a medication clearly, they can't benefit from that medication, right? We know that if a patient had neutropenia, very quickly they were withheld and the doses reduced. And this was continued if the patient developed neutropenia after the dose had been reduced to 75 mg, then they were no longer able to continue on the study. Unfortunately, a post hoc analysis reviewing various subgroups did not show that any of the various subsets benefited from the addition of palbociclib.

Then looking at the PENELOPE-B trial, many of the patients in the study at the time of surgery had a low Ki-67 expression. Only 25% of them had tumors with a high Ki-67 expression. Also, the palbociclib was only given for 1 year, and the endocrine therapy in this study was given for 5 years. And is 1 year, perhaps, not long enough to really see the benefit?

Approximately 20% of patients did not complete all 13 cycles or didn't stay on the drug for

that entire year. At the 3-year data analysis, the invasive disease-free survival in the palbociclib arm was 81.2% compared with 77% in the placebo arm. So that was an absolute difference or an absolute benefit, at that point, of 3.5%. That's almost exactly what we see in the abemaciclib in the monarchE trial. Now at 4 years, those curves came together, and no statistically significant improvement was demonstrated. So again, this bears the fact that we really need to follow the data and allow these studies to mature.

The NATALEE trial has now completed enrollment. And we know that in this particular trial, the CDK4/6 is actually going to be given for 36 months so for 3 years, and will that make a difference? We also know that the endocrine therapy will last up to 60 months, and that the dosing of the ribociclib was decreased in the adjuvant study. It's 400 mg daily in this adjuvant trial. However, it might be more tolerable from a bone marrow standpoint, and that patients could stay on it and, therefore, hopefully benefit from it. Again, the trial has completed enrollment, and we will just have to wait and see.



So as we consider these studies—the monarchE, the PALLAS, the PENELOPE-B, and the NATALEE—things that we want to consider are if study fails, one of the very first questions we ask is did we have the wrong hypothesis? Was the trial, perhaps, not set up appropriately—the drug duration, the drug exposure? If a patient can't take the drug, it doesn't matter how good that drug is. If it's in the bottle and not in the patient, there's no way the patient can benefit from that. So does the duration of the CDK4/6 treatment matter? Does it need to be longer than 1 year? Is 2 years the appropriate number, is 3 years the appropriate number? And then, of course, the discontinuation rate—if we can't keep the patient on the regimen, they're not going to benefit from it.

So the data we've reviewed I hope you find it as interesting as I do. I also hope you find it as hopeful, potentially. But I think the caveat is we need to allow all of these data to mature so we can get more answers to many of these questions that we have just discussed.

Implications of Side Effects, Adherence, and Shared Decision Making

An Advanced Practitioner Roundtable Discussion

So, I'd like to welcome back my colleagues, Theresa and Val. We're going to talk about how we get a patient on medication, help set them up for success so they can adhere to the medication regimen, help talk about watching for any potential toxicities and how we might mitigate that, and how we'll use our entire team. So, Theresa, in your practice, what are some of the factors that you find contribute to most patients discontinuing their therapy?

Theresa W. Gillespie, PhD, MA, RN, FAAN: So the data are clear that patients who are older, patients who have a lot of polypharmacy, patients who perhaps have less health literacy or understanding of what they're doing, I want to make the point that educational attainment does not necessarily or always translate to comprehension of what's going on. Regardless of the educational attainment of the patient or the family members who are supporting that patient, all of us, as providers, need to implement a variety of techniques to make sure that the patient and the family understand what the drugs are, what potential side effects are, what is the particular regimen and the schedule.

And I think one of the things that is often missed is talking about the goal of therapy. Patients may have metastatic disease and be thinking that well, I'm going to take this, and this is going to be a finite amount of time, and this is going to cure me. And they don't, necessarily, understand or can articulate the goal of therapy. So I think that probably is one of the very first things. And then to ascertain, perhaps, from other drugs that the patient might be on for other chronic diseases what has been their level of adherence? Are they prone to missed doses or be confused or not be very compliant or adhere rigidly? And that all combined together to help maybe just highlight we need to spend a little bit more time talking with this patient and family, and maybe think of some tools or some other strategies to help that patient.

Orbaugh: Thank you very much for that. Val, I tell you, I have the highest respect for pharmacists. I am very blessed, at my facility, to work with just a great pharmacy team. And I just wonder in your practice in your experience, what are some practical tactics for ensuing care coordination and communication among an interdisciplinary team? You know, let's face it—not one patient just has one doctor. How do you keep all of that together and make sure that the team is communication?

Val R. Adams, PharmD, FCCP, BCOP, FHOPA: First I really appreciate all the things that Theresa said. It really starts with the patient and trying to understand their expectations but also their track record. And then, as you just mentioned, the big key is communication because we have splintered care. We've got a multimodality breast cancer clinic; so our surgeons come, our oncologists come, our radiation oncologists come, a social worker comes, pharmacy comes.

But you're exactly right—all of those people have to be part of the same plan and again, it has to involve the patient. But once it's started, how are we doing it, who's doing it, who's going to get preauthorization, who's following side effects? And the other element that's not in our room directly is our specialty pharmacy. Because, as we know, these are all oral, and they're going to come from a specialty pharmacy, and that's probably different. So, having a good clinical pharmacist at the site helps us because someone needs to review all of their meds, and there are so many potential drug interactions it's hard to get them on the same computer when they're getting filled at different pharmacies versus a specialty pharmacy that is functionally going to be a mail order, but they're going to follow the patient, ask about toxicities, all of the financial issues.

Somebody has to make sure there's good communication among everybody. And there's a number of different successful things, but I think the key is exactly what you said—it's communication. It's getting harder and harder to know everything, right? So, we're all involved, and I think good communication channels are the key.

Gillespie: I was just going to add that I like to think that there needs to be a quarterback for the team. And whether that is the advanced practice nurse or the clinical pharmacist or someone, but someone needs to be sort of the point person. And it's usually not going to be the physician who may be very busy, or perhaps that person is off and someone else is covering for that person. But as Val said, to have that clear coordination and have someone leading that part of the team. So the drugs, the polypharmacy, the drug-drug interactions—if someone isn't minding the store, it's very easy for so much to slip through the cracks, and then patients can get into real trouble.

Orbaugh: Absolutely. I couldn't agree with that more. One thing that's been vital when we do education on oral therapies with patients and their support team or their caregivers is to make sure they understand that that oral treatment is just as important as the IV treatment. And sometimes I really think they get in the mindset well this is just a pill—it can't make me as sick, there aren't as many toxicities; or more importantly, it's not as important because it's just a pill. And so I think making sure they understand that this is their cancer treatment. This pill going into their mouth on a regular basis is what's treating their cancer right now is really important.

What are some of the tactics you use for anticipating, monitoring, and managing any side effects with these CDK4/6 inhibitors?

Adams: Maybe I can start here. This is something that's not always widely known, and it bridges back to the communication. Specialty pharmacies, to be accredited, have to call and follow the patient for toxicities. It's part of their jobs to call and follow-up with patients. And when I talk about communication, it's helped us a lot. We have our own specialty pharmacy. But because insurance companies sometimes mandate who the long term is, we'll fill the first one, then we'll have to transfer it to a different specialty pharmacy or something like that. And that's fine. But we don't always have as good a communication back because they are following up. A lot of times if it's just a mild or moderate toxicity, they'll make recommendation. We don't even know it happened, right?

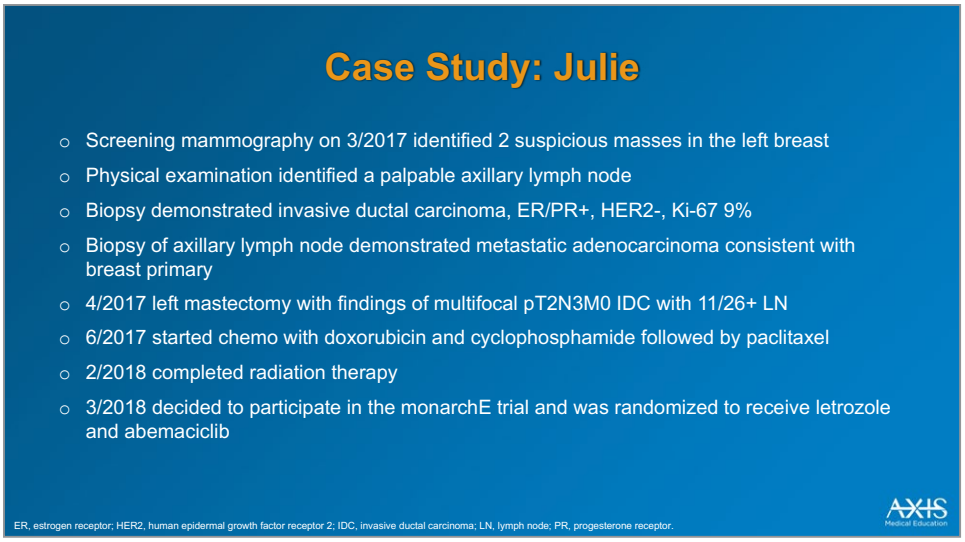
Those are the things that it's hard, it's not great, and we need to anticipate. Some of the communication is probably key. For these drugs, in particular, with abemaciclib, we're going to look at diarrhea is one of the things that's symptomatic, and it's a tolerability issue. But hopefully we're all getting the right labs and looking at those for all of the neutropenia and those types of events and asking about infections and some of the other more common types of toxicities that we do see with this group of drugs.

Gillespie: Whatever the techniques or tactics that are chosen, they need to be compatible with what is going to work with that individual patient. And so, many of these women or men with this breast cancer usually metastatic or what have you are going to be a little older, and some of them may or may not be technology

savvy. We cannot assume that because our patient is 70 years old, that she or he doesn't understand or doesn't use technology. That's very stereotypical, and we need to get beyond that. We need to have the conversation and ask them is it a classic phone call, are people texting, are they using the patient portal?

During the pandemic, many patients became very comfortable with telehealth for those centers that were utilizing that for follow-up visits or assessments of toxicities or how patients were doing in the interim. And so there's a wide variety of ways to monitor and to conduct ongoing surveillance about toxicity status and how people are tolerating and if they need an intervention. And that upfront conversation, in terms of if you're experiencing X, Y, Z, different symptoms or problems, that's immediately when you need to make that phone call.

And of course, we like it when patients have to come in for IV therapy because they're in our chairs, and we can see them and put our hands on them and eyeball them and do all the things that we like to do. But with these patients, with oral therapies, a lot of that's on their own. And so we need to be creative, and we need to be consistent, and we need to have creative ways that are where the patient is in terms of what's most comfortable and what they're able to really engage with. So lots of options, but it needs to be compatible with the patient.



Orbaugh: Let me share a patient of mine. And I'd like to hear some of your thoughts about the patient and how you would manage this particular patient, how you would include the patient in shared decision making, those types of things. So let me introduce you to her. Her name is Julie. She underwent a screening mammogram in March 2017, and she had two suspicious masses in her left breast. Unfortunately, she also had palpable lymphadenopathy on examination. She had a biopsy-proven invasive ductal carcinoma and was ER/PR-positive, HER2-negative, Ki-67 is 9%.

The biopsy specimen of her axillary lymph node also demonstrated metastatic adenocarcinoma consistent with a breast primary. In April 2017, she underwent a left mastectomy with findings of multifocal invasive ductal cell carcinoma. She had 11

of 26 nodes positive for metastatic disease. She started chemo with doxorubicin and cyclophosphamide followed by paclitaxel. She then went through radiation. She is a very savvy woman and works in the community with a breast cancer support group. She was a very big advocate for herself and decided that she wanted to pursue the monarchE trial, and she was randomized to receive letrozole and abemaciclib.

So now with that in mind, let's talk about how are we going to help her be adherent, and what are some things we need to think about with her? So, Theresa, I'll start with you—what strategies or resources do you use in your clinical practice to help facilitate oral therapy compliance? Or how would you talk to Julie?

Gillespie: Right. And I want to get back to a point you made earlier, Kristi, that patients think that because it's a pill, it couldn't possibly be that important. And there have been studies looking at women who were on adjuvant therapy with both chemo followed by endocrine therapy, and while they were extremely adherent to the regimen for the chemotherapy, they often dropped off with their endocrine therapy. Now part of that is because you're probably giving at least some of that chemotherapy IV, so they have to show up.

But the other rationale that these patients have was that I had the big guns, I had the IV chemo, and these are just pills, and these are just mocking it up. Even though we know for many of these women, it was the endocrine therapy that was probably going to do more of the therapeutic work than even the chemotherapy. So the first thing I would do with Julie is assess her understanding of the goals of therapy, what does she understand about these particular CDK4/6 inhibitors and this particular one, which is given continuously, which in some ways is easier than the other two CDK4/6 inhibitors where they're given 3 weeks on and then 1 week off. Because it's similar to birth control where you need to have something to keep them going during that week off, or they can get off schedule pretty easily.

But I would ask Julie about what kinds of things does she use, for example, as reminders? I think one of the things that even older people can adapt to pretty easily is using a smart speaker. So you're asking Alexa to remind you at 10 am to take your pill and remind you at 8 pm—or whatever it is—in terms of making sure that you're following up with that. Knowing what her regular schedule is is there a particular time of day where that might be really easy for her to comment on that this is where I need to be taking these pills consistently. And use technology as well as there are a lot of pharmaceutical services, that can help organize pill taking. So whatever drugs is she on already, the whole drug-drug interaction, but also scheduling because that can get really complicated.

I was just home with my parents this past weekend—they're in their nineties—and their pill bottles just cover the dining room table. It takes my father hours every Sunday to set up all the pills for the week. So you have to think about how can we make it easy? Because if it's not easy and it's not almost automatic, I think that's where some of this adherence falls off.

Orbaugh: Absolutely. Val, in your practice, how do you all assess for patient adherence?

Adams: That's such a great question, and Theresa said so many things that resonate with me. My mother's the same thing—so pill burden is a real thing, I get it now. And there are a number of tools. At the start, to go back to your original question, one of the things that's really important to try to understand is what's their background, how many other medicines are they on, how do they take them? And to try to make it part of their routine. And that's the strategy, to get back to your original question, even though I know you posed it differently than that.

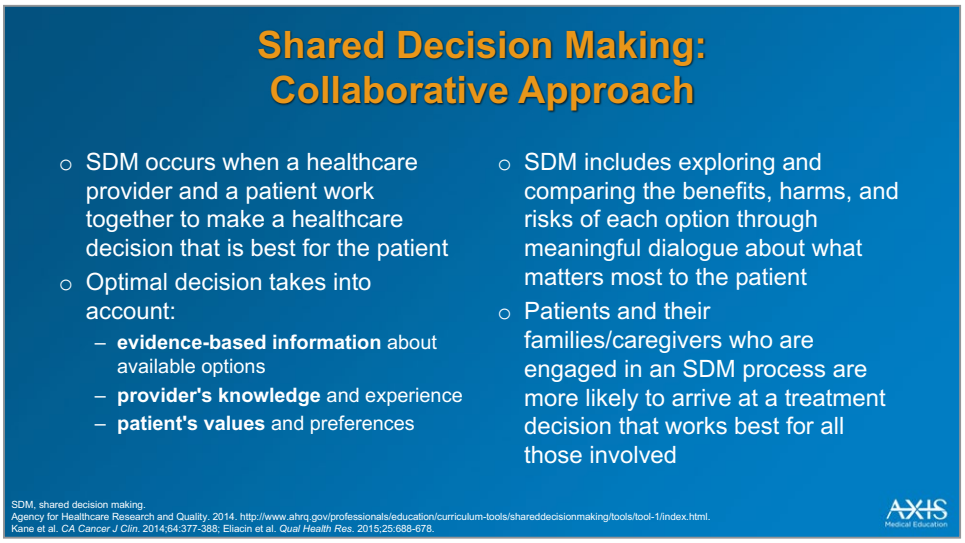
That's really important to make sure it's part of their routine. As I reflect, I'm on a statin just at bedtime, and now it's part of my routine, and I've got one. But there are a lot of people, like my mother, I think she's got probably six or eight pills in the morning and another eight or nine at night. And the pill burden and just adding to that trying to figure out what's a good time, how can we work with that, what systems have they already got in place that we could just add to I think is really key?

In terms of talking to them and assessing adherence, I think this comes with communication. A lot of this, again, it's going to go to a specialty pharmacy, it may take a day or two. You may never see it. I think in challenging cases, it's nice to have patients, especially if they've got dosing changes or other things going with their medications, ask them to

bring all their pills with them when they come to clinic. And a clinical pharmacist or a nurse practitioner somebody should sit down and see. There's nothing more scary, as a pharmacist, to find out somebody's on warfarin, and they've got a 5 mg bottle and a 7.5. And they're like oh yeah, they just bumped me up to 7.5, but I've just been taking one of each so I can finish the old 5s. And you're like no!

So those are the kinds of things that I think that it catches, and it does because the pill burden and the adherence, as they get older and more forgetful, is really a problem. I don't have great strategies. I'm a huge fan of pill boxes, somebody helping fill those. But if they're already doing something else that works, join in that. It has to be personalized for the patient.

Orbaugh: There's been a lot of talk, a lot written about shared decision making and including that patient in helping guide their treatment journey. What does shared decision making look like at your facility, or what does it look like in your mind, your professional mind?

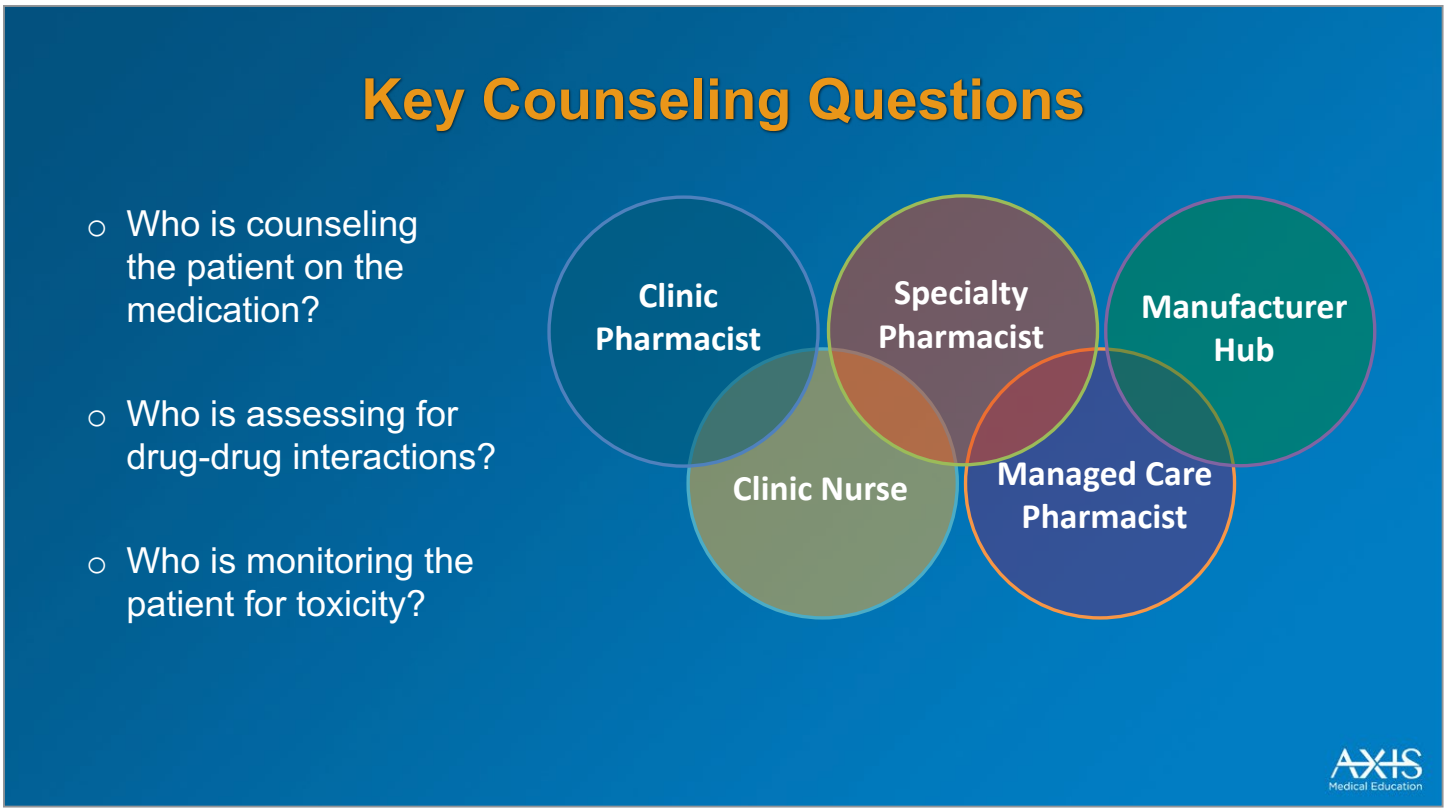


Gillespie: So I'll just jump in, and then Val can add as well. But there is a tendency when we get to that decision point and the healthcare provider or the team has described the options, and a lot of it is well, doc, whatever you recommend that's fine, or you know best, or what would you do if it was your wife? All of those kinds of scenarios and that's not everyone. But particularly older patients they tend to go with what the recommendation is from the healthcare team. Whereas, perhaps, some other subgroups might be more wanting to be involved and engaged in the decision making.

And so, you have to be where the patient is and work with that patient from where they're coming from. Because even then, they still have concept of what their goals are or what they hope to achieve or what is going to happen with this particular treatment, and that impacts their adherence to the schedule, their follow-ups, their reporting of toxicities. When you look at the numbers and rates of people who discontinue these drugs, even on a clinical trial, then you have to sort of extrapolate that to community practice. And what does that mean about our patient population?

So, it's very important, even in patients and practices where there's sort of this more traditional perhaps more paternalistic kind of view about recommending treatment and going along with that, that those patients are fully informed and engaged. And so they're part of that sharing of whatever that decision is. We have to make it easy for the patient. If we make it complicated and there's all these data over here and something over there, some patients may want to know that, but many of them may not. So we need to be able to make it easy for them to understand and to adhere to and follow along and then we're all part of that team.

Orbaugh: I absolutely agree. Val, did you want to add anything to that?



Adams: I do. I see it very similarly, but I would just add a slightly different view of the same process. Having a multimodality sort of communication is important so everybody on the team knows. And the reason that that's most important is we've got a variety of docs that communicate—some more intimidating than others—and I completely agree with Theresa. But all the way along the line, they're going to ask the nurse, they're going to ask the nurse practitioner, they're going to ask the pharmacist is this really the best?

If we're all on the same team upfront and we all understand the plan, and the other thing that's part of that, and we've got a number of our docs that do this really nicely is they figure out a way to describe benefit versus risk and number needed to treat.

Orbaugh: I agree. Part of shared decision making is understanding what brings that particular patient quality of life. How do they define quality of life?

Adams: Yeah, I couldn't agree more. I think it has to be personalized to the patient, absolutely. People with a long commute probably aren't going to tolerate diarrhea as a toxicity, even though it might be grade 1 or grade 2, that might be intolerable for them if they do a lot of driving. I think having good communication with the patients and understanding what they value and how valuable because, as a scientist, I find myself efficacy trumps toxicity. That's how my brain's wired, and I would say that's why we transplant people.

Orbaugh: I agree. I'd like to just add another point about toxicity, as we begin to tie up things here. And that is—again, speaking about patients as individuals—I think with each and every person we put on a treatment regimen, regardless of what it is, we need to think about those toxicities and make sure that patients have a plan. They need to have a plan in place if they have diarrhea or if they have developed nausea or vomiting, if they develop a fever. They've got to know okay, this is the first thing I do, this is the second thing I do. I think that empowers them if they know what to do. And let's face it, Murphy's Law—they're never going to have a really bad toxicity between 9 and 5 Monday through Friday. They are always going to have their worse toxicity in the middle of the night. Their doctor's never on call when they're having their toxicity, right?

So you mentioned something about diarrhea. So let's think

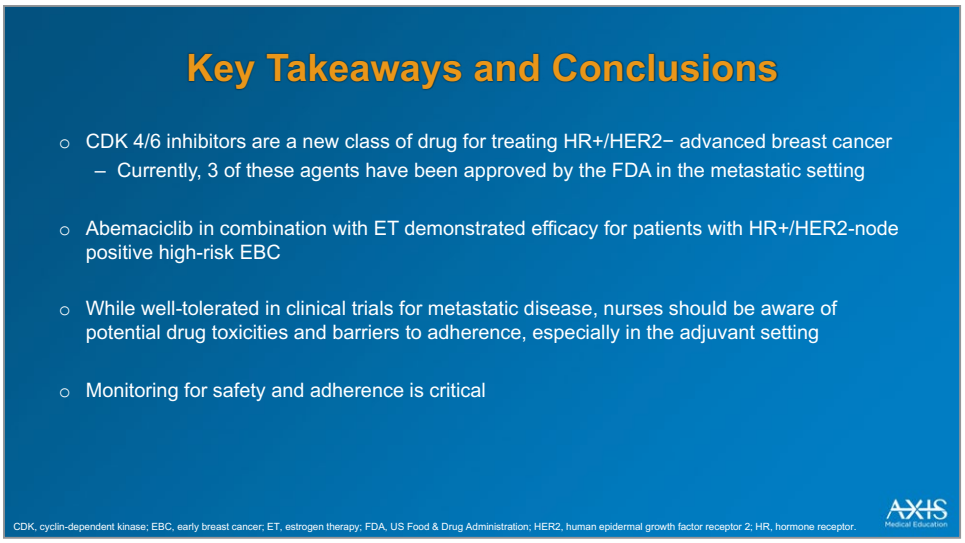
about my patient, Julie, that she's now completed the monarchE study. We made sure she had an antidiarrheal medicine at home. We made sure she understood, at the very first sign, when to start that medication, how to increase her fluids, when to call the office. Really made very concrete this is step 1, this is step 2, this is step 3. And I think that empowers patients if they feel like they know what to do.

Adams: It's always nice to make sure we give it to them in writing. Because information overload sometimes is a real thing, too. So if they've got it in writing, they can refer back to it or even share with a caregiver that's always good. And at my shop, we've got a triage nurse that answers the phone. So make sure they've got the triage nurse's phone. I know that maybe throws a few of you folks under the bus, but that's how it works at my shop.

Gillespie: That's right. And I would just also add—because you were primarily talking about more acute toxicities like diarrhea or something like that—there are also chronic toxicities like fatigue. And fatigue can really impact quality of life, and that can be incredibly important to patients to have the energy to do the things that are important to them. And sometimes I've found that patients won't really report fatigue because they think well that's just part and parcel to having cancer or having cancer treatment.

And the other side of that is that there's a counterintuitive approach to fatigue in terms of encouraging more exercise. Because patients are like well I'm tired, why would I want to exert more energy? So, that's something that you have to approach it a little differently than if you have diarrhea, you take an antidiarrheal. But if you're fatigued, you actually want to try to exercise more. So you have to, again, assess the patient individually and make sure that even these more chronic kinds of toxicities that may not seem life threatening but can definitely impact quality of life are also addressed.

Orbaugh: I think that's great. I'd like to thank you both for joining me and for sharing your valuable experience and expertise with us.



I'm going to leave us with just a few takeaways as we conclude this program. CDK4/6 inhibitors are a relatively new class of drugs for treating hormone receptor–positive/HER2-negative advanced breast cancer. In many ways, the addition of these drugs has revolutionized a patient population. They are well tolerated in clinical trials for metastatic disease; however, nurses, pharmacists, advance practice we all need to be very aware of the potential drug toxicities and how those toxicities, at times, can be a barrier to adherence. But there are also other barriers to adherence. And when we move medications from a metastatic setting into an adjuvant setting, sometimes we may find that patients are a little tolerant of any toxicities in that adjuvant setting. We have reviewed data looking at abemaciclib and palbociclib in the adjuvant setting. Abemaciclib in combination with endocrine therapy demonstrated efficacy for patients with hormone-positive/HER2-negative/node-positive/high-risk early breast cancer.

But I think you might agree that when we reviewed and compared these trials, there still are questions. We still have probably more questions in the adjuvant setting with these drugs than we were able to provide answers. I think we need to continue to watch these data closely as it matures and be on the lookout as new updates are released.

So I'd like to thank you all for joining us.

Gillespie: Thank you. Thank you for having me.

Adams: It's been a pleasure, absolute pleasure. Thank you.

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