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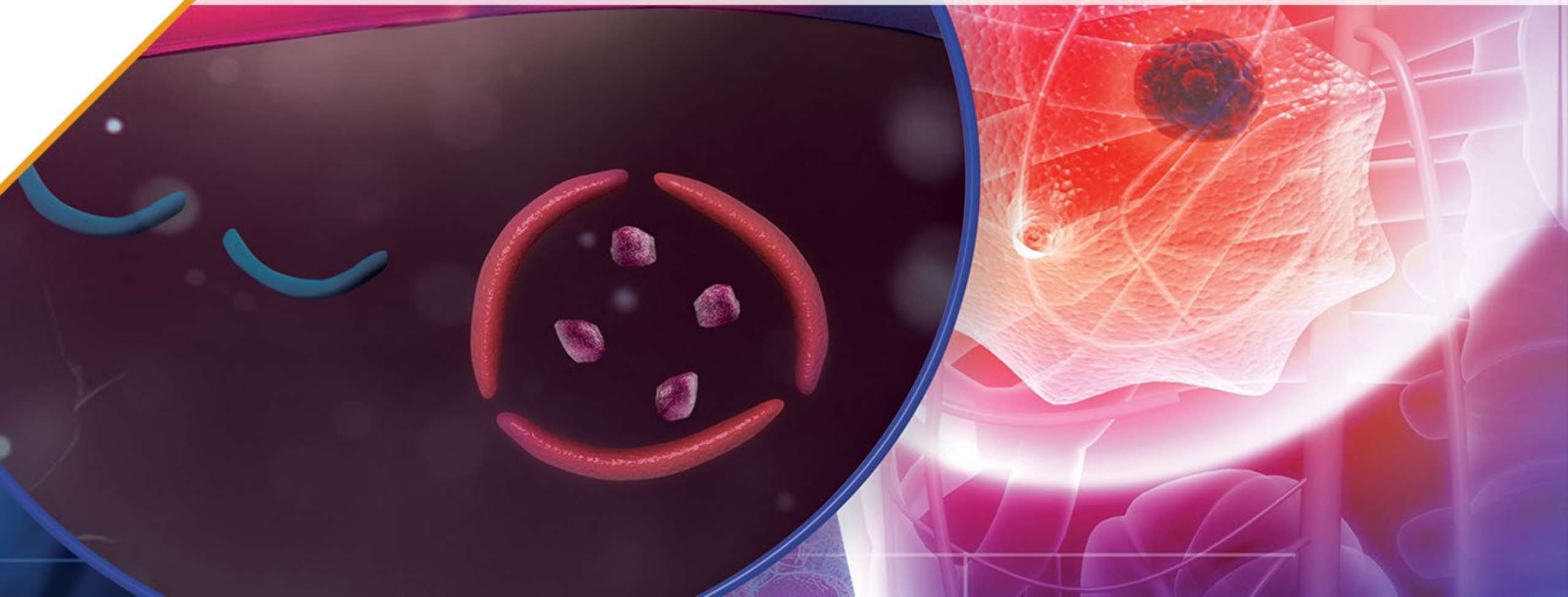
# Improving Outcomes and Addressing Racial Disparities in Patients With HR+/HER2- Early Breast Cancer



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# Learning Objectives

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

1. Outline evidence-based molecular testing and risk assessment strategies for patients with eBC
2. Appraise emerging data and accumulating evidence supporting the efficacy of CDK4/6 inhibitors for appropriate HR+/HER2− eBC patients
3. Examine disparities in the diagnosis and management of patients with eBC leading to poor outcomes
4. Select appropriate mitigation and management strategies for CDK4/6 inhibitor-related and ET-related AEs to prevent and reduce toxicities, treatment delays, and discontinuation

# Clinical Significance of Molecular Testing and Assessment of Risk of Recurrence in eBC

# Early Breast Cancer

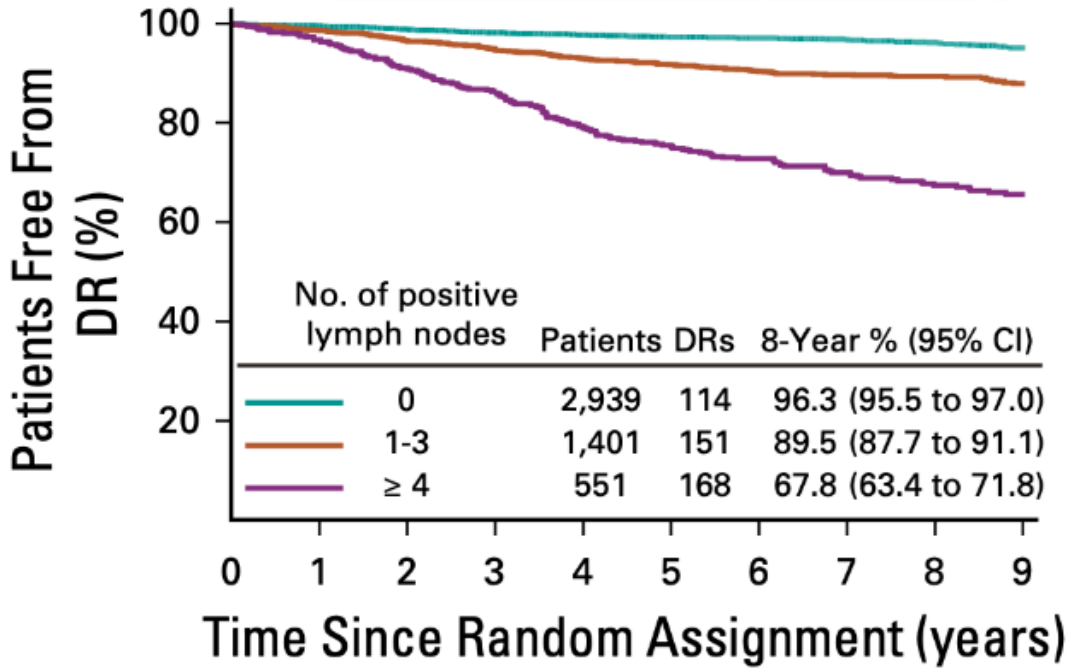
- Disease confined within the breast and/or neighboring lymph nodes
- ~90% of breast cancer diagnoses are early breast cancer (eBC)
  - ~70% of patients with eBC are HR+, HER2-
  - ~20% of patients with eBC experience disease recurrence within 10 years
    - > Risk of recurrence is highest in the first 2 years following diagnosis
    - > Patients with disease recurrence have a worse prognosis
    - > Patients with high-risk clinical and/or pathologic features are more likely to experience recurrence or distant metastases
- Goal of HR+, HER2- eBC treatment: eradicate cancer and prevent disease recurrence
- Standard of care for HR+, HER2- eBC includes locoregional therapies (surgery, radiation therapy) and adjuvant/neoadjuvant systemic therapies (chemotherapy, endocrine therapy)

Redig AJ, McAllister SS. *J Intern Med.* 2013;274(2):113-126. Wang et al. *BMC Cancer*. 2019;19(1):1091. Sheffield KM, et al. *Future Oncol.* 2022;18(21):2667-2682. Huppert LA, et al. *CA Cancer J Clin.* 2023;73(5):480-515. Colleoni M, et al. *J Clin Oncol.* 2016;34(9):927-935. Pan H, Gray R, Braybrooke J, et al. *N Engl J Med.* 2017;377(19):1836-1846. Richman J, Dowsett M. *Nat Rev Clin Oncol.* 2019;16(5):296-311.
HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

# HR+ eBC: Assessing Risk

- Clinical + pathologic features
- 10-year estimated risk of relapse with current therapies:
  - >30% (ALN ≥4)
  - >20% (ALN 1-3 + another poor prognostic factor)

**HR+/HER2– Operable BC**




Pagani O, et al. *J Clin Oncol*. 2020;38:1293-1303.

ALN, axillary lymph node; BC, breast cancer; eBC, early breast cancer; DR, distant recurrence; HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

# Risk of Early Breast Cancer Recurrence

**Approximately 20-30% of patients with eBC experience relapse[1,2]**

## Factors that affect risk of recurrence in people with eBC[3-6]:

- Young age at diagnosis
- Tumor morphology (ductal versus lobular)
- Larger tumor size
- Higher tumor grade
- Symptomatic presentation
- Presence of lymphovascular invasion
- Axillary node involvement
- Negative ER or HER2 overexpression
- Positive or close margins
- PR negativity
- High proliferation rate (eg, high Ki-67)
- Metaplastic (vs. non-metaplastic) carcinoma

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1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2005;365(9472):1687-1717. 2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2015;386(10001):1341-1352. 3. Győrffy B, et al. *Breast Cancer Res*. 2015;17(1):11. 4. Dang CM, Giuliano AE. *Oncology (Williston Park)*. 2011;25(10):895-899. 5. Stuart-Harris R, et al. *Breast.* 2019;44:153-159. 6. Reddy TP, et al. *Breast Cancer Res.* 2020;22(1):121.
eBC, early breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

# Molecular Testing In Breast Cancer

- Biomarker testing for tumor ER, PR, and HER2 status is recommended for all patients
  - Ki-67 testing recently removed as a recommendation for HR+/HER2− patients who are being considered for abemaciclib
  - Methods for testing include: PCR, NGS, FISH, and IHC
- Genetic counseling and testing is recommended for patients considered to be at high risk for hereditary BC, who have TNBC, or who may be candidates for adjuvant olaparib
- Molecular profiling tests help to determine whether to add chemotherapy to ET for patients with HR+/HER2− eBC
- Gene expression assays critical in determining need for adjuvant chemotherapy:
  - The 21-gene assay (Oncotype Dx) is preferred by the NCCN for prognosis and prediction of chemotherapy benefit
  - Other prognostic assays: 70-gene (MammaPrint), 50-gene (Prosigna), 12-gene (EndoPredict), and Breast Cancer Index (BCI)

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Gradishar WJ, et al. NCCN Guidelines. Breast Cancer. Version 2.2024. Markopoulos C, et al. *Eur J Surg Oncol*. 2020;46(4 Pt A):656-666. Blanchette P, et al. *Curr Oncol*. 2022;29(4):2599-2615.

BC, breast cancer; eBC, early breast cancer; ER, estrogen receptor; ET, endocrine therapy; FISH, flourescence in situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PCR, polymerase chain reaction; PR, progesterone receptor; TNBC, triple-negative breast cancer.

# Aligning Clinical Practice With the Latest Clinical Evidence in Treating HR+/HER2− eBC

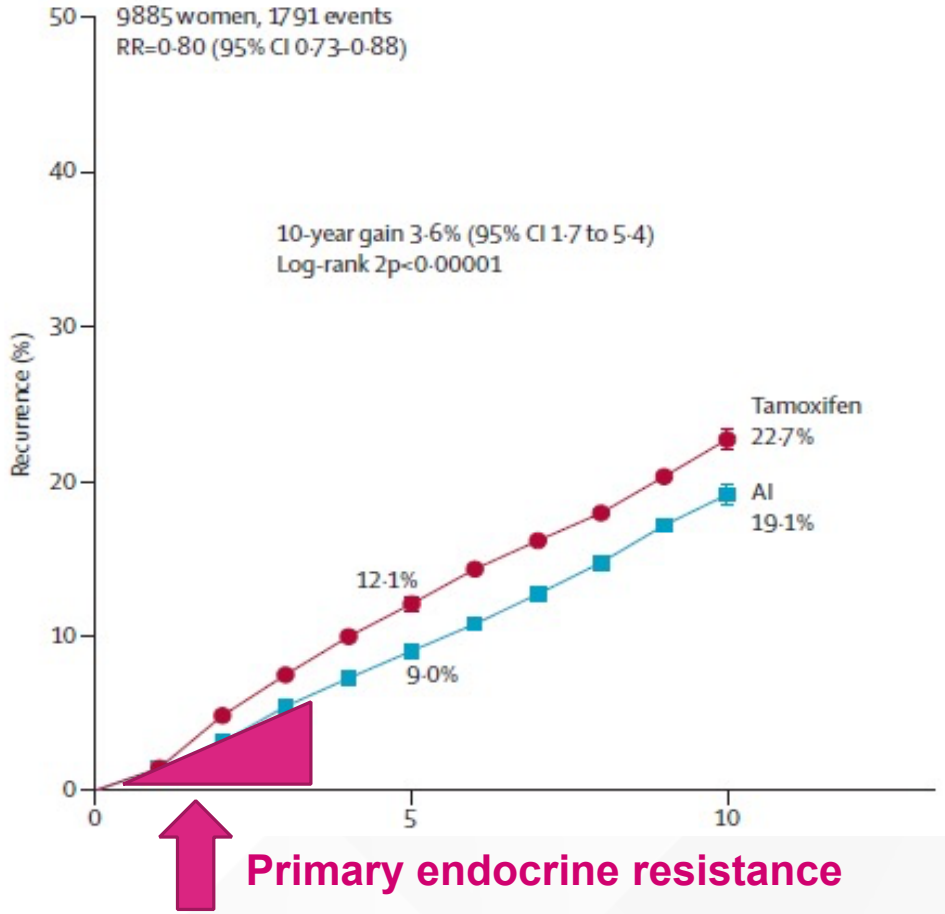
# Endocrine Therapy in ER+ EBC

## Endocrine Therapy

- Tamoxifen, aromatase inhibitors
- Ovarian suppression (LHRH analogues) in high-risk premenopausal women
- Extended adjuvant therapy (10 years vs. 5 years)

## Unmet Need

- Understanding who does/does not need adjuvant chemotherapy
- Identifying those with primary endocrine resistance HR-positive BC, and preventing or delaying recurrence with additional therapy





Cardoso F, et al. *Ann Oncol.* 2019;30(8):1194-1220.
Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet.* 2015;386(10001):1341-1352.

AI, aromatase inhibitor; BC, breast cancer; eBC, early breast cancer; ER, estrogen receptor, HR, hormone receptor; LHRH, luteinizing hormone-releasing hormone.

# Guidelines Overview: Adjuvant Endocrine Therapy

- Adjuvant ET for 5 years results in a substantial reduction in the risk of local recurrence, contralateral BC, distant recurrence, and risk of death
- The addition of chemotherapy to adjuvant ET is recommended in certain patients with HR+/HER2- breast cancer based on recurrence risk (Oncotype Dx 21-gene assay)
  - Postmenopausal patients with pT1-3, and pN0 and pN1 (1-3 positive nodes) tumors and a risk score ≥26
  - Premenopausal patients with pN0 tumors and a risk score ≥26
  - Premenopausal patients with pT1-3 and pN1 (1-3 positive nodes) tumors and a risk score ≥26
- The NCCN recommends considering the addition of a CDK4/6 inhibitor, abemaciclib, to systemic adjuvant ET for certain HR+/HER2−, high-risk eBC patients
  - ≥4 positive lymph nodes (confirmed preoperatively and/or at surgery)

    or
  - 1-3 positive lymph nodes with either grade 3 disease or tumor size ≥ 5cm (on pre-operative imaging and/or at surgery)
- Select patients may also be eligible for adjuvant abemaciclib after preoperative systemic therapy

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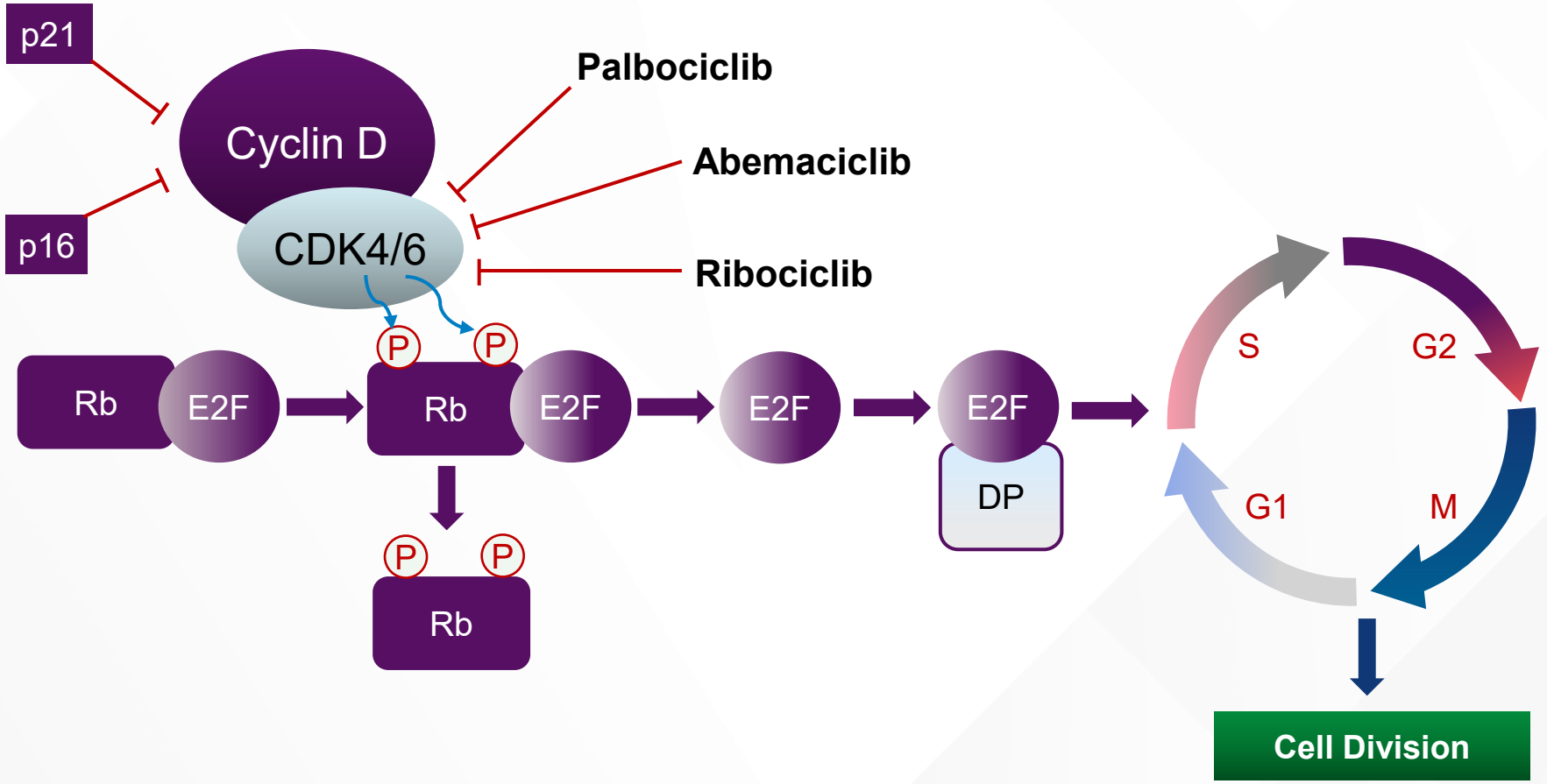
Pan H, et al. *N Engl J Med.* 2017;377(19):1836-1846. Sheffield KM, et al. *Future Oncol.* 2022;18(21):2667-2682. Johnston SRD, et al. *Lancet Oncol.* 2023;24(1):77-90. Gradishar WJ, et al. NCCN Guidelines. Breast Cancer. Version 2.2024.

BC, breast cancer; CDK, cyclin-dependent kinase; eBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NCCN, National Comprehensive Cancer Network.

# Efficacy Data of CDK4/6 Inhibitors in HR+/HER2− eBC

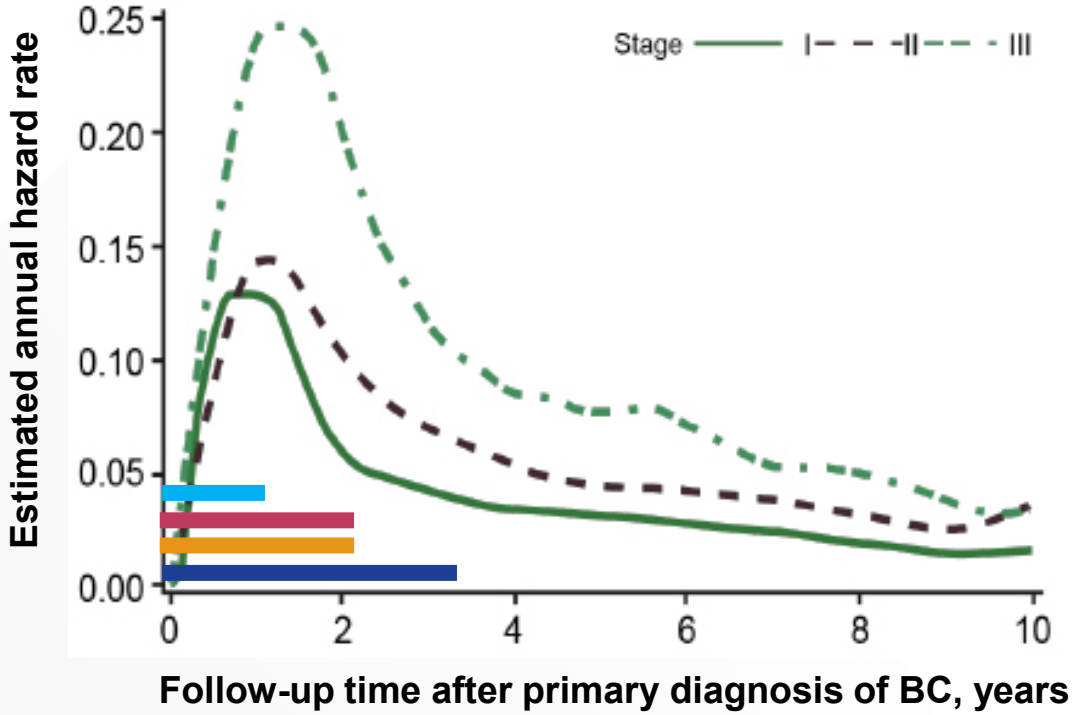
# Inhibition of CDK4/6 is Critical to Improving Outcomes in ER+ Breast Cancer




Slide courtesy of Sara M. Tolaney, MD, MPH.
CDK, cyclin-dependent kinase; ER, estrogen receptor.

# CDK4/6 Inhibitors for High-Risk, HR+ eBC

## Risk of recurrence by tumor stage




- PENELOPE-B: palbociclib (after neoadjuvant, high risk)[1]
- monarchE: abemaciclib (high-risk CPR factors, Ki-67)[2,3]
- PALLAS: palbociclib (stage II, III)[4]
- NATALEE: ribociclib (stage II, III)[5]

1. Loibl S, et al. *J Clin Oncol.* 2021;39(14):1518-1530. 2. Johnston S, et al. *J Clin Oncol.* 2020;38(34):3987-3998. 3. Harbeck N, et al. *Ann Oncol.* 2021;32(12):1571-1581.
4. Mayer EL, et al. *Lancet Oncol*. 2021;22(2):212-222. 5. Slamon DJ, et al. *J Clin Oncol.* 2019;37(15_suppl):TPS597.
BC, breast cancer; CDK, cyclin-dependent kinase; CPR, clinicopathologic recurrence; eBC, early breast cancer; HR, hormone receptor.

# PALLAS Primary Endpoint: iDFS

- Stage II-III HR+/HER2- breast cancer
- Completion of prior surgery, ± chemo, RT
- Within 12 months of diagnosis
- Within 6 months of starting adjuvant endocrine treatment
- FFPE tumor block submitted

**Stratification factors**
- Stage (IIA vs IIB/III)
- Chemotherapy (yes vs no)
- Age (≤50 vs >50)
- Geographic region (North America vs Europe vs other)

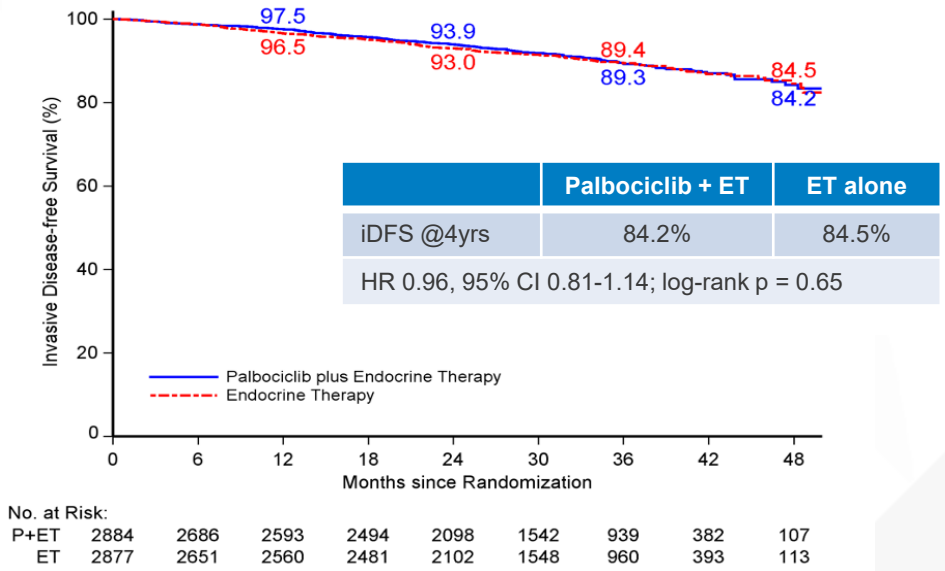
**R 1:1**
N = 5,600

**Arm A**
**Palbociclib x 2 years**
(125 mg QD, 3 weeks on/1 week off)
**+ endocrine treatment**

**Arm B**
**Endocrine treatment**

**Primary endpoint:** invasive disease-free survival (iDFS)

**PALLAS: Palbociclib**




| | Palbociclib + ET | ET alone |
|---|---|---|
| iDFS @4yrs | 84.2% | 84.5% |
| HR 0.96, 95% CI 0.81-1.14; log-rank p = 0.65 | | |

- There were 253 vs 263 iDFS events in the palbociclib + ET vs ET only arms, but no difference in event categories, including distant recurrences, second primaries, local, regional, contralateral, or deaths without recurrence
- At a median follow-up of 31 months, no significant difference in 4-year iDFS was observed
- Most common AEs in palbociclib + ET arm: neutropenia, leukopenia, fatigue
- Anemia, thrombocytopenia, alopecia, and upper respiratory tract infections also more common in Palbociclib + ET arm
- 13.0% of patients in palbociclib + ET arm experienced ≥1 SAE (versus 7.9% in ET arm)
- No deaths related to study treatment in either arm

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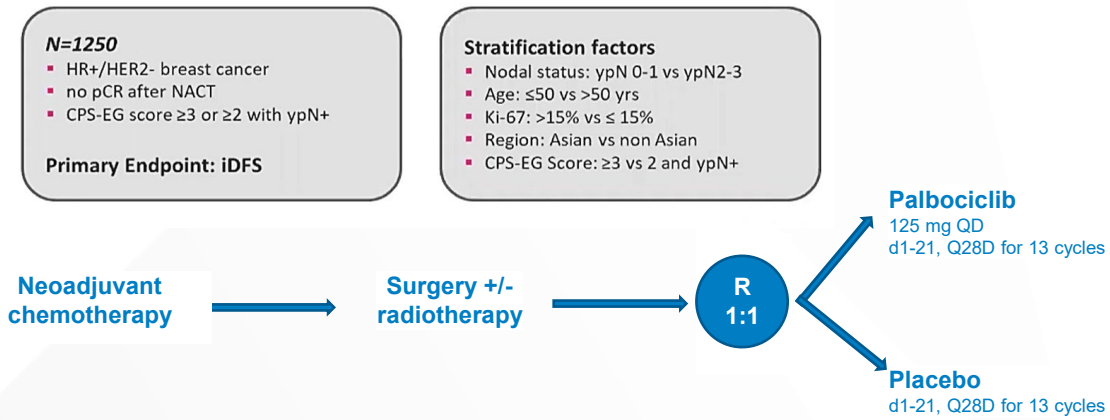
Mayer EL, et al. *Ann Oncol*. 2020;31(suppl_4):LBA12. Mayer EL, et al. *Lancet Onc*ol. 2021;22(2):212-222. Mayer EL, et al. ESMO 2020. Abstract LBA12. Gnant M. SABCS 2021. Abstract GS1-07. Gnant M, et al. *J Clin Oncol*. 2022;40(3):282-293.

AE, adverse event; ET, endocrine therapy; FFPE, formalin-fixed, paraffin-embedded; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; QD, once a day; RT, radiotherapy; SAE, serious adverse event.

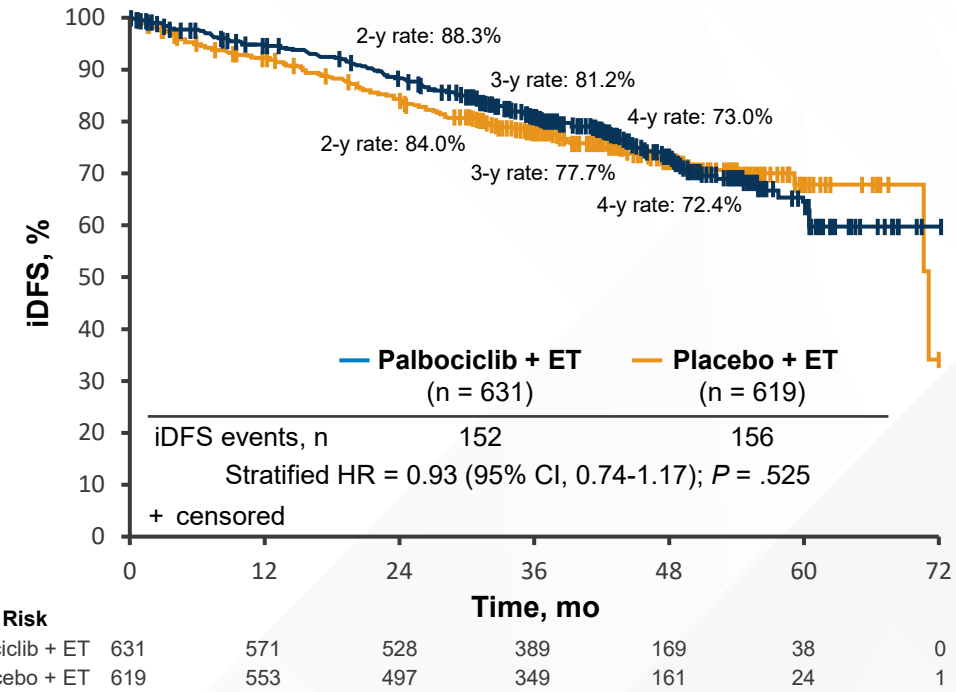
# PENELOPE-B: Palbociclib + Endocrine Therapy in HR+/HER2- With Residual Disease After Neoadjuvant Chemo + Surgery

## Study Design




## iDFS

Median follow-up 42.8 mo




**No. at Risk**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Palbociclib + ET | 631 | 571 | 528 | 389 | 169 | 38 | 0 |
| Placebo + ET | 619 | 553 | 497 | 349 | 161 | 24 | 1 |

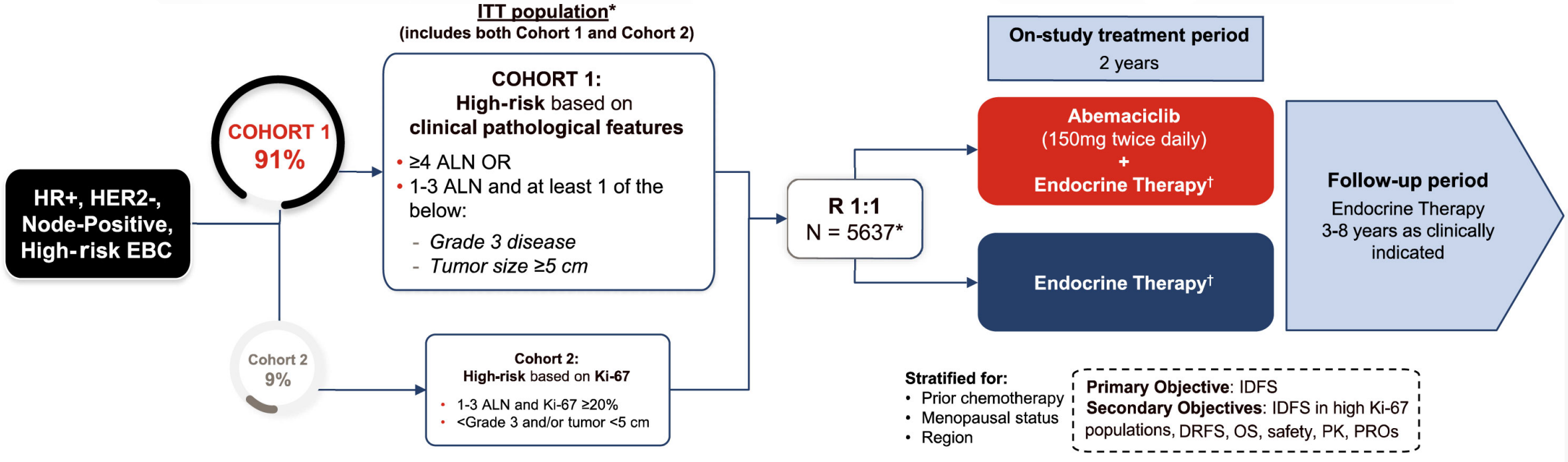
- The most frequent AEs in the palbociclib arm were hematologic in nature (any grade: neutropenia 95.7%, leukopenia 99.2%, thrombocytopenia 56.6%, anemia 73.9%)
- Most common related serious adverse events were infections and vascular disorders
- 2 deaths in palbociclib arm (not related to study drug), 6 deaths in placebo arm

Slide courtesy of Joyce A. O'Shaughnessy, MD.

Loibl S, et al. *J Clin Oncol*. 2021;39(14):1518-1530.

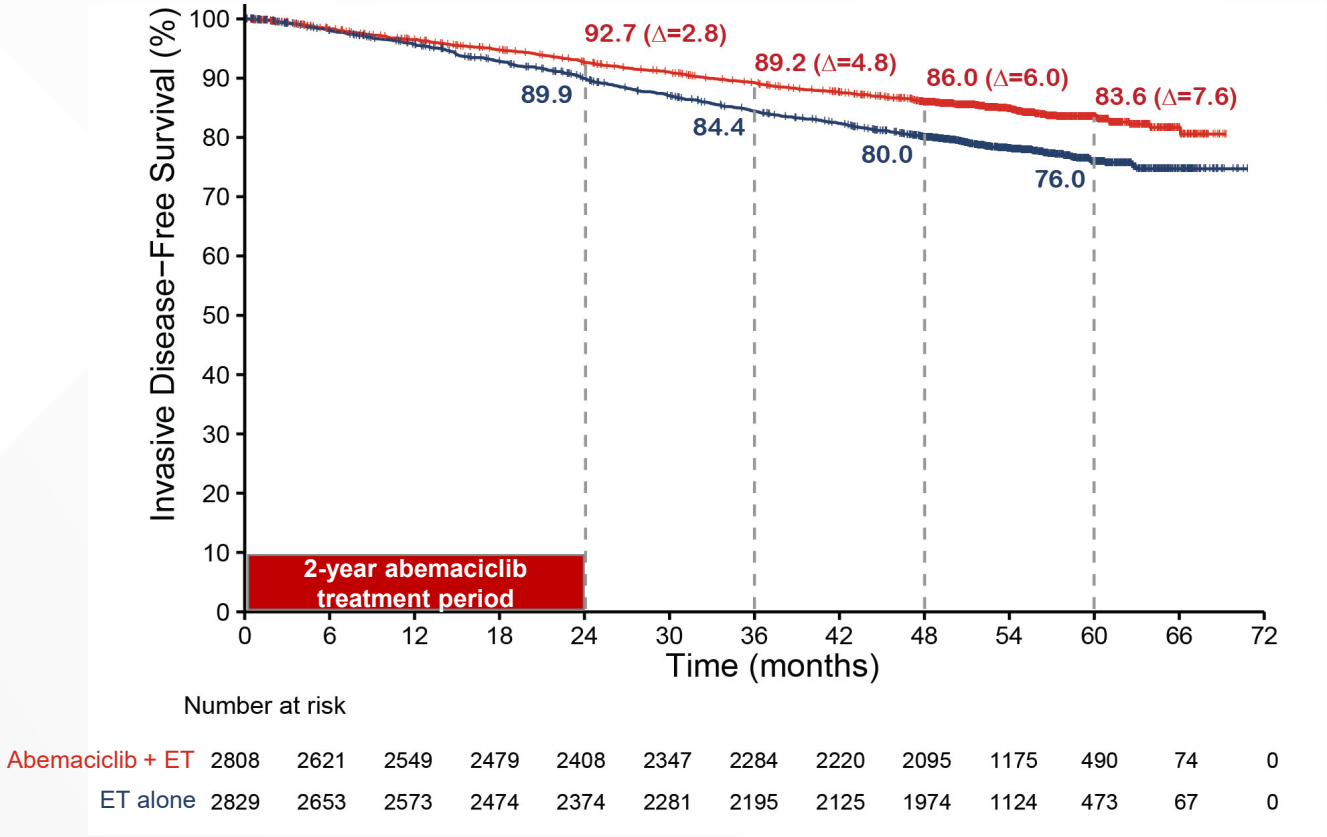
AE, adverse events; CPS-EG, pre-treatment clinical and post-treatment pathological stage, estrogen-receptor status, and grade; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; QD, once a day; Q28D, every 28 days; NACT, neoadjuvant chemotherapy; pCR, pathological complete response.

# monarchE Study Design (NCT03155997)




*Recruitment from July 2017 to August 2019.
†Endocrine therapy of physician's choice [eg, aromatase inhibitors, tamoxifen, GnRH agonist].
Harbeck N, et al. Adjuvant ESMO 2023. Abstract LBA17.
ALN, axillary lymph node; DRFS, distant relapse-free survival; EBC, early breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; ITT, intention-to-treat; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcome.

# monarchE: Sustained iDFS Benefit in ITT




| Number of iDFS events | |
|---|---|
| Abemaciclib + ET | ET Alone |
| 407 | 585 |

**HR (95% CI): 0.680 (0.599, 0.772)**
Nominal p <0.001

**32% reduction in the risk of developing an iDFS event**
**The KM curves continue to separate and the absolute difference in iDFS rates between arms was 7.6% at 5 years**

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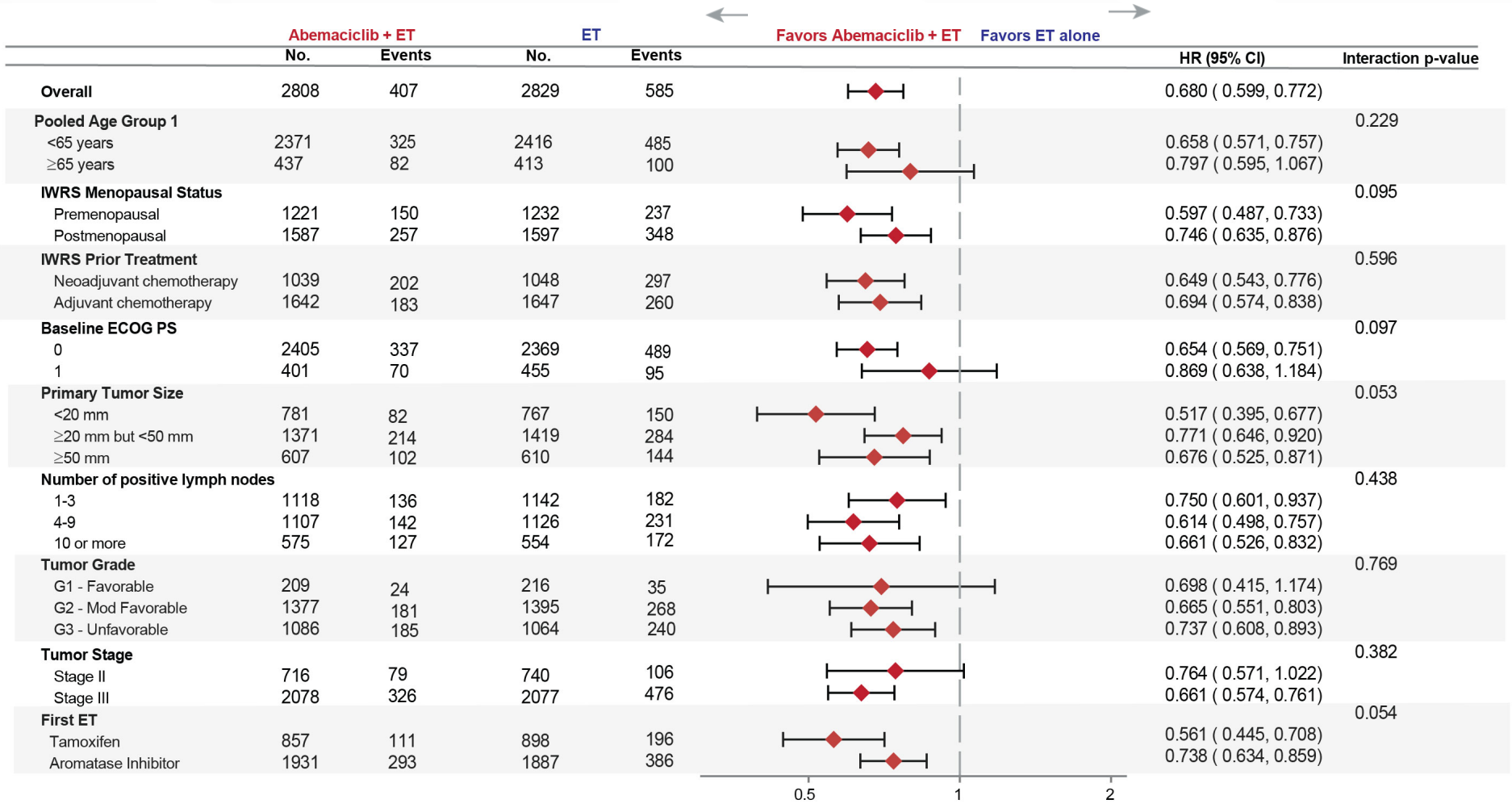
Harbeck N, et al. Adjuvant ESMO 2023. Abstract LBA17.
ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival; ITT, intent-to-treat; KM, Kaplan–Meier.

# monarchE: Consistent iDFS Benefit Observed in Selected Subgroups*

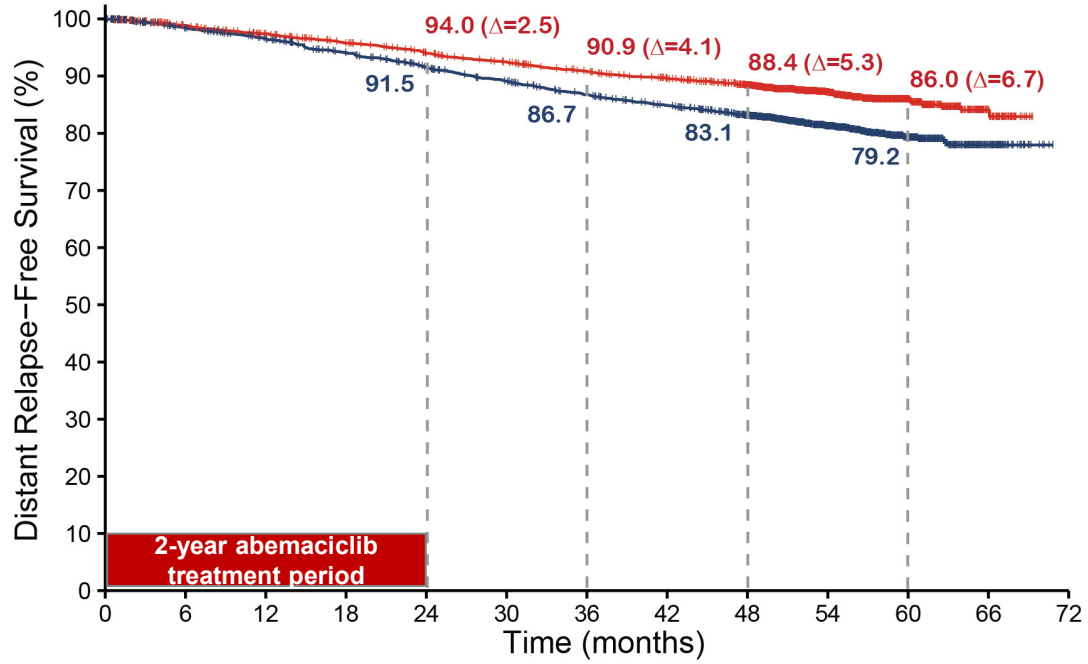



*Region of enrollment and Progesterone status data not shown

Harbeck N, et al. Adjuvant ESMO 2023. Abstract LBA17.

ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; iDFS, invasive disease-free survival; IWRS Interactive Web Response Systems; PS, performance status.

# monarchE: Sustained DRFS Benefit in ITT




| Number of DRFS events | |
|---|---|
| Abemaciclib + ET | ET Alone |
| 345 | 501 |

**HR (95% CI): 0.675 (0.588, 0.774)**
Nominal p <0.001

**32.5% reduction in the risk of developing a DRFS event**
**The KM curves continue to separate and the absolute difference in DRFS rates between arms was 6.7% at 5 years**

Harbeck N, et al. Adjuvant ESMO 2023. Abstract LBA17.
DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; ITT, intent-to-treat; KM, Kaplan–Meier.

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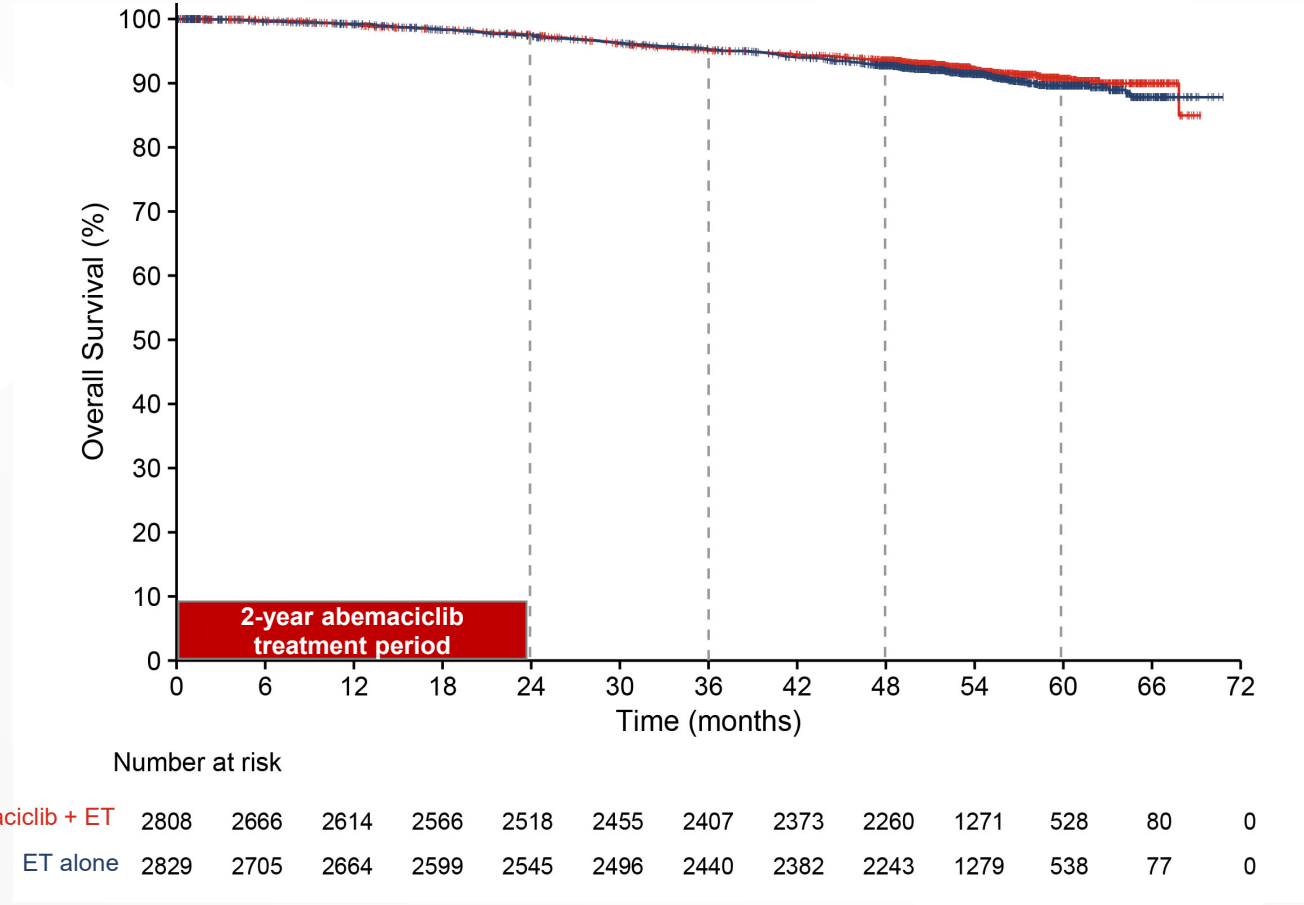
# monarchE: Fewer Deaths in the ITT Abemaciclib Arm



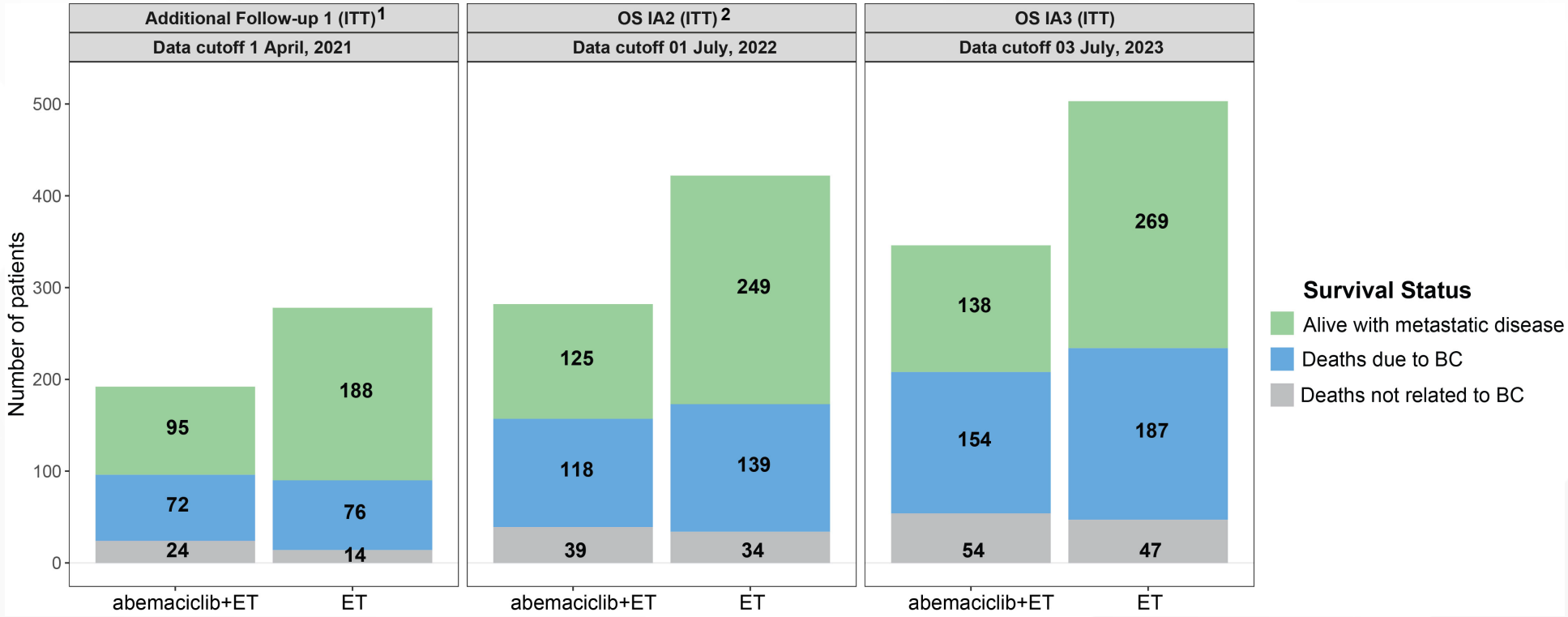

| Number of OS events | |
|---|---|
| Abemaciclib + ET | ET Alone |
| 208 | 234 |

**HR (95% CI): 0.903 (0.749, 1.088)**
p=0.284

**At OS IA3 statistical significance was not reached for OS**

Harbeck N, et al. Adjuvant ESMO 2023. Abstract LBA17.
ET, endocrine therapy; HR, hazard ratio; IA, interim analysis; ITT, intent-to-treat; KM, Kaplan–Meier; OS, overall survival.

# monarchE: Fewer Patients with Metastatic Disease in the Abemaciclib Arm




**The imbalance of incurable metastatic recurrence continues to be substantial at OS IA3**

Harbeck N, et al. Adjuvant ESMO 2023. Abstract LBA17. Harbeck N, et al. *Ann Oncol.* 2021;32(12):1571-1581. Johnston SRD, et al. *Lancet Oncol.* 2023;24(1):77-90.
BC, breast cancer; ET, endocrine therapy; IA, interim analysis; ITT, intent-to-treat; OS, overall survival.

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# monarchE: Efficacy Outcomes by Cohorts

| | Cohort 1 | | Cohort 2 | |
|---|---|---|---|---|
| | Abemaciclib + ET | ET | Abemaciclib + ET | ET |
| | n=2555 | n= 2565 | n=253 | n=264 |
| **iDFS** | | | | |
| Number of events, n | 382 | 553 | 25 | 32 |
| HR (95% CI) | **0.670 (0.588, 0.764)** | | **0.827 (0.484, 1.414)** | |
| Nominal p-value | p<0.001 | | p=0.488 | |
| 5-year iDFS rate, % (95% CI) | 83.2 (81.5, 84.7) | 75.3 (73.4, 77.2) | NR | NR |
| **DRFS** | | | | |
| Number of events, n | 325 | 477 | 20 | 24 |
| HR (95% CI) | **0.665 (0.577, 0.765)** | | **0.892 (0.485, 1.643)** | |
| Nominal p-value | p<0.001 | | p=0.714 | |
| 5-year DRFS rate, % (95% CI) | 85.6 (84.0, 87.1) | 78.5 (76.6, 80.3) | NR | NR |
| **OS (immature)** | | | | |
| Number of events, n | 197 | 223 | 11 | 11 |
| HR (95% CI) | **0.894 (0.738, 1.084)** | | **1.078 (0.465, 2.501)** | |
| Nominal p-value | p=0.254 | | p=0.861 | |

**Treatment benefit in Cohort 1 was consistent with ITT. Cohort 2 data remain immature**

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Harbeck N, et al. Adjuvant ESMO 2023. Abstract LBA17.

DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival; ITT, intent-to-treat; NR, not reached; OS, overall survival.

# monarchE: Efficacy Outcomes by Ki-67 Index in Cohort 1

| | Cohort 1 Ki-67 High | | Cohort 1 Ki-67 Low | |
|---|---|---|---|---|
| | Abemaciclib + ET | ET | Abemaciclib + ET | ET |
| | n=1017 | n= 986 | n=946 | n=968 |
| **iDFS** | | | | |
| Number of events, n | 176 | 251 | 116 | 171 |
| HR (95% CI) | **0.643 (0.530, 0.781)** | | **0.662 (0.522, 0.839)** | |
| Nominal p-value | p<0.001 | | p<0.001 | |
| 5-year iDFS rate, % (95% CI) | 81.0 (78.1, 83.4) | 72.0 (68.7, 75.0) | 86.3 (83.6, 88.6) | 80.2 (77.2, 82.9) |
| **DRFS** | | | | |
| Number of events, n | 152 | 221 | 96 | 143 |
| HR (95% CI) | **0.634 (0.515, 0.781)** | | **0.664 (0.512, 0.861)** | |
| Nominal p-value | p<0.001 | | p=0.002 | |
| 5-year DRFS rate, % (95% CI) | 83.4 (80.7, 85.8) | 75.2 (72.1, 78.0) | 88.6 (86.1, 90.7) | 83.5 (80.7, 86.0) |
| **OS (immature)** | | | | |
| Number of events, n | 92 | 121 | 56 | 62 |
| HR (95% CI) | **0.717 (0.546, 0.941)** | | **0.911 (0.633, 1.309)** | |
| Nominal p-value | p=0.016 | | p=0.613 | |

**Within Cohort 1, similar abemaciclib treatment effects were observed regardless of Ki-67 index**

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Harbeck N, et al. Adjuvant ESMO 2023. Abstract LBA17.

DRFS, distant relapse-free survival; ET, endocrine therapy; HR, hazard ratio; iDFS, invasive disease-free survival; OS, overall survival.

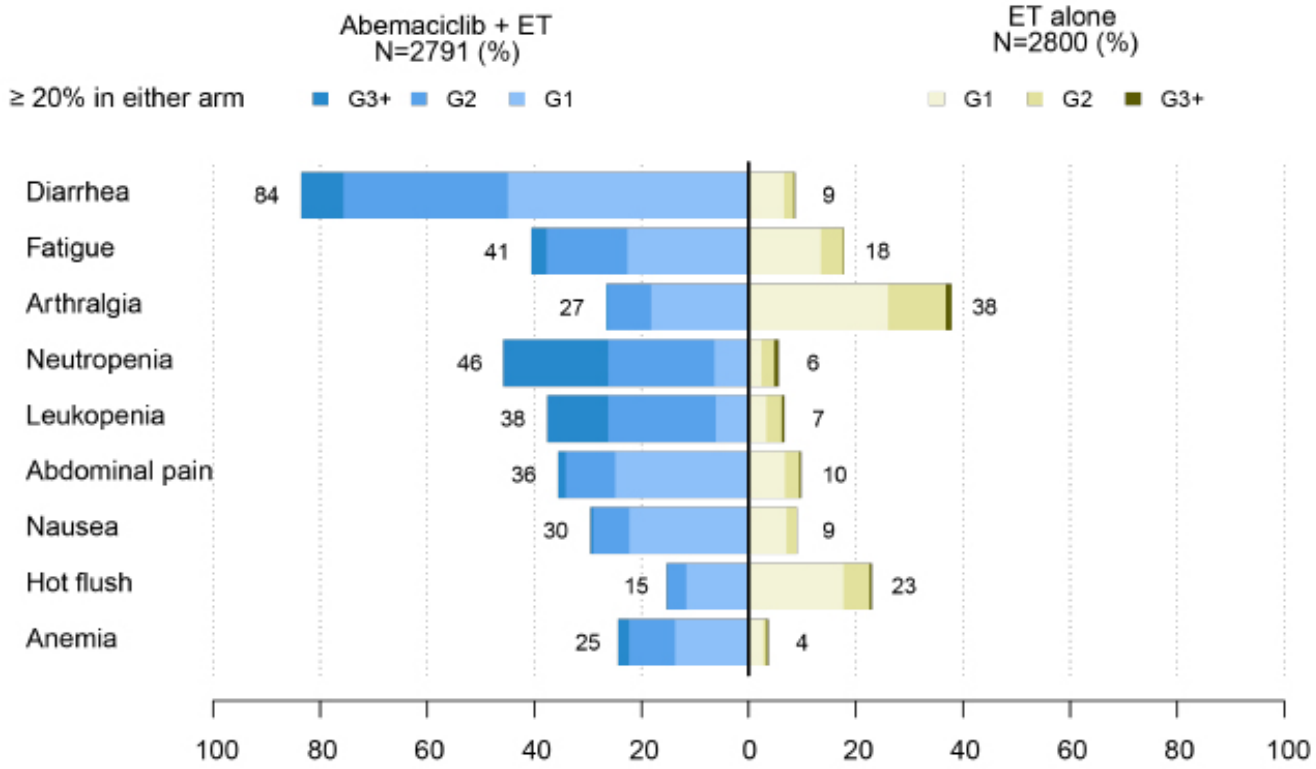
# Current Labels and Guidelines for Abemaciclib in High-Risk Early Breast Cancer

| | FDA[1] | ASCO[2] | NCCN[3] | EMA[4] | ESMO[5] |
|---|---|---|---|---|---|
| **Treatment/ Duration** | Abemaciclib + ET approved for 2 years | Abemaciclib + ET may be offered for 2 years + ET for ≥5 years | Abemaciclib + ET can be considered for 2 years + ET for ≥5 years | Abemaciclib + ET is indicated | Abemaciclib + ET could be considered for use in high-risk groups, when approved |
| **Patient Population** | HR+/HER2−, node-positive eBC at high risk of recurrence | Resected HR+/HER2−, node-positive EBC with high risk of recurrence | HR+/HER2− high-risk breast cancer | HR+/HER2−, node-positive EBC at high risk of recurrence | HR+/HER2− high-risk breast cancer |
| **High-risk Criteria** | • ≥4 positive ALNs, or<br>• 1 to 3 positive ALNs and at least one:<br>  • Grade 3<br>  • Tumor ≥5 cm<br>Previous requirement for a Ki-67 score >20% has been removed | • ≥ 4 positive ALNs, or<br>• 1 to 3 positive ALNs and one of the following:<br>  • Grade 3<br>  • Tumor ≥5 cm<br>  • Ki-67 ≥20% | | • ≥4 positive ALNs, or<br>• 1 to 3 positive ALNs and one of the following:<br>  • Grade 3<br>  • Tumor ≥5 cm | |

1. FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-early-breast-cancer-indication-abemaciclib-endocrine-therapy. 2. Giordano SH, et al; Optimal Adjuvant Chemotherapy and Targeted Therapy Guideline Expert Panel. *J Clin Oncol.* 2022;40(3):307-309. 3. Gradishar WJ, et al. NCCN Guidelines. Breast Cancer. Version 2.2024. 4. European Medicines Agency. Assessment report. Abemaciclib. https://www.ema.europa.eu/en/documents/variation-report/verzenios-h-c-004302-ii-0013-epar-assessment-report-variation_en.pdf. 5. Loibl S, et al. *Ann Oncol.* 2024;35(2):159-182.

ALN, axillary lymph node; ASCO, American Society of Clinical Oncology; eBC, early breast cancer; EMA, European Medicines Agency; ESMO, European Society for Medical Oncology; ET, endocrine therapy; FDA, U.S. Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NCCN, National Comprehensive Cancer Network.

# monarchE: Safety Findings Consistent With Previous Analyses




**Median duration of abemaciclib: 23.7 months**

| Other events of interest, any grade | Abemaciclib + ET N = 2791, % | ET Alone N = 2800, % |
|---|---|---|
| VTE | 2.5 | 0.7 |
| PE | 1.0 | 0.1 |
| ILD | 3.3 | 1.3 |

Abemaciclib dose adjustments due to AEs

- Dose holds: 61.7%
- Dose reductions: 43.6%
- Discontinuations: 18.5% [8.9% after dose reduction]

**All patients who received at least one dose of study treatment were included in the safety population. The safety profile of abemaciclib is considered manageable and acceptable for this high-risk population.**

Johnston SRD, et al. SABCS 2022. Abstract GS1-09.
AE, adverse events; ET, endocrine therapy; ILD, interstitial lung disease; PE, pulmonary embolism; VTE, venous thromboembolism.

# monarchE: Dose Adjustments Were More Common in Older Patients

| Abemaciclib dose adjustments due to AEs, % | Abemaciclib + ET | | |
|---|---|---|---|
| | Overall | <65 | ≥65* |
| | n=2791 | n=2361 | n=430 |
| Interruptions | 62 | 60 | 68 |
| Reductions | 44 | 42 | 55 |
| Discontinuations | 18 | 15 | 38 |
| Discontinuations without prior dose reductions | 10 | 8 | 19 |

**Adverse event rates were similar in older vs younger patients**
**Patients ≥75 years had more grade 3 diarrhea and grade 2/3 fatigue**

*Patients ≥ 75 years had higher rates of abemaciclib dose adjustments and discontinuations due to AEs
Hamilton EP, et al. ASCO 2023. Abstract 501.
AE, adverse event; ET, endocrine therapy.

# Abemaciclib Efficacy Is Not Compromised By Dose Reductions

**Time dependent Cox model in patients treated with abemaciclib**

| Efficacy Endpoint | HR (95% CI)<br>Staying at full dose vs<br>Being reduced to lower doses |
|---|---|
| **ITT** | |
| iDFS | 0.905 (0.727, 1.125) |
| DRFS | 0.942 (0.742, 1.195) |
| **Cohort 1** | |
| iDFS | 0.899 (0.718, 1.125) |
| DRFS | 0.958 (0.750, 1.223) |

**Abemaciclib benefit was similar when given at the full dose of 150 mg compared to reduced doses of 100 mg or 50 mg**

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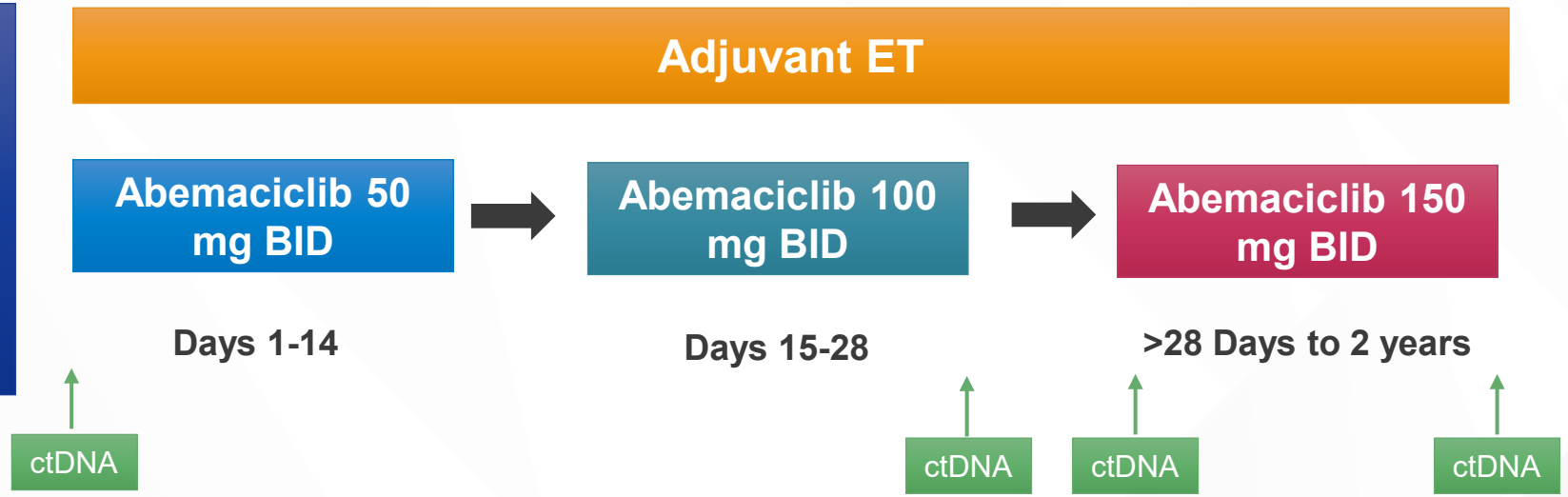
O'Shaughnessy J, et al. ESMO 2023. Abstract 274P.
DRFS, distant relapse-free survival; HR, hazard ratio; iDFS, invasive disease-free survival; ITT, intent-to-treat.

# TRADE: A Phase 2, Single Arm, Dose-Escalation Trial of Adjuvant Abemaciclib and Endocrine Therapy

- HR-positive, HER2-negative, node positive early breast cancer
- Adjuvant abemaciclib indicated based on patient risk/stage

**N=90**




**Primary endpoint: 12-week Composite Adverse Rate:**
Discontinuation of abemaciclib for any reason, and/or need to dose reduce, and/or inability to reach-maintain the full dose.
**Secondary endpoints:** TRAEs, discontinuation/hold rates, incidence of Grade ≥2 diarrhea, adherence to therapy, dose intensity, QOL
**Correlative endpoints:** serial ctDNA, PBMC, stool studies

NCT06001762 PI: Erica Mayer

AXIS Medical Education

ClinicalTrials.gov. NCT06001762.
BID, twice a day; ctDNA, circulating tumor DNA; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PBMC, peripheral blood mononuclear cells QOL, quality of life; TRAE, treatment-related adverse events.

# What ET Should Be Combined With Abemaciclib?

## Venous thromboembolic events (VTE)

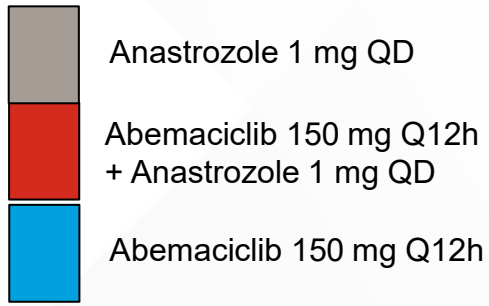
| Event term, n (%) | Abemaciclib + ET (N=2791) | | | |
|---|---|---|---|---|
| | Any Grade | G1 | G2 | G≥3 |
| *VTE* | 67 (2.4) | 3 (0.1) | 27 (1.0) | 37 (1.3) |
| Pe[a] | 26 (0.9) | 0 | 0 | 26 (0.9) |
| Serious *VTE* | 33 (1.2) | | | |
| *VTE* by First ET | Abemaciclib + ET | | | |
| Tamoxifen (Nx=857 [abemaciclib + ET]; 898 [ET alone]) | 35 (4.1) | 2 (0.2) | 14 (1.6) | 19 (2.2) |
| Aromatase Inhibitors (Nx=1929 [abemaciclib + ET]; 1892 [ET alone]) | 32 (1.7) | 1 (0.1) | 13 (0.7) | 18 (0.9) |
| Time to onset of first *VTE* event (days); median (range) | 182.0 (8.0 – 714.0) | | | |
| Discontinuation due to *VTE* | 13 (0.5) | | | |

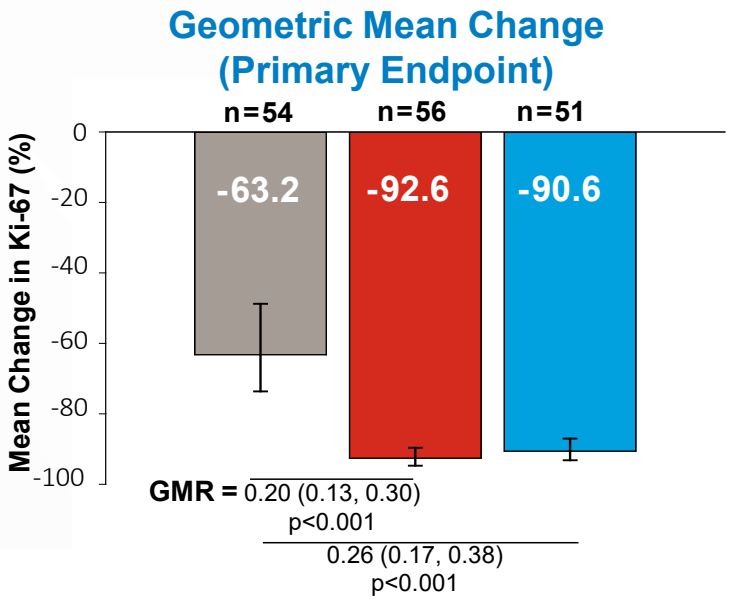
**Use abemaciclib + tamoxifen with caution in patients with risk factors for VTE**

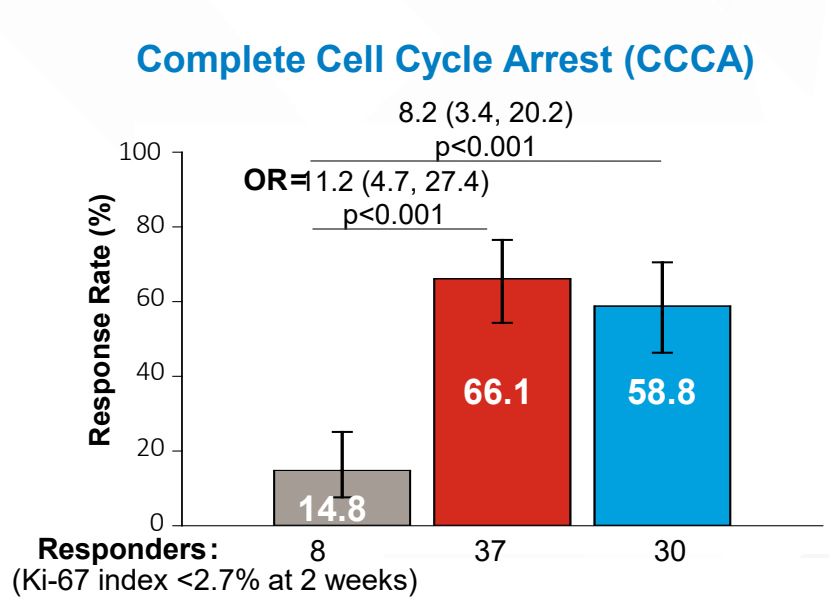
TAMOXIFEN → 4.1% any-grade VTE
AI → 1.7% any-grade VTE

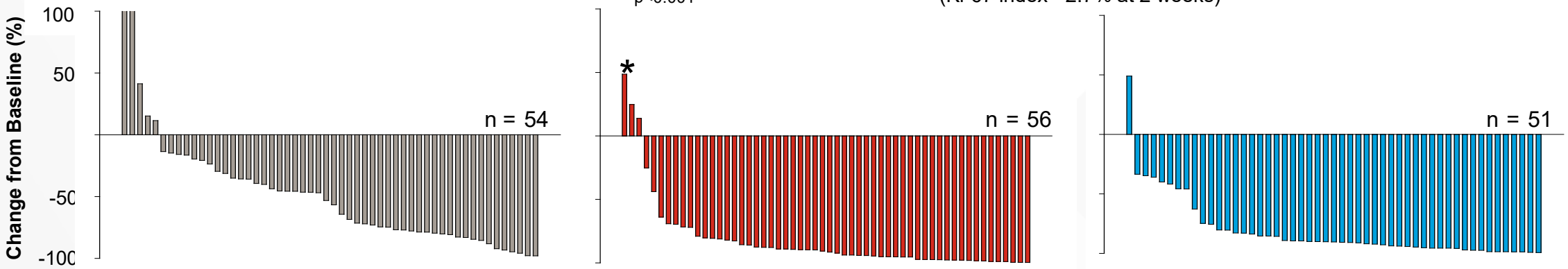
Toi M, et al. *Ann Oncol.* 2021;32(suppl_2):S37-S47.
AI, aromatase inhibitor; ET, endocrine therapy; PE, pulmonary embolism; VTE, venous thromboembolism.

# What About Patients Who Need Preop Therapy? neoMONARCH: Ki-67 Expression and Response at Wk 2




Hurvitz S, et al. *Cancer Res.* 2017;77(4_Supplement):S4-06. Hurvitz SA, et al. *Clin Cancer Res*. 2020;26:566-580.
GMR, geometric mean ratios; OR, odds ratio; Q12h, every 12 hours; QD once daily.

# What About Patients With gBRCAm?

**Prioritize adjuvant olaparib (1 year)**

Consider sequential administration of abemaciclib after olaparib in patients with the highest risk of relapse



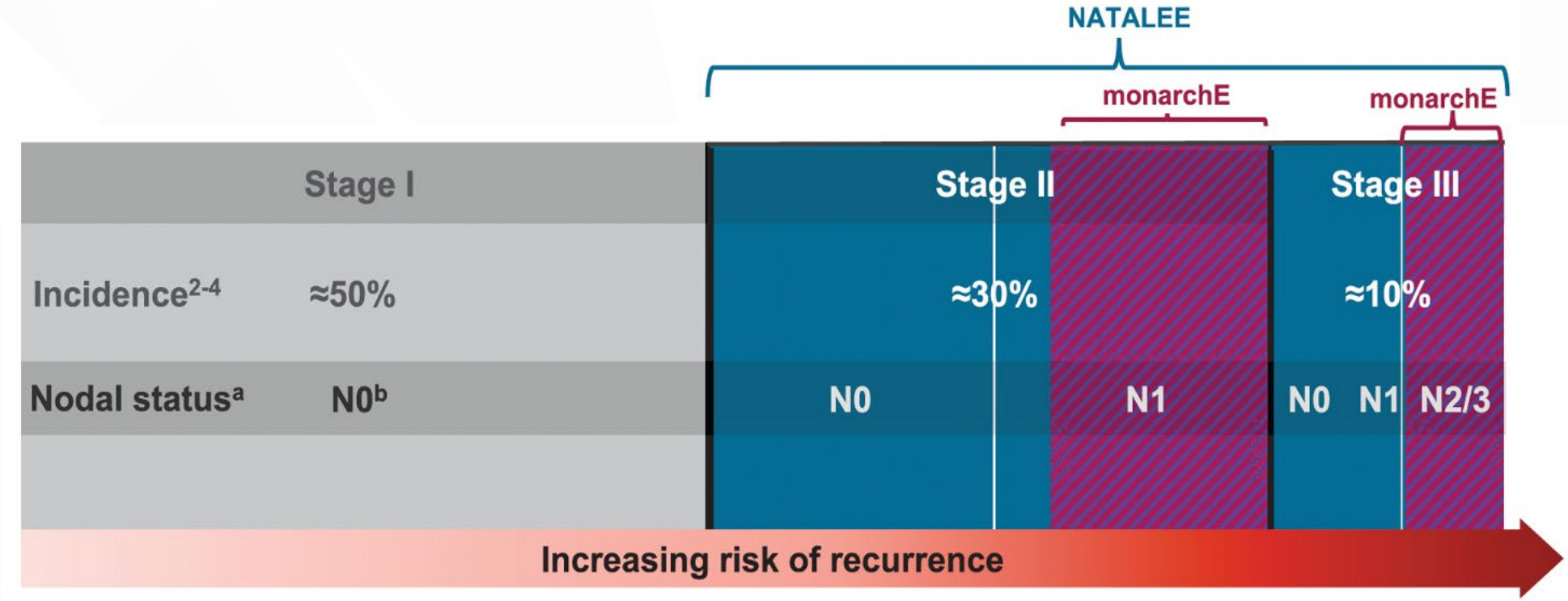
Tutt ANJ, et al. *N Engl J Med.* 2021;384(25):2394-2405.
gBRCAm, germline BRCA-mutated.

# Which Patients Should Be Considered for Adjuvant Abemaciclib with N+, High-Risk Early-Stage BC?

- ≥4 positive lymph nodes (any T, grade)
- T3, N1-3 (any grade)
- T1-2, N1-3, AND grade 3

Slide courtesy of Sara M. Tolaney, MD, MPH.|
BC, breast cancer; N, node; T, tumor.

# NATALEE: Potential for Expanding Adjuvant CDK4/6i Use

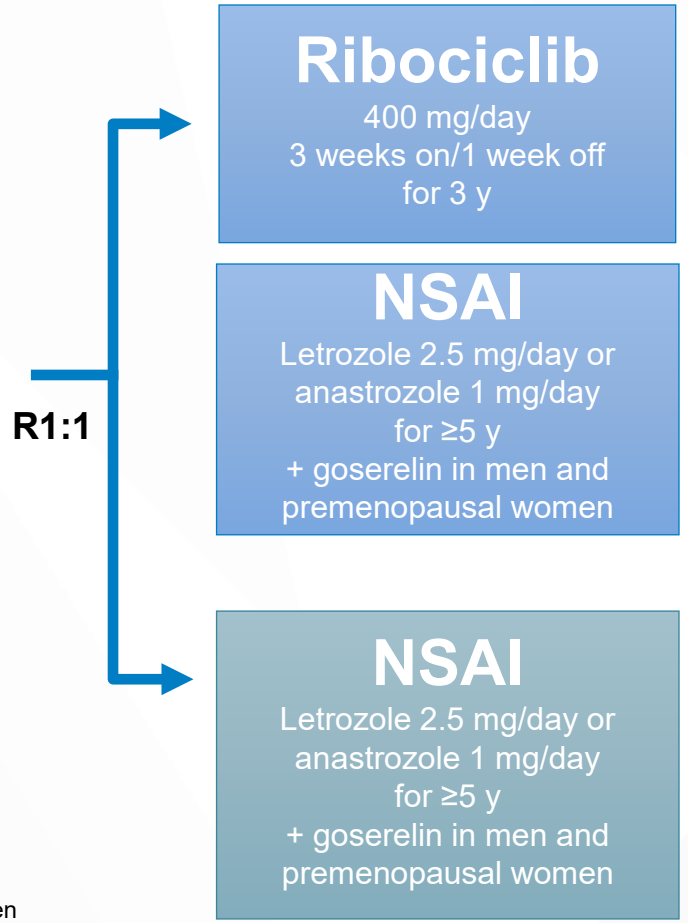



Slide courtesy of Sara M. Tolaney, MD, MPH.|
Slamon DJ, et al. *Ther Adv Med Oncol.* 2023;15:17588359231178125.
CDK, cyclin-dependent kinase; N, node.

# NATALEE: Study Design: Unique Features

- Adult patients with HR+/HER2− EBC
- Prior ET allowed up to 12 months
- **Anatomic stage IIA**
  - **N0** with:
    - > Grade 2 and evidence of high risk:
      - Ki-67 ≥20%
      - Oncotype DX Breast Recurrence Score ≥26 or
      - High risk via genomic risk profiling
    - > Grade 3
  - **N1**
- **Anatomic stage IIB**
  - N0 or N1
- **Anatomic stage III**
  - N0, N1, N2, or N3

N = 5,101




- **Primary Endpoint**
  - iDFS using STEEP criteria
- **Secondary Endpoints**
  - Recurrence-free survival
  - Distant disease-free survival
  - OS
  - PROs
  - Safety and tolerability
  - PK
- **Exploratory Endpoints**
  - Locoregional recurrence-free survival
  - Gene expression and alterations in tumor ctDNA/ctRNA samples

**Randomization stratification**
**Anatomical stage:** II vs III
**Menopausal status:** men and premenopausal women vs postmenopausal women
**Receipt of prior (neo)adjuvant chemotherapy:** yes vs no
**Geographic location:** North America/Western Europe/Oceania vs rest of world



Hortobagyi G, et al. SABCS 2023. Abstract GS03-03.
1. ClinicalTrials.gov. NCT03701334. 2. Slamon D, et al. ASCO 2023. Abstract LBA500.
ctDNA/RNA, circulating tumor DNA/RNA; EBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; iDFS, invasive disease-free survival; N, node; NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; PK, pharmacokinetics; PRO, patient-reported outcomes; R, randomized; STEEP, Standardized Definitions for Efficacy End Points in Adjuvant Breast Cancer Trials; y, years.

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    - High risk via genomic risk profiling
  - Grade 3
- **N1**

**Anatomical stage IIB**
- N0 or N1

**Anatomical stage III**
- N0, N1, N2, or N3

N = 5,101

**Ribociclib**
400 mg/day
3 weeks on/1 week off for 3 y

premenopausal women

**Rationale for Broad Population of Patients**

Patients with stage II and III HR+/HER2− EBC, including those with no nodal involvement, are at risk of disease recurrence for decades after initial diagnosis

- **Primary Endpoint**
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**Anatomical stage III**

- N0, N1, N2, or N3

N = 5,101

**Ribociclib**

**400 mg/day**

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premenopausal women

**Rationale for Broad Population of Patients**

Patients with stage II and III HR+/HER2− EBC, including those with no nodal involvement, are at risk of disease recurrence for decades after initial diagnosis

- **Primary Endpoint**
- survival
  - OS
  - PROs
  - Safety and tolerability
  - PK
- **Exploratory Endpoints**
  - Locoregional recurrence-free survival
  - Gene expression and alterations in tumor ctDNA/ctRNA samples

**Rationale for 400 mg RIBOCICLIB**

To improve tolerability while maintaining efficacy

**Randomization stratification**
**Anatomical stage:** II vs III
**Menopausal status:** men and premenopausal women vs postmenopausal women
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N = 5,101

**Ribociclib**
**400 mg/day**
3 weeks on/1 week off for
**for 3 y**

premenopausal women

**Rationale for Broad Population of Patients**

Patients with stage II and III HR+/HER2− EBC, including those with no nodal involvement, are at risk of disease recurrence for decades after initial diagnosis

- **Primary Endpoint**

survival

**Rationale for 400 mg RIBOCICLIB**

To improve tolerability while maintaining efficacy

**Rationale for 3-year Treatment Duration**

Extended duration of treatment is crucial to prolong cell cycle arrest and drive more tumor cells into irreversible senescence

- Gene expression and alterations in tumor ctDNA/ctRNA samples

**Randomization stratification**
**Anatomical stage:** II vs III
**Menopausal status:** men and premenopausal women vs postmenopausal women
**Receipt of prior (neo)adjuvant chemotherapy:** yes vs no
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# NATALEE and monarchE: Difference in Patient Populations

| NATALEE (N=5,101) | | |
|---|---|---|
| | ribociclib+ET (N= 2549) | ET (N= 2552) |
| Stage II | 1011 (40%) | 1033 (40%) |
| Stage III | 1528 (60%) | 1512 (59%) |
| Prior chemo (neo) adjuvant | | |
| Yes | 2249 (88%) | 2245 (88%) |
| Premenopausal/ Men | 1126 (44%) | 1132 (44%) |
| Postmenopausal | 1423 (56%) | 1420 (56%) |
| Age, median (min-max) | 52 (24-90) | 52 (24-89) |
| ALN | | |
| NX | 272 (11%) | 264 (10%) |
| N0 | 694 (27%) | 737 (29%) |
| N1 1-3 | 1050 (41%) | 1049 (41%) |
| N2, N3 ≥4 | 483 (19%) | 467 (18%) |
| ECOG PS | | |
| 0 | 2106 (83%) | 2132 (84%) |
| 1 | 440 (17%) | 418 (16%) |

| monarchE (N=5,637) | | |
|---|---|---|
| | Abema + ET (N= 2808) | ET (N=2879) |
| Stage II (derived) | 25.5% | 26.2% |
| Stage III (derived) | 73.9% | 73.4% |
| Prior chemo | | |
| Neoadjuvant | 1025 (36.5%) | 1031(36.4%) |
| Adjuvant | 1631 (58.1%) | 1633 (57.7%) |
| None | 152 (5.4%) | 165 (5.8%) |
| Premenopausal | 1221 (43.5%) | 1232 (43.5%) |
| Postmenopausal | 1587 (56.5%) | 1597 (56.5%) |
| Age, (median IQR), years | 51 (44-60) | 51 (44-60) |
| <65 | 2371 (84.4%) | 2416 (85.4%) |
| ≥65 | 437 (15.6%) | 413 (14.6%) |
| ALN | | |
| N0 | 7 (0.2%) | 7 (0.2%) |
| N1 1-3 | 1118 (39.8%) | 1142 (40.4%) |
| N2, N3 ≥4 | 1682 (59.9%) | 1680 (59.4%) |
| ECOG PS | | |
| 0 | 2405 (85.7%) | 2369 (83.8%) |
| 1 | 401 (14.3%) | 455 (16.1%) |

12% at SURGERY

Hortobagyi G, et al. SABCS 2023. Abstract GS03-03.
ALN, axillary lymph node; ECOG, Eastern Cooperative Oncology Group; ET, endocrine therapy; IQR, interquartile range; N, node; PS, performance status.

# NATALEE: Patient Disposition

## Second Interim Efficacy Analysis

Data cutoff: January 11, 2023

iDFS events: n=426

### Ribociclib + NSAI, n=2549

- NSAI ongoing: 1984 (77.8%)
  - **RIB ongoing: 1147 (45.0%)**
- Stopped RIB: 1377 (54.0%)
  - **Completed 3 years: 515 (20.2%)**
  - **Early discontinuation: 862 (33.8%)**
    - Discontinued due to AEs: 477 (18.7%)

### NSAI Alone, n=2552

- NSAI ongoing: 1826 (71.6%)
- Discontinued NSAI: 617 (24.2%)

## Final iDFS Analysis

Data cutoff: July 21, 2023

iDFS events: n=509

### Ribociclib + NSAI, n=2549

- NSAI ongoing: 1914 (75.1%)
  - **RIB ongoing: 528 (20.7%)**
- Stopped RIB: 1996 (78.3%)
  - **Completed 3 years: 1091 (42.8%)**
  - **Early discontinuation: 905 (35.5%)**
    - Discontinued due to AEs: 498 (19.5%)

### NSAI Alone, n=2552

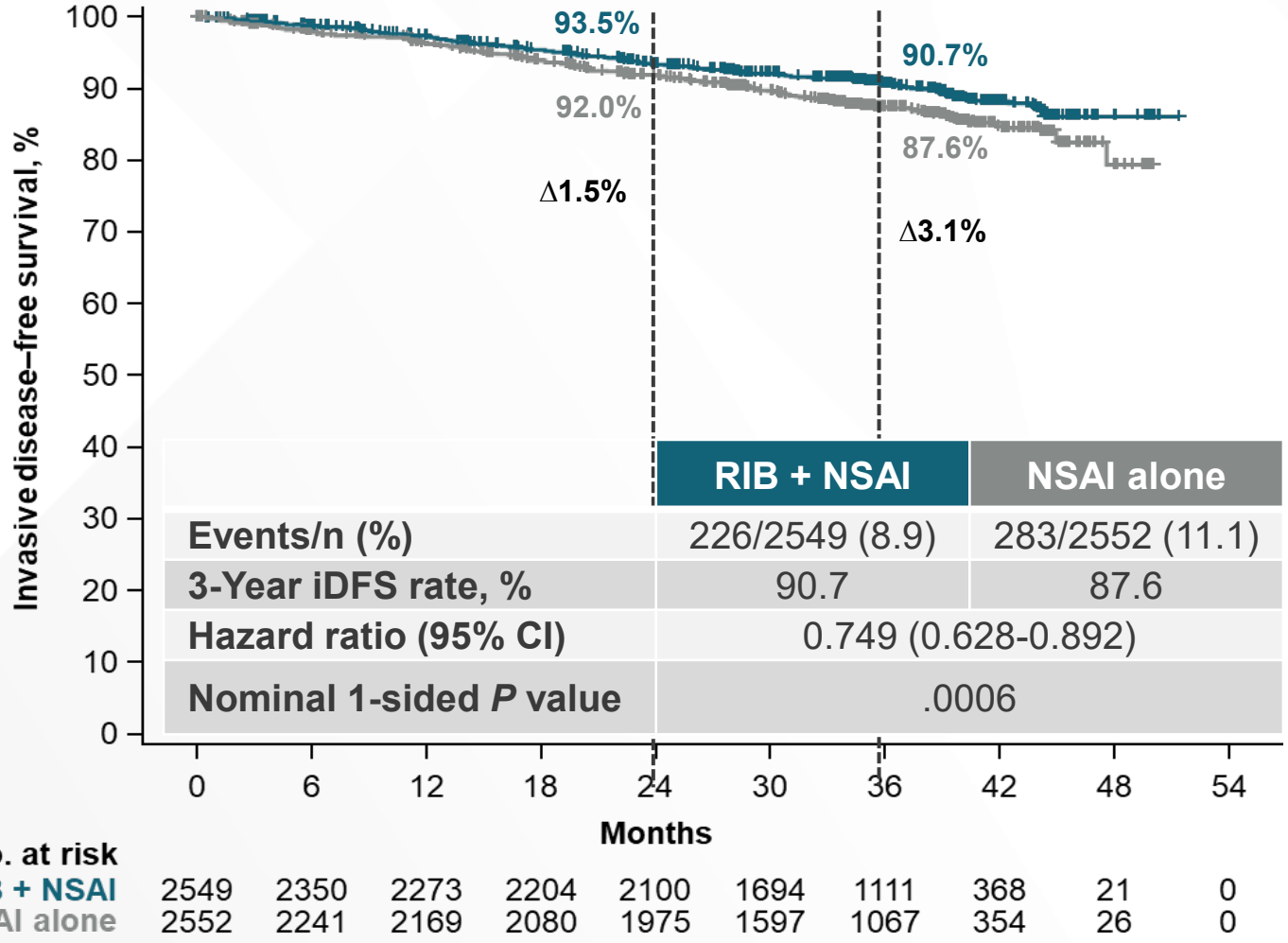
- NSAI ongoing: 1748 (68.5%)
- Discontinued NSAI: 693 (27.2%)

AXIS Medical Education

Hortobagyi G, et al. SABCS 2023. Abstract GS03-03.
Slamon D, et al. ASCO 2023. Abstract LBA500.

AE, adverse event; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

# NATALEE: Invasive Disease–Free Survival




| | RIB + NSAI | NSAI alone |
|---|---|---|
| Events/n (%) | 226/2549 (8.9) | 283/2552 (11.1) |
| 3-Year iDFS rate, % | 90.7 | 87.6 |
| Hazard ratio (95% CI) | 0.749 (0.628-0.892) | |
| Nominal 1-sided *P* value | .0006 | |

| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| RIB + NSAI | 2549 | 2350 | 2273 | 2204 | 2100 | 1694 | 1111 | 368 | 21 | 0 |
| NSAI alone | 2552 | 2241 | 2169 | 2080 | 1975 | 1597 | 1067 | 354 | 26 | 0 |

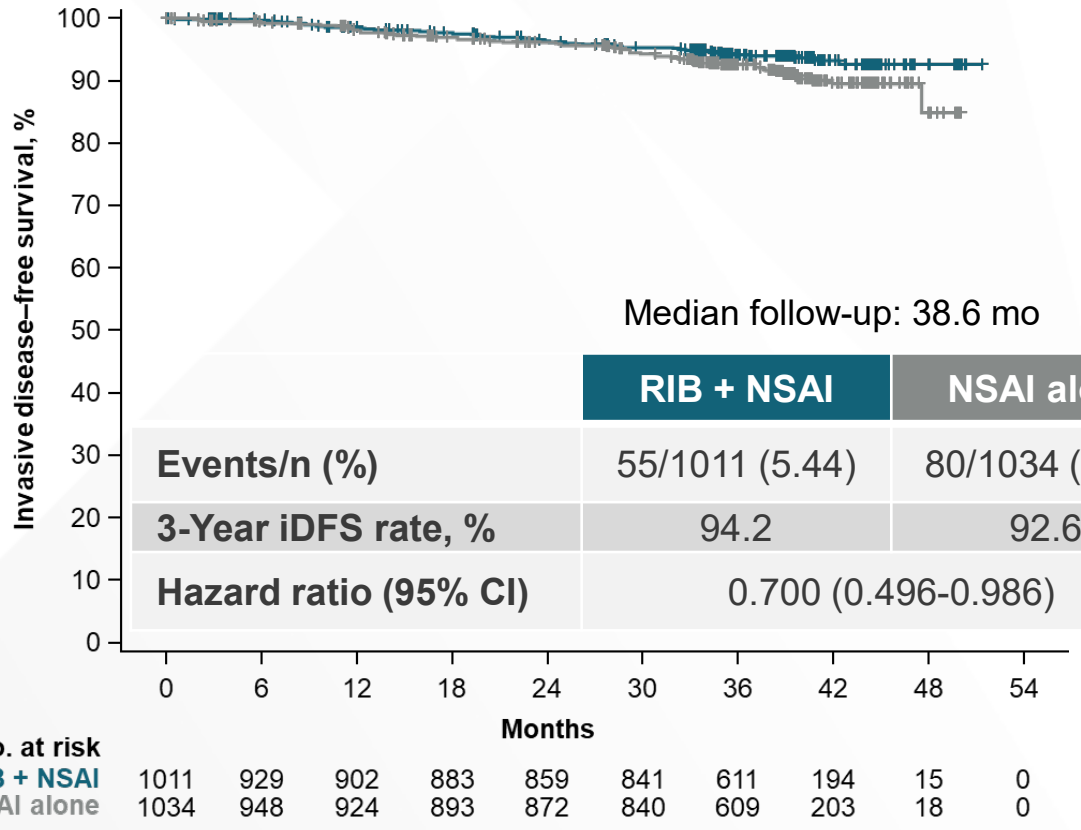
- The median follow-up for iDFS was 33.3 months (maximum, 51 months)—an additional 5.6 months from the second interim efficacy analysis
- The absolute iDFS benefit with ribociclib plus NSAI was 3.1% at 3 years
- The risk of invasive disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone

AXIS Medical Education

Hortobagyi G, et al. SABCS 2023. Abstract GS03-03; Slamon D, et al. ASCO 2023. Abstract LBA500.
iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

# NATALEE: iDFS by Anatomical Stage

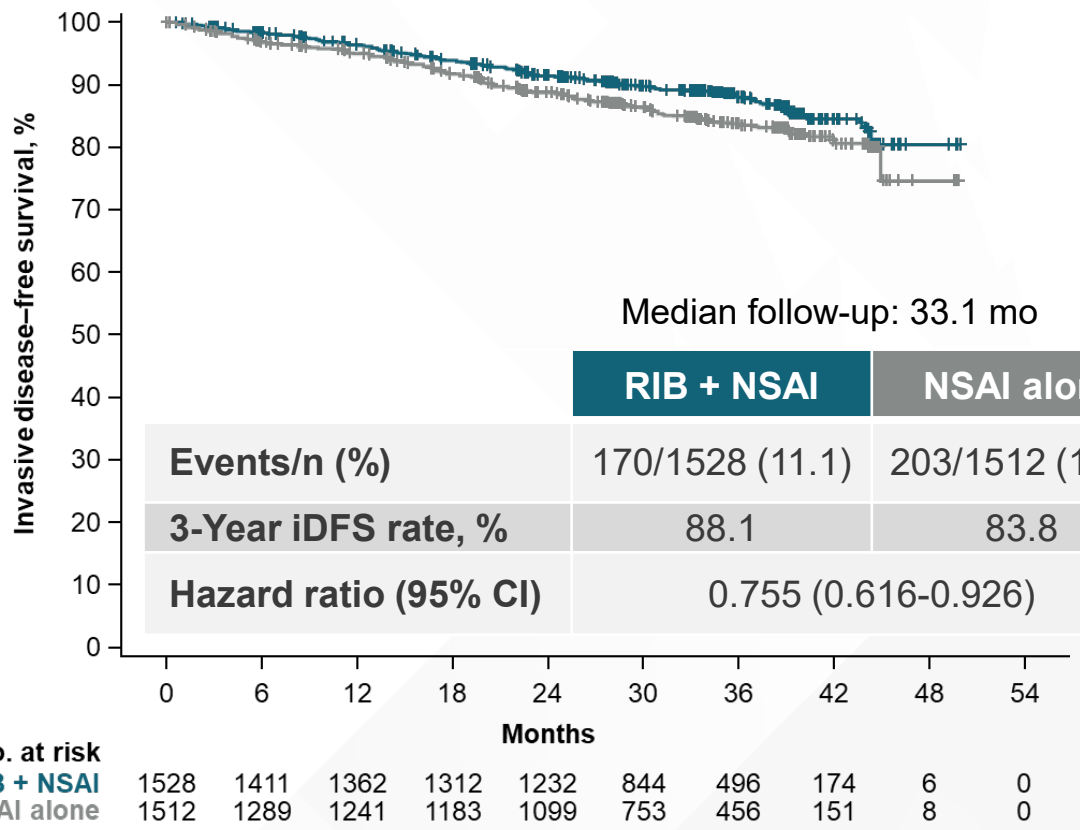
## Stage II




Median follow-up: 38.6 mo

| | RIB + NSAI | NSAI alone |
|---|---|---|
| **Events/n (%)** | 55/1011 (5.44) | 80/1034 (7.74) |
| **3-Year iDFS rate, %** | 94.2 | 92.6 |
| **Hazard ratio (95% CI)** | 0.700 (0.496-0.986) | |

## Stage III




Median follow-up: 33.1 mo

| | RIB + NSAI | NSAI alone |
|---|---|---|
| **Events/n (%)** | 170/1528 (11.1) | 203/1512 (13.4) |
| **3-Year iDFS rate, %** | 88.1 | 83.8 |
| **Hazard ratio (95% CI)** | 0.755 (0.616-0.926) | |

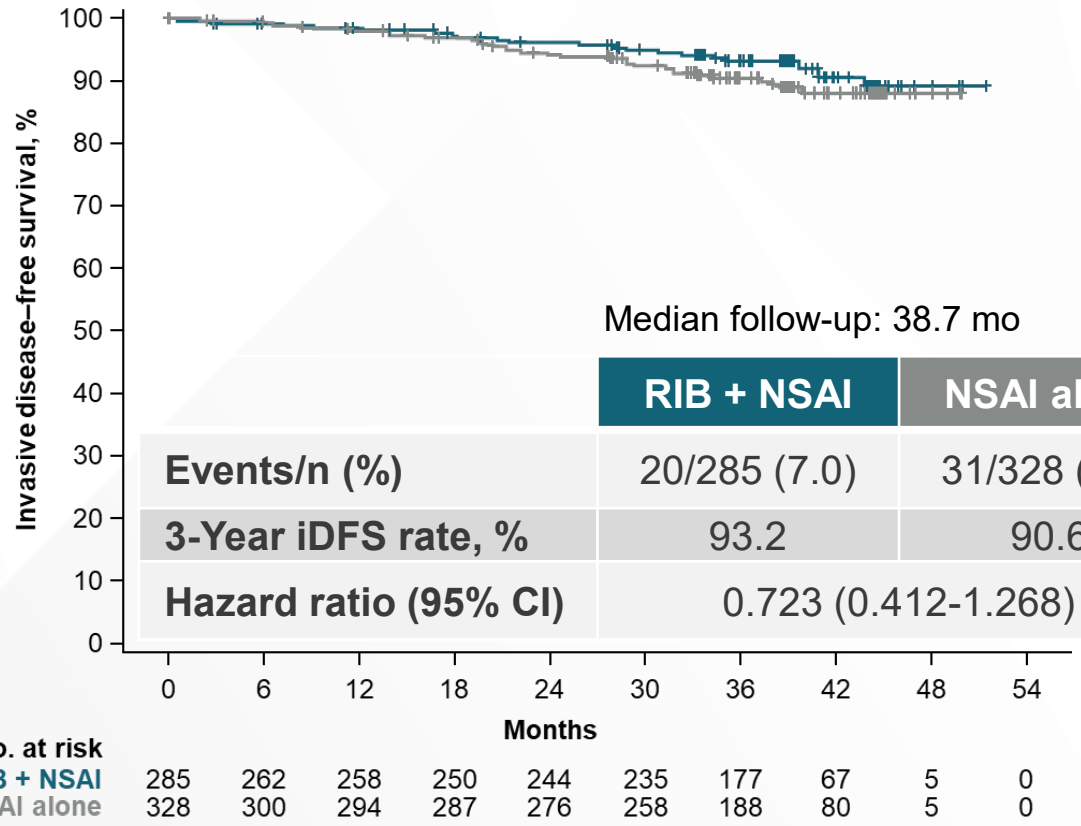
**The risk of invasive disease was reduced by 30% for stage II and by 24.5% for stage III disease with ribociclib plus NSAI vs NSAI alone**

AXIS Medical Education

Hortobagyi G, et al. SABCS 2023. Abstract GS03-03.
iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

# NATALEE: iDFS by Nodal Status

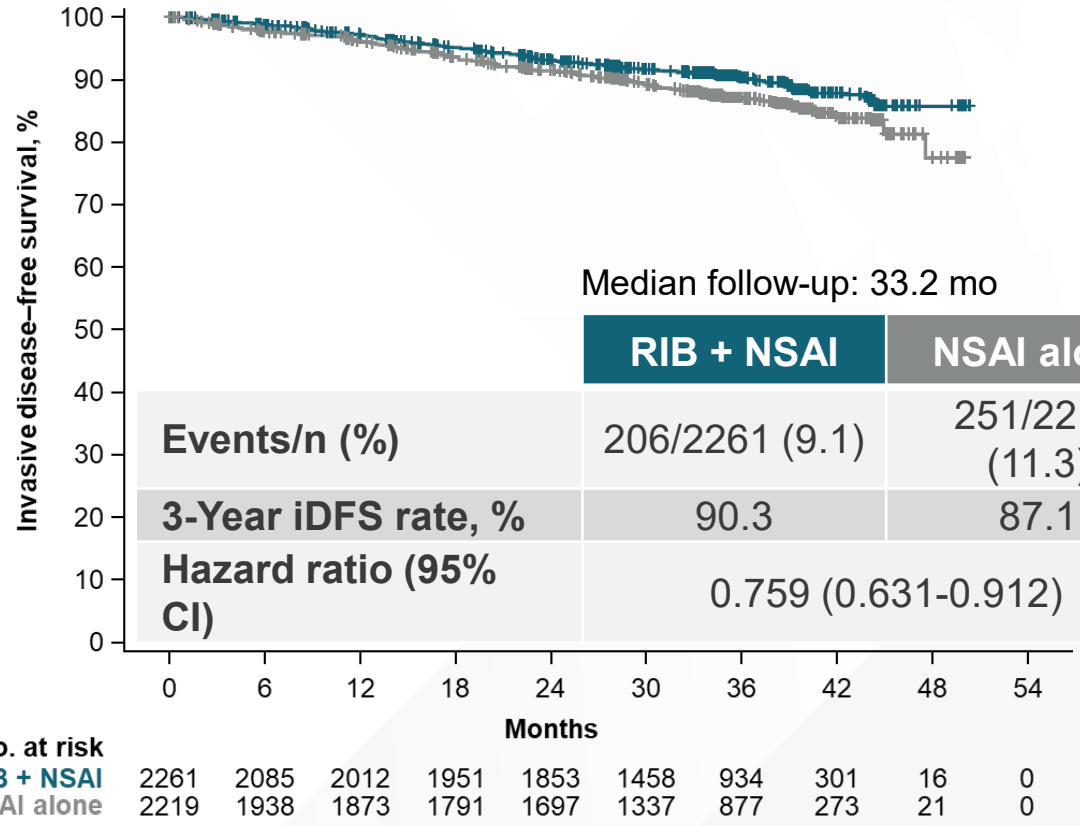
## N0




Median follow-up: 38.7 mo

| | RIB + NSAI | NSAI alone |
|---|---|---|
| **Events/n (%)** | 20/285 (7.0) | 31/328 (9.5) |
| **3-Year iDFS rate, %** | 93.2 | 90.6 |
| **Hazard ratio (95% CI)** | 0.723 (0.412-1.268) | |

## N1-N3




Median follow-up: 33.2 mo

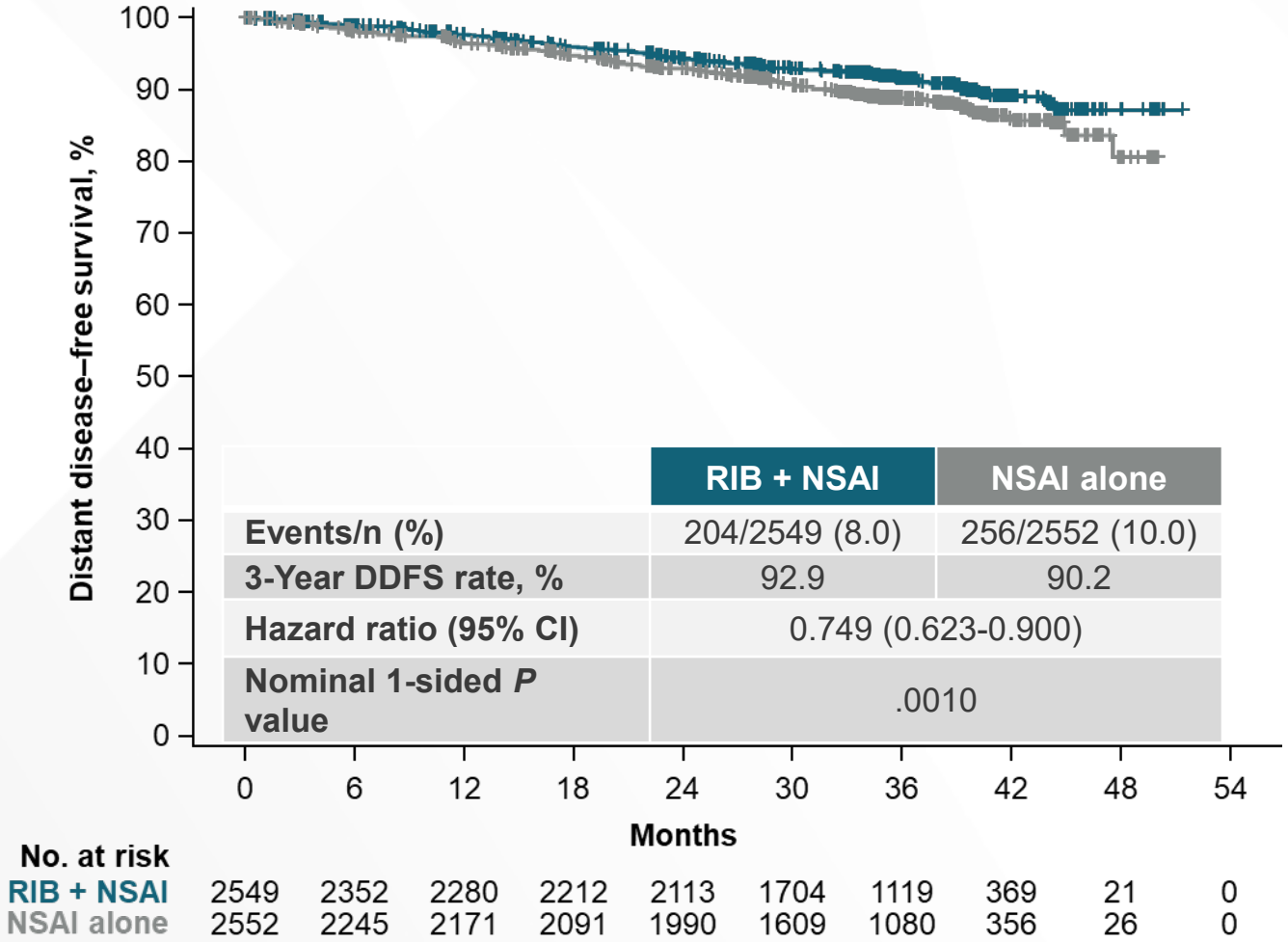
| | RIB + NSAI | NSAI alone |
|---|---|---|
| **Events/n (%)** | 206/2261 (9.1) | 251/2219 (11.3) |
| **3-Year iDFS rate, %** | 90.3 | 87.1 |
| **Hazard ratio (95% CI)** | 0.759 (0.631-0.912) | |

**The risk of invasive disease was reduced by 27.7% for node-negative and by 24.1% for node-positive disease with ribociclib plus NSAI vs NSAI alone**

AXIS Medical Education

Hortobagyi G, et al. SABCS 2023. Abstract GS03-03.
iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

# NATALEE: Distant Disease–Free Survival




| | RIB + NSAI | NSAI alone |
|---|---|---|
| Events/n (%) | 204/2549 (8.0) | 256/2552 (10.0) |
| 3-Year DDFS rate, % | 92.9 | 90.2 |
| Hazard ratio (95% CI) | 0.749 (0.623-0.900) | |
| Nominal 1-sided *P* value | .0010 | |

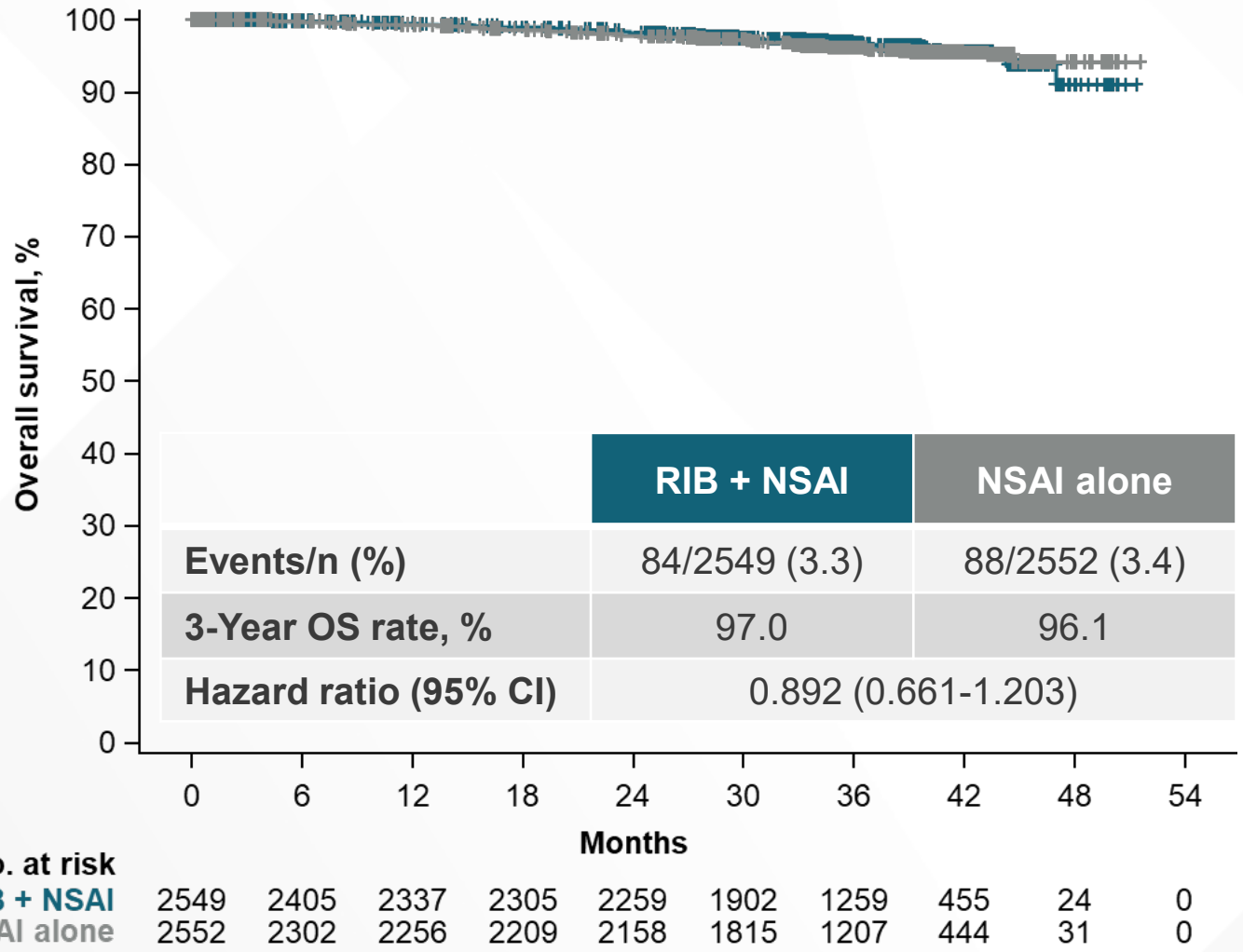
- The absolute DDFS[a] benefit with ribociclib plus NSAI was 2.7% at 3 years
- The risk of distant disease was reduced by 25.1% with ribociclib plus NSAI vs NSAI alone at the final analysis

[a]DDFS is the time from randomization to the date of the first event of distant recurrence, death by any cause, or second primary nonbreast invasive cancer (excluding basal and squamous cell carcinomas of the skin).

Hortobagyi G, et al. SABCS 2023. Abstract GS03-03.

DDFS, distant disease-free survival; iDFS, invasive disease-free survival; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib.

# NATALEE: Overall Survival




| | RIB + NSAI | NSAI alone |
|---|---|---|
| **Events/n (%)** | 84/2549 (3.3) | 88/2552 (3.4) |
| **3-Year OS rate, %** | 97.0 | 96.1 |
| **Hazard ratio (95% CI)** | 0.892 (0.661-1.203) | |

| No. at risk | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| RIB + NSAI | 2549 | 2405 | 2337 | 2305 | 2259 | 1902 | 1259 | 455 | 24 | 0 |
| NSAI alone | 2552 | 2302 | 2256 | 2209 | 2158 | 1815 | 1207 | 444 | 31 | 0 |

- The median follow-up for OS was 35.9 months at the final analysis
- The OS data require longer-term follow-up, as there were so few events in both treatment arms (4%)

Hortobagyi G, et al. SABCS 2023. Abstract GS03-03.
NSAI, nonsteroidal aromatase inhibitor; OS, overall survival; RIB, ribociclib.

# NATALEE: Safety Profile of Ribociclib at 400 mg

| | RIB + NSAI n=2525 | | NSAI alone n=2442 | |
|---|---|---|---|---|
| **AESIs, %** | **Any grade** | **Grade ≥3** | **Any grade** | **Grade ≥3** |
| Neutropenia[a] | 62.5 | 44.3 | 4.6 | 0.9 |
| Febrile neutropenia | 0.3 | 0.3 | 0 | 0 |
| Liver-related AEs[b] | 26.4 | 8.6 | 11.2 | 1.7 |
| QT interval prolongation[c] | 5.3 | 1.0 | 1.4 | 0.6 |
| ECG QT prolonged | 4.3 | 0.3 | 0.7 | 0 |
| Interstitial lung disease/pneumonitis[d] | 1.5 | 0 | 0.9 | 0.1 |
| **Other clinically relevant AEs, %** | | | | |
| Arthralgia | 37.3 | 1.0 | 43.3 | 1.3 |
| Nausea | 23.3 | 0.2 | 7.8 | 0.0 |
| Headache | 22.8 | 0.4 | 17.0 | 0.2 |
| Fatigue | 22.3 | 0.8 | 13.2 | 0.2 |
| Diarrhea | 14.5 | 0.6 | 5.5 | 0.1 |
| VTE[e] | 1.5 | 0.6 | 0.8 | 0.4 |

- In this updated analysis:
  - No AESIs
  - No >1% increase in clinically relevant AEs
  - Only an 0.8% increase in discontinuations
- The most frequent all-grade AEs (with ribociclib + NSAI vs NSAI alone) leading to discontinuation in both treatment arms were:
  - Liver-related AEs
  - Arthralgia

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[a]Grouped term that combines neutropenia and neutrophil count decreased. [b]Grouped term that includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders. [c]Grouped term. [d]Grouped term that includes all preferred terms identified by standardized MedDRA queries for interstitial lung disease. [e]Grouped term that includes all preferred terms identified by standardized MedDRA queries for venous thromboembolism.
Hortobagyi G, et al. SABCS 2023. Abstract GS03-03. Slamon D, et al. ASCO 2023. Abstract LBA500.
AE, adverse event; AESI, adverse event of special interest; ECG, electrocardiogram; MedDRA, Medical Dictionary for Regulatory Activities; NSAI, nonsteroidal aromatase inhibitor; RIB, ribociclib; VTE, venous thromboembolism.

# NATALEE: Subgroup Analysis of Patients with High-risk, Node-negative (N0) HR+/HER2- EBC

- Ribociclib +ET, compared to ET alone, showed an improvement in rates of iDFS, DRFS, and DDFS in high-risk EBC patients with N0 disease
  - 28% risk reduction in iDFS in subgroup of patients with node-negative (N0) disease at high risk of recurrence

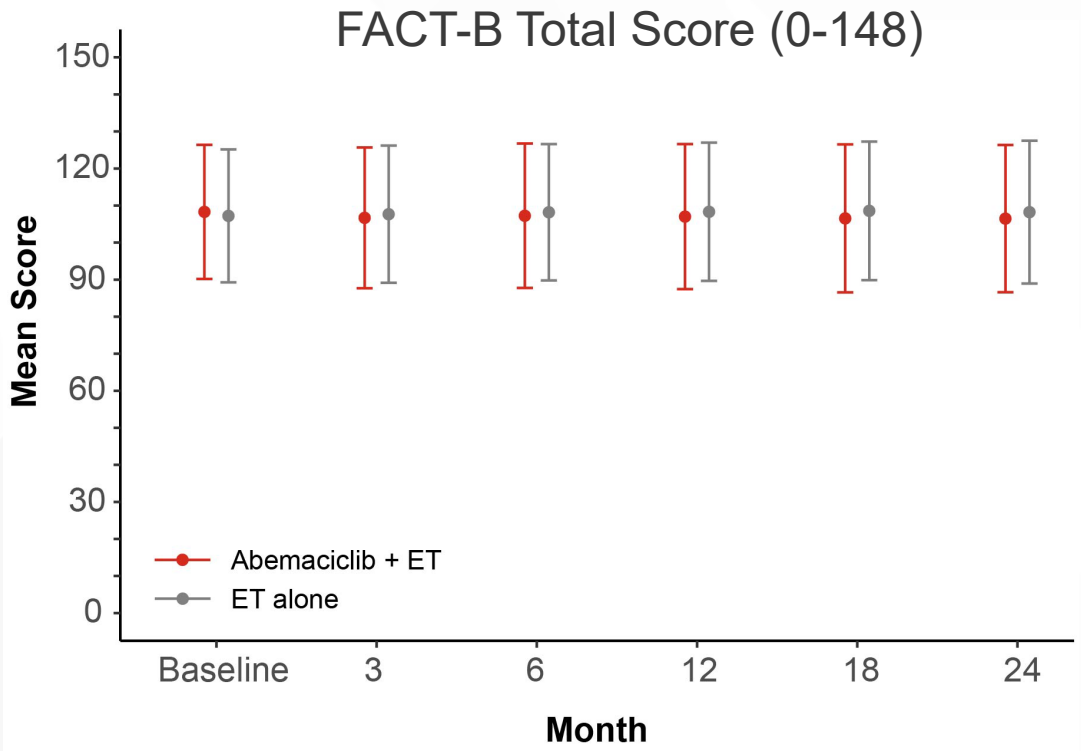
| | Ribociclib + ET | ET Alone | HR |
|---|---|---|---|
| 3-year iDFS rate, % | 93.2 | 90.6 | 0.72 |
| 3-year DRFS rate, % | 96.3 | 92.5 | 0.58 |
| 3-year DDFS rate, % | 94.3 | 91.5 | 0.70 |

AXIS Medical Education

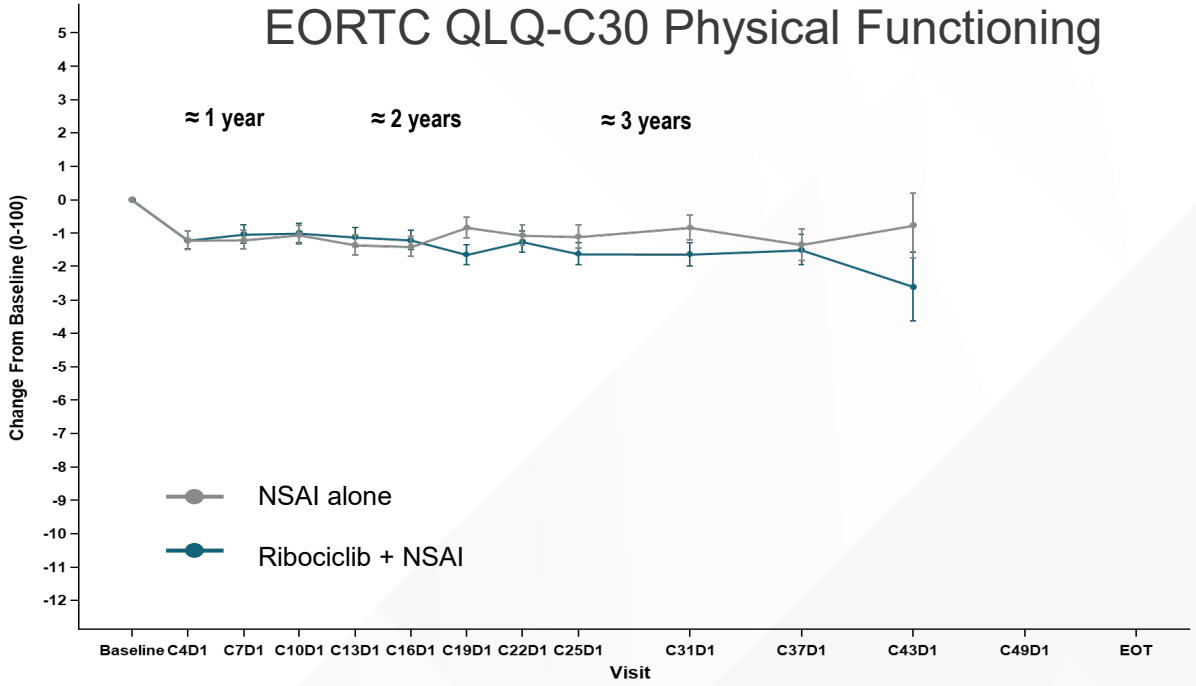
Yardley DA, et al. *J Clin Oncol*. 2024; https://doi.org/10.1200/JCO.2024.42.16_suppl.512.
iDFS, invasive disease-free survival; DRFS, distant recurrence-free survival; DDFS, distant disease-free survival.

# Adjuvant CDK 4/6 Inhibitors in ER+ EBC
# QOL Scores Maintained Over Time on Treatment

## MONARCH-E




## NATALEE




Harbeck N, et al. ESMO Breast Cancer Congress 2023. Abstract 93MO. Fasching P. Virtual Plenary 2023.

CDK, cyclin-dependent kinase; FACT-B, Functional Assessment of Cancer Therapy - Breast; EBC, early breast cancer; EORTC, European Organisation for Research and Treatment of Cancer; ER, estrogen receptor; ET, endocrine therapy; QLQ-C30, EORTC Quality of Life Group Core Questionnaire; QOL, quality of life.

# CDK4/6 Inhibitors in Early Breast Cancer Summary

| CDK4/6 Inhibitor | Trial | Approval/Status |
|---|---|---|
| **Abemaciclib** | monarchE | FDA-approved with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with HR+, HER2-, node-positive, early breast cancer at high risk of recurrence.<br>• High risk: either ≥4 pALN or 1-3 pALN and either tumor grade 3 or a tumor size ≥50 mm<br>• Previously approved for the above high-risk population with the additional requirement of having a Ki-67 score ≥20%. Ki-67 testing requirement now removed |
| **Ribociclib** | NATALEE | FDA-approved with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor HR+, HER2- stage II and III early breast cancer at high risk of recurrence.<br>The FDA also approved the ribociclib and letrozole co-pack for the same indication. |
| **Palbociclib** | PALLAS<br>Penelope-B | Palbociclib did not show a benefit in this setting |

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FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-expands-early-breast-cancer-indication-abemaciclib-endocrine-therapy; FDA.gov. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-kisqali-aromatase-inhibitor-and-kisqali-femara-co-pack-early-high-risk-breast-cancer?utm_medium=email&utm_source=govdelivery.Gradishar WJ, et al. NCCN Guidelines. Breast Cancer. Version 2.2024. Hamilton EP, et al. ASCO 2023. Abstract 501. Slamon D, et al. ASCO 2023. Abstract LBA500. Loibl S, et al. *J Clin Oncol.* 2021;39(14):1518-1530. Gnant M, et al. *J Clin Oncol.* 2022;40(3):282-293.
CDK, cyclin-dependent kinase; EBC, early breast cancer; FDA, Food and Drug Administration; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; pALN, pathologic axillary lymph nodes.

# Other Ongoing Randomized Phase III Trials of CDK4/6 Inhibitors in HR+/HER2- eBC

## POETIC-A (NCT04584853)

**Target N = 2500**

**Patient Population**: Postmenopausal and high baseline Ki-67 ≥20% or predicted Ki-67 ≥8% after 2 wk of AI therapy by clinicopathologic factors

Randomization of patients with Ki-67 ≥8% after 2 wk of AI therapy given prior to surgery

**Regimen:**
ET alone **VS** ET + abemaciclib

## ADAPTcycle (NCT04055493)

**N = 1670**

**Patient Population:** Pre/postmenopausal with intermediate risk: RS ≤25 and $Ki67_{postendocrine}$>10%, RS >25 and $Ki67_{postendocrine}$<10% in p/cN0-1 pts, or RS ≤25 and $Ki67_{postendocrine}$<10% in c/pN2-3 pt

Preoperative ET

**Regimen:**
ET + ribociclib → adjuvant ET **VS**
SoC chemotherapy → adjuvant ET

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ClinicalTrials.gov. NCT04584853. ClinicalTrials.gov. NCT04055493.
AI, aromatase inhibitor; CDK, cyclin-dependent kinase; eBC, early breast cancer; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; p/cN, pathological/clinical node; RS, recurrence score; SoC, standard of care.

# Adverse Events Related to CDK4/6 Inhibitor Therapies and ET

Ribociclib was associated with higher rates of hematological toxicity, primarily neutropenia, and liver—related adverse events

Abemaciclib was associated with a high rate of gastrointestinal toxicities, primarily diarrhea (grade 1–2)

Adjuvant abemaciclib has a tolerable safety profile with symptoms that are reversible and can be managed by dose reductions without compromising efficacy

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Rastogi P, et al. *J Clin Oncol*. 2024;42(9):987-993.
CDK, cyclin-dependent kinase; ET, endocrine therapy.

# Monitoring and Managing Common Adverse Events

## Diarrhea

- Take action immediately at the first signs of symptoms
  1. Start an over-the-counter anti-diarrheal and call your doctor
  2. Stay hydrated and drink clear fluids
  3. Watch for improvement and follow up with your doctor
- Dietary suggestions
  - Eat smaller meals more frequently
  - Choose foods that are easy to digest
    - Look for soft, bland foods
    - Eat foods that are high in sodium and potassium
  - Avoid:
    - Dairy products
    - High-fiber foods
    - Fatty or greasy foods
    - Spicy foods
    - Sugar-free candy or gum made with sugar alcohol
    - Food or drinks that have caffeine
    - Alcoholic drinks
    - Food or drinks that are too hot or too cold

## Neutropenia and Liver Problems

- CBCs: Monitor complete blood counts prior to the start of therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated
- LFTs: Monitor ALT, AST, and serum bilirubin prior to the start of therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated

**Generally managed by dose adjustments**

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VERZENIO (abemaciclib). Prescribing information. Eli Lilly and Company; 2024.
KISQALI (ribociclib). Prescribing information. Novartis; 2023.
ALT, alanine transaminase; AST, aspartate transaminase; CBC, complete blood count; LFT, liver function test.

# Summary: HR+ eBC

- Adjuvant abemaciclib reduces risk of recurrence by one-third in high-risk HR+ breast cancer and should be considered for patients meeting monarchE eligibility
  - LN ≥4 OR 1-3+ LNs and T ≥5 cm or grade 3
  - Benefit seen in patients with both low and high Ki-67 tumors
- Ribociclib is now also FDA-approved in combination with an aromatase inhibitor for the adjuvant treatment of adults with HR+/HER2- stage II and III early breast cancer at high risk of recurrence
- Olaparib is the preferred standard adjuvant therapy for *gBRCA*m patients
- Trials ongoing to evaluate the role of SERDs in the immediate and extended adjuvant settings

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eBC, early breast cancer; gBRCAm, germline BRCA-mutated; HR, hormone receptor; LN, lymph node; SERD, selective estrogen receptor degrader; T, tumor.

# Racial/Ethnic Disparities Among Minority Patients With HR+/HER2− BC

# Improving Health Outcomes of Racial/Ethnic Minorities

- BC mortality has been steadily decreasing for the past few decades
- However, there are persistent racial and ethnic disparities in US outcomes
  - Black patients have a 40% higher mortality rate compared to White patients
  - BC is the leading cause of cancer death for Black and Hispanic women
  - Black patients have higher mortality rates for HR+/HER2− BC compared to other subgroups

*"Increased frequency of non-luminal A/high risk of recurrence breast tumors coupled with suboptimal provision of prognostic tests and adjuvant treatment contribute significantly to the higher mortality rates in Black compared to White women with breast cancer."*

– Lovejoy et al, 2023

- Unconscious or implicit bias refers to associations or attitudes that reflexively alter our perceptions, thereby affecting behavior, interactions, and decision-making.
  - May influence the way information about an individual is processed, leading to unintended disparities
- Implementing organizational and individual strategies to recognize and mitigate unconscious bias can contribute to reducing these disparities
  - Meaningful diversity training
  - Self-reflection on personal biases
  - Questioning and actively countering stereotypes
  - Mentorship and sponsorship
  - Cultural humility and curiosity
  - Intentionally diversifying experiences

AXIS Medical Education

CDC. https://www.cdc.gov/cancer/dcpc/research/articles/disparities-breast-cancer-deaths.htm. McDowell S. https://www.cancer.org/research/acs-research-news/breast-cancer-death-rates-are-highest-for-black-women-again.html. Schermerhorn MC, et al. *Ann Surg Oncol.* 2022;29(12):7652-7658. Lovejoy LA, et al. *J Environ Res Public Health.* 2023;20(4):2903. Moore JX, et al. *Breast Cancer Res Treat.* 2023;197(3):633-645. Terman E, et al. *Breast Cancer Res Treat.* 2023;200(1):75-83. O'Brien KM, et al. *Clin Cancer Res.* 2010;16(24):6100-6110. Warner ET, et al. *J Clin Oncol.* 2015;33(20):2254-2261. FitzGerald C, Hurst S. *BMC Med Ethics.* 2017;18(1):19.
BC, breast cancer; HER2, human epidermal growth factor receptor 2; HR, hormone receptor;

# Improving Health Outcomes of Racial/Ethnic Minorities

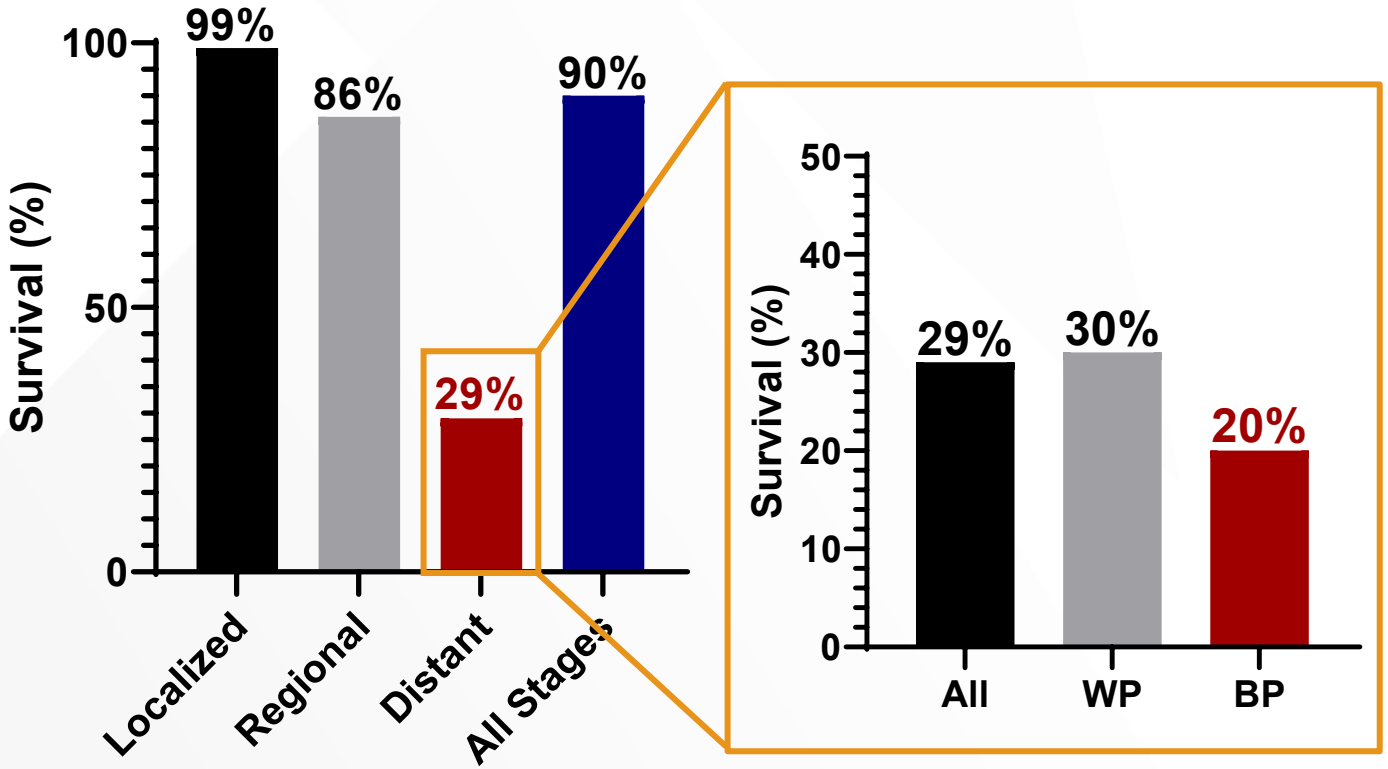
- Racial disparity in breast cancer outcomes is complex
- Various factors contribute to difference in survival rates and outcomes among Black, Hispanic, and White breast cancer patients
  - Non-biological:
    - Access to care including adherence to endocrine therapy
    - Access and engagement with screening, mammography, and molecular risk assessment
    - Delay in referral to cancer providers
  - Biological:
    - Higher incidence of non-luminal A subtypes (associated with less favorable outcomes)
    - Higher gene expression-based risk scores
    - Higher disease stage at presentation for younger patients
    - Higher 5-year recurrence risk
  - Decreased awareness of cancer risk and/or distrust of the medical system



CDC. https://www.cdc.gov/cancer/dcpc/research/articles/disparities-breast-cancer-deaths.htm. McDowell S. https://www.cancer.org/research/acs-research-news/breast-cancer-death-rates-are-highest-for-black-women-again.html. Schermerhorn MC, et al. *Ann Surg Oncol.* 2022;29(12):7652-7658. Lovejoy LA, et al. *J Environ Res Public Health.* 2023;20(4):2903. Moore JX, et al. *Breast Cancer Res Treat.* 2023;197(3):633-645. Terman E, et al. *Breast Cancer Res Treat.* 2023;200(1):75-83. O'Brien KM, et al. *Clin Cancer Res.* 2010;16(24):6100-6110. Warner ET, et al. *J Clin Oncol.* 2015;33(20):2254-2261. FitzGerald C, Hurst S. *BMC Med Ethics.* 2017;18(1):19.
BC, breast cancer.

# Distant Metastasis is the Main Reason for Cancer Related Deaths

Five-year relative survival of females with breast cancer, United States 2011-2017




**Majority of the breast cancer-related deaths are caused by DISTANT METASTASES**

**Black patients (BP) with breast cancer have 40% higher death rates compared to White patients (WP)**

Adapted from Siegel RL, et al. *CA Cancer J Clin.* 2022;72(1):7-33.
DeSantis CE, et al. *CA Cancer J Clin.* 2019;69(6):438-451.

# Black Women with ER+ Disease Have Higher Risk of Recurrence

Black race is associated with distant recurrence in ER+/HER2-, but not in TN or HER2+ disease

## Randomized Adjuvant Breast Cancer Trials

| Study/Cohort | No. | Black | Stage | Black race and risk of recurrence |
|---|---|---|---|---|
| **E1199 (NCT00004125)**<br>Sparano JA, et al. *J Natl Cancer Inst*., 2012 | 4,817 | 405 (8.4%) | II-III | ↑**1.58-fold** (p=0.002) in ER+/HER2- disease |
| **E5103 (NCT00433511)**<br>Schneider BP, et al. *JCO Precision Oncol*., 2017 | 2,859 | 386 (13.5%) | II-III | ↑**1.5-fold** (p=0.027) in ER+/HER2- disease |
| **Montefiore-Einstein cohort**<br>Kabat GC, et al. *J Racial Ethn Health Disparities*, 2017 | 3,890 | 1,394 (35.8%) | I-III | ↑**1.84-fold** (p<0.05) in ER+/HER2- disease |

↑ Increased

AXIS Medical Education

Sparano JA, et al. *J Natl Cancer Inst.* 2012;104(5):406-414. Schneider BP, et al. *JCO Precis Oncol.* 2017;2017:PO.17.00059.
Kabat GC, et al. *J Racial Ethn Health Disparities.* 2017;4(6):1181-1188.
ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; TN, triple-negative.

# Case-Based Learning Lab

# Case Study Patient Presentation and History

- A 48-year-old premenopausal Black woman palpated a mass in her right breast
- Imaging revealed a 3.5 cm mass
- Biopsy demonstrated a grade 2 invasive lobular carcinoma, ER 95%, PR 95%, HER2 1+
- An enlarged node was noted on axillary ultrasound and FNA was positive for malignant cells
- She underwent upfront surgery and was found to have a 4.1 cm grade 2 invasive lobular cancer, with 2/7 lymph nodes

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ER, estrogen receptor; FNA, fine-needle aspiration; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

# Case Study Audience Question

What would be your next step for this patient?

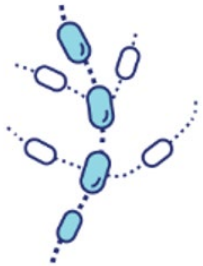
a) Ki-67 testing
b) Oncotype Dx testing
c) Start adjuvant endocrine therapy
d) Start adjuvant endocrine therapy + chemotherapy
e) Unsure

# Discussion: Risk Assessment

- What factors increase her risk of recurrence?
  - Nodal positivity
  - Grade and stage of disease
  - Positive margins
  - High proliferation rate
  - Younger age
  - HR and HER2 status
- High risk of recurrence based on:
  - Extent of nodal involvement
  - Tumor size
  - Tumor grade

**Node-Positive Patients**

4+ positive nodes



**OR**

1-3 positive nodes at least one of the following:


Tumor size ≥ 5cm

Grade 3

# Which Patients Should Be Considered for Adjuvant Abemaciclib with N+, High-Risk Early-Stage BC?

- ≥ 4 positive lymph nodes (any T, grade)
- T3, N1-3 (any grade)
- T1-2, N1-3, AND grade 3

BC, breast cancer; N, node; T, tumor.

# Risk of Early Breast Cancer Recurrence

**Approximately 20-30% of patients with eBC experience relapse[1,2]**

## Factors that affect risk of recurrence in people with eBC[3-6]:

- Young age at diagnosis
- Tumor morphology (ductal versus lobular)
- Larger tumor size
- Higher tumor grade
- Symptomatic presentation
- Presence of lymphovascular invasion
- Axillary node involvement
- Negative ER or HER2 overexpression
- Positive or close margins
- PR negativity
- High proliferation rate (eg, high Ki-67)
- Metaplastic (vs. non-metaplastic) carcinoma

AXIS Medical Education

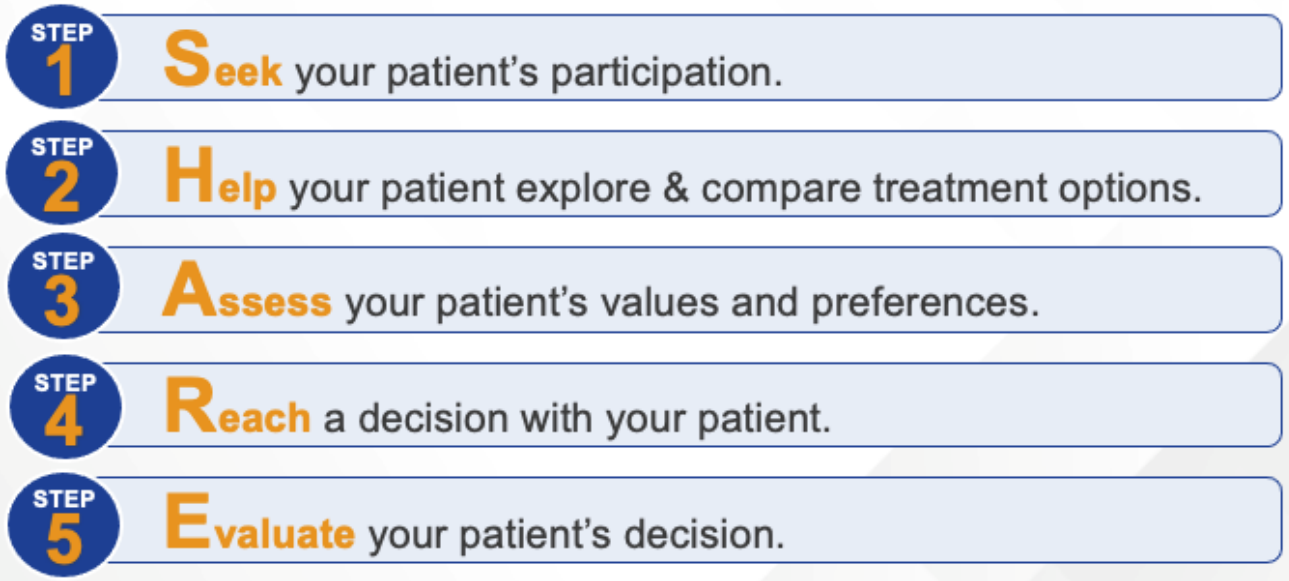
1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2005;365(9472):1687-1717. 2. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). *Lancet*. 2015;386(10001):1341-1352. 3. Győrffy B, et al. *Breast Cancer Res*. 2015;17(1):11. 4. Dang CM, Giuliano AE. *Oncology (Williston Park)*. 2011;25(10):895-899. 5. Stuart-Harris R, et al. *Breast*. 2019;44:153-159. 6. Reddy TP, et al. *Breast Cancer Res*. 2020;22(1):121.

eBC, early breast cancer; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

# Case Study Clinical Course

- Oncotype Dx Recurrence Score returned at 11
- Discussed recurrence risk, treatment options, and goals and preferences with patient
- Elected not to administer adjuvant chemotherapy and started her on leuprolide + letrozole

## SHARE Decision-Making Model

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AHRQ. The SHARE Approach. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html

# Case Study Audience Question

Would you add a CDK4/6 inhibitor?

a) Yes
b) No
c) Unsure

# Case Study Audience Question

Which CDK4/6 inhibitor would you use?

a) Abemaciclib
b) Ribociclib
c) I would not use a CDK4/6 inhibitor
d) Unsure

# Case Study Clinical Course

- You explain to the patient that adding a CDK 4/6 inhibitor to hormone therapy can reduce her risk of recurrence vs hormone therapy alone by helping to kill cancer cells left behind after surgery, chemotherapy, or radiation
  - 35% reduction in the risk of cancer returning compared with hormone therapy alone
  - Reduces risk of cancer from progressing to incurable metastatic disease

- She was started on abemaciclib
  - For the treatment of HR+, HER2–, node-positive high-risk early breast cancer, NCCN® recommends considering the addition of 2 years of abemaciclib + ET as a Category 1 treatment option
  - High risk defined as ≥4 positive lymph nodes, or 1-3 positive lymph nodes with one or more of the following: grade 3 disease, tumor size ≥5cm

- Ribociclib is now also FDA-approved
  - In combination with an aromatase inhibitor for the adjuvant treatment of adults with HR+/HER2- stage II and III early breast cancer at high risk of recurrence

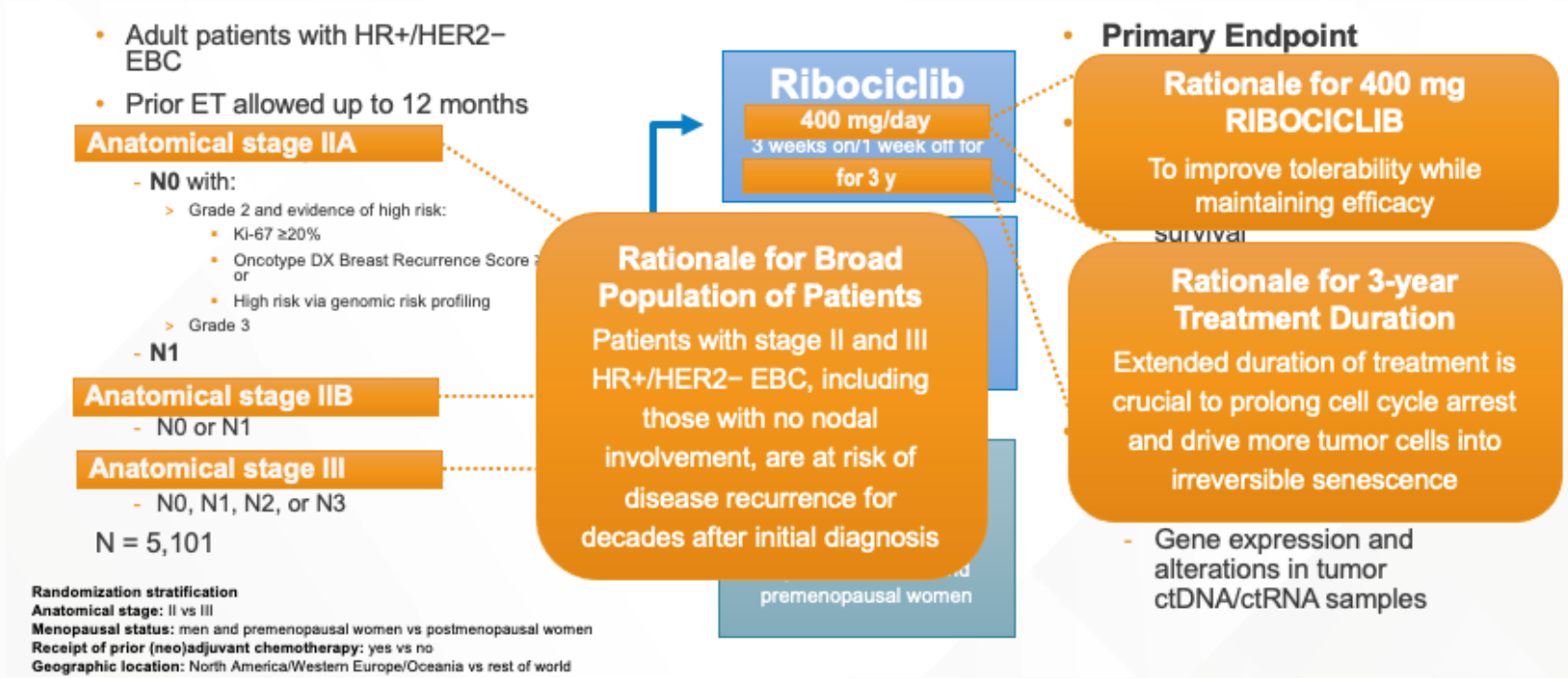
AXIS Medical Education

CDK, cyclin-dependent kinase; ET, endocrine therapy; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; NCCN, National Comprehensive Cancer Network®.

# Discussion: Choosing a CDK 4/6 Inhibitor

**When would you consider treatment with ribociclib?**

## NATALEE: Study Design Unique Features



# Case Study Audience Question

- 8 days after starting abemaciclib, the patient developed diarrhea with up to 4 bowel movements per day

- What would you do?
  a) Discontinue abemaciclib
  b) Hold abemaciclib and utilize anti-diarrheal therapy; once diarrhea is resolved, re-initiate abemaciclib at a lower dose
  c) Dose reduce abemaciclib
  d) Continue abemaciclib and use anti-diarrheal therapy
  e) Unsure

# Case Study Conclusion

- Hold abemaciclib and utilize anti-diarrheal therapy
- Once diarrhea is resolved, re-initiate abemaciclib at a lower dose

- Most cases of diarrhea with abemaciclib + ET were low grade and manageable
- Dose modifications can help improve tolerability
- Increase intake of oral fluids

# Case Study: Discussion

- How can we best address and mitigate factors surrounding racial/ethnic disparities among minority patients?
  - Higher risk of recurrent breast tumors
    - Black race is associated with distant recurrence in ER+/HER2-
  - Access to care
    - Delay in referral to cancer providers
  - Prognostic testing and risk assessment
    - Access and engagement with screening, mammography, and molecular risk assessment
  - Intervention: adjuvant treatment
  - Assessing and encouraging adherence to endocrine therapy
  - Discussing recurrence risk
    - Decreased awareness of cancer risk and/or distrust of the medical system

# Shared Decision-Making Guide


## The SHARE Decision-Making Approach

- STEP 1 SEEK your patient's participation.
- STEP 2 HELP your patient explore & compare treatment options.
- STEP 3 ASSESS your patient's values and preferences.
- STEP 4 REACH a decision with your patient.
- STEP 5 EVALUATE your patient's decision.

AHRQ. The SHARE Approach. https://www.ahrq.gov/health-literacy/professional-training/shared-decision/index.html

## Early Breast Cancer

- Disease confined within the breast and/or neighboring lymph nodes
- ~90% of breast cancer diagnoses are early breast cancer (EBC)
- ~70% of patients with EBC are HR+, HER2-
- ~20% of patients with EBC experience recurrence within 10 years
  - Risk of recurrence is highest in the first 2 years following diagnosis
  - Patients with disease recurrence have a worse prognosis
  - Patients with high-risk clinical and/or pathologic features are more likely to experience recurrence or distant metastases

Redig AJ, McAllister SS. *J Intern Med*. 2013;274(2):113-126. Wang R, et al. *BMC Cancer*. 2019;19(1):1091. Sheffield KM, et al. *Future Oncol*. 2022;18(21):2667-2682. Huppert LA, et al. *CA Cancer J Clin*. 2023;73(5):480-515. Colleoni M, et al. *J Clin Oncol*. 2016;34(9):927-935. Pan H, et al. *N Engl J Med*. 2017;377(19):1836-1846. Richman J, Dowsett M. *Nat Rev Clin Oncol*. 2019;16(5):296-311.
HER2, human epidermal growth factor receptor 2; HR, hormone receptor.

## Treatment Options for HR+/HER2- EBC

- Biomarker testing for tumor ER, PR, and HER2 status is recommended for all patients
  - Methods for testing include: PCR, NGS, FISH, and IHC
- Goal of HR+, HER2- EBC treatment: eradicate cancer and prevent disease recurrence
- Standard of care for HR+, HER2- EBC includes locoregional therapies (surgery, radiation therapy) and adjuvant/neoadjuvant systemic therapies (chemotherapy, endocrine therapy)
  - Endocrine Therapy
    - Tamoxifen, aromatase inhibitors
    - Ovarian suppression (LHRH analogues) in high risk premenopausal women
    - Extended adjuvant therapy (10 years vs. 5 years)
  - Adjuvant ET for 5 years results in a substantial reduction in the risk of local recurrence, contralateral BC, distant recurrence, and risk of death
- The addition of chemotherapy to adjuvant ET is recommended in certain patients with HR+/HER2- breast cancer based on recurrence risk
  - Molecular profiling tests help to determine whether to add chemotherapy to ET for patients with HR+/HER2- EBC
  - Gene expression assays critical in determining need for adjuvant chemotherapy:
    - The 21-gene assay (Oncotype Dx) is preferredby the NCCN® for prognosis and prediction of chemotherapy benefit
  - High risk of recurrence based on:
    - Extent of nodal involvement
    - Tumor size
    - Tumor grade
  - Clinical practice guidelines (NCCN®) recommend to consider the addition of a CDK4/6 inhibitor (abemaciclib) to systemic adjuvant ET for node-positive, high-risk, HR+/HER2- EBC patients

**Node-Positive Patients**

| 4+ positive nodes | OR | 1-3 positive nodes at least one of the following: |
|---|---|---|
| | | ≥ 5cm Tumor size ≥ 5cm; Grade 3 |

- Potential for expanding adjuvant CDK4/6 inhibitor (ribociclib) use in a broader patient population
  - Stage II and III HR+/HER2- EBC, including those with no nodal involvement

Pan H, et al. *N Engl J Med*. 2017;377(19):1836-1846. Sheffield KM, et al. *Future Oncol*. 2022;18(21):2667-2682. Johnston SRD, et al. *Lancet Oncol*. 2023;24(1):77-90. Gradishar WJ, et al. NCCN Guidelines: Breast Cancer. Version 2.2024. Markopoulos C, et al. *Eur J Surg Oncol*. 2020;46(4 Pt A):656-666. Blanchette P, et al. *Curr Oncol*. 2022;29(4):2599-2615. Harbeck N, et al. ESMO 2023. Abstract LBA17. Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:17588359231178925.
BC, breast cancer; CDK, cyclin-dependent kinase; EBC, early breast cancer; ER, estrogen receptor; ET, endocrine therapy; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; PCR, polymerase chain reaction; PR, progesterone receptor.

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# Improving Outcomes and Addressing Racial Disparities in Patients With HR+/HER2- Early Breast Cancer