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Consensus Statement Regarding use of Adjuvant Abemaciclib in Patients with Early-Stage, Hormone-Receptor-Positive Breast Cancer

Dana-Farber Brigham Cancer Center
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I. Introduction

Based on the significant improvement in invasive-disease-free survival (iDFS) observed in the phase III monarchE trial^{1,2}, on October 12, 2021 the US Food and Drug Administration (FDA) approved the use of abemaciclib in combination with endocrine therapy (ET) for the adjuvant treatment of high-risk, node-positive, early-stage, hormone-receptor-positive (HR+), HER2-negative breast cancer with a Ki-67 score $\geq 20\%$, as determined by an FDA-approved test.³

The purpose of the Dana-Farber Brigham Breast Oncology Center (BOC) meetings held on October 15 and November 5, 2021, was to discuss recommendations for the use of abemaciclib in patients with early-stage, high-risk, HR+ breast cancer. Data were reviewed from the following randomized phase III trials that evaluated the addition of CDK4/6 inhibitors to adjuvant endocrine treatment for early-stage, HR+ breast cancer: monarchE², PALLAS⁴ and PENELOPE-B⁵. Data regarding adjuvant olaparib (OLYMPIA⁶) for high-risk breast cancer were also reviewed. Additional relevant data were reviewed to address the questions in this document as noted below.

	monarchE	PALLAS	PENELOPE-B
N (exp/control)	5637	5760	1250
Primary endpoint	iDFS	iDFS	iDFS
Adjuvant ET	AI or Tam	AI or Tam	AI or Tam
CDK4/6 inhibitor	Abemaciclib	Palbociclib	Palbociclib
Duration	2 years	2 years	1 year
Population	Patients with HR+ BC and high-risk features (Cohort 1: ≥ 4 ALNs, or 1-3 positive ALNs and either grade 3 disease or tumor ≥ 5 cm; Cohort 2: 1-3 positive ALNs and Ki-67 $\geq 20\%$)	Patients with stage II or stage III HR+ BC	Patients with HR+ BC, residual disease after NACT and high-risk features (CPS ≥ 3 or CPS ≥ 2 and ypN+)
Median F-UP	27 months	23.7 months	42.8 months
iDFS outcome	In ITT: 3-year iDFS 88.8% vs 83.4% (HR 0.70, p<0.001), delta 5.4%	3-year iDFS 88.2% vs 88.5% (HR 0.93, p=0.51)	3-year iDFS 81.2% vs 77.7% (HR 0.93, p=0.525)

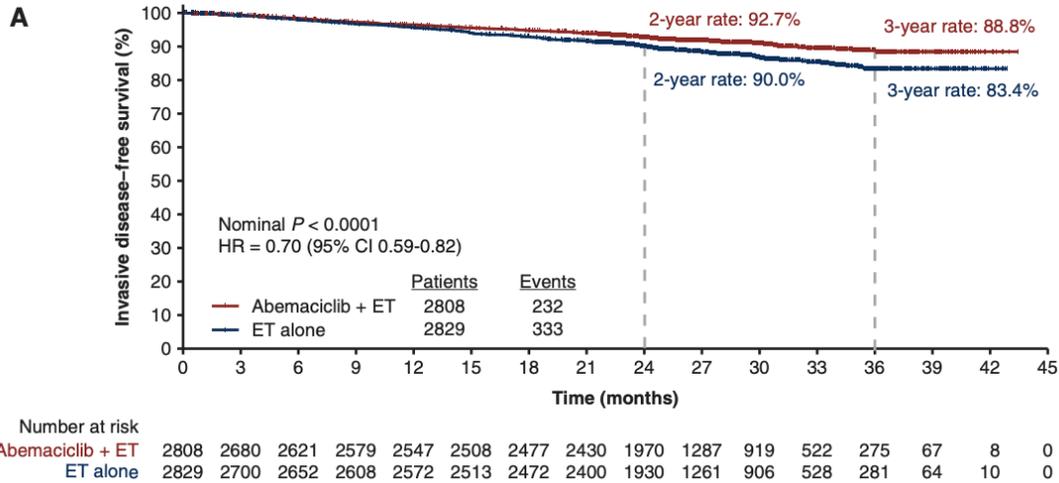


Figure 1 - MonarchE iDFS curves in ITT population at a median follow up of 27 months

A) Outcomes in monarchE according to Ki-67

The FDA restriction of abemaciclib approval to Ki-67-high ($\geq 20\%$) tumors derived from a secondary endpoint of monarchE. Among patients with high-risk, Ki-67-high disease, the addition of abemaciclib further improved statistical iDFS benefit (HR=0.66, P=0.0002) compared with the ITT, with an absolute improvement of 7.1% in 3-year iDFS rate.

A similar relative reduction in risk of relapse was observed with abemaciclib in the populations of patients with Ki-67-high and Ki-67-low tumors, suggesting no predictive value for this biomarker in the context of monarchE. However, due to the prognostic value of Ki-67, the ultimate absolute benefit in 3-year iDFS differed in the two cohorts, being 7.1% in the Ki-67-high cohort (86.1% vs 79%) and 4.5% in the Ki-67-low population (91.7% vs 87.2%).

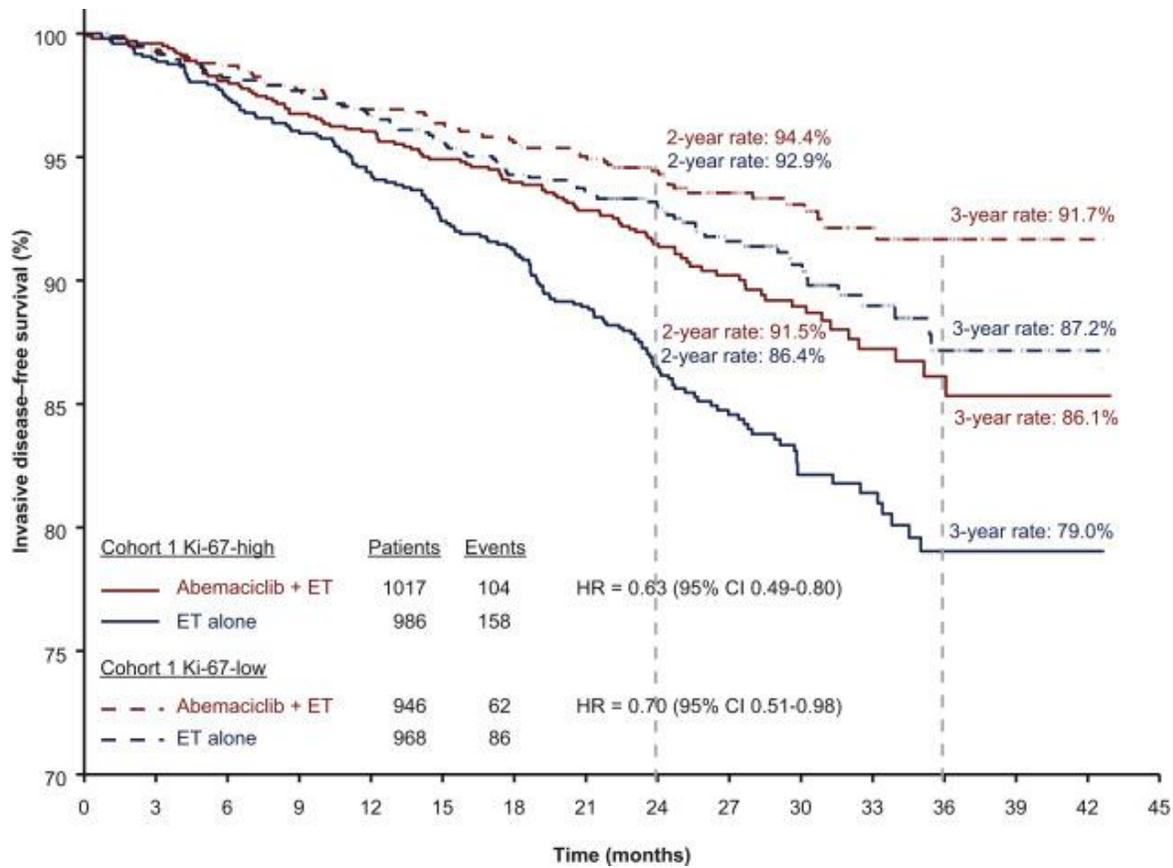


Figure 2 - Kaplan-Meier curves of invasive-disease-free survival in Cohort 1 Ki-67 high versus Ki-67 low at additional follow-up 1

Importantly, the Ki-67 selection required by the FDA approval excludes from treatment with abemaciclib a cohort of patients expected to have a particularly high risk of recurrence, namely patients with ≥ 4 lymph nodes involved.⁷ These patients were particularly enriched in the Ki-67-low cohort, as detailed in the figure below, with 55% of all patients with ≥ 4 lymph nodes involved in monarchE being Ki-67-low.

Cohort 1 Ki-67 High versus Ki-67 Low

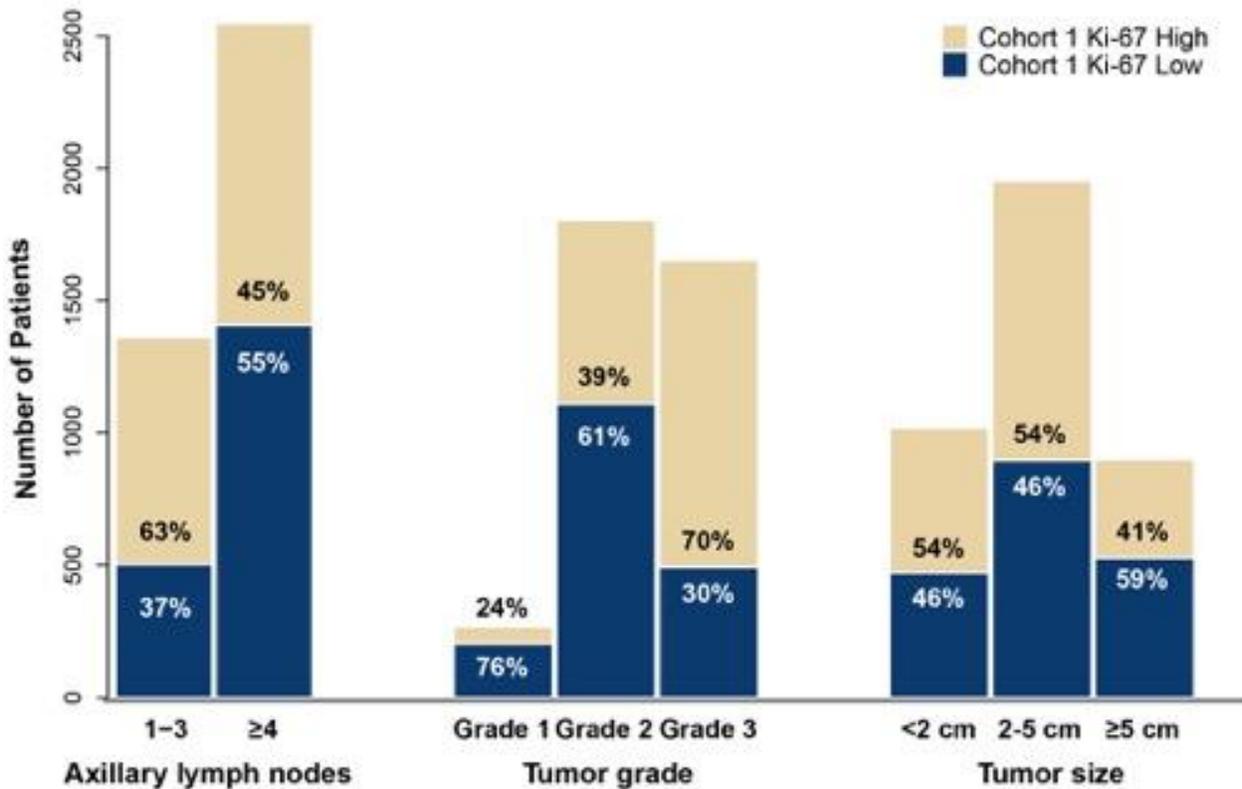


Figure 3 - Ki-67 distribution within each clinicopathological feature in Cohort 1

B) Preliminary overall survival in monarchE

Overall survival (OS) was a secondary endpoint in monarchE and is expected to be still immature at median follow up of 27 months, due to the natural history of HR+ early breast cancer. In a letter to the editor published in *Annals of Oncology*, two OS curves from monarchE were released: OS for the ITT population showed a HR of 1.091 (95%CI 0.818-1.455), with a comparable number of deaths in both study arms (3.4% vs 3.2%), whereas OS in the FDA indicated population (high-risk features, Ki-67 ≥20%) showed a HR of 0.767 (95%CI 0.511 – 1.152), with slightly less deaths in the abemaciclib arm (4.1% vs 5.4%).

The consensus of the BOC group was to wait for updates on this endpoint after longer follow up before drawing conclusions on the efficacy of adjuvant abemaciclib in different populations.

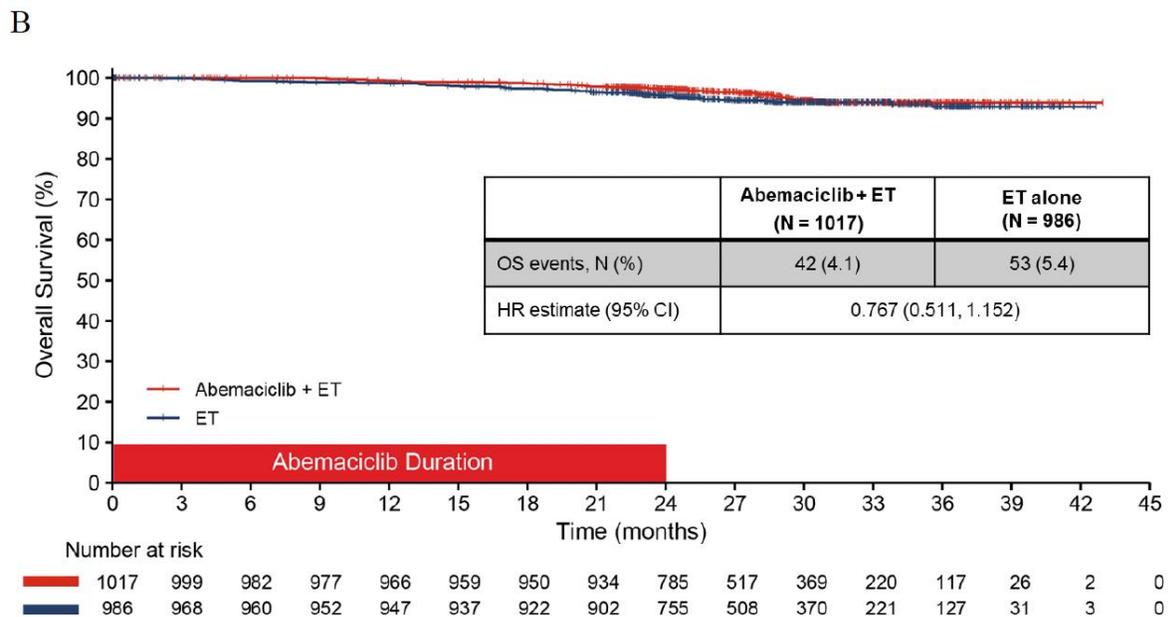
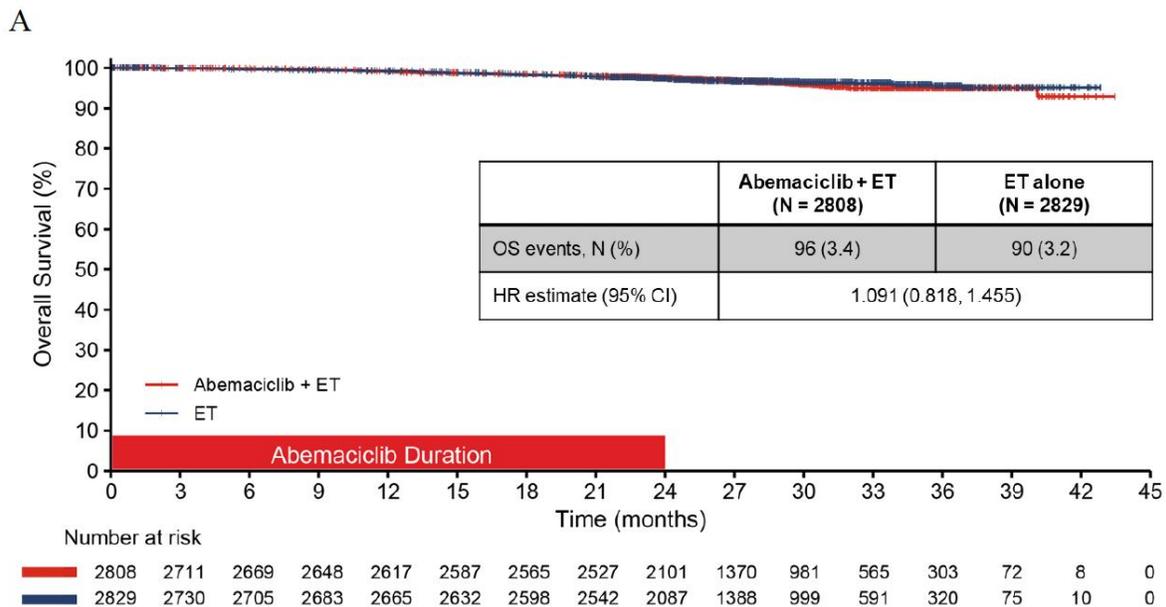


Figure 4: Kaplan-Meier analysis of overall survival in Intent-to-Treat Population (A) and in the FDA Indicated Population (B) according to additional follow-up data cut performed on 1-APR-2021

This document summarizes the discussions and consensus among the Dana-Farber Brigham BOC regarding the following:

Consensus Statement Regarding use of Adjuvant Abemaciclib in Patients with Early-Stage, Hormone-Receptor-Positive Breast Cancer

- **Q1: Which patients should receive adjuvant abemaciclib?**
- **Q2: How should abemaciclib be administered?**
- **Q3: How should the toxicities of abemaciclib be managed?**

Additional considerations:

- Potential toxicities and benefits of adjuvant abemaciclib should be discussed with the patient before initiating adjuvant treatment.
- Guidelines are subject to change with evolution of data from existing and future trials. The BOC will plan to reconvene in 12 months to review patterns of care for high-risk, early-stage HR+ breast cancer.

II. Which patients should receive adjuvant abemaciclib?

The following considerations, including A) clinical stage at diagnosis, B) Ki-67 score, C) prior receipt of chemotherapy, and D) *BRCA* mutation status, for recommendations on the use of adjuvant abemaciclib are detailed below.

A) Clinical anatomic stage at diagnosis:

After review of the data noted above, the consensus among the group was to consider adjuvant abemaciclib for patients with node-positive, HR+ breast cancer and either ≥ 4 positive lymph nodes or 1-3 lymph nodes and high-risk features (grade 3 disease or tumor ≥ 5 cm), as per monarchE inclusion criteria.

B) Ki-67 score:

The group agreed regarding the significant challenges of implementing Ki-67 testing in clinical practice to select patients for treatment with abemaciclib.

Ki-67 is a continuous value by nature, as well as a biomarker for which standardization of pre-analytic, analytic, and post-analytic factors has yet to be achieved. Unacceptably wide inter-observer and/or inter-laboratory variability of Ki-67 scoring has been documented in multiple concordance studies⁸, highlighting the difficulties of using Ki-67 thresholds for clinical decision-making, particularly when small differences in the intermediate range could impact therapy choice. For illustration, in an international Ki-67 reproducibility study, eight highly experienced laboratories in North America and Europe received 100 breast cancer cases, either locally or centrally stained with the same Ki-67 assay (MIB-1 from Dako). Interlaboratory reproducibility (quantified by intraclass correlation coefficient [ICC]) was suboptimal, with ICC=0.71 for centrally stained and IC=0.59 for locally stained samples, highlighting a substantial variability in Ki-67 scoring despite the relevant expertise of the laboratories involved.⁹ Subsequent research attempts to improve reproducibility have not

yet led to clinically satisfying results, particularly in the Ki67 range of 10%-20%, where kappa values of interobserver agreement were near 0.6 across studies.⁸

Based on the abovementioned issues characterizing Ki-67 staining and the lack of predictive value shown by Ki-67 in monarchE, the group agreed to avoid routine testing of Ki-67 in HR+ breast cancer patients.

The consensus among the group was to:

- Offer adjuvant abemaciclib to HR+ breast cancer patients with ≥ 4 lymph nodes involved, regardless of the Ki-67 score
- Offer adjuvant abemaciclib for patients with 1-3 lymph nodes involved and high-risk features (T3-4 or G3), with Ki-67 to be assessed only if required for reimbursement purposes
- In cases with an OncotypeDX recurrence score ≥ 26 (high risk), determination of Ki-67 may be avoided, unless required for reimbursement purposes

Ki-67 testing will not follow reflex testing, but will be requested as needed, per physician discretion, on selected cases of node-positive, HR+ breast cancers. Ki-67 will be assessed with the Mib-1 clone assay, through manual count (minimum 200 cells counted; whole area stained reviewed; hotspots included in count) - consistent with criteria adopted in monarchE trial - and will be provided as an absolute score. In locally advanced HR+ breast cancers, Ki-67 should be tested off core biopsies prior to systemic treatment and surgery.

C) Adjuvant abemaciclib in patients without prior receipt of chemotherapy:

In monarchE, 95% of the enrolled patients had received prior (neo)adjuvant chemotherapy. However, since the presentation of the results from the RxPONDER trial at SABCS 2020, the use of chemotherapy in HR+, lymph-node positive patients has substantially decreased.¹⁰

Despite this modification in treatment standards, it is reasonable to offer adjuvant abemaciclib regardless of prior receipt of chemotherapy, since the benefit of abemaciclib is expected to be retained in this context based on current biological and clinical knowledge.

D) *BRCA*-mutation status:

For patients with high-risk, HR+ breast cancer and with germline pathogenic or likely pathogenic variants in *BRCA1* or *BRCA2*, the OLYMPIA phase 3 trial established the significant DFS benefit of administering one year of adjuvant olaparib after surgery.⁶ Although data is not available for outcomes of patients within monarchE with g*BRCA* mutations, and acknowledging the pitfalls of cross-trials comparisons, the extent of iDFS benefit in OLYMPIA (8.8% at 3 years) currently appears higher than observed in monarchE (5.4% in the ITT). Thus, the consensus among the group was to prioritize adjuvant olaparib over abemaciclib for this subgroup of patients.

One or two years of additional adjuvant abemaciclib administered sequentially after olaparib may be considered in patients with the highest risks of relapse, on a case-by-case basis.

III. Treatment regimen and schedule

In the monarchE trial, adjuvant abemaciclib was administered in combination with either an aromatase inhibitor or tamoxifen. Notably, a higher risk of venous thrombo-embolism (VTE) was observed when abemaciclib was combined with tamoxifen (any-grade VTE 4.1%, G \geq 3 VTE 2.2%) compared with aromatase inhibitors (any-grade VTE 1.7%, G \geq 3 VTE 0.9%).

The consensus among the group was to avoid combining adjuvant abemaciclib with tamoxifen, and preferentially combine abemaciclib with aromatase inhibitors in the adjuvant setting.

For selected cases for which treatment with tamoxifen may be clinically preferred, a hematological consultation for consideration of prophylactic anticoagulation is recommended before adding abemaciclib.

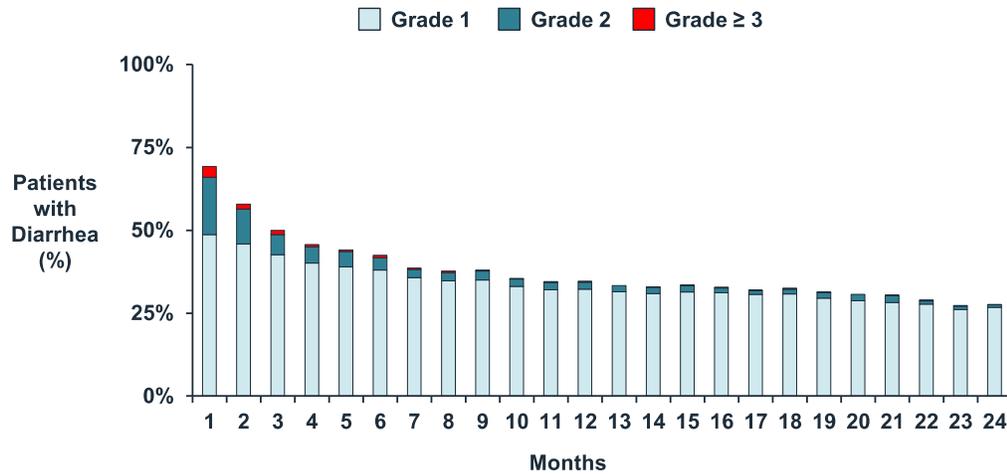
The initial dose of abemaciclib should be 150 mg twice daily, administered orally. Dose modifications in case of adverse events should adhere to the following table:

Dose Level	Abemaciclib dose
Recommended starting dose	150 mg twice daily
First dose reduction	100 mg twice daily
Second dose reduction	50 mg twice daily

For patients unable to tolerate a dose of 50 mg twice daily, abemaciclib should be discontinued.

IV. Toxicity monitoring and management:

The most common toxicity observed in the abemaciclib arm of monarchE was diarrhea (any-grade 83%, grade 3 7.8%, no grade 4, one grade 5 event). The incidence of diarrhea decreased with time, with virtually no severe events after 6 months of treatment. Despite the occurrence of diarrhea, patient-reported outcomes highlighted no clinically meaningful differences in patients being bothered by treatment side effects between monarchE arms.¹¹



Across abemaciclib studies, the median time to onset of diarrhea was 6-8 days.¹² Anti-diarrheal prophylaxis is contraindicated, due to the high risk of constipation.

Always instruct patients to have available over-the-counter anti-diarrhea medications (e.g., loperamide) available at home, to be started at the first sign of loose stools. Concomitantly, patients should increase oral fluids and notify their treating physician for further instructions and appropriate follow up.

The following dose modifications should be applied in case of diarrhea with abemaciclib:

CTCAE Grade	Abemaciclib dose modifications
Grade 1	No dose modification is required.
Grade 2	If toxicity does not resolve within 24 hours to ≤Grade 1, suspend dose until resolution. <i>No dose reduction is required.</i>
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to ≤Grade 1. <i>Resume at next lower dose.</i>
Grade 3 or 4 or requires hospitalization	Suspend dose until toxicity resolves to ≤Grade 1. <i>Resume at next lower dose.</i>

The most common grade ≥3 adverse event in monarchE was neutropenia (any-grade 45.8%, grade 3 18.9%, grade 4 0.7%). Across abemaciclib studies, the median time to the first episode of Grade ≥3 neutropenia was 29-33 days, and the median duration of Grade ≥3 neutropenia was 11-16 days.¹²

Monitoring involves every-two-week CBC and CMP (consider cystatin C if elevated creatinine) for the first two months, then monthly CBC and CMP for the following two months, and every-two-months CBC and CMP thereafter (from the fourth month). Continuing monthly (or shorter-term) monitoring to be considered for patients experimenting significant laboratory abnormalities

The following dose modifications should be applied in case of neutropenia with abemaciclib:

CTCAE Grade	Abemaciclib dose modifications
Grade 1 or 2	No dose modification is required.
Grade 3	Suspend dose until toxicity resolves to ≤Grade 2. Dose reduction is not required.
Grade 3 recurrent, or Grade 4	Suspend dose until toxicity resolves to ≤Grade 2. Resume at next lower dose.

Other frequent toxicities in monarchE were fatigue (any-grade 40%), abdominal pain (any-grade 36%), nausea (any-grade 30%) and anemia (any-grade 24%), all of which were rarely >grade 2 in severity.

The incidence of any-grade interstitial lung disease (ILD) was 3.2% (0.4% grade 3, no grade 4, one fatal case). Patients should be monitored for symptoms consistent with ILD (hypoxia, cough, dyspnea) or interstitial infiltrates on radiologic exams. Dose interruption or dose reduction is recommended for patients who develop persistent or recurrent grade 2 ILD. Permanently discontinue abemaciclib in all patients with Grade 3 or 4 ILD.

References

1. Johnston SRD, Harbeck N, Hegg R, et al. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR1, HER22, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol*. 2020;38(34):3987-3998. doi:10.1200/JCO.20.02514
2. Harbeck N, Rastogi P, Martin M, et al. Adjuvant Abemaciclib Combined With Endocrine Therapy for High-Risk Early Breast Cancer: Updated Efficacy and Ki-67 Analysis From the monarchE Study. (Online first). *Ann Oncol*. 2021. doi:10.1016/j.annonc.2021.09.015
3. Abemaciclib U.S. Food and Drugs Administration prescribing information. Link: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/208716s006s007s008lbl.pdf.
4. Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2021;22(2):212-222. doi:10.1016/S1470-2045(20)30642-2
5. Loibl S, Marmé F, Martin M, et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer—The Penelope-B Trial. *J Clin Oncol*. 2021;39(14):1518-1530. doi:10.1200/JCO.20.03639
6. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with BRCA1 - or BRCA2 -Mutated Breast Cancer . *N Engl J Med*. 2021;384(25):2394-2405. doi:10.1056/nejmoa2105215
7. Pan H, Gray R, Braybrooke J, et al. 20-Year Risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 Years. *N Engl J Med*. 2017;377(19):1836-1846. doi:10.1056/NEJMoa1701830
8. Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in Breast Cancer: Updated Recommendations From the International Ki67 in Breast Cancer Working Group. *JNCI J Natl Cancer Inst*. 2021;113(7):808-819. doi:10.1093/jnci/djaa201

9. Polley M-YC, Leung SCY, Gao D, et al. An international study to increase concordance in Ki67 scoring. *Mod Pathol*. 2015;28(6):778-786.
doi:10.1038/modpathol.2015.38
10. Kalinsky K, Barlow WE, Meric-Bernstam F, et al. Abstract GS3-00: First results from a phase III randomized clinical trial of standard adjuvant endocrine therapy (ET) +/- chemotherapy (CT) in patients (pts) with 1-3 positive nodes, hormone receptor-positive (HR+) and HER2-negative (HER2-) breast cancer. In: *General Session Abstracts*. American Association for Cancer Research; 2021:GS3-00-GS3-00.
doi:10.1158/1538-7445.SABCS20-GS3-00
11. Tolaney SM, Blancas I, Im Y-H, Rastogi P, Brown J, Shahir A. Patients' Quality of Life and Side-Effect Perceptions in monarchE, a Study of Abemaciclib plus Endocrine Therapy in Adjuvant Treatment of HR+, HER2-, Node-positive, High-risk, Early Breast Cancer. *St Gall Breast Cancer Conf 2021*. 2021.
12. Rugo HS, Tolaney SM, Huober J, et al. Management of abemaciclib associated adverse events in patients with hormone receptor positive (HR+), HER2- advanced breast cancer: Analysis of the MONARCH trials. *Ann Oncol*. 2018;29:viii110-viii111.
doi:10.1093/annonc/mdy272.329