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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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Disclosure of Conflicts of Interest

- **Kristi K. Orbaugh, MSN, NP, AOCN®**, reported a financial interest/relationship or affiliation in the form of *Serve(d) as a speaker or a member of a speakers' bureau for:* Bristol-Myers Squibb Co; Pfizer, Inc; AstraZeneca Pharmaceuticals LP; Daiichi-Sankyo, Inc; Astellas Pharma US, Inc; Lilly USA; MorphoSys; Immunomedics, Inc; Gilead; and Coherus BioSciences.
- **Val R. Adams, PharmD, FCCP, BCOP, FHOPA**, reported a financial interest/relationship or affiliation in the form of *Research grant*: Bristol-Myers Squibb Co. *Consultant*: Regeneron Pharmaceuticals, Inc.
- **Theresa W. Gillespie, PhD, MA, RN, FAAN**, has no real or apparent conflicts of interest to report.

Learning Objectives

Upon completion of this activity, participants should be better able to:

- Evaluate recent evidence supporting the use of CDK 4/6 inhibitors for the adjuvant treatment of HR+, HER2- early breast cancer to prevent early disease recurrences and reduce the risk of distant metastases
- Assess the efficacy of CDK 4/6 inhibitors as adjuvant therapy in high-risk early breast cancer
- Integrate strategies to promote and improve adherence in patients receiving oral CDK 4/6 inhibitors for the treatment of breast cancer
- Develop a plan for assessing, monitoring, and managing side effects that may occur with oral CDK 4/6 inhibitors to prevent and reduce toxicities, treatment delays, and treatment discontinuation
- Implement shared decision-making to foster co-creation of treatment plans, optimal adherence, and management of side effects with patients and their families

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Currently Approved CDK 4/6 Inhibitors in HR+, HER2− Advanced/Metastatic Breast Cancer

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.

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.

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 at 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.

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.

CDK 4/6 Inhibitor Trials Summary

- No head-to-head trials among any of the 3 agents
- Similarities
  - All oral agents
  - All indicated for HR+/HER2– advanced or metastatic disease
  - All are given until disease progression or unacceptable toxicity
  - All improved PFS
  - OS benefits have recently been reported

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

Exploring Emerging Evidence: CDK 4/6 Inhibitors in Adjuvant Early Breast Cancer

Up to 30% of patients with high-risk clinical and/or pathologic features may experience distant recurrence, many in the first few years

Adjuvant treatment: to prevent early recurrence and development of metastases

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.

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.

monarchE Trial Design

HR+/HER2-, node+ high risk early breast cancer N=5,637[a]

- Women or men
- Pre-/post menopausal
- With or without prior neo- and/or adjuvant chemotherapy
- No distant metastasis
- Maximum of 16 months from surgery to randomization and 12 weeks of ET following the last non-ET

Cohort 1: Inclusion based on clinicopathological risk factors:

- ≥4 ALN or
- 1–3 ALN and at least 1 of the below:
  - G3 disease
  - Tumor size ≥5 cm

Cohort 2: Inclusion based on Ki-67:

- 1–3 ALN and
- Centrally tested Ki-67 ≥20%[d]
- No G3 or tumor size ≥5 cm

ITT includes both C1 and C2

R 1:1

Abemaciclib
150 mg twice daily for up to 2 years[b]
+ standard of care endocrine therapy[c]
5–10 years as clinically indicated

Standard of care endocrine therapy[b,c]
5–10 years as clinically indicated

Primary Endpoint:
- iDFS (STEEP criteria)

Key Secondary Objectives:
- iDFS in Ki-67 high (≥20%) population, DRFS, overall survival, safety, patient reported outcomes, and pharmacokinetics

Stratified for:
- Prior chemotherapy
- Menopausal status
- Region

[a]Recruitment from July 2017 to August 2019, [b]Treatment period = first 2 years on study treatment after randomization, [c]Endocrine therapy of physician's choice (e.g. aromatase inhibitors, tamoxifen, LHRH agonist), [d]Ki-67 expression assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochermistry Assay by Dako/Agilent.
ALN, axillary lymph nodes; C, cohort; DRFS, distant relapse-free survival; ET, endocrine therapy; G, grade; HER, human epidermal growth factor receptor; HR, hormone receptor; iDFS, invasive disease-free survival; ITT, intention-to-treat; LHRH, luteiniing hormone; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials.
Rastogi P et al. Presented at: San Antonio Breast Cancer Symposium, December 8-11, 2020: abstract GS1-01.

monarchE Trial: Key Endpoints

- Primary key endpoint: invasive disease-free survival
- Secondary endpoints:
  - Invasive disease-free survival in patients with high Ki-67expression
  - Distant relapse-free survival
  - Overall survival
  - Safety
  - Patient-related outcomes
- Median follow-up: 19.1 months in both arms

Johnston et al. *J Clin Oncol*. 2020;38:3987-3998; *Ann Oncol*. 2020;31(suppl 4):LBA5_PR; O'Shaughnessy et al. *Cancer Res*. 2021;81:GS1-01.

monarchE Trial

- Phase 3 trial
- Comparing adjuvant abemaciclib 150 mg bid + endocrine therapy vs endocrine therapy alone for a 2-year duration
- Patients with HR+, HER2-, node positive, high-risk early breast cancer
- Patients continued their standard of care endocrine therapy for a total of 5-10 years as clinically indicated
- Included pre- and postmenopausal women and men
- All patients underwent surgery, radiation therapy, and /or chemotherapy as clinically indicated

- Eligible patients were at increased risk for recurrence based on clinicopathologic risk factors including:
  - **Number of positive nodes**
  - **Tumor size**
  - **Histologic grade**
  - **Ki-67 expression**

HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

Johnston et al. *J Clin Oncol*. 2020;38:3987-3998; Johnston et al. *Ann Oncol*. 2020;31(suppl 4):LBA5_PR; O'Shaughnessy et al. *Cancer Res*. 2021;81:GS1-01.

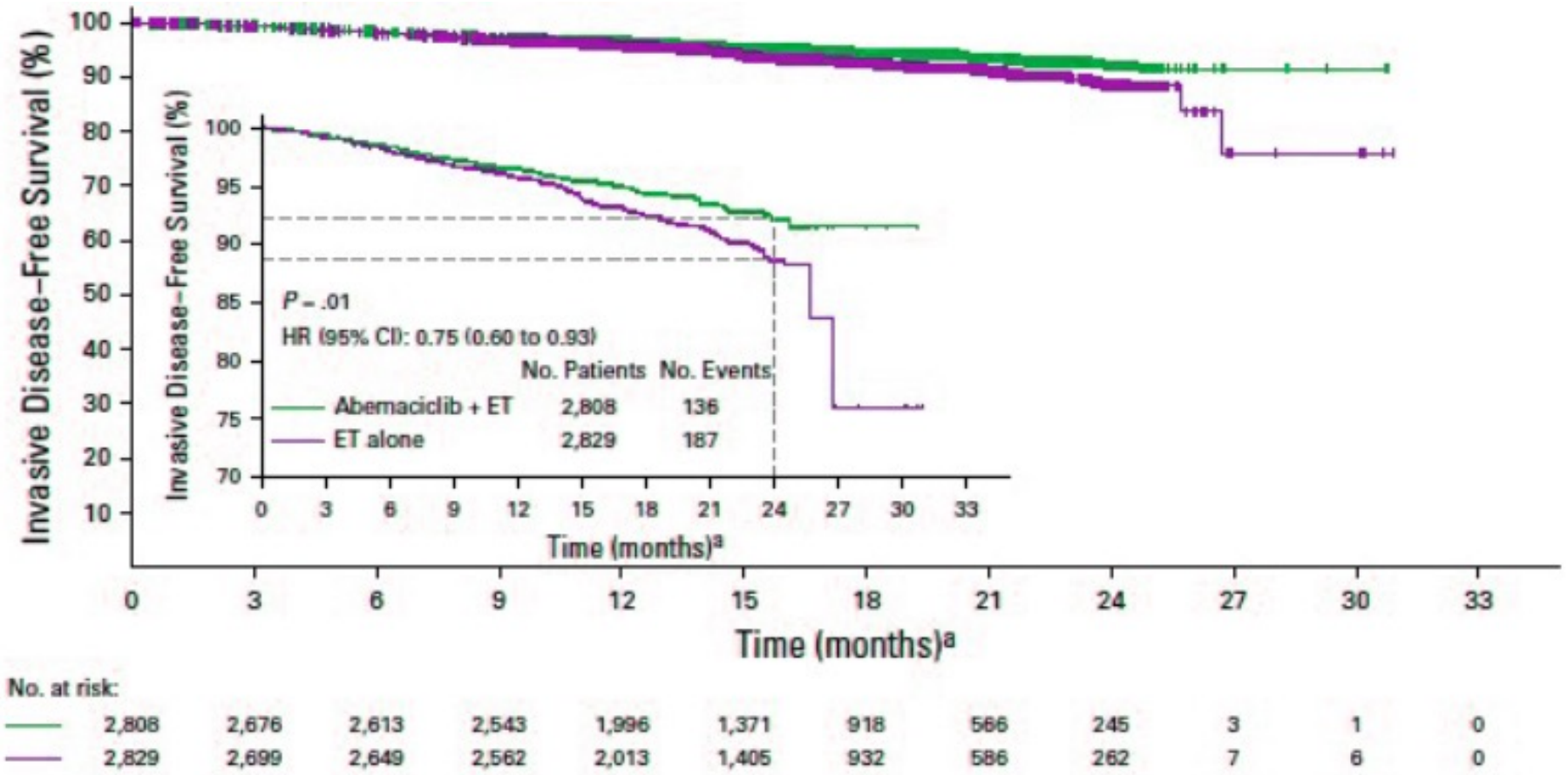
monarchE Trial: Key Findings

- Statistically significant and clinically meaningful improvement in iDFS in patients treated with abemaciclib compared to endocrine therapy alone:
  - 2-year iDFS: 92.3% vs 89.3%
  - Nominal *P* = .0009
  - HR 0.713
- Abemaciclib used in combination with standard endocrine therapy significantly decreased the risk of invasive disease by 28.7% compared to standard adjuvant endocrine therapy alone in people with HR+, HER2-, node-positive, high-risk early breast cancer
- Ki-67 ≥20% shown to be a clinicopathological feature that could be used for identifying high-risk patients
  - Benefit from abemaciclib was seen independent of Ki-67 level
  - 2-year iDFS rate in Ki-67 high population: 91.6% vs 87.1%
    - *P* = .0111
    - HR 0.691

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival.

O'Shaughnessy et al. *Cancer Res*. 2021;81:GS1-01.

monarchE Trial: Key Findings



Johnston et al. *J Clin Oncol*. 2020;38:3987-3998; O'Shaughnessy et al. *Cancer Res*. 2021;81:GS1-01.

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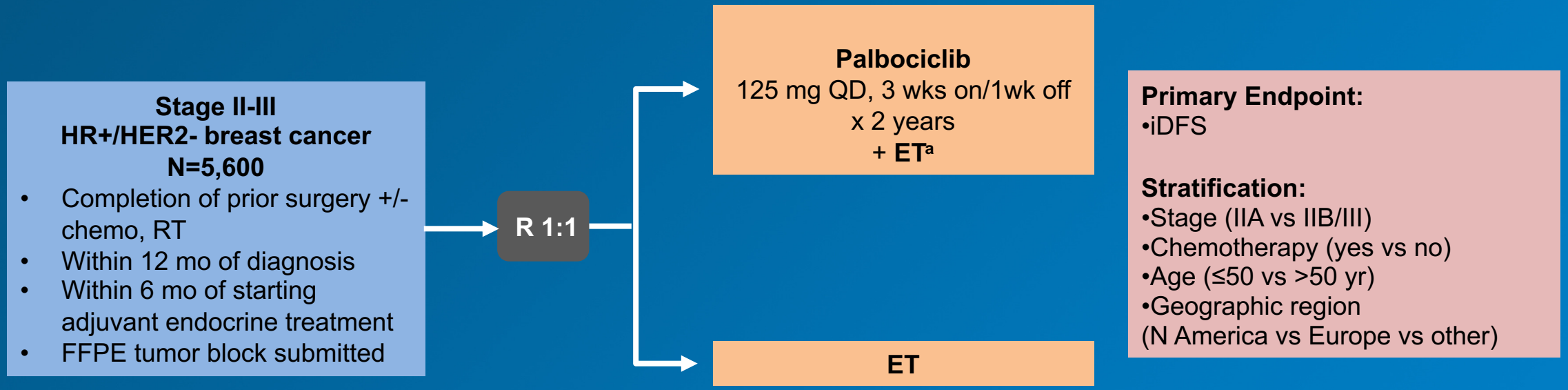
PALLAS Trial Design



[a]aromatase inhibitor or tamoxifen, +/- LHRH agonist.
ET, endocrine therapy; FFPE, formalin-fixed paraffin-embedded; HER, human epidermal growth factor receptor; HER, hormone receptor; LHRH, Luteinizing hormone-releasing hormone; QD, once daily; RT, radiation therapy.
Mayer et al. *Ann Oncol*. 2020;31(Suppl.4):LBA12; *Lancet Oncol*. 2021;22(2):212-222.

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PALLAS Trial

- Phase 3 trial
- Investigating the addition of 2 years of palbociclib to standard adjuvant endocrine treatment (HR+, HER2-)
- Patients with stage II and stage III invasive breast cancer were included
- Had to have completed definitive breast surgery, adjuvant or neoadjuvant chemotherapy, and/or RT
- Stratified by anatomic stage, previous adjuvant or neoadjuvant chemotherapy, age, and region
- Randomized 1:1 to palbociclib 125 mg po daily d1-21 every 28 days plus standard adjuvant endocrine therapy vs endocrine therapy alone
- Palbociclib was given for 2 years; endocrine therapy was given for at least 5 years

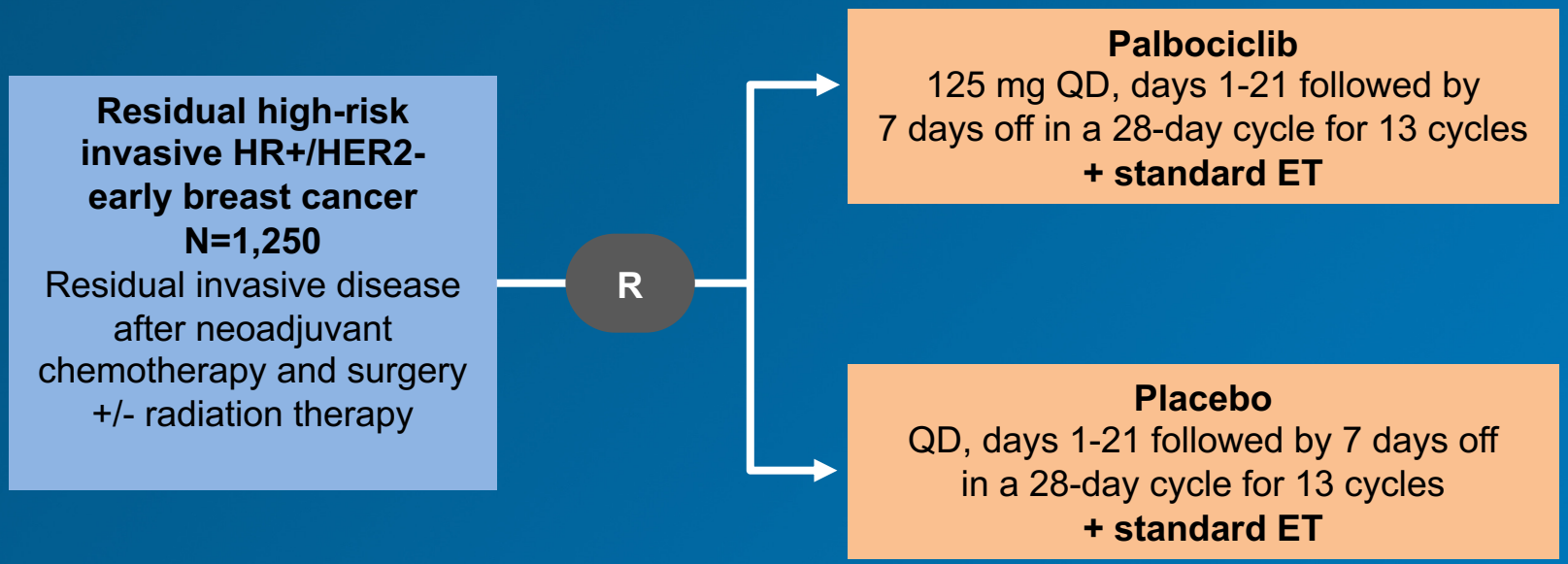
HER2, human epidermal growth factor receptor 2; HR, hormone receptor; po, orally; RT, radiation therapy.
Mayer EL, et al. *Ann Oncol*. 2020;31(Suppl.4):LBA12; Mayer et al. *Lancet Oncol*. 2021;22(2):212-222.

PALLAS Trial: Results

- In the second interim analysis, the addition of palbociclib to adjuvant endocrine therapy did not improve invasive disease-free survival compared to endocrine therapy alone
  - 3-year invasive disease-free survival: 88.2% vs 88.5%
  - HR 0.93
  - log-rank *P* = .51
- Analysis was done after 67% of expected invasive disease-free survival events had occurred
- Post-hoc analyses did not demonstrate any subgroups that appeared to benefit from the addition of palbociclib

Mayer EL, et al. *Ann Oncol*. 2020;31(Suppl.4):LBA12; Mayer et al. *Lancet Oncol*. 2021;22(2):212-222.

PENELOPE-B Trial Design



Primary Endpoint:
- iDFS

Secondary Endpoints:
- iDFS excluding second primary invasive non-BC, safety, DRFS, LRRFS, OS

Stratification:
- Lymph node status (at surgery)
- Age
- Ki-67
- Global region
- CPS-EG score

BC, breast cancer; CPS-EG, pretreatment clinical stage and post-treatment pathologic stage + estrogen receptor status and tumor grade; DRFS, distant recurrence-free survival; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; LRRFS, locoregional recurrence-free survival; OS, overall survival; QD, once daily; R, randomized.

Loibl S, et al. Presented at: San Antonio Breast Cancer Symposium, December 8-11, 2020:abstract GS1-02.

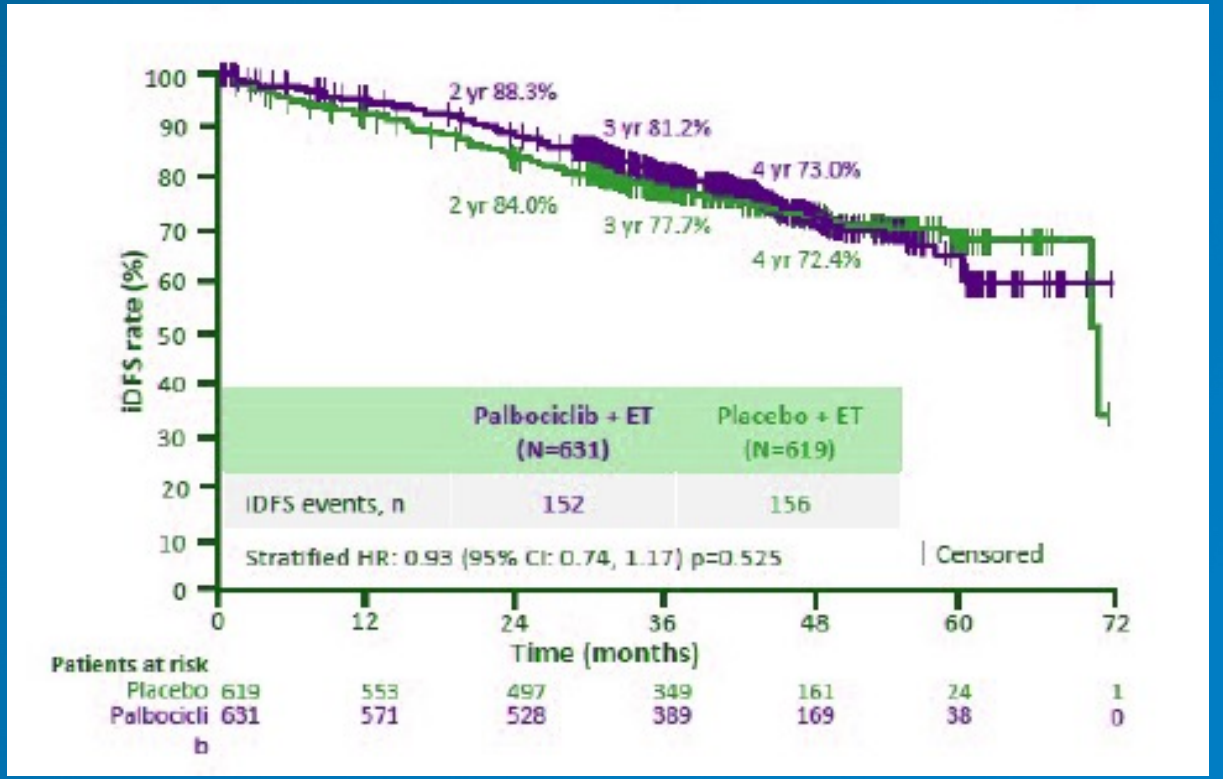
PENELOPE-B Trial

- Phase 3 double blind study
- Women with HR+, HER2- breast cancer without a complete pathologic response after a neoadjuvant taxane-containing regimen
- Randomized 1:1 to receive 13 cycles of palbociclib 125 mg daily days 1-21 in a 28-day cycle plus ET vs placebo plus ET, which was given for at least 5 years
- Primary endpoint: iDFS
- Median follow-up: 42.8 months

ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone therapy; iDFS, invasive disease-free survival.
Loibl et al. *J Clin Oncol*. 2021;39:1518-1530.

PENELOPE-B Trial: Results

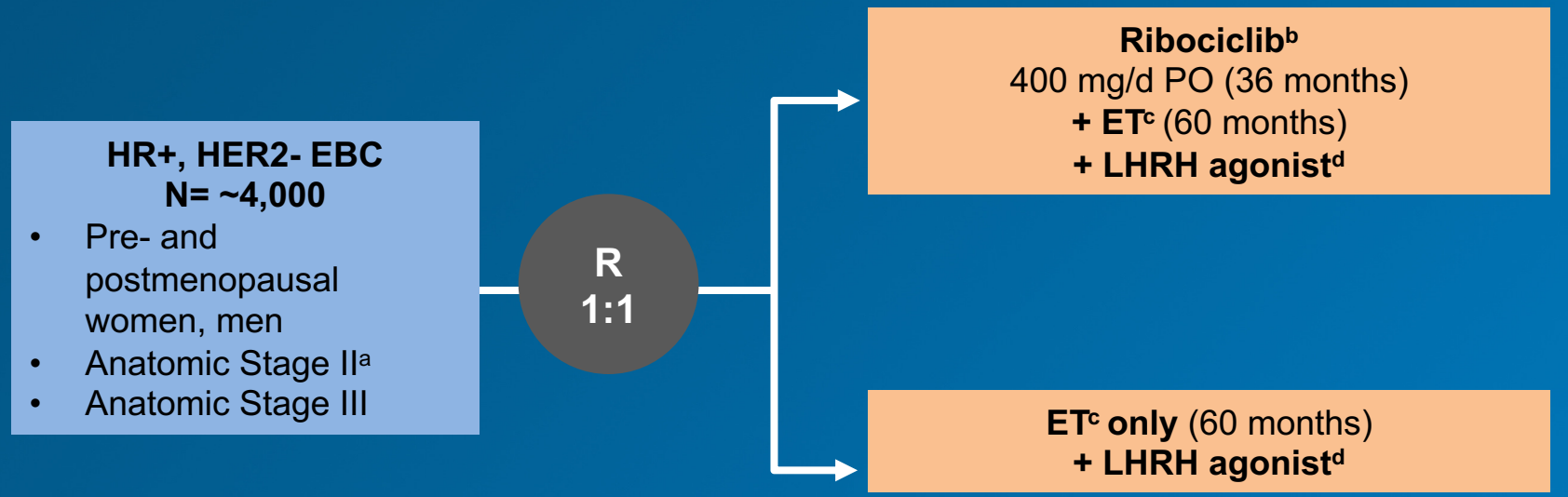
- Palbociclib for 1 year in addition to standard of care ET did not improve iDFS in women with residual invasive disease after neoadjuvant chemotherapy
  - Estimated 3-year iDFS: 81.2% vs 77.7%
  - HR 0.93



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; Loibl et al. *J Clin Oncol*. 2021;39:1518-1530.

NATALEE Trial Design



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 offl, 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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NATALEE Trial

- Phase 3, open label trial evaluating the efficacy and safety of ribociclib plus ET vs ET alone as adjuvant treatment in women and men with HR+, HER2- early breast cancer
- Includes stage II and III patients
- Two interim analyses are planned
- Patients will be stratified by anatomic stage, menopausal status, prior (neo)adjuvant chemotherapy and geographical region
- Dose of ribociclib will be 400 mg po daily for 21 days on and 7 days off

ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; po, orally.

Slamon et al. *J Clin Oncol*. 2019;37(15):TPS597.

Understanding What Constitutes a “High-Risk” Patient and How This May Inform Which Patients Will Most Likely Benefit From a CDK 4/6 Inhibitor in Early-Stage Disease

Disease Staging

- T,N,M classificastion
- Size of primary tumor
- Nodal status
- Metastatic sites

Carter et al. *Cancer* 1989; 63:181; Anderson et al. *J Clin Oncol*. 2010;28:2868.

Pathology

- Tumor morphology
- Histologic grade
- Differentiation
- Hormone status
- HER2 status
- Ki-67 expression

HER2, human epidermal growth factor receptor 2.

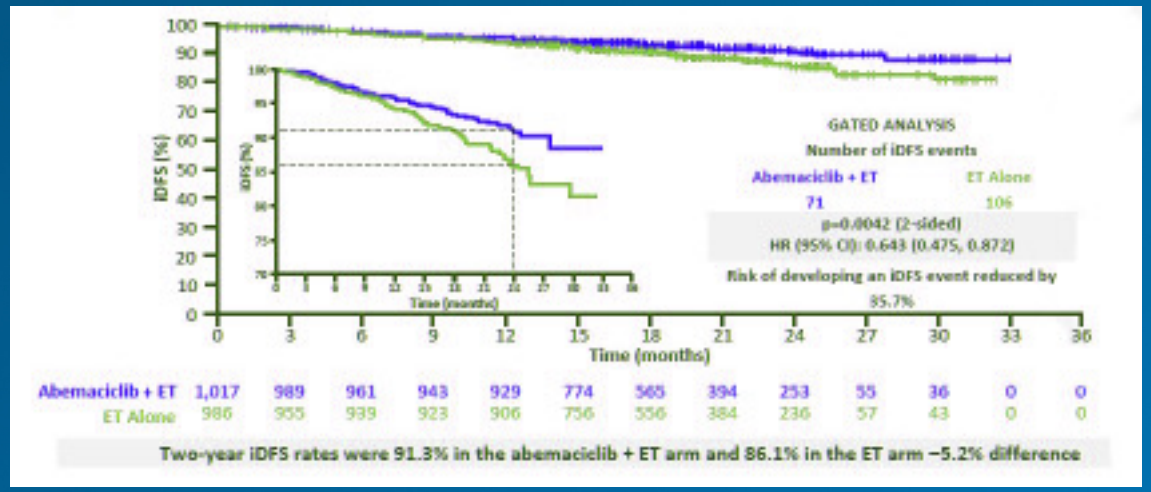
Li et al. *Br J Cancer* 2005; 93:1046; Luporsi et al. *Breast Cancer Res Treat*. 2012;132:895; Rakha et al. *J Clin Oncol*. 2008; Bartlett et al. *J Clin Oncol*. 2011: 29:1531; Li et al. *JAMA Netw Open* 2020;3:e1918160; Perez et al. *J Natl Cancer Inst*. 2017: 109:1.

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

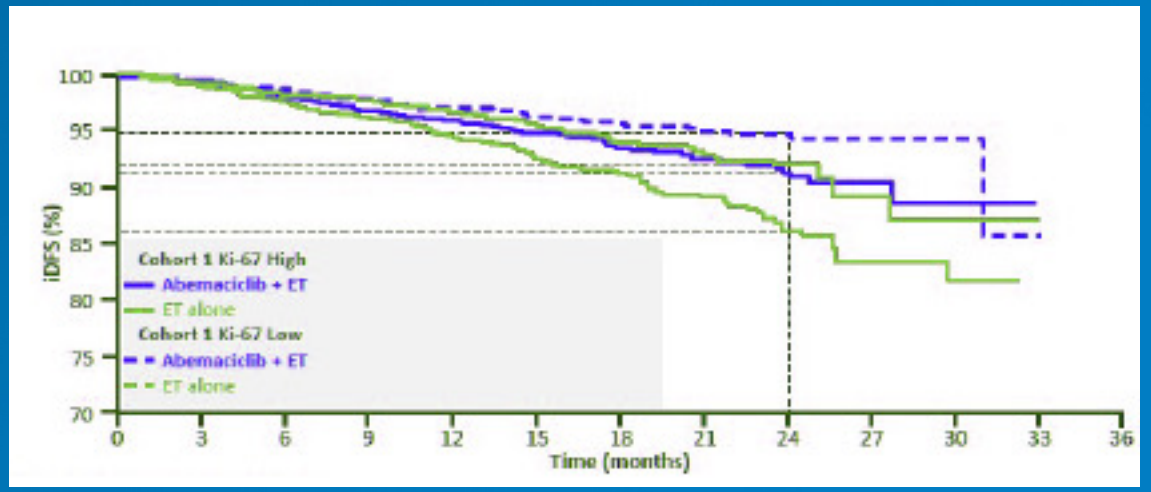
monarchE: High Ki-67 as a Biomarker for Identifying Patients With High-Risk EBC

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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Other Factors to Consider

- Age
- Menopausal status (SOFT trial)
- Race
- Molecular subtypes
  - Luminal A – HR+/HER2-
  - Luminal B – HR+/HER2+
  - Triple Negative – HR-/HER2-
  - HER2-positive

Billena et al. *Int J Radiat Oncol Biol Phys*. 2021;109:1007; Patridge et al. *J Clin Oncol*. 2016;34:3308; Silber et al. *JAMA* 2013;310:389; Loi et al. *J Clin Oncol*. 2007;25:1239.

Gene Expression Assays

- Oncotype DX
- MammaPrint
- Category 1 NCCN Guidelines®

Cronin et al. *Clin Chem*. 2007;53(6):1084-1091; Sparano et al. *J Clin Oncol*. 2008;26(5):721-728; Harris et al. *J Clin Oncol*. 2016;34:1134-1150; Cardoso et al. *N Engl J Med*. 2016:375:717-729.

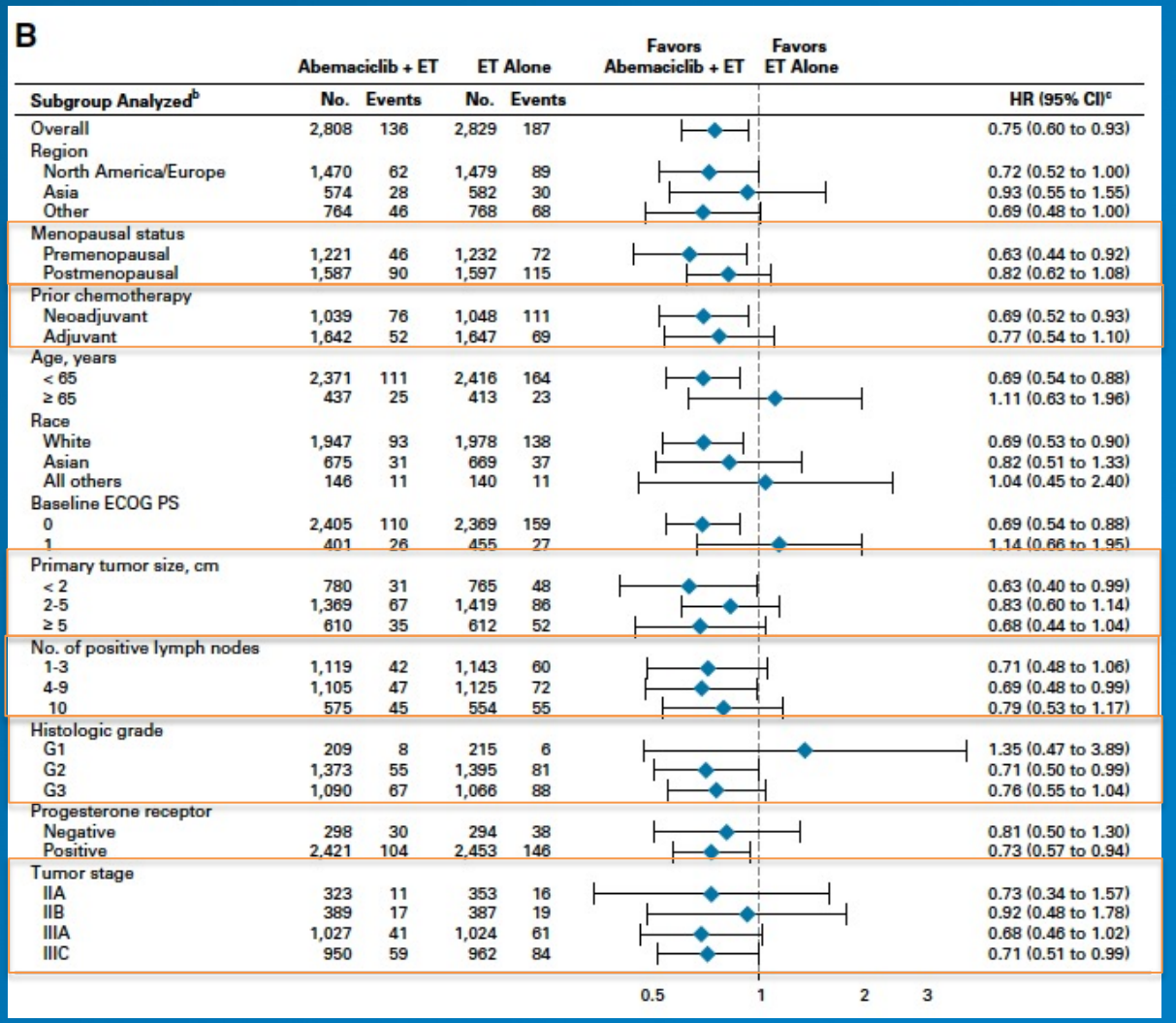
monarchE: High-Risk Disease and Subgroup Analysis

- 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

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.

Evaluating Nuances Across Early Breast Cancer 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 ll 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.

Points To Consider

- Drug duration and drug exposure
- Discontinuation rate
- Intermittent dosing
- Heterogenicity of breast cancer
- Tumor type: luminal A and luminal B
- Length of follow-up
- Differences in CDK 4/6 inhibitor
- Currently no biomarker is available to select which patient would benefit from CDK 4/6 inhibitors

CDK, cyclin-dependent kinase.

Shared Decision Making: Collaborative Approach

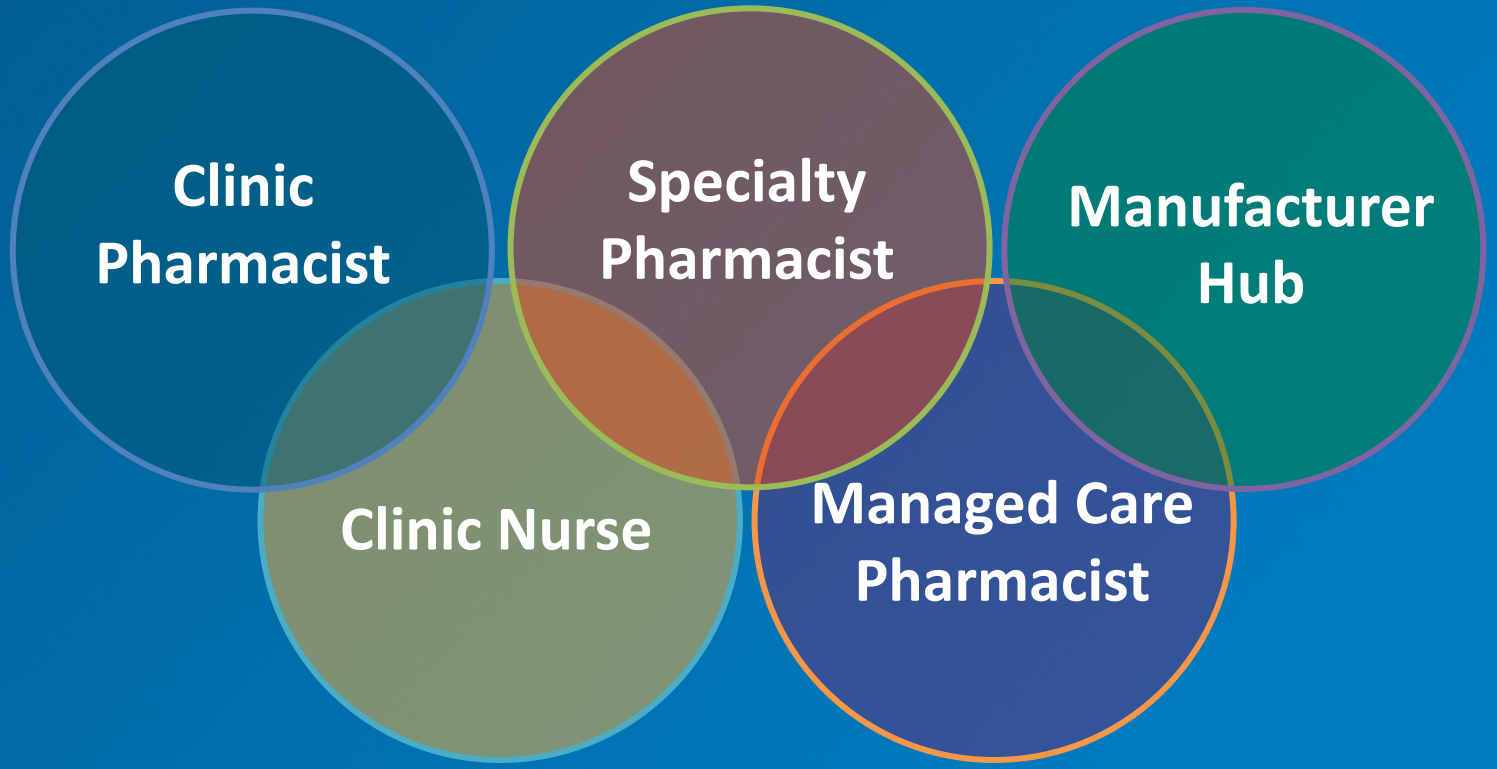
- SDM occurs when a healthcare provider and a patient work together to make a healthcare decision that is best for the patient
- Optimal decision takes into account:
  - **evidence-based information** about available options
  - **provider's knowledge** and experience
  - **patient's values** and preferences
- SDM includes exploring and comparing the benefits, harms, and risks of each option through meaningful dialogue about what matters most to the patient
- Patients and their families/caregivers who are engaged in an SDM process are more likely to arrive at a treatment decision that works best for all those involved

SDM, shared decision making.

Agency for Healthcare Research and Quality. 2014. http://www.ahrq.gov/professionals/education/curriculum-tools/shareddecisionmaking/tools/tool-1/index.html.
Kane et al. *CA Cancer J Clin*. 2014;64:377-388; Eliacin et al. *Qual Health Res*. 2015;25:688-678.

Key Counseling Questions

- Who is counseling the patient on the medication?
- Who is assessing for drug-drug interactions?
- Who is monitoring the patient for toxicity?



Key Takeaways and Conclusions

- CDK 4/6 inhibitors are a new class of drug for treating HR+/HER2− advanced breast cancer
  - Currently, 3 of these agents have been approved by the FDA in the metastatic setting
- Abemaciclib in combination with ET demonstrated efficacy for patients with HR+/HER2-node positive high-risk EBC
- While well-tolerated in clinical trials for metastatic disease, nurses should be aware of potential drug toxicities and barriers to adherence, especially in the adjuvant setting
- Monitoring for safety and adherence is critical

CDK, cyclin-dependent kinase; EBC, early breast cancer; ET, estrogen therapy; FDA, US Food & Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

AXIS Medical Education

Advanced Practice Perspectives on CDK 4/6 Inhibitors:

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