DID YOU KNOW?

Beyond the Data

CDK4/6 Inhibitors for Treatment of Node-Positive, High-Risk, HR-Positive/HER2-Negative Early Breast Cancer: Addressing Tolerability to Maximize Treatment Persistence

Dose Modifications: Preserved Clinical Trial Efficacy and Real-World Tolerability

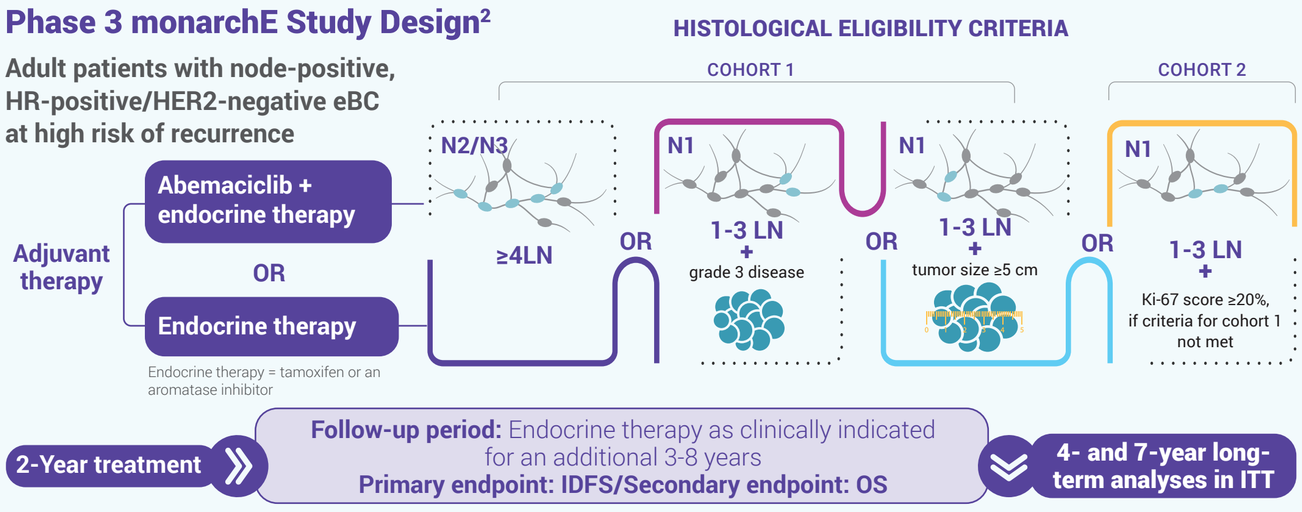
Currently, there are 2 cyclin-dependent kinase (CDK)4/6 inhibitors approved for adjuvant use in node-positive, high-risk, hormone receptor (HR)-positive/HER2-negative early breast cancer (eBC):

- Abemaciclib was approved in 2021 in combination with endocrine therapy (ET) (tamoxifen or an aromatase inhibitor [AI]) for the adjuvant treatment of adult patients with node-positive, HR-positive/HER2-negative eBC at high risk of recurrence based on data from the phase 3 monarchE study[1,2]
- Ribociclib was approved in 2024 in combination with an AI for the adjuvant treatment of adults with HR-positive/HER2-negative stage II and III eBC at high risk of recurrence based on the results of the phase 3 NATALEE study[3]

Experience From monarchE: Abemaciclib Dose Reductions Do Not Compromise Efficacy

Phase 3 monarchE Study Design[2]

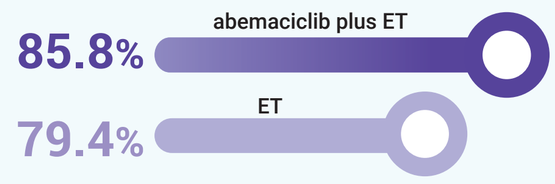
Adult patients with node-positive, HR-positive/HER2-negative eBC at high risk of recurrence



Abemaciclib Plus ET Shows Sustained IDFS Benefit in Long-Term Analyses (ITT) Compared with ET alone

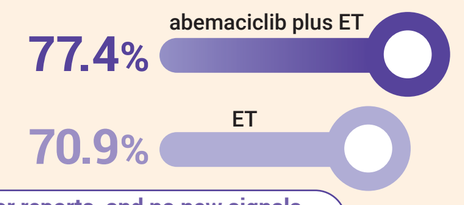
4 years: Analysis update[4]

- **Hazard ratio**, 0.66; 95% CI, 0.58-0.76; 2-sided *P*<.0001
- Median follow-up of 42 months; median IDFS not yet reached



7 years: Results from ESMO 2025[5,6]

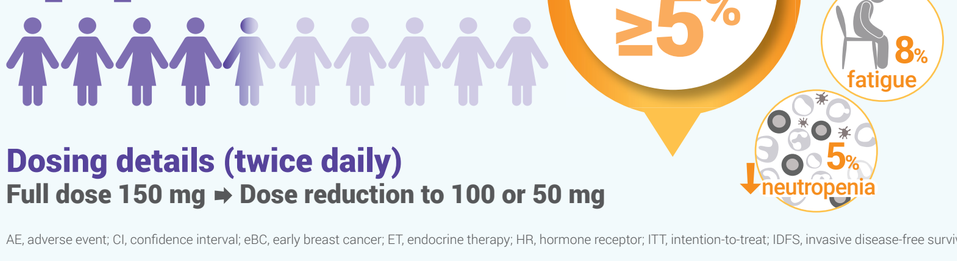
- **Hazard ratio**, 0.84; 95% CI, 0.72-0.98; 2-sided *P*=.027
- Median follow-up of 76 months



Safety was consistent with prior reports, and no new signals related to delayed toxicities were identified

A Portion of Patients in monarchE Required Abemaciclib Dose Reductions (Safety Set)[2]

44% of patients required dose reduction due to AEs



Dosing details (twice daily)

Full dose 150 mg ➡ Dose reduction to 100 or 50 mg

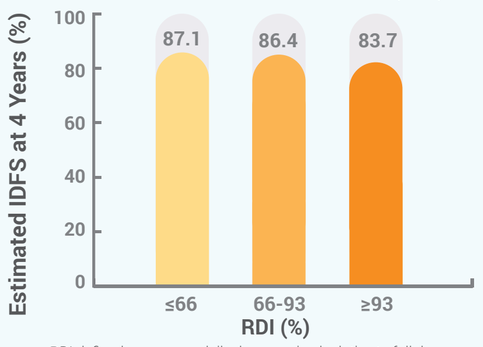
monarchE: Impact Analysis of Dose Reductions on Adjuvant Abemaciclib Efficacy[7]

Using data from the 4-year long-term analysis, this study evaluated the impact of abemaciclib dose reductions on treatment outcomes by relative dose intensity (RDI), with patients divided into 3 equally sized subgroups. IDFS was estimated within each subgroup using the Kaplan-Meier method, and a time-dependent Cox proportional hazards model was used to assess the effect of dose reductions on IDFS while accounting for the timing and duration of dose changes.

IDFS benefit was not significantly impacted by dose reductions

- **Adjusted hazard ratio,** 0.92; 95% CI, 0.74-1.15; *P* value not reported

Dose-Reduced Abemaciclib Plus ET Shows Sustained IDFS Benefit at 4 Years (ITT)



RDI defined as average daily dose received relative to full dose

AE, adverse event; CI, confidence interval; eBC, early breast cancer; ET, endocrine therapy; HR, hormone receptor; ITT, intention-to-treat; IDFS, invasive disease-free survival; LN, lymph nodes; OS, overall survival.

Real-World Evidence Suggests Abemaciclib is Well Tolerated by Most Patients in US Clinical Practice Beyond 3 Months of Treatment With Tailored Dose-Modification Strategies

Findings Presented at San Antonio Breast Cancer Symposium 2024[8]

A real-world, retrospective study evaluated dose-reduction patterns and 3-month treatment persistence of abemaciclib using the US Flatiron Health database. A 60-day medication gap was allowed in analysis of persistence rates.

- Median time to first dose reduction was ~2 months

AE, adverse event; eBC, early breast cancer; HR, hormone receptor.

Real-World Study of Abemaciclib Shows Half of Patients Had at Least 1 Dose Reduction[8]

Adult patients with node-positive, HR-positive/HER2-negative eBC who initiated abemaciclib in the adjuvant setting in the first year following FDA approval

Real-world cohort initiating abemaciclib at full dose
150 mg twice daily (n=354)

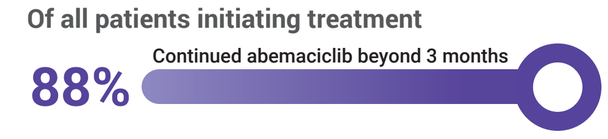
- **49% of patients had no dose change or dose hold**
- **51% of patients had a dose decrease**

- First dose change (n=180)
- 100 mg twice daily, n=143 (79%)
- 150 mg once daily, n=19 (11%)
- 50 mg twice daily, n=11 (6%)
- 100 mg once daily, n=5 (3%)
- 50 mg once daily, n=1 (1%)

48 patients underwent a second dose adjustment

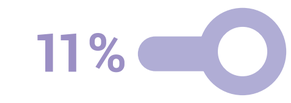
The Option of Modifying Dosing Allowed the Majority of Patients to Continue Abemaciclib Beyond 3 Months

Of all patients initiating treatment



Among patients with dose reductions

93% continued abemaciclib beyond 3 months



Among patients who discontinued

70% were not dose reduced

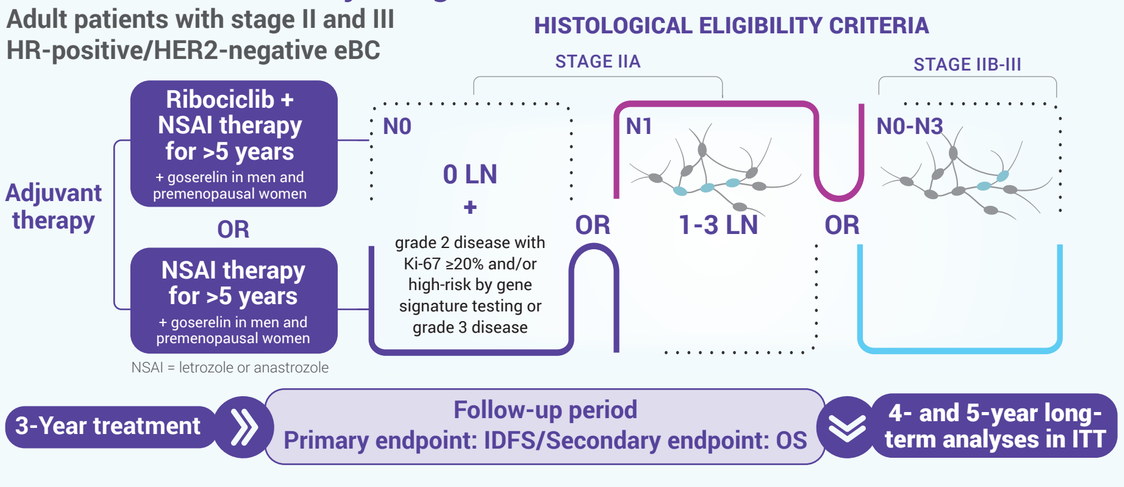
Common side effects leading to discontinuation

- Diarrhea, fatigue, nausea/vomiting

Experience From NATALEE: Ribociclib Dose Reductions Do Not Compromise Efficacy

Phase 3 NATALEE Study Design[3]

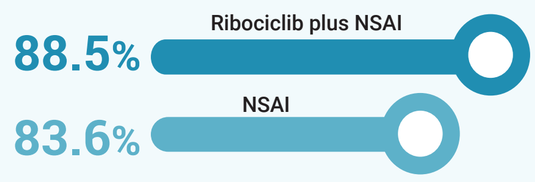
Adult patients with stage II and III HR-positive/HER2-negative eBC



Ribociclib Plus NSAI Shows Sustained IDFS Benefit in Long-Term Analysis Compared With NSAI Alone (ITT)

4 years: Analysis update[9]

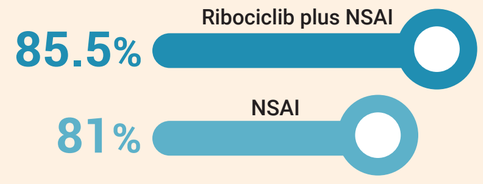
- **Hazard ratio,** 0.72; 95% CI, 0.61-0.84; *P* values not reported
- Median follow-up of 44.2 months



5 years: Results from ESMO 2025[9,10]

- **Hazard ratio,** 0.72; 95% CI, 0.62-0.83; 1-sided *P*<.0001
- Median follow-up of 55.4 months

No new safety signals were identified



NATALEE: Impact Analysis of Dose Reductions on Adjuvant Ribociclib Efficacy[11]

This **4-year exploratory analysis** evaluated the impact of ribociclib dose reductions on treatment outcomes by RDI. Unstratified Cox proportional hazards models were used to compare IDFS rates across RDI tertiles. Cox proportional hazards models were used to compare IDFS rates across RDI while accounting for timing and early discontinuation. The median IDFS follow-up time was 44.2 months.

AE, adverse event; ALT, alanine transaminase; CI, confidence interval; eBC, early breast cancer; ET, endocrine therapy; HR, hormone receptor; IDFS, invasive disease-free survival; ITT, intention-to-treat; LN, lymph node; NSAI, nonsteroidal aromatase inhibitor.

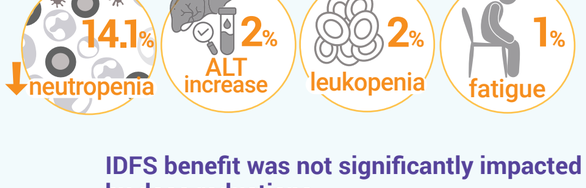
A Portion of Patients in NATALEE Required Ribociclib Dose Reductions (Safety Set)

27.2% of patients required a ribociclib dose reduction

Dosing details (3-week-on/1-week-off schedule)

Full dose 400 mg ➡
Dose reduction to 200 mg per day

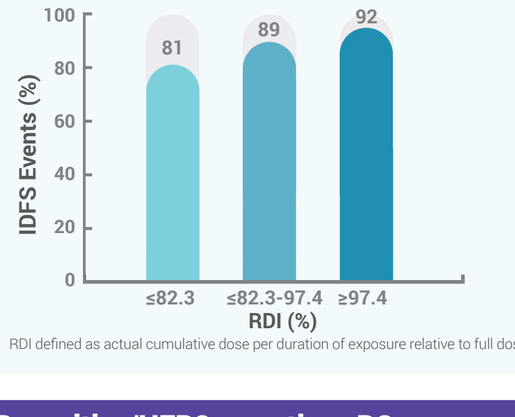
Adverse events that led to dose reductions:



IDFS benefit was not significantly impacted by dose reductions

- Unadjusted and adjusted hazard ratios crossed 1 for all model and comparisons

Dose-Reduced Ribociclib Plus ET Shows Sustained IDFS Benefit at 4-Year Exploratory Analysis (Safety Set)



RDI defined as actual cumulative dose per duration of exposure relative to full dose

In clinical trials, dose reductions of CDK4/6 inhibitors did not compromise IDFS benefit in patients with node-positive, HR-positive/HER2-negative eBC at high risk of recurrence. Real-world studies showed that dose reductions were associated with higher treatment persistence

References

1. VERZENIO [prescribing information]. 2021. Lilly USA, LLC; Indianapolis, IN.
2. VERZENIO [prescribing information]. 2025. Lilly USA, LLC; Indianapolis, IN.
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4. Johnston SRD, Toi M, O'Shaughnessy J, et al. Abemaciclib plus endocrine therapy for hormone receptor-positive, HER2-negative, node-positive, high-risk early breast cancer (monarchE): results from a preplanned interim analysis of a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2023;24:77-90.
5. Johnston SR, Martin M, O'Shaughnessy J, et al. monarchE: primary overall survival (OS) results of adjuvant abemaciclib + endocrine therapy (ET) for HR+, HER2-, high-risk early breast cancer (EBC). Presented at: ESMO Congress 2025. October 17, 2025; Berlin, Germany. Abstract LBA13.
6. Johnston S, Martin M, O'Shaughnessy J, et al. Overall survival with abemaciclib in early breast cancer. *Ann Oncol*. 2025;S0923-7534:04948-8.
7. Goetz MP, Cicin I, Testa L, et al. Impact of dose reductions on adjuvant abemaciclib efficacy for patients with high-risk early breast cancer: analyses from the monarchE study. *NPJ Breast Cancer*. 2024;10:34.
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10. Crown JP, Stroyakovskiy D, Yardley D, et al. Adjuvant ribociclib (RIB) plus nonsteroidal aromatase inhibitor (NSAI) in patients (pts) with HR+/HER2− early breast cancer (EBC): NATALEE 5-year outcomes. Presented at: ESMO Congress 2025. October 17, 2025; Berlin, Germany. Abstract LBA14.
11. Hamilton E, Decker T, Rugo HS, et al. Impact of ribociclib dose reduction on efficacy in patients with hormone receptor-positive/human epidermal growth factor receptor 2-negative early breast cancer in NATALEE. Presented at: San Antonio Breast Cancer Symposium. December 10-13, 2024; San Antonio, TX. Poster P1-11-16.

For full prescribing information see:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/208716s019lbl.pdf
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