CDK4/6 INHIBITORS + ET IN HR+, HER2- EARLY BREAST CANCER

THIS PRESENTATION WAS COMMISSIONED BY LILLY MEDICAL AND IS INTENDED TO BE USED BY HCPs FOR MEDICAL, SCIENTIFIC, AND EDUCATIONAL PURPOSES

Table of Contents

CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; FDA=US Food and Drug Administration; HER2=human epidermal growth factor receptor 2; HR=hormone receptor.

Learning Objectives

After reviewing this educational slide deck on key concepts in high-risk HR+, HER2- EBC, HCPs will be able to:

Address Unmet Need:
Understand the critical unmet need in the treatment of high-risk HR+, HER2- EBC and explore strategies to address these gaps in practice

Identify Patients With High-Risk:
Learn to accurately identify patients with HR+, HER2- EBC who are at high risk of disease recurrence

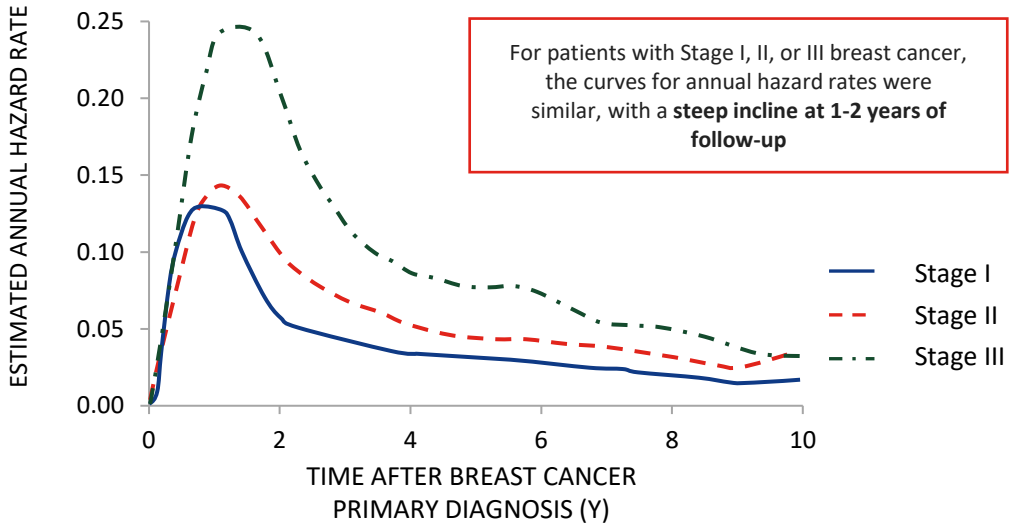
Incorporate Emerging Data Into Clinical Practice:
Gain practical insights into ongoing clinical trials involving CDK4/6i combined with ET for HR+, HER2- EBC

CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; EBC=early breast cancer; ET=endocrine therapy; HCP=healthcare provider; HER2=human epidermal growth factor receptor 2; HR=hormone receptor.

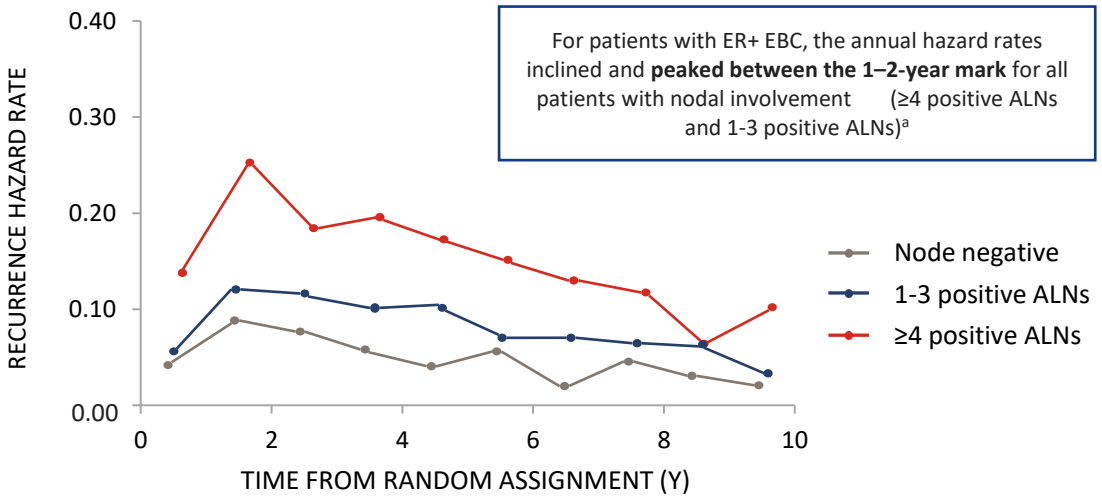
UNMET NEED IN HIGH-RISK HR+, HER2- EARLY BREAST CANCER

Risk of Recurrence Peaks Within 1-3 Years After Diagnosis in Patients With HR+, HER2- EBC

Risk of Recurrence by Stage in Patients With HR+ EBC[1]



Risk of Recurrence by Nodal Status in Patients With ER+ EBC[2]



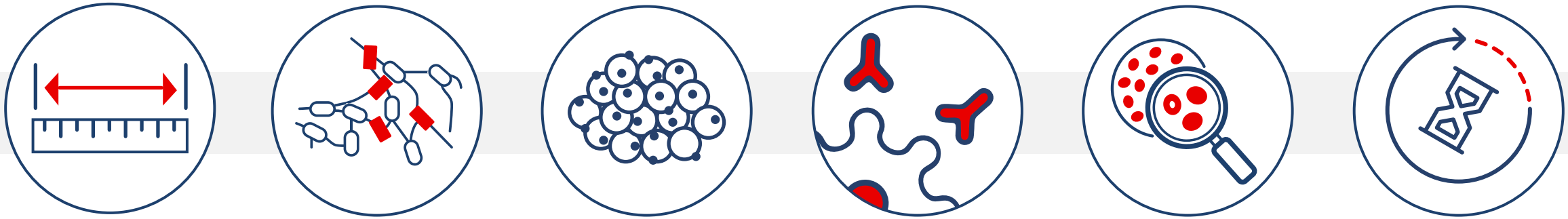
This highlights a **substantial unmet need for additional therapies** during the time when breast cancer recurrence peaks

[a]ER levels of 10 fmol/mg or greater of cytosol protein based on biochemical assay were classified as positive.
ALN=axillary lymph node; EBC=early breast cancer; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; HR=hormone receptor.
1. Cheng L, et al. *Cancer Epidemiol Biomarkers Prev*. 2012;21(5):800-809. 2. Colleoni M, et al. *J Clin Oncol.* 2016;34(9):927-935.

Identification of HR+, HER2- EBC Patients at High Risk of Disease Recurrence

Not all patients with EBC will experience recurrence. It is important to identify patients with HR+, HER2- EBC at high risk of recurrence and their **appropriate treatment** while still in the **adjuvant setting**[1]

Clinical and Pathological Factors That Influence Risk of Recurrence Include[2,3]:



- Tumor size
- Lymph node involvement
- Tumor grade
- PR and ER expression; HER2 status
- Other Biomarkers (eg, Ki-67)
- Age

EBC=early breast cancer; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; PR= progesterone receptor.

1. Johnston SRD, et al. *J Clin Oncol*. 2020;38(34):3987-3998. 2. Győrffy B, et al. *Breast Cancer Res*. 2015;17(1):11. 3. Dang CM, Giuliano AE. *Oncology (Williston Park).* 2011;25(10):895-896, 899.

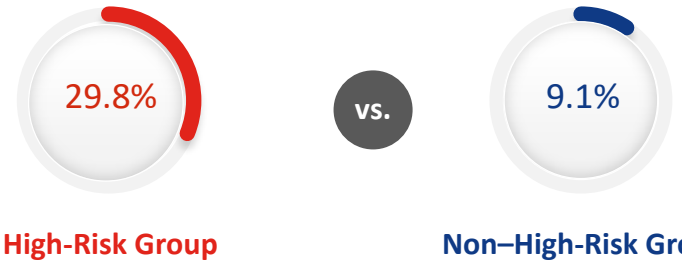
Unmet Need for Patients With HR+, HER2- EBC at High Risk of Disease Recurrence

In a real-world US study of electronic health records, approximately **14% of patients** with HR+, HER2- were classified as having node-positive, high-risk EBC[a]

High Risk vs Non–High Risk of Recurrence[a,b]

3× Patients with high-risk characteristics have a 3× higher rate of recurrence compared with those who lack these high-risk characteristics

5-Year Risk of Recurrence



Rate of Recurrence

Within **5 years** of initiating ET:

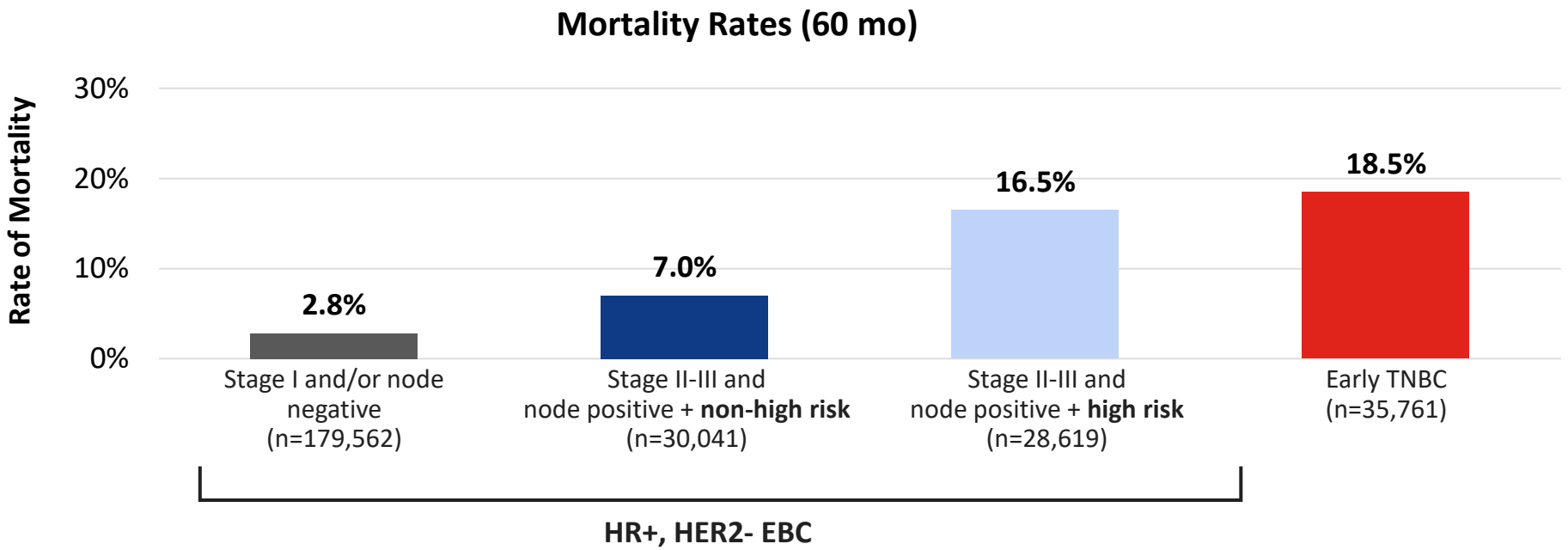
3 in 10 patients with node-positive, high-risk HR+, HER2- EBC will experience disease recurrence or death

[a]**High risk was based on monarchE inclusion criteria: ≥4 positive ALNs, or 1-3 positive ALNs and ≥1 of the following: Grade 3, tumor size ≥5 cm, or Ki-67≥20% . In this study, more than 1 in 10 patients with HR+, HER2- EBC have high-risk features.** [b]IDFS rate was used to calculate risk of recurrence.
ALN=axillary lymph node; EBC=early breast cancer; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IDFS=invasive disease-free survival.
Sheffield KM, et al. *Future Oncol.* 2022;18(21):2667-2682.

Patients With Node-Positive, High-Risk HR+, HER2- EBC Have a 5-Year Mortality Risk Similar to Patients With Early TNBC

A 5-year study of Surveillance, Epidemiology, and End Results data (SEER, 2010-2015) found that patients with node-positive, HR+, HER2- EBC who met clinical-pathological high-risk criteria had nearly the same high risk of mortality as patients with early TNBC

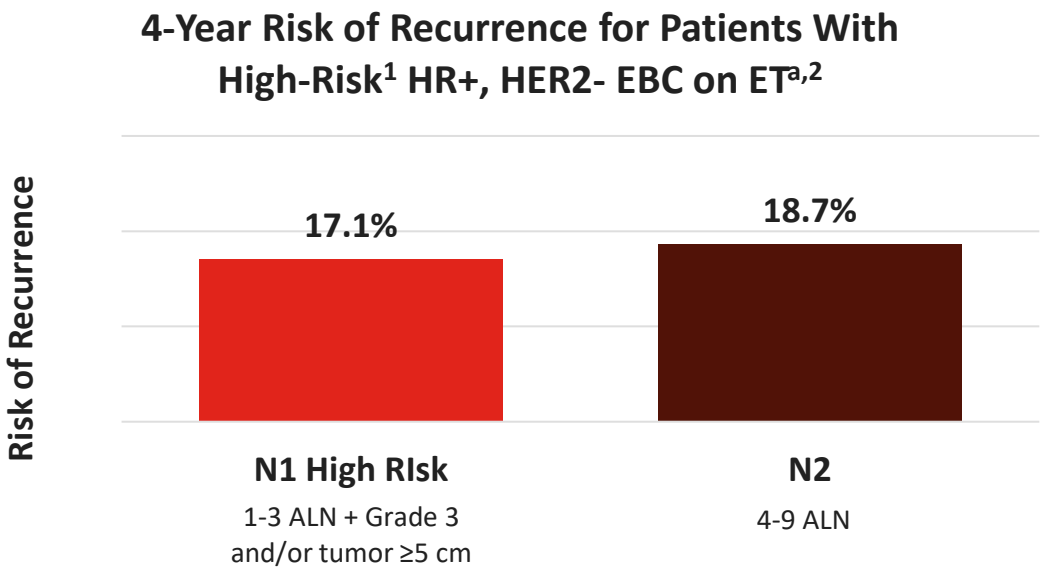
High risk was based on monarchE inclusion criteria: ≥4 positive ALNs, or 1-3 positive ALN and at least one of the following: Grade 3 or tumor size ≥5 cm



ALN=axillary lymph node; EBC=early breast cancer; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; TNBC= triple-negative breast cancer.

Nelson D, et al. *PLoS One.* 2022;17(2):e0264637.

Similar Risk of Recurrence in N1 High-Risk and N2 Disease in HR+, HER2- EBC



At a median follow-up of 54 months, the 4-year risk of recurrence for patients with HR+, HER2- EBC and **N1 high-risk disease was similar to** that for patients with **N2 disease**

These data highlight the **comparable risk of recurrence in the N1 high-risk and N2 populations** and the similar need for additional treatments

[a]**The risk of recurrence was calculated from the 4-year IDFS rates of Cohort 1 from the monarchE trial, where high risk was defined as: ≥4 positive ALNs, or 1-3 positive ALNs and at least one of the following: Grade 3 or tumor size ≥5 cm.**

ALN=axillary lymph node; EBC=early breast cancer; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IDFS=invasive disease-free survival; N=node.

1. Fasching PA, et al. *Geburtshilfe Frauenheilkd*. 2024;84(2):164-184. 2. Rastogi P, et al. *J Clin Oncol.* 2024;42(9):987-993.

HR+, HER2- EBC and Risk of Recurrence: Summary

Despite the benefits of SOC therapies for HR+, HER2- EBC, patients may still be at risk for recurrence[1,2]

Patients with node-positive and node-negative, high-risk HR+, HER2- EBC may be at risk for disease recurrence[3,4]

Patients with node-positive, high-risk clinicopathological features have 3× higher rate of recurrence than those who lack high-risk features[1]

Proper identification of patients at high risk of recurrence is vital to select appropriate therapy while in the adjuvant setting[5]

EBC=early breast cancer; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; SOC=standard of care.

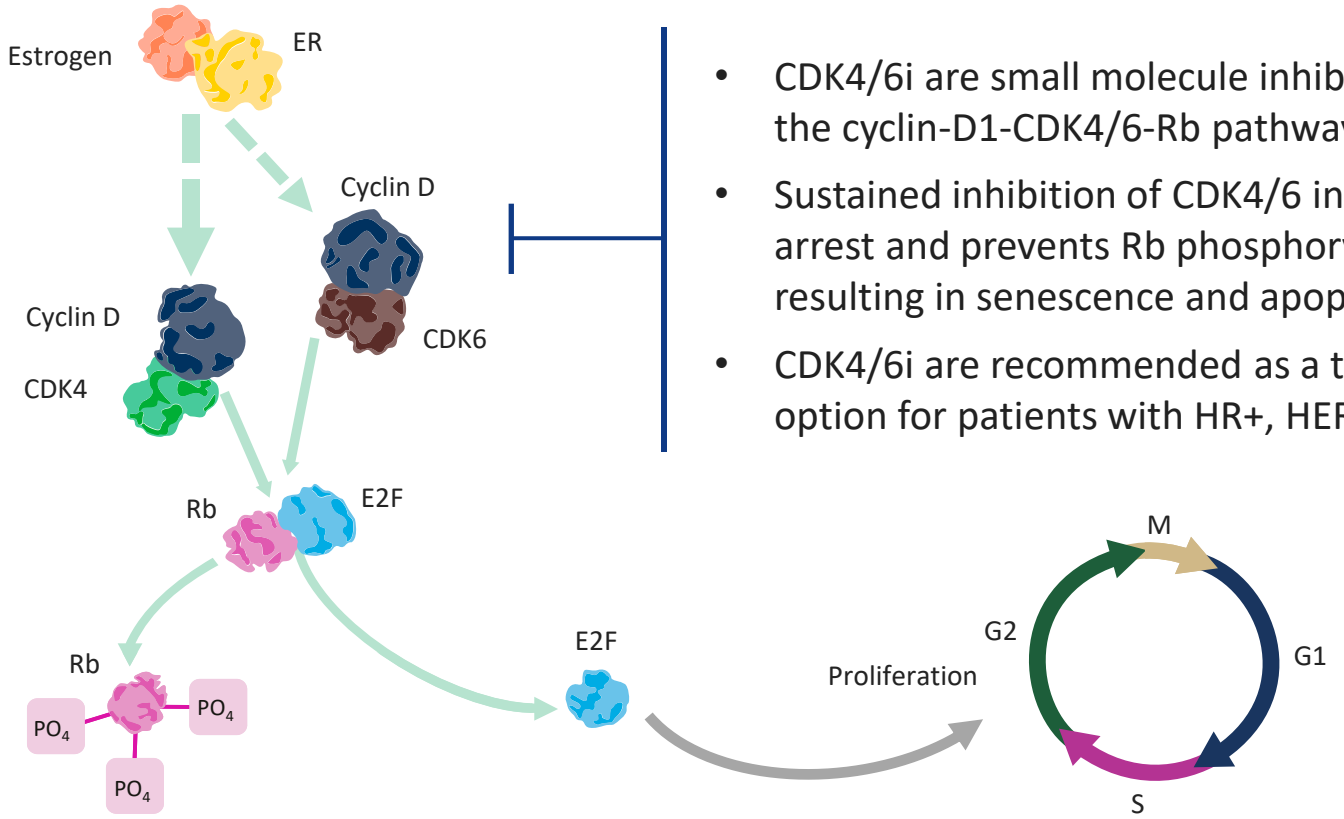
1. Sheffield KM, et al. *Future Oncol.* 2022;18(21):2667-2682. 2. Burstein HJ, et al. *Ann Oncol*. 2021;32(10):1216-1235. 3. Colleoni M, et al. *J Clin Oncol.* 2016;34(9):927-935.
4. Nelson D, et al. *PLoS One.* 2022;17(2):e0264637. 5. Fasching PA, et al. *Geburtshilfe Frauenheilkd*. 2024;84(2):164-184.

THE USE OF CDK4/6i IN HR+, HER2- EARLY BREAST CANCER

CDK4/6i in Breast Cancer: Mechanism of Action

Activation of CDK4 and CDK6 through the cyclin D1-CDK4/6-Rb pathway leads to cellular proliferation[1]

This pathway is deregulated in most tumors[1,2]



- CDK4/6i are small molecule inhibitors that target the cyclin-D1-CDK4/6-Rb pathway[1,3]
- Sustained inhibition of CDK4/6 induces cell cycle arrest and prevents Rb phosphorylation, resulting in senescence and apoptosis[3,4]
- CDK4/6i are recommended as a treatment option for patients with HR+, HER2- MBC[1]

Recently, CDK4/6i have emerged as a new treatment option in the EBC setting in combination with adjuvant ET[1]

CDK4/6=cyclin-dependent kinase 4/6; CDK4/6i=CDK4/6 inhibitor; E2F=E2F transcription factor; EBC=early breast cancer; ER=estrogen receptor; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; M, G1, S, G2=phases of the cell cycle; MBC=metastatic breast cancer; PO_4=phosphate; Rb=retinoblastoma protein.

1. Braal CL, et al. *Drugs*. 2021;81(3):317-331. 2. Vermeulen K, et al. *Cell Prolif.* 2003;36(3):131-149. 3. Schettini F, et al. *Front Oncol*. 2018;8:608. 4. Torres-Guzmán R, et al. *Oncotarget*. 2017;8(41):69493-69507.

CDK4/6i in HR+, HER2- EBC: Trial Designs

	PENELOPE-B[a,1-4]	PALLAS[a,5-8]	monarchE[b,9-11]	NATALEE[b,12-14]
CDK4/6i	Palbociclib		Abemaciclib	Ribociclib
Design	Phase 3, randomized, placebo-controlled	Phase 3, randomized, open label	Phase 3, randomized, open label	Phase 3, randomized, open label
Sample size	1250	5796	5637	5101
Study population	High risk by CPS-EG score (Select Stage IIB-III)	Stage II-III	Stages IB-III Node positive, high risk N1/N1mi + Grade 3 and/or tumor ≥5 cm, N2/N3	Stage II-III Node positive and N0 (Select higher-risk Stage IIA N0)
CDK4/6i dose	Palbociclib 125 mg QD (3 wk on/1 wk off) + ET (Continuous dosing)	Palbociclib 125 mg QD (3 wk on/1 wk off) + ET (Continuous dosing)	Abemaciclib 150 mg BID + ET (Continuous dosing)	Ribociclib 400 mg QD (3 wk on/1 wk off) + NSAI (Continuous dosing)
ET partner	Physician's choice (Tamoxifen or AI)	Physician's choice (Tamoxifen or AI)	Physician's choice (Tamoxifen or AI)[c]	NSAI (Letrozole or anastrozole)[d]
Duration of CDK4/6i treatment	1 year	2 years	2 years	3 years
First results reported	2020	2020	2020	2023
Primary endpoint	Invasive Disease-Free Survival (IDFS)			

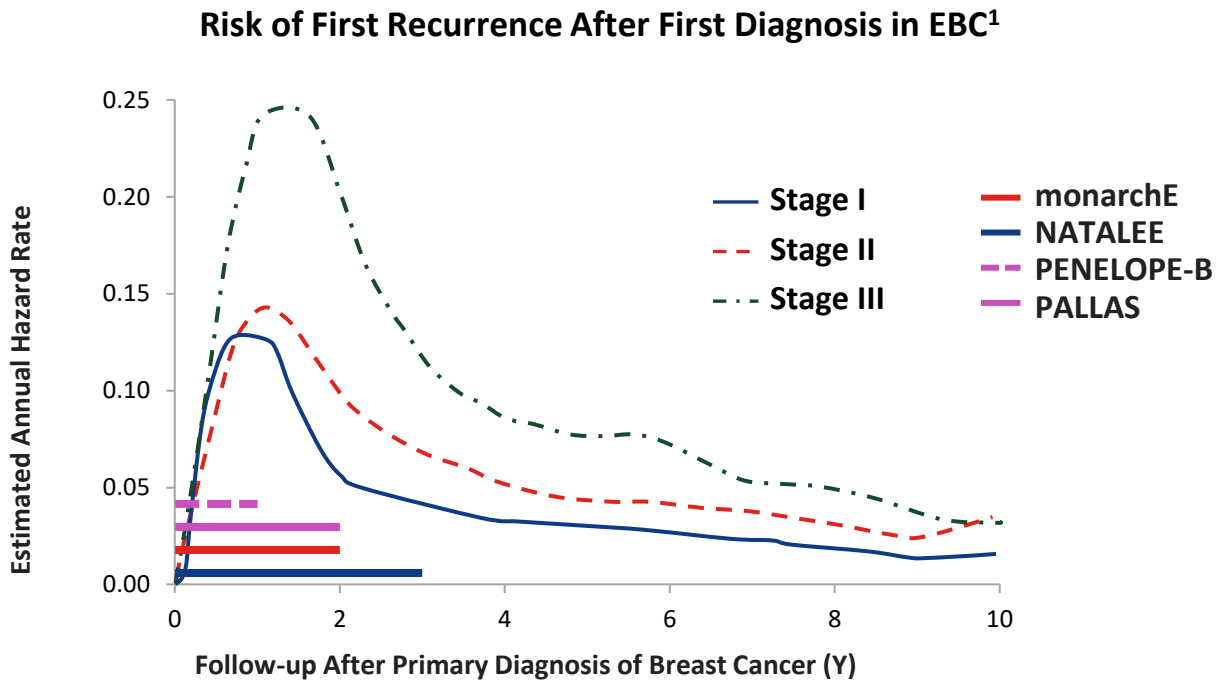
Note: The table above is not intended as a head-to-head trial comparison. Cross-trial comparison of efficacy, tolerability, and safety cannot be made.

These trials were conducted in patients with HR+, HER2- EBC who had an increased risk of recurrence.
The trials differed in **study design**, **patient populations**, and **treatment durations**

[a]Trial did not meet statistical significance. [b]Trial met statistical significance. [c]With or without ovarian suppression per standard practice.
[d]NSAI was investigator choice; men and premenopausal women also received LHRH agonists as per standard of care.
AI=aromatase inhibitor; BID=twice a day; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; CPS-EG=pretreatment clinical and posttreatment pathological stage, estrogen-receptor status and grade; EBC=early breast cancer; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IDFS=invasive disease-free survival; LHRH=luteinizing hormone-releasing hormone; N=node; NSAI=nonsteroidal aromatase inhibitor; mi=micrometastases; QD=once daily.

1. https://www.clinicaltrials.gov/ct2/show/NCT01864746. (Accessed April 24, 2023). 2. https://www.pfizer.com/news/press-release/press-release-detail/penelope-b-trial-ibrancer-palbociclib-early-breast-cancer. (Accessed April 3, 2024). 3. Loibl S, et al. *J Clin Oncol.* 2021;39(14):1518-1530. 4. Loibl S, et al. Oral presentation at: *SABCS 2020*. Abstract GS1-02. 5. https://www.clinicaltrials.gov/ct2/show/NCT02513394. (Accessed April 3, 2024). 6. https://investors.pfizer.com/Investors/News/news-details/2020/Pfizer-Provides-Update-on-Phase-3-PALLAS-Trial-of-IBRANCE-palbociclib-Plus-Endocrine-Therapy-in-HR-HER2--Early-Breast-Cancer-05-29-2020/default.aspx. (Accessed September 24, 2023). 7. Mayer EL, et al. *Lancet Oncol.* 2021;22(2):212-222. 8. Mayer E, et al. Oral presentation at: *ESMO 2020*. Abstract LBA12. 9. https://www.clinicaltrials.gov/ct2/show/NCT03155997. (Accessed April 4, 2024). 10. Rastogi P, et al. Oral presentation at: *SABCS 2020.* Abstract GS1-01. 11. Johnston SRD, et al. *J Clin Oncol.* 2020;38(34):3987-3998. 12. https://clinicaltrials.gov/study/NCT03701334. (Accessed March 4, 2024). 13. Slamon DJ, et al. *ASCO 2023.* Abstract LBA500. 14. Slamon D, et al. *N Engl J Med*. 2024;390(12):1080-1091.

CDK4/6i in HR+, HER2- EBC: Duration of Treatment



CDK4/6i trials in EBC have focused on **1-3 years** of adjuvant treatment, during the time when **recurrence peaks**[2-5]

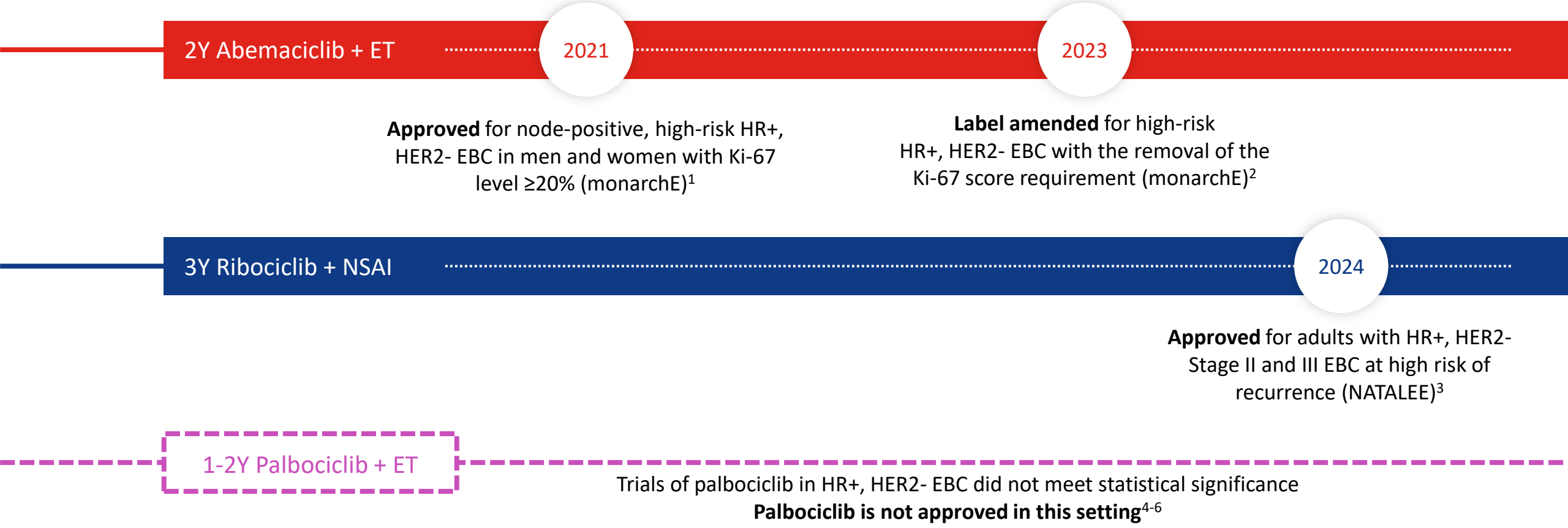
	PENELOPE-B[2]	PALLAS[3]	monarchE[4]	NATALEE[5]
CDK4/6i	Palbociclib		Abemaciclib	Ribociclib
Duration of CDK4/6i treatment	1 year	2 years	2 years	3 years

Note: The table above is not intended for comparison as the information is not from any head-to-head trials. Cross-trial comparison of efficacy, tolerability, and safety cannot be made.

CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; EBC=early breast cancer; HER2=human epidermal growth factor receptor 2; HR=hormone receptor.

1. Cheng L, et al. *Cancer Epidemiol Biomarkers Prev*. 2012;21(5):800-809. 2. https://clinicaltrials.gov/study/NCT01864746. (Accessed July 16, 2024). 3. https://clinicaltrials.gov/study/NCT02513394. (Accessed July 16, 2024). 4. https://clinicaltrials.gov/study/NCT03155997. (Accessed July 16, 2024). 5. https://clinicaltrials.gov/study/NCT03701334. (Accessed July 16, 2024).

CDK4/6i in HR+, HER2- EBC: Timeline of FDA Approvals

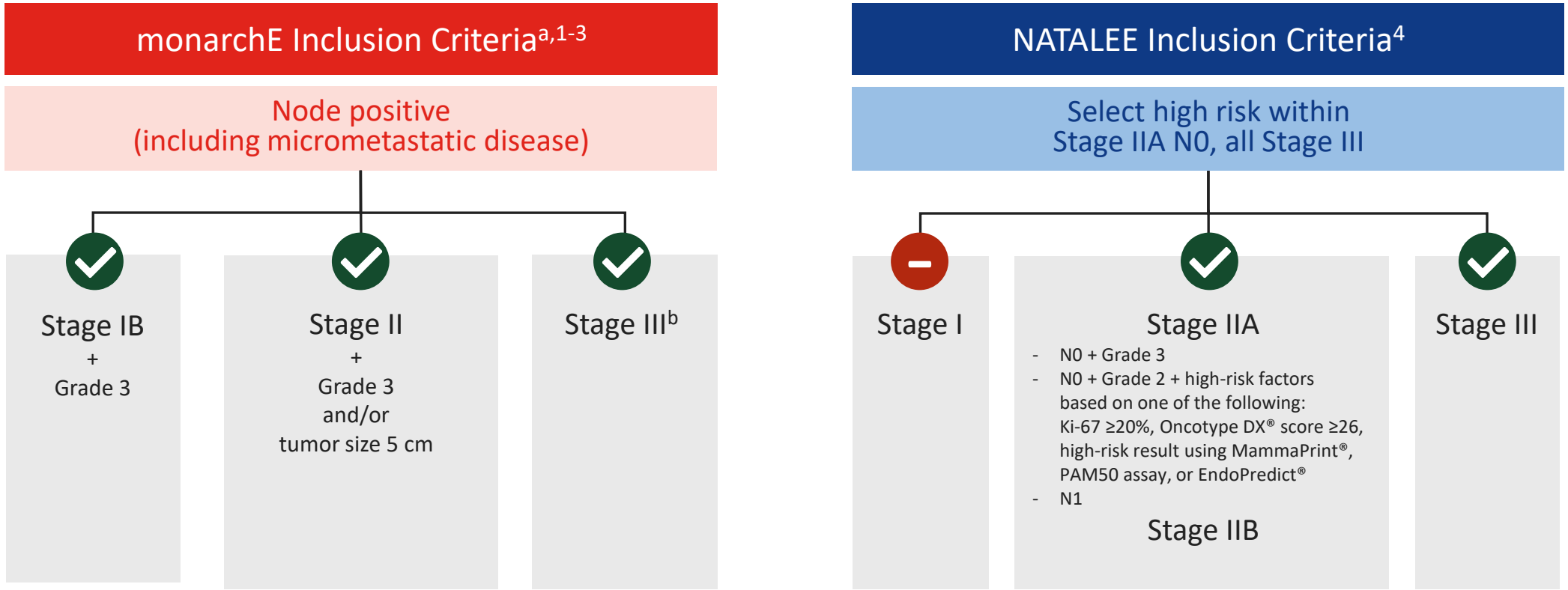


CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; EBC=early breast cancer; ET=endocrine therapy; FDA=US Food and Drug Administration; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; NSAI=nonsteroidal aromatase inhibitor.

1. https://investor.lilly.com/news-releases/news-release-details/fda-approves-verzenior-abemaciclib-first-and-only-cdk46. (Accessed April 4, 2024). 2. https://investor.lilly.com/news-releases/news-release-details/us-fda-broadens-indication-verzenior-abemaciclib-hr-her2-node. (Accessed April 3, 2024). 3. https://www.novartis.com/news/media-releases/fda-approves-novartis-kisqali-reduce-risk-recurrence-people-hrher2-early-breast-cancer. (Accessed September 21, 2024). 4. Loibl S, et al. *J Clin Oncol*. 2021;39(14):1518-1530. 5. Gnant M, et al. *J Clin Oncol*. 2022;40(3):282-293. 6. DeMichele A, et al. Oral presentation at: *ASCO 2023*. Abstract 390216.

High-Risk Criteria: monarchE and NATALEE

The criteria for defining and including patients with high-risk HR+, HER2- EBC varied across adjuvant trials



Note: This table is not intended as a head-to-head trial comparison. Cross-trial comparison of efficacy, tolerability, and safety cannot be made. All the product/company names mentioned herein are trademarks of their respective owners.

[a]Patients in monarchE were required to have at least 1 positive ALN. In monarchE, AJCC stage was derived based on pathological tumor size and number of positive lymph nodes following primary surgery.[5] Cytological evaluation of lymph node status was used where patients received NAC. [b]Stage IIIB T4N1 can be included if Grade 3 and/ or tumor ≥5 cm.

AJCC=American Joint Committee on Cancer; ALN=axillary lymph node; EBC=early breast cancer; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; N=node; NAC=neoadjuvant chemotherapy.

1. Johnston SRD, et al. *J Clin Oncol.* 2020;38(34):3987-3998. 2. Rastogi P, et al. *J Clin Oncol*. 2024;42(9):987-93; 3. Abemaciclib [US PI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2024. 4. Slamon DJ, et al. *Ther Adv Med Oncol*. 2023;15:17588359231178125. 5. Amin MB, et al. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer, 2017.

FDA Approved Populations: monarchE and NATALEE[1-6]

AJCC anatomical staging	TN (M0)	monarchE	NATALEE
Stage IB*	T1N1mi	If Grade 3	Not eligible
Stage IIA	T1N1	If Grade 3	✓
	T2N0	Not eligible	If Grade 3, or Grade 2 and Ki-67 ≥20% or high genomic risk[a]
Stage IIB	T2N1	If Grade 3 or tumor size 5 cm	✓
	T3N0	Not eligible	✓
Stage IIIA	T1N2	✓	✓
	T2N2	✓	✓
	T3N1	✓	✓
	T3N2	✓	✓
Stage IIIB	T4N0	Not eligible	✓
	T4N1	If Grade 3 or tumor size ≥5 cm	✓
	T4N2	✓	✓
Stage IIIC	Any T size, N3	✓	✓

Patients in monarchE were required to have at least 1 positive ALN. Staging in monarchE: Any patient with 1-3 ALN, regardless of the presence of micrometastases or macrometastases were designated N1 for the purposes deriving stage. Rare occult T0N1 (Stage IIA), T0N2 (Stage IIIA) breast cancers were not permitted in monarchE but were part of the inclusion criteria in NATALEE.

[a]High genomic risk was based on one of the following assays: OncotypeDX score of ≥26, Prosigna PAM50, Mammaprint or Endopredict AJCC=American Joint Committee on Cancer; ALN=axillary lymph nodes; G=grade; M=metastasis; N=node; NAC=neoadjuvant chemotherapy; T=tumor.

1. Amin MB, et al. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer, 2017. 2. Johnston SRD et al. *Lancet Oncol*. 2023; 24(1):77-90. 3. Rastogi P et al. *J Clin Oncol*. 2024;42(9):987-993. 4. Abemaciclib [US PI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2024. 5. Slamon D et al. *N Engl J Med*. 2024;390(12):1080-1091. 6. Ribociclib [US PI]. East Hanover, NJ, USA: Novartis Pharmaceuticals Corporation, 2024.

TRIALS OF FDA-APPROVED CDK4/6i IN HR+, HER2- EARLY BREAST CANCER

- monarchE
- NATALEE

Abemaciclib in EBC: FDA Prescribing Information

Abemaciclib Indication in EBC

Abemaciclib is indicated in combination with endocrine therapy (tamoxifen or an aromatase inhibitor) for the adjuvant treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive, early breast cancer at high risk of recurrence

Warnings and Precautions

The FDA label carries warnings for diarrhea, neutropenia, ILD/pneumonitis, hepatotoxicity, venous thromboembolism, and embryo-fetal toxicity

Blood count and liver function monitoring are recommended before treatment initiation, in the early treatment cycles, and as clinically indicated

EBC=early breast cancer; FDA=US Food and Drug Administration; ILD=interstitial lung disease.

Abemaciclib [US PI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2024.

Abemaciclib in EBC: Timeline of FDA Approval

2021

In **2021**, the **FDA approved abemaciclib plus ET for the adjuvant treatment** of HR+, HER2-, node-positive EBC at high risk of recurrence and a Ki-67 score ≥20%, a prespecified population in cohort 1[1]

In **2022**, monarchE 4-year data showed an improved benefit in IDFS beyond the 2-year treatment course with adjuvant abemaciclib, primarily attributed to cohort 1[2]

2023

In **2023**, the **label was amended to remove Ki-67** as a testing requirement based on the 4-year data[3]

Abemaciclib plus ET is approved for the adjuvant treatment of adult patients with HR+, HER2-, node-positive EBC at high risk of recurrence[4]

EBC=early breast cancer; ET=endocrine therapy; FDA=US Food and Drug Administration; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IDFS=invasive disease-free survival.

1. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-abemaciclib-endocrine-therapy-early-breast-cancer. (Accessed April 4, 2024). 2. Johnston SRD, et al. *Lancet Oncol.* 2023;24(1):77-90. 3. https://investor.lilly.com/news-releases/news-release-details/us-fda-broadens-indication-verzenior-abemaciclib-hr-her2-node. (Accessed April 4, 2024). 4. Abemaciclib [US PI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2024.

Abemaciclib in EBC: Guideline Recommendations

National Comprehensive Cancer Network® (NCCN®) Recommendation[1]

For the treatment of HR+, HER2-, node-positive, high-risk EBC, the NCCN recommends consideration of 2 years of abemaciclib in combination with ET as an **NCCN Category 1, Preferred** treatment option[a]

American Society of Clinical Oncology® (ASCO®) Recommendation[2,3]

Abemaciclib for 2 years plus ET for ≥5 years may be offered to patients meeting the criteria of the ITT monarchE population with resected, HR+, HER2-, node-positive EBC at high risk of recurrence[b]

The panel promotes the use of abemaciclib primarily in those who would have been eligible for monarchE based on that trial's eligibility criteria

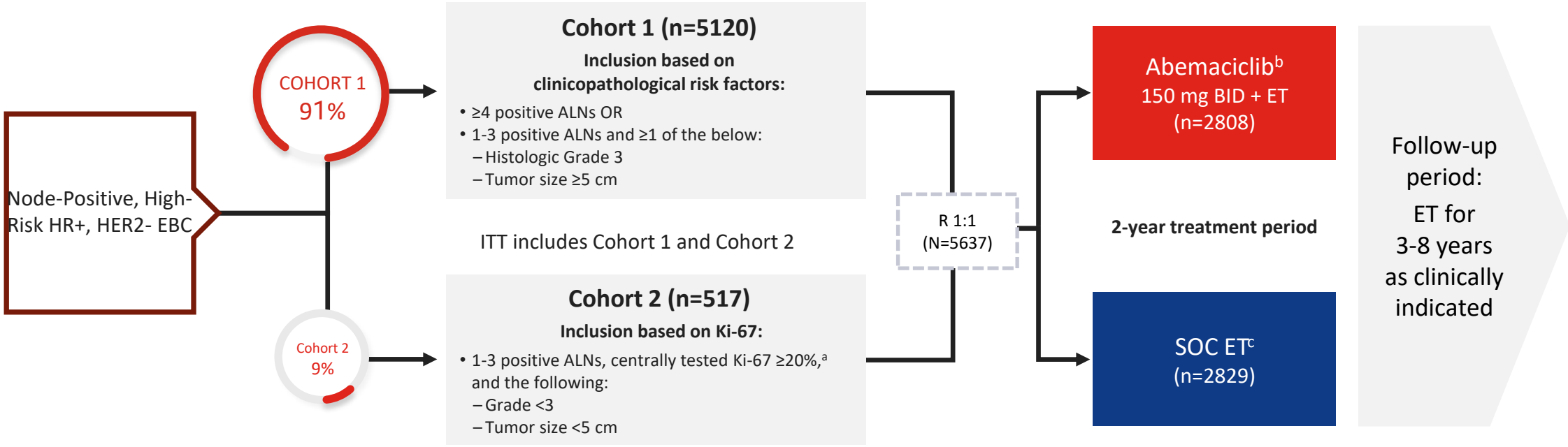
(Evidence quality: **High**; strength of recommendation: **Strong**)

[a]Based on NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer Version 6.2024. High risk is defined as ≥4 positive ALNs (confirmed preoperatively and/or at surgery), or 1-3 positive ALNs with either Grade 3 disease or tumor size ≥5 cm (on pre-operative imaging and/or at surgery). VTE risk should be considered when combining abemaciclib with tamoxifen. Category 1 is based upon high-level evidence (≥1 randomized Phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN® consensus (≥85% support of the Panel) that the intervention is appropriate. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
[b]Based on the ASCO 2024 Rapid Recommendation Update. High risk of recurrence is defined as having ≥4 positive ALNs or 1-3 positive ALNs with at least one of the following: Grade 3 disease, tumor size ≥5 cm, or Ki-67 ≥20%.
ALN=axillary lymph node; EBC=early breast cancer; ET=endocrine therapy; FDA=US Food and Drug Administration; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; ITT=intention-to-treat; VTE=venous thromboembolism.

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.6.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed November 18, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org.
2. Freedman RA, et al. *J Clin Oncol*. 2024;42(18):2233-2235. 3. Caswell-Jin JL, et al. *JCO Oncol Pract.* 2024. doi.org/10.1200/OP-24-00663 (Ahead of print).

monarchE: Study Design[1-5]

Phase 3, open-label study of abemaciclib in addition to ET in patients with high-risk, node-positive, HR+, HER2- EBC



Prior treatment:
Neoadjuvant ET was allowed. No more than 16 months from definitive breast surgery to randomization. Adjuvant ET could start any time after definitive surgery. After completion of last non-ET adjuvant treatment (surgery, chemotherapy, radiation therapy), an additional 12 weeks of adjuvant ET were allowed

Stratified for:
- Prior chemotherapy: neo(adjuvant) vs. none
- Menopausal status[d]
- Region: North America/Europe vs. Asia vs. other

Primary Objective: IDFS[e]
Secondary Objectives: IDFS in high Ki-67 index, DRFS, OS, safety, PK, PROs

[a]Ki-67 expression was centrally assessed in all patients from both cohorts with suitable untreated breast tissue using Ki-67 immunohistochemistry assay by Dako/Agilent.
[b]Treatment period was the first 2 years on study treatment after randomization. [c]ET of physician's choice (eg, AIs, tamoxifen, LHRH agonist). [d]As determined during diagnosis.
[e]The primary endpoint was met at a preplanned interim analysis with a medium follow-up of 15.5 months.
AI=aromatase inhibitor; ALN=axillary lymph node; BID=twice a day; DRFS=distant relapse-free survival; EBC=early breast cancer; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IDFS=invasive disease-free survival; ITT=intention-to-treat; LHRH=luteinizing hormone-releasing hormone; OS=overall survival; PK=pharmacokinetics; PRO=patient-reported outcome; R=randomization; SOC=standard of care.
1. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03155997. (Accessed April 24, 2023). 2. Harbeck N, et al. *Ann Oncol.* 2021;32(12):1571-1581. 3. Johnston SRD, et al. *Lancet Oncol*. 2023;24(1):77-90.
4. Rastogi P, et al. *J Clin Oncol*. 2024;42(9):987-993. 5. Abemaciclib [US PI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2024.

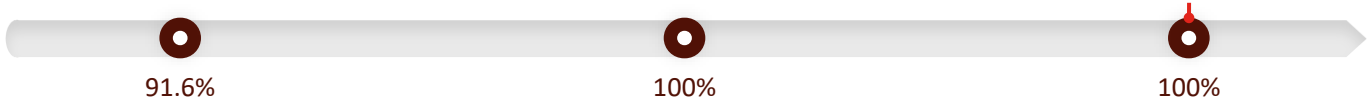
monarchE: Evolution of Data

Totality of evidence demonstrates **continuing benefit** of abemaciclib + ET for the treatment of patients with HR+, HER2- EBC at high risk of recurrence

Safety remains consistent across monarchE analyses and the known safety profile of abemaciclib + ET

Abemaciclib benefit beyond 2Y treatment period	Abemaciclib benefit improved beyond 2Y treatment period	Abemaciclib benefit continues to improve beyond 2Y treatment
28 mo mF/U[1]	**42 mo mF/U[2,3]**	**54 mo mF/U[4,5]**
32% risk reduction in IDFS	**35% risk reduction in IDFS**	**33% risk reduction in IDFS**
IDFS Hazard ratio: 0.68 (0.57-0.81)	**IDFS** Hazard ratio: 0.65 (0.57-0.75)	**IDFS** Hazard ratio: 0.67 (0.59-0.76)
DRFS Hazard ratio: 0.67 (0.55-0.81)	**DRFS** Hazard ratio: 0.65 (0.56-0.76)	**DRFS** Hazard ratio: 0.67 (0.58-0.77)
3.0% absolute benefit at 2Y	**6.9% absolute benefit at 4Y**	**7.9% absolute benefit at 5Y**
2.9% absolute benefit at 2Y	**6.1% absolute benefit at 4Y**	**7.1% absolute benefit at 5Y**

PATIENTS OFF ABEMACICLIB TREATMENT[b]



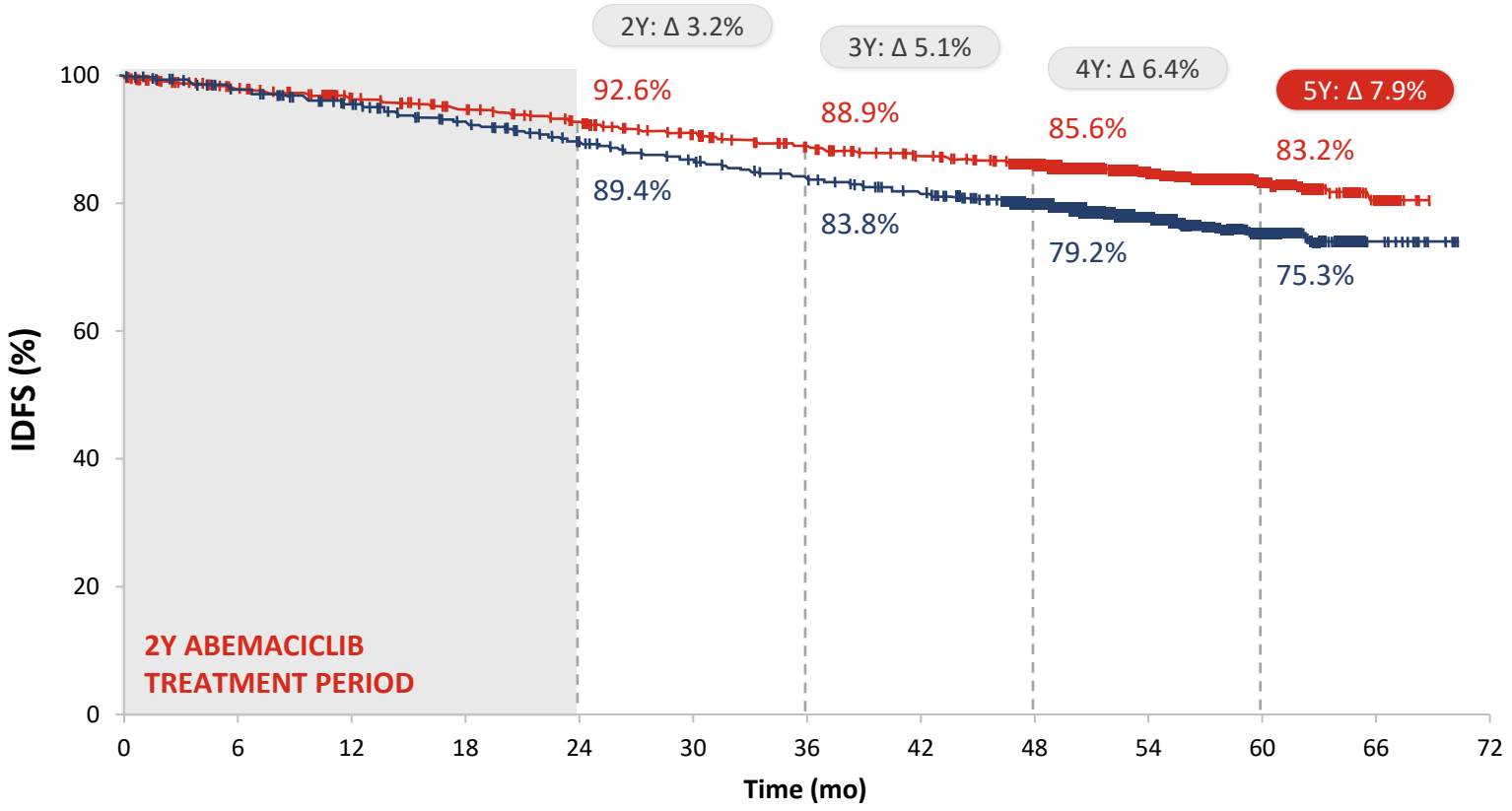
[a]**The Cohort 1 subgroup was not powered or alpha controlled for testing statistical significance.** [b]Includes patients (0.8%) who were randomized but never treated.
DRFS=distant relapse-free survival; EBC=early breast cancer; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IDFS=invasive disease-free survival; mF/U=median follow-up.

1. Toi M, et al. *Oncologist.* 2023;18;28(1):e77-e81. 2. Johnston SRD, et al. Oral presentation at: *SABCS 2022*. Abstract GS1-09. 3. Johnston SRD, et al. *Lancet Oncol.* 2023;24(1):77-90. 4. Harbeck N, et al. Oral presentation at: *ESMO Congress 2023*. Abstract LBA17. 5. Rastogi P, et al. *J Clin Oncol.* 2024;42(9):987-993.

Cohort 1

54 mo mF/U

monarchE: IDFS



No. at risk													
Abemaciclib + ET	2555	2387	2322	2256	2189	2129	2068	2006	1913	1111	490	74	0
ET	2565	2405	2328	2236	2143	2059	1979	1915	1795	1056	473	67	0

33%

REDUCTION IN THE RISK OF DEVELOPING AN IDFS EVENT[a]

Hazard ratio=0.670
(95% CI: 0.588-0.764),
nominal p<.001

# IDFS Events	Abemaciclib + ET	382
	ET Alone	553

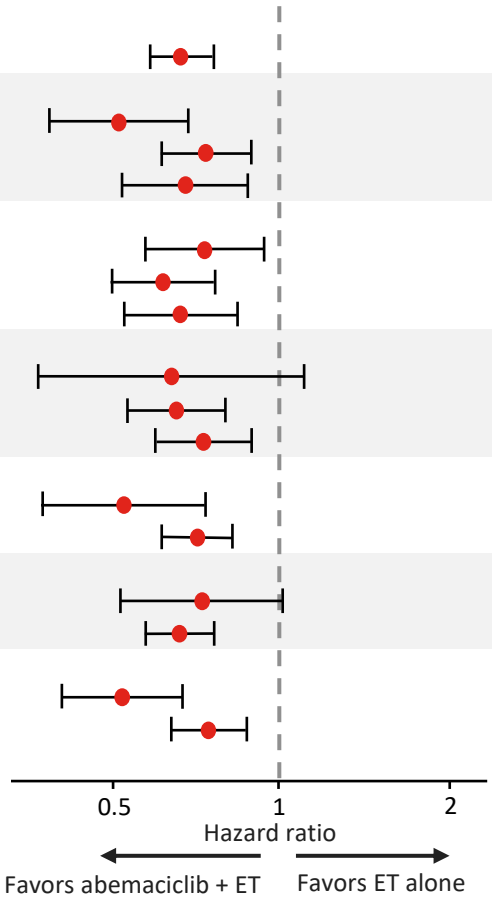
[a]**Not powered or alpha controlled for testing statistical significance.**
ET=endocrine therapy; IDFS=invasive disease-free survival; mF/U=median follow-up.
Rastogi P, et al. *J Clin Oncol*. 2024;42(9):987-993.

Cohort 1

54 mo mF/U

monarchE: IDFS for Key Prespecified Subgroups[a]

	Abemaciclib + ET		ET			
	n/Events	4Y IDFS Rate	n/Events	4Y IDFS Rate	Hazard Ratio (95% CI)	Interaction p-Value
Overall	2555/382	85.6 (84.1, 86.9)	2565/553	79.2 (77.6, 80.8)	0.670 (0.58-0.764)	
Primary tumor size						0.108
<20 mm	676/75	88.8 (86.0, 91.0)	656/136	80.5 (77.1, 83.4)	0.519 (0.391-0.688)	
≥20 mm but <50 mm	1232/197	84.7 (82.5, 86.7)	1278/270	79.7 (77.3, 81.9)	0.744 (0.619-0.894)	
≥50 mm	600/101	84.2 (80.9, 87.0)	606/142	76.6 (72.8, 79.9)	0.683 (0.529-0.882)	
Number of positive lymph nodes						0.587
1-3	873/113	87.5 (85.0, 89.6)	888/154	82.9 (80.1, 85.3)	0.733 (0.575-0.934)	
4-9	1104/142	88.1 (86.0, 90.0)	1119/229	81.3 (78.8, 83.5)	0.618 (0.501-0.762)	
10 or more	571/126	78.0 (74.2, 81.2)	552/170	68.8 (64.6, 72.7)	0.666 (0.529-0.839)	
Tumor grade						0.730
Grade 1 - favorable	186/21	89.5 (83.9, 93.3)	190/33	85.8 (79.8, 90.2)	0.640 (0.370-1.106)	
Grade 2 – moderately favorable	1181/164	86.4 (84.2, 88.3)	1193/245	80.4 (77.9, 82.6)	0.656 (0.538-0.799)	
Grade 3 – unfavorable	1063/180	83.7 (81.2, 85.8)	1050/237	77.8 (75.1, 80.3)	0.732 (0.603-0.888)	
Progesterone receptor						0.087
Negative	268/54	81.2 (75.7, 85.5)	269/97	67.3 (61.2, 72.7)	0.526 (0.377-0.733)	
Positive	2208/320	86.0 (84.4, 87.4)	2226/442	80.7 (78.9, 82.3)	0.712 (0.617-0.822)	
Tumor stage						0.635
Stage II	510/59	88.8 (85.6, 91.3)	534/84	84.2 (80.7, 87.1)	0.725 (0.519-1.011)	
Stage III	2034/322	84.8 (83.1, 86.3)	2027/468	77.9 (76.0, 79.7)	0.664 (0.576-0.765)	
First ET						0.015
Tamoxifen	783/100	87.7 (85.2, 89.9)	805/185	77.5 (74.4, 80.3)	0.522 (0.409-0.666)	
Aromatase inhibitor	1753/279	84.8 (82.9, 86.4)	1725/366	80.0 (78.0, 81.9)	0.746 (0.639-0.872)	

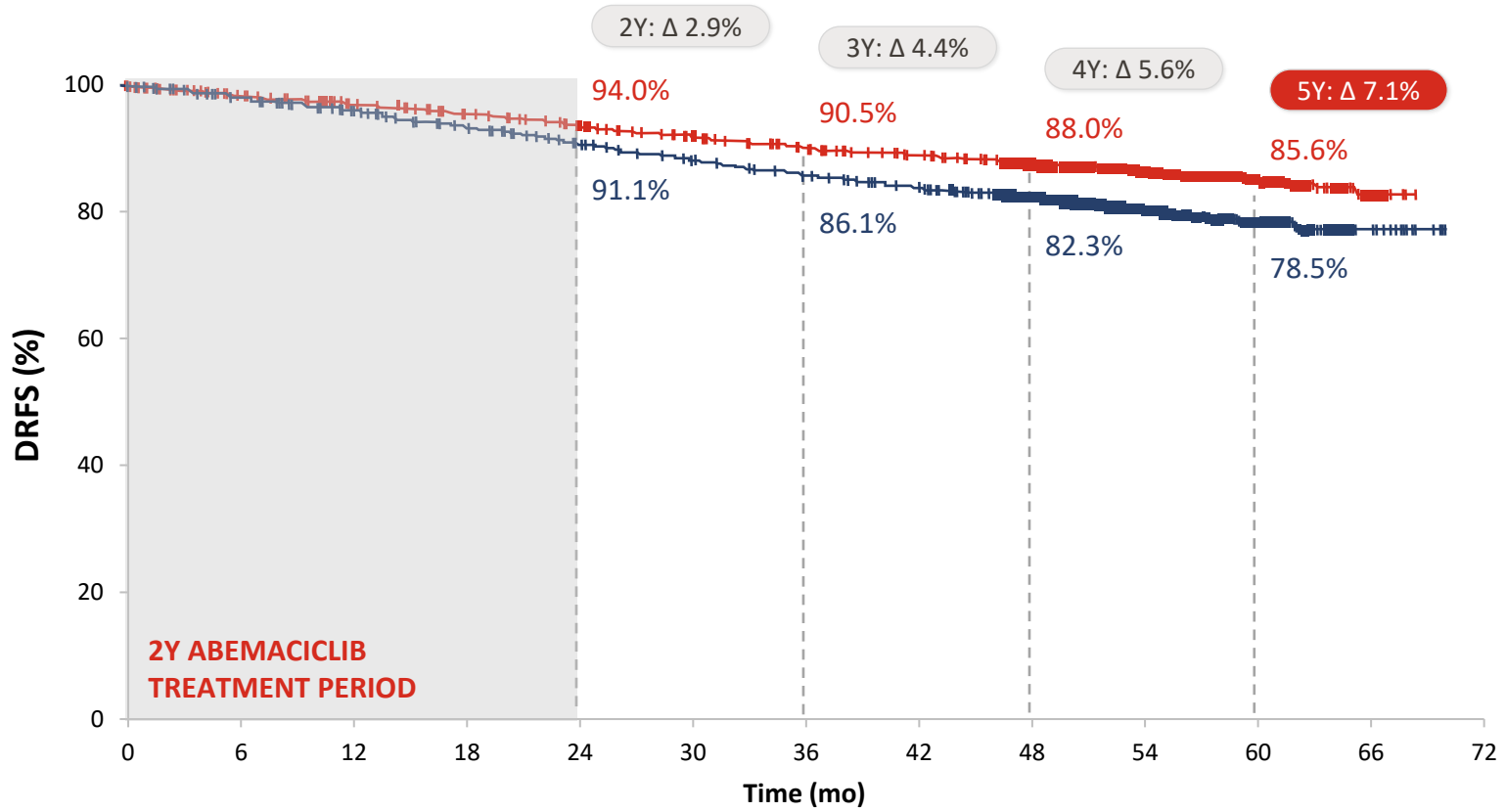


[a]Not powered or alpha controlled for testing statistical significance.
ET=endocrine therapy; IDFS=invasive disease-free survival; mF/U=median follow-up.
Rastogi P, et al. *J Clin Oncol*. 2024;42(9):987-993.

Cohort 1

54 mo mF/U

monarchE: DRFS



No. at risk													
Abemaciclib + ET	2555	2396	2339	2274	2213	2155	2095	2040	1953	1136	500	75	0
ET	2565	2412	2345	2259	2177	2102	2023	1960	1849	1092	488	72	0

33.5%

REDUCTION IN THE RISK OF DEVELOPING A DRFS EVENT[a]

Hazard ratio=0.665
(95% CI: 0.577-0.765),
nominal p<.001

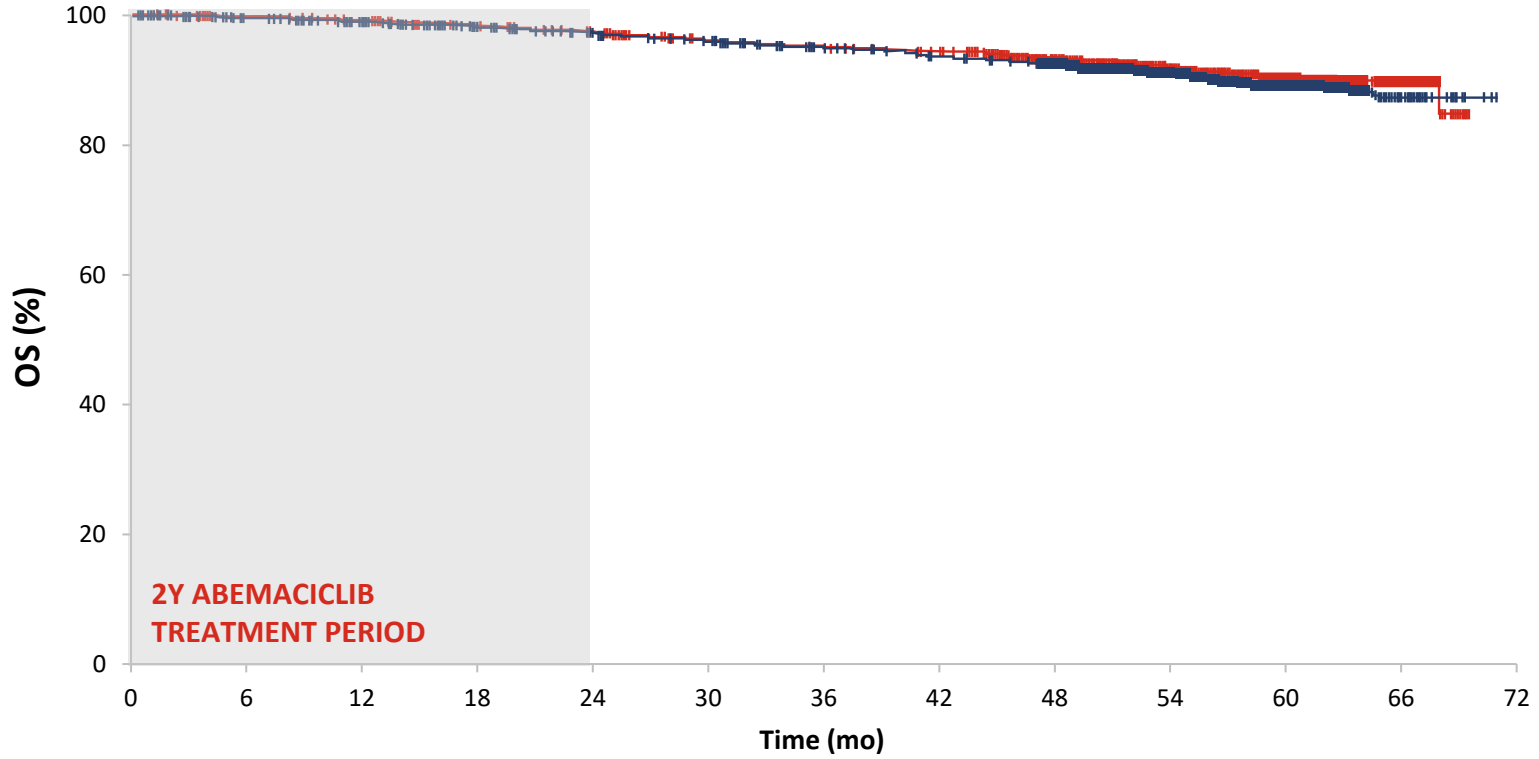
# DRFS Events	Abemaciclib + ET	325
	ET Alone	477

[a]**Not powered or alpha controlled for testing statistical significance.**
DRFS=distant relapse-free survival; ET=endocrine therapy; mF/U=median follow-up.
Rastogi P, et al. *J Clin Oncol*. 2024;42(9):987-993.

Cohort 1

54 mo mF/U

monarchE: OS



No. at risk													
Abemaciclib + ET	2555	2429	2381	2333	2290	2232	2186	2153	2066	1202	527	80	0
ET	2565	2455	2416	2356	2304	2262	2208	2156	2050	1207	538	77	0

OS DATA ARE IMMATURE

HR stratified=0.894
(95% CI: 0.738-1.084),
nominal p=.254

# OS Events	Abemaciclib + ET	197
	ET Alone	223

ET=endocrine therapy; mF/U=median follow-up; OS, overall survival.
Rastogi P, et al. *J Clin Oncol*. 2024;42(9):987-993.

ITT

42 mo mF/U

monarchE: Treatment-Emergent AEs

AEs in Either Arm (≥20%), %	Abemaciclib + ET (n=2791)		ET Only (n=2800)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Diarrhea[a]	83.6	7.8	8.7	0.2
Neutropenia	45.9	19.6	5.6	0.9
Fatigue[b]	40.8	2.9	18.0	0.1
Leukopenia	37.7	11.4	6.6	0.4
Abdominal pain[b]	35.7	1.4	9.9	0.3
Nausea	29.6	0.5	9.0	0.1
Arthralgia[b]	26.5	0.3	37.9	1.0
Anemia	24.5	2.1	3.9	0.4
Hot flush[b]	15.4	0.1	23.0	0.4

[a]One Grade 5 event of diarrhea. [b]Patient has a maximum CTCAE Grade of 3.

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; ET=endocrine therapy; ITT=intention-to-treat; mF/U=median follow-up.

Johnston SRD, et al. *Lancet Oncol.* 2023;24(1):77-90.

ITT

42-54 mo mF/U

monarchE: Discontinuation Rates and Treatment Completion

100%
of monarchE patients are off abemaciclib treatment[1]

~80% have been followed for ≥2Y since treatment with abemaciclib[2]

Abemaciclib dose adjustments due to AEs

- Dose holds: 61.7%[1]
- Dose reductions: 43.6%[1]
- Discontinuations: 18.5% (8.9% after dose reduction)[3]

AE=adverse event; ITT=intention-to-treat; mF/U=median follow-up.

1. Johnston SRD, et al. *Lancet Oncol.* 2023;24(1):77-90. 2. Rastogi P, et al. *J Clin Oncol.* 2024;42(9):987-993. 3. Rugo HS, et al. *Ann Oncol.* 2022;33(6):616-627.

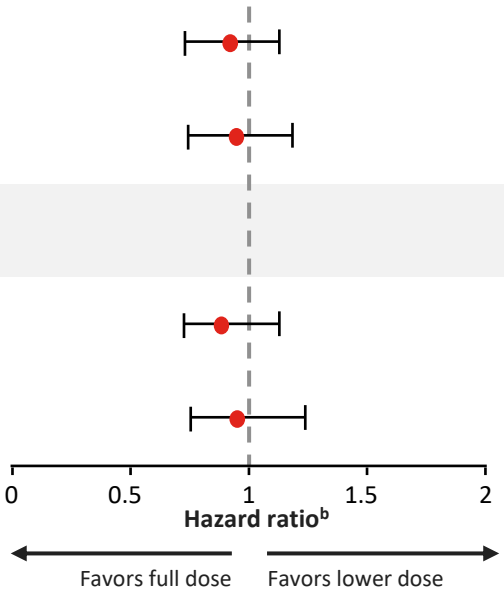
ITT/Cohort 1

42 mo mF/U

monarchE: Efficacy Maintained With Dose Reductions

In EBC, abemaciclib efficacy was not shown to be compromised by dose reductions[a,1,2]

Efficacy Endpoint	Hazard Ratio (95% CI)
ITT	
IDFS **150 mg abemaciclib + ET vs 100 mg or 50 mg**	0.905 (0.727-1.125)
DRFS **150 mg abemaciclib + ET vs 100 mg or 50 mg**	0.942 (0.742-1.195)
Cohort 1	
IDFS **150 mg abemaciclib + ET vs 100 mg or 50 mg**	0.899 (0.718-1.125)
DRFS **150 mg abemaciclib + ET vs 100 mg or 50 mg**	0.958 (0.750-1.223)



Abemaciclib Recommended Dose[3]

150 mg BID

1st dose reduction: 100 mg BID

2nd dose reduction: 50 mg BID

[a]The analyses were conducted using a time-dependent Cox proportional hazard model. [b]Closer to 1 signifies no difference.

BID=twice a day; EBC=early breast cancer; DRFS=distant relapse-free survival; IDFS=invasive disease-free survival; ITT=intention-to-treat; mF/U=median follow-up.

1. O'Shaughnessy J, et al. Oral presentation at: *ESMO 2023*. Abstract 274P. 2. Goetz MP, et al. *NPJ Breast Cancer*. 2024;10(1):34. 3. Abemaciclib [US PI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2024.

ITT/Cohort 1

42 mo mF/U

monarchE: Dose Reductions Were Associated With Improved Patient Retention

	No Dose Reduction **(n=1570)**	1 Dose Reduction **(n=832)**	2 Dose Reductions **(n=389)**
Treatment duration, months			
Median (Q1-Q3)	23.7 (14.9-23.8)	23.7 (20.6-23.8)	23.7 (13.2-23.8)
>3 months, %	**86**	**95**	**94**
>6 months, %	**81**	**90**	**86**

ITT=intention-to-treat; mF/U=median follow-up; Q=quarter.

Goetz MP, et al. *NPJ Breast Cancer*. 2024;10(1):34.

Cohort 1

54 mo mF/U

monarchE: Efficacy Summary

Treatment benefit at 54 months median follow-up[a]

	IDFS	DRFS
Relative risk reduction	33.0%	33.5%
Absolute benefit at 5Y	7.9%	7.1%

[a]IDFS includes invasive disease and death; DRFS includes distant recurrence and death. Relative risk reduction is measured over the trial duration and is based on the hazard ratio. Absolute benefit measures the difference in event rate at a single timepoint between 2 treatment arms and was calculated by subtraction of the IDFS/DRFS rates between the 2 arms at each year.

DRFS=distant relapse-free survival; IDFS=invasive disease-free survival; mF/U=median follow-up.

Rastogi P, et al. *J Clin Oncol*. 2024;42(9):987-993.

monarchE: Safety Summary[a]

Safety Data[1,2]

100% of patients are off abemaciclib treatment[b]

AEs were mainly low grade, and generally manageable with comedication and/or dose adjustments[1-3]

Most frequent AEs: any grade (Grade ≥3)[3]

Diarrhea	Neutropenia	Fatigue
84% (7.8%)	46% (19.6%)	41% (2.9%)

Serious AEs occurred in 15.5% of patients in the abemaciclib arm vs. 9.1% in the ET only arm[2]

[a]Latest available safety data. [b]Includes patients (0.8%) who were randomized but never treated.
AE=adverse event; ET=endocrine therapy; ITT=intention-to-treat.
1. Johnston SRD, et al. Oral presentation at: *SABCS 2022.* Abstract GS1-09. 2. Johnston SRD, et al. *Lancet Oncol.* 2023;24(1):77-90. 3. Rugo HS, et al. *Ann Oncol.* 2022;33(6):616-627.

Ribociclib in EBC: FDA Prescribing Information

Ribociclib Indication in EBC

Ribociclib is indicated in combination with an aromatase inhibitor for the adjuvant treatment of adults with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative Stage II and III early breast cancer at high risk of recurrence

Warning and Precautions

The FDA label carries warnings for ILD/pneumonitis, severe cutaneous adverse reactions, QT interval prolongation, increased QT prolongation with concomitant use of tamoxifen, liver toxicity, neutropenia, and embryo-fetal toxicity

ECG, electrolytes, liver function tests, and blood counts should be performed before treatment initiation, in the early treatment cycles, and as clinically indicated

EBC=early breast cancer; ECG=electrocardiogram; FDA=US Food and Drug Administration; ILD=interstitial lung disease.

Ribociclib [US PI]. East Hanover, NJ, USA: Novartis Pharmaceuticals Corporation, 2024.

Ribociclib in EBC: Guideline Recommendations

NCCN Recommendation[1]

For the treatment of HR+, HER2- EBC with any lymph node involvement (excluding microscopic nodal involvement), or if no nodal involvement either tumor size >5 cm, or if tumor size 2-5 cm, either Grade 2 (and high genomic risk or Ki-67 ≥20%), or Grade 3, the NCCN recommends consideration of 3 years of ribociclib with AI as an **NCCN Category 1, Preferred** treatment option[a]

ASCO Recommendation[2,3]

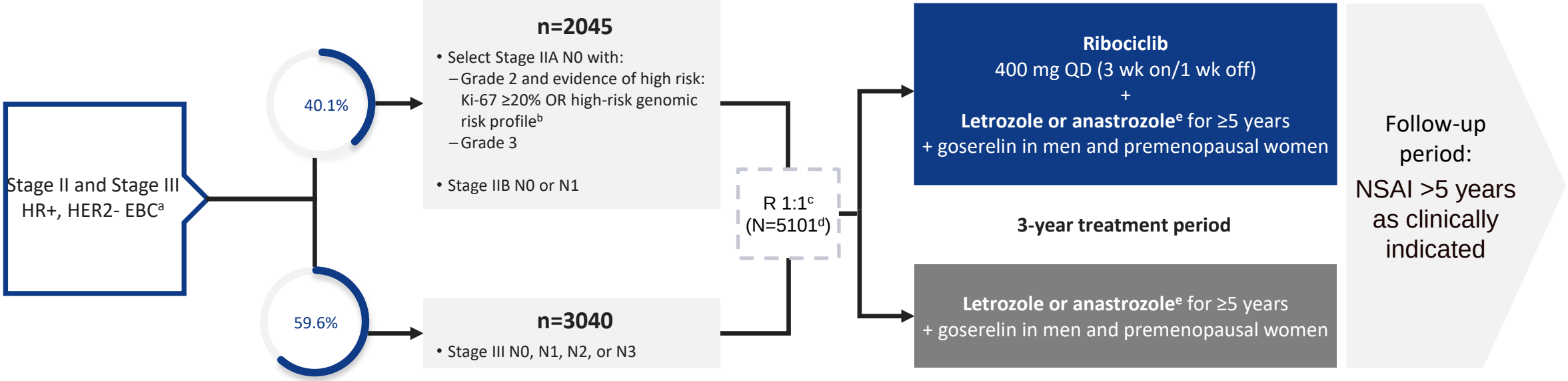
The Panel recommends, based on the Phase III NATALEE trial, that adjuvant ribociclib (400 mg once daily, 3 weeks on followed by 1 week off) for 3 years plus ET may be offered to patients with anatomic Stage II or III breast cancer who would have met criteria for study entry and have a high risk of recurrence

(Evidence quality: **High**; strength of recommendation: **Conditional**)

[a]Based on NCCN Guidelines® for Breast Cancer Version 6.2024. Category 1 is based upon high-level evidence (≥1 randomized Phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN® consensus (≥85% support of the Panel) that the intervention is appropriate. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
AI=aromatase inhibitor; EBC=early breast cancer; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor.
1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.6.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed November 18, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. 2. Freedman RA, et al. *J Clin Oncol*. 2024;42(18):2233-2235. 3. Caswell-Jin JL, et al. *JCO Oncol Pract.* 2024. doi.org/10.1200/OP-24-00663 (Ahead of print).

NATALEE: Study Design[1-4]

Phase 3, open-label study of ribociclib in addition to ET in patients with HR+, HER2- EBC



Prior treatment:

Patients could have received up to 12 months of neoadjuvant or adjuvant ET to random assignment

Stratified for:

- Anatomical stage: II vs. III
- Menopausal status: men and premenopausal women vs. postmenopausal women
- Prior (neo)adjuvant chemotherapy: yes vs. no
- Geographic location: North America/Western Europe/Oceania vs. rest of world

Primary Objective: IDFS using STEEP criteria[f]

Secondary Objectives: RFS, DDFS, OS, PROs, safety and tolerability, PK

Exploratory Endpoints: Locoregional RFS, gene expression and alterations in tumor ctDNA/ctRNA samples

[a]Enrollment of patients with Stage II disease was capped at 40%. Fourteen patients had Stage I disease and 2 had missing data. [b]High genomic risk was based on one of the following assays: Oncotype DX score of ≥26, Prosigna PAM50, Mammaprint, or Endopredict. [c]Open-label design. [d]Between January 10, 2019, and April 20, 2021. [e]Depending on the investigator.
[f]The primary endpoint was met at the second interim efficacy analysis with a medium follow-up of 27.7 months.
ctDNA=circulating tumor DNA; ctRNA=circulating tumor RNA; DDFS=distant disease-free survival; 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 outcome; QD=once daily; R=randomization; RFS=recurrence-free survival; STEEP=Standardized Definitions for Efficacy Endpoints.

1. https://www.clinicaltrials.gov/ct2/show/NCT03701334. (Accessed March 4, 2024). 2. Slamon D, et al. *N Engl J Med*. 2024;390(12):1080-1091.
3. Ribociclib [US PI]. East Hanover, NJ, USA: Novartis Pharmaceuticals Corporation, 2024. 4. Hortobagyi G, et al. Oral presentation at: *SABCS 2023.* Abstract GS03-03.

ITT

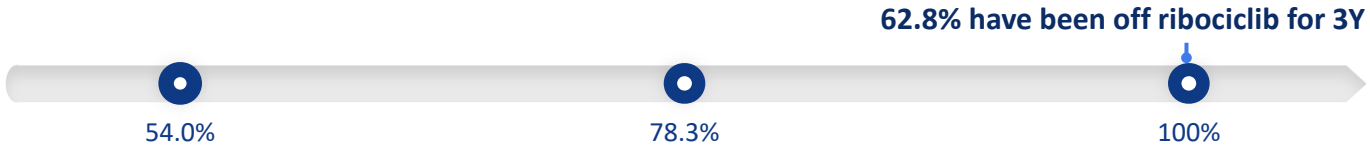
NATALEE: Evolution of Data

Totality of evidence demonstrates the utility of ribociclib + NSAI for the treatment of patients with HR+, HER2- Stage II and III EBC at high risk of recurrence

Safety profile of ribociclib + NSAI remain stable with additional follow-up

Primary endpoint IDFS met	Final IDFS analysis	Additional follow-up
27.7 mo mF/U[1-3]	33.3 mo mF/U[4,5]	44.2 mo mF/U[6]
25% risk reduction in IDFS	**25% risk reduction in IDFS**	**28.5% risk reduction in IDFS**
IDFS Hazard ratio: 0.748 (0.618-0.906)	**IDFS** Hazard ratio: 0.749 (0.628-0.892)	**IDFS** Hazard ratio: 0.715 (0.609-0.840)
3.3% absolute benefit at 2Y	**3.1% absolute benefit at 3Y**	**4.9% absolute benefit at 4Y**
DDFS Hazard ratio: 0.739 (0.603-0.905)	**DDFS** Hazard ratio: 0.749 (0.623-0.900)	**DDFS** Hazard ratio: 0.715 (0.604-0.847)
2.2% absolute benefit at 2Y	**2.7% absolute benefit at 3Y**	**NR**

PATIENTS OFF RIBOCICLIB TREATMENT[a]



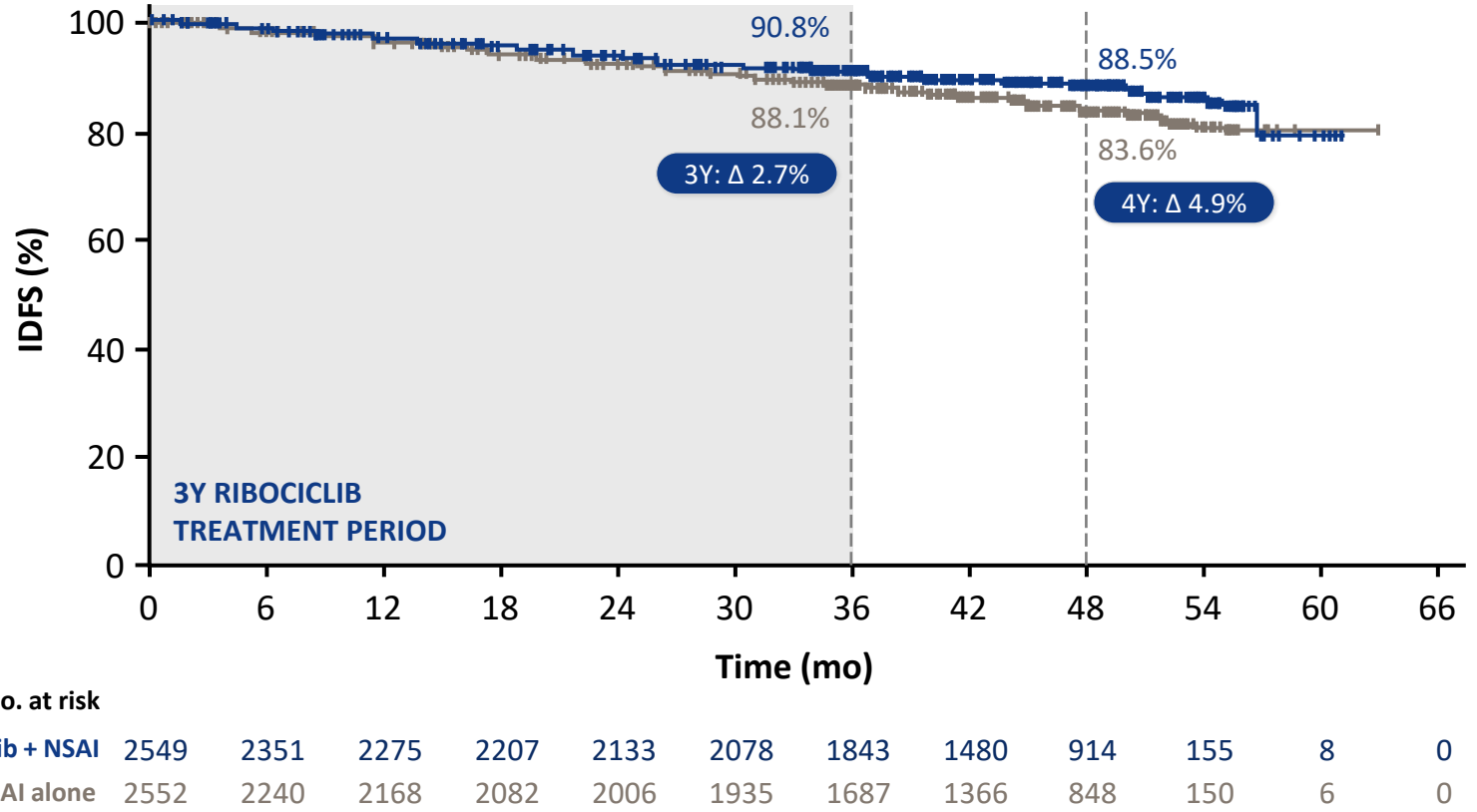
[a]A total of 1% of patients were randomized but not administered treatment.
DDFS=distant disease-free survival; EBC=early breast cancer; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; IDFS=invasive disease-free survival; ITT=Intention-to-treat; NSAI=nonsteroidal aromatase inhibitor; mF/U=median follow-up; NR=not reported.

1. Slamon DJ, et al. Oral presentation at: *ASCO 2023*. Abstract LBA500. 2. Bardia A, et al. Oral presentation at: *ESMO 2023.* Abstract LBA23. 3. Slamon D, et al. *N Engl J Med*. 2024;390(12):1080-1091. 4. Hortobagyi G, et al. Oral presentation at: *SABCS 2023*. Abstract GS03-03. 5. Barrios C, et al. Oral presentation at: *ESMO Breast 2024*. Abstract 113MO. 6. Fasching PA, et al. Oral presentation at: *ESMO 2024*. Abstract LBA13.

ITT

44.2 mo mF/U

NATALEE: IDFS[a]



No. at risk												
Ribociclib + NSAI	2549	2351	2275	2207	2133	2078	1843	1480	914	155	8	0
NSAI alone	2552	2240	2168	2082	2006	1935	1687	1366	848	150	6	0

28.5%

REDUCTION IN THE RISK OF DEVELOPING AN IDFS EVENT

Hazard ratio=0.715
(95% CI: 0.609-0.840)
nominal 1-sided p<.0001

# IDFS Events	**Ribociclib + NSAI**	263
	NSAI alone	340

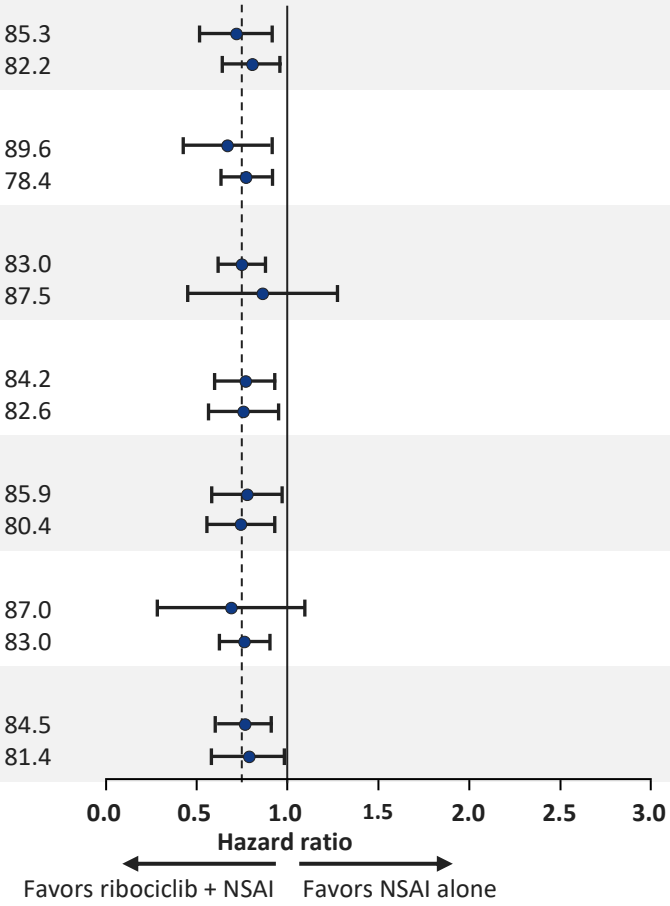
[a]An additional 10.9 mo of follow-up compared with the protocol-specified final IDFS analysis.
IDFS=invasive disease-free survival; ITT=intention-to-treat; mF/U=median follow-up; NSAI=nonsteroidal aromatase inhibitor.
Fasching PA, et al. Oral presentation at: *ESMO 2024*. Abstract LBA13.

ITT

44.2 mo mF/U

NATALEE: IDFS for Key Prespecified Subgroups

Subgroup	Ribociclib + NSAI		NSAI alone		Hazard Ratio	95% CI
	Events/n	4Y IDFS Rate, %	Events/n	4Y IDFS Rate, %		
Menopausal status						
Men and premenopausal women	99/1125	90.7	137/1132	85.3	0.677	0.523-0.877
Postmenopausal women	164/1424	86.8	203/1420	82.2	0.760	0.619-0.933
AJCC stage						
Stage II	62/1012	93.9	96/1034	89.6	0.644	0.468-0.887
Stage III	200/1527	84.3	244/1512	78.4	0.737	0.611-0.888
Prior chemotherapy						
Yes	238/2249	88.2	309/2245	83.0	0.715	0.604-0.846
No	25/300	90.7	31/307	87.5	0.827	0.488-1.401
Region						
North America/Western Europe/Oceania	151/1563	88.9	195/1565	84.2	0.726	0.587-0.898
Rest of world	112/986	88.0	145/987	82.6	0.722	0.564-0.925
Ki-67 status[a]						
Ki-67 ≤20%	106/1199	89.9	142/1236	85.9	0.737	0.573-0.948
Ki-67 >20%	113/920	86.3	149/937	80.4	0.709	0.555-0.905
Nodal status[b,c]						
N0	23/285	92.1	38/328	87.0	0.666	0.397-1.118
N1-N3	240/2261	88.0	301/2219	83.0	0.731	0.617-0.866
Prior ET						
Yes	176/1830	89.2	227/1807	84.5	0.718	0.589-0.874
No	87/719	86.7	113/745	81.4	0.752	0.568-0.994

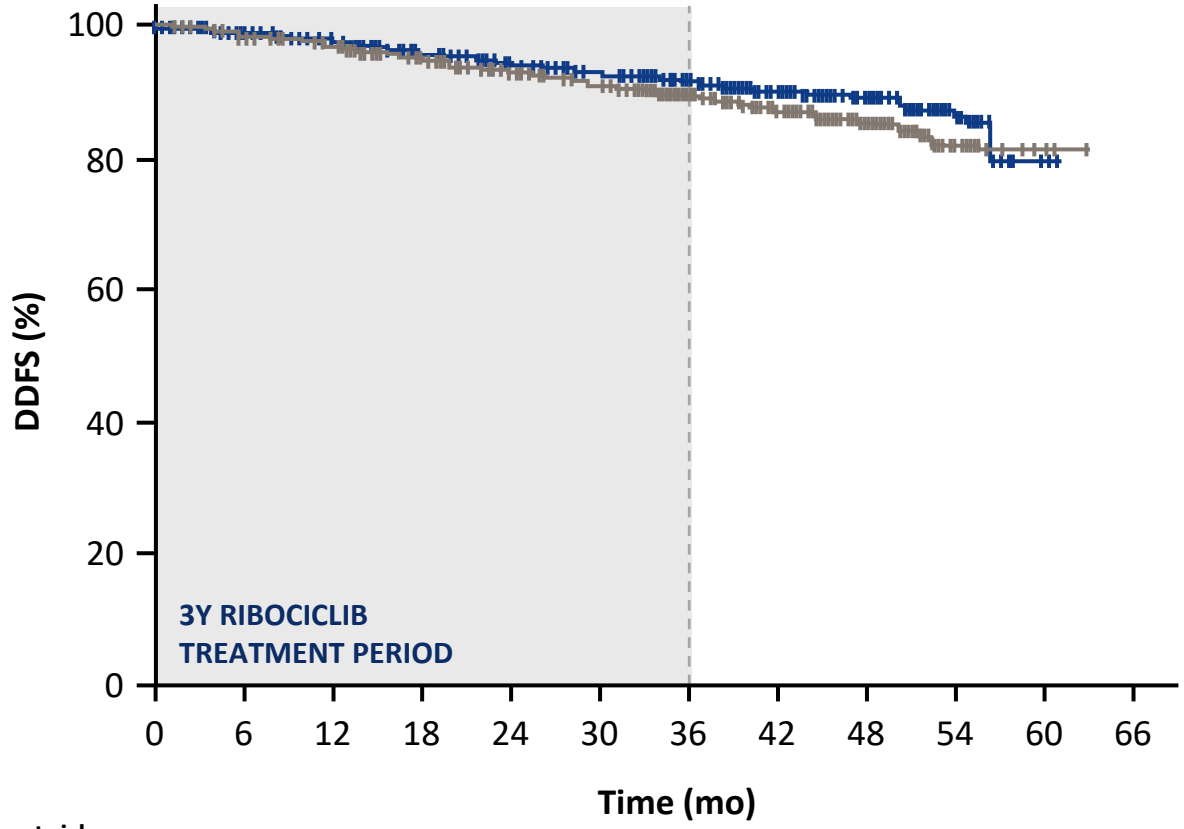


[a]From archival tumor tissue. [b]Nodal status classification according to AJCC staging. [c]Nodal status is from the worst stage derived per surgical specimen or at diagnosis.
AJCC=American Joint Committee on Cancer; ET=endocrine therapy; IDFS=invasive disease-free survival; ITT=intention-to-treat; mF/U=median follow-up; N=node; NSAI=nonsteroidal aromatase inhibitor.
Fasching PA, et al. Oral presentation at: *ESMO 2024*. Abstract LBA13.

ITT

44.2 mo mF/U

NATALEE: DDFS



No. at risk												
Ribociclib + NSAI	2549	2353	2282	2215	2146	2089	1854	1487	918	155	8	0
NSAI alone	2552	2244	2171	2093	2021	1949	1701	1376	856	152	6	0

28.5%

REDUCTION IN THE RISK OF DEVELOPING A DDFS EVENT

Hazard ratio=0.715
(95% CI: 0.604-0.847)
nominal 1-sided p<.0001

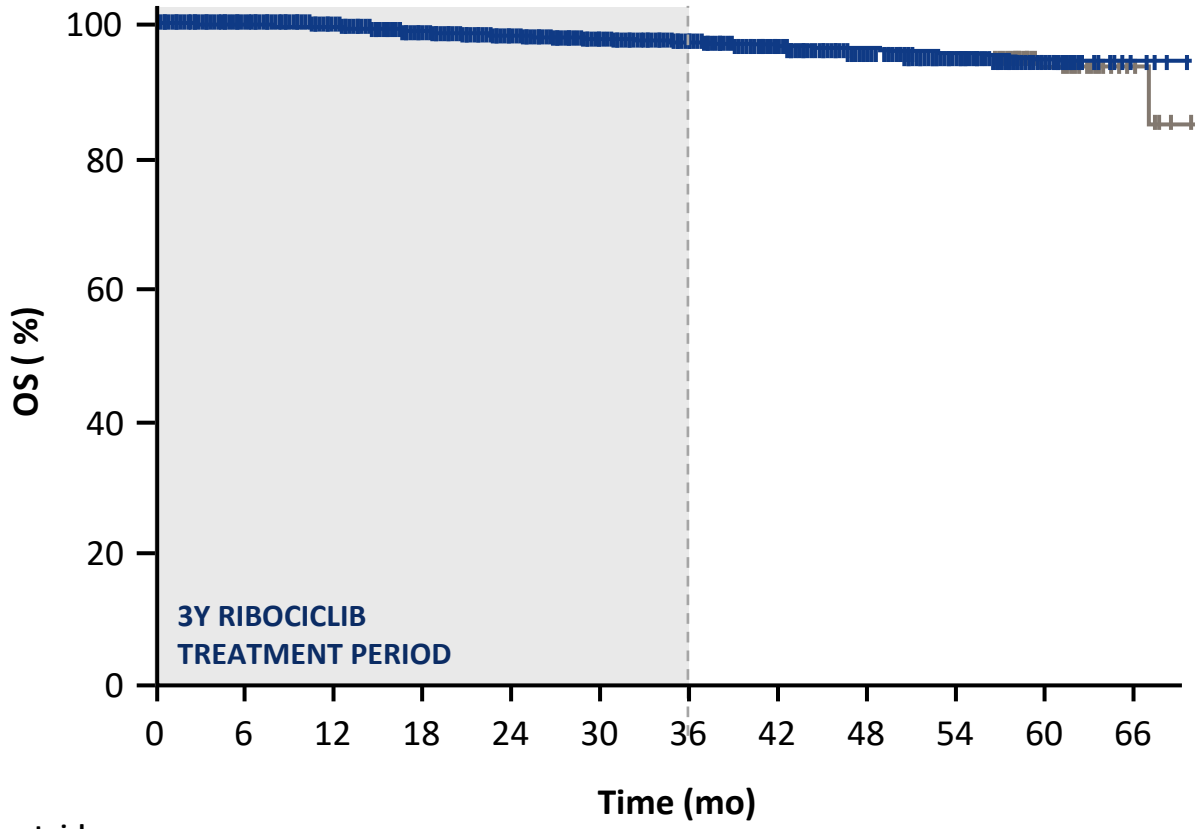
# DDFS Events	**Ribociclib + NSAI**	240
	NSAI alone	311

DDFS=distant disease-free survival; ITT=intention-to-treat; mF/U=median follow-up; NSAI=nonsteroidal aromatase inhibitor.
Fasching PA, et al. Oral presentation at: *ESMO 2024*. Abstract LBA13.

ITT

44.3 mo mF/U

NATALEE: OS



No. at risk												
Ribociclib + NSAI	2549	2404	2336	2300	2260	2217	2080	1648	1032	195	11	0
NSAI alone	2552	2302	2256	2210	2164	2117	1945	1571	991	204	13	0

OS DATA ARE IMMATURE

Hazard ratio=0.827
(95% CI: 0.636-1.074)
nominal 1-sided p=.0766

# OS Events	Ribociclib + NSAI	105
	NSAI alone	121

ITT=intention-to-treat; mF/U=median follow-up; NSAI=nonsteroidal aromatase inhibitor; OS=overall survival.
Fasching PA, et al. Oral presentation at: *ESMO 2024*. Abstract LBA13.

ITT

44.2 mo mF/U

NATALEE: Treatment-Emergent AEs

AEs of Special Interest in Either Arm (≥20%), %	Ribociclib + NSAI (n=2526)		NSAI Alone (n=2441)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Neutropenia[a]	62.8	44.4	4.5	0.9
Febrile neutropenia	0.3	0.3	0	0
Arthralgia	38.8	1.0	44.4	1.3
Liver-related AEs[b]	26.7	8.6	11.4	1.7
Nausea	23.5	0.2	7.9	<0.1
Headache	22.9	0.4	17.2	0.2
Fatigue	22.8	0.8	13.5	0.2

[a]Includes neutropenia and neutrophil count decreased. [b]Includes all preferred terms identified by standardized MedDRA queries for drug-related hepatic disorders.
AE=adverse event; ITT=intention-to-treat; MedDRA=Medical Dictionary for Regulatory Activities; mF/U=median follow-up; NSAI=nonsteroidal aromatase inhibitor.
Fasching PA, et al. Oral presentation at: *ESMO 2024*. Abstract LBA13.

ITT

44.2 mo mF/U

NATALEE: Discontinuation Rates and Treatment Completion

100%
of NATALEE patients are off ribociclib treatment[1]

62.8% of patients completed the 3Y treatment with ribociclib[1]

Ribociclib dose adjustments due to AEs

- Dose reductions: 22.8%[a,2]
- Discontinuations: 20.0%[1]

[a]mF/U of 33.3 mo.
AE=adverse event; ITT=intention-to-treat; mF/U=median follow-up.
1. Fasching PA, et al. Oral presentation at: *ESMO 2024*. Abstract LBA13. 2. Barrios C, et al. Oral presentation at: *ESMO Breast 2024*. Abstract 113MO.

ITT

33.3 mo mF/U

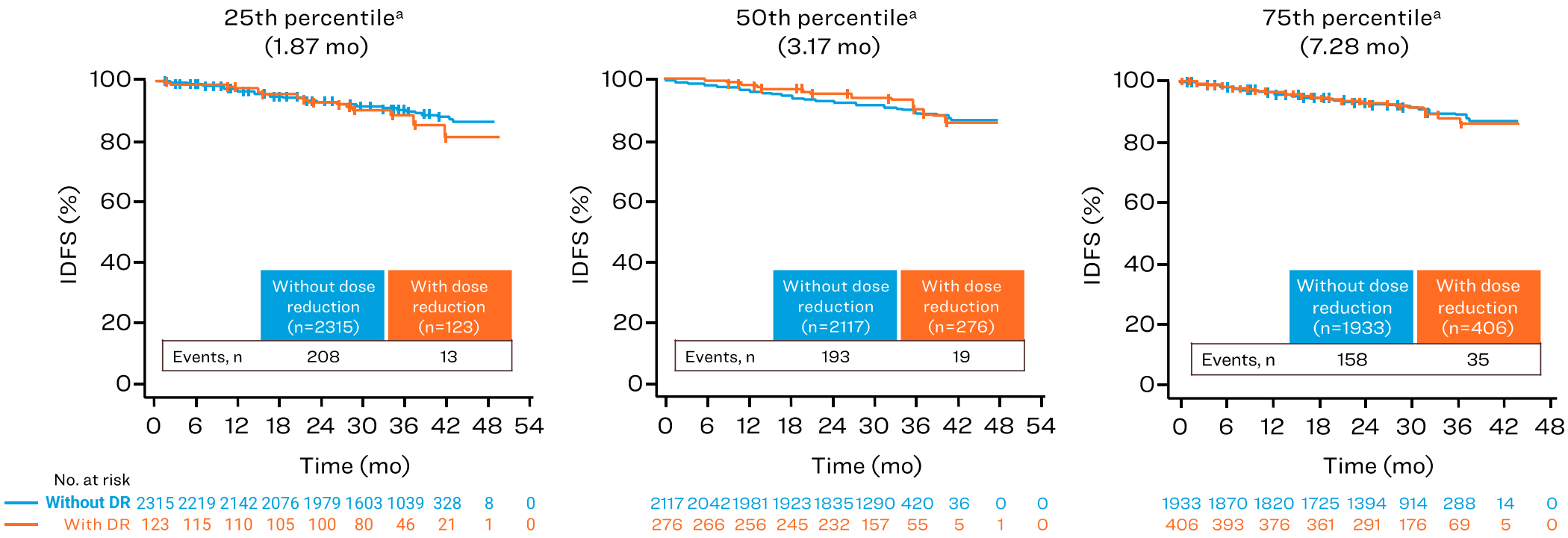
NATALEE: Efficacy Maintained With Dose Reduction

Ribociclib Recommended Dose[2]

400 mg QD

1st dose reduction: 200 mg QD

Invasive Disease-Free Survival by Dose Reductions



[a]Of dose reduction time, calculated from randomization.

DR=dose reduction; IDFS=invasive disease-free survival; ITT=intention-to-treat; mF/U=median follow-up; QD=once daily.

1. Barrios C, et al. Oral presentation at: *ESMO Breast 2024*. Abstract 113MO. 2. Ribociclib [US PI]. East Hanover, NJ, USA: Novartis Pharmaceuticals Corporation, 2024.

ITT

44.2 mo mF/U

NATALEE: Efficacy Summary at Additional IDFS Follow-Up

Treatment benefit at 44.2 months median follow-up[a]

	IDFS	DDFS
Relative risk reduction	28.5%	28.5%
Absolute benefit at 4Y	4.9%	NR

[a]IDFS, as defined by Standardized Definitions for Efficacy End Points criteria (version 1.0), was evaluated by the Kaplan-Meier method. DDFS was calculated as time from randomization to the date of the first event of distant recurrence, death by any cause, or second primary non-breast invasive cancer (excluding basal and squamous cell carcinomas of the skin).
DDFS=distant disease-free survival; IDFS=invasive disease-free survival; ITT=intention-to-treat; mF/U=median follow-up; NR=not reported.
Fasching PA, et al. Oral presentation at: *ESMO 2024*. Abstract LBA13.

ITT

44.2 mo mF/U

NATALEE: Safety Summary

Safety Data[1]

100% of patients are off ribociclib treatment

AEs of special interest were mainly low grade, except for neutropenia, and the safety profile of ribociclib + NSAI remained stable with additional follow-up[1]

Most frequent AEs of special interest: any grade (Grade ≥3)[1]

Neutropenia	Arthralgia	Liver-related
63% (44.4%)	39% (1.0%)	27% (8.6%)

The most frequent reason for discontinuation of ribociclib due to AEs was liver-related AEs[2]

AE=adverse event; ITT=intention-to-treat; mF/U=median follow-up; NSAI=nonsteroidal aromatase inhibitor.
1.Fasching PA, et al. Oral presentation at: *ESMO 2024*. Abstract LBA13. 2.Hortobagyi G, et al. Oral presentation at: *SABCS 2023.* Abstract GS03-03.

Summary

CDK4/6i + ET in HR+, HER2- EBC

1. **Patients with high-risk, HR+, HER2- EBC may benefit from additional treatments to reduce their risk of disease recurrence[1-3]**
2. **Understanding features associated with node-positive and node-negative, high-risk, HR+, HER2- EBC will help identify patients who could benefit from a CDK4/6i in the adjuvant setting[4-6]**
3. **Two CDK4/6i are approved for patients with high-risk, HR+, HER2- EBC, offering a potential for improved clinical outcomes[7,8]**

CDK4/6i=cyclin-dependent kinases 4/6 inhibitor; EBC=early breast cancer; ET=endocrine therapy; HER2=human epidermal growth factor receptor 2; HR=hormone receptor.

1. Burstein HJ, et al. *J Clin Oncol.* 2019;37(5):423-438. 2. Sheffield KM, et al. *Future Oncol*. 2022;18(21):2667-2682. 3. Caswell-Jin JL, et al. *JAMA*. 2024;331(3):233-241.
4. Colleoni M, et al. *J Clin Oncol.* 2016;34(9):927-935. 5. https://www.clinicaltrials.gov/ct2/show/NCT03155997. (Accessed April 4, 2023).
6. https://www.clinicaltrials.gov/ct2/show/NCT03701334. (Accessed March 4, 2024). 7. Ribociclib [US PI]. East Hanover, NJ, USA: Novartis Pharmaceuticals Corporation, 2024. 8. Abemaciclib [US PI]. Indianapolis, IN, USA: Eli Lilly USA LLC, 2024.

CDK4/6i USPI Links

Abemaciclib

https://e.lilly/3w30f5X

Palbociclib

https://e.lilly/30sGQBS

Ribociclib

https://e.lilly/3HInDZ9