How is Verzenio® (abemaciclib) administered?

SUMMARY

- Depending on the indication, the recommended dose of abemaciclib is
  - 150 mg orally, twice daily in combination with ET (EBC or Advanced or MBC), or[1-3]
  - 200 mg orally twice daily as a single agent (Advanced or MBC).[1,4]
- Abemaciclib should be taken at approximately the same time every day.[1]
- Abemaciclib may be taken with or without food.[1]
- Patients should avoid grapefruit products.[1]
- If a patient cannot swallow the abemaciclib tablet, the intact tablet may be placed in a glass with at least 10 mL of water. Allow the tablet to break apart (disperse) in the water. Please note that the tablet will not dissolve in the water to a clear solution. Once the tablet has dispersed the patient must drink all of the solution immediately (i.e., within 10 minutes of dispersing it in at least 10 mL of water).[5]
- In case of overdose, use general supportive measures. There is no known antidote for abemaciclib overdose.[5]
- Abemaciclib dose modification is recommended based on individual safety and tolerability. Management of some adverse reactions may require dose interruption and/or dose reduction. If dose reduction is necessary, reduce dose by decrements of 50 mg as shown in Table 4.[5]
  - In patients with severe hepatic impairment, decrease the dosing frequency to once daily.[1]
- Abemaciclib is primarily metabolized by CYP3A.[1]
  - Avoid concomitant use of strong CYP3A inhibitors and use caution with coadministered moderate or weak CYP3A inhibitors.[1]
  - If coadministration with a CYP3A inhibitor is unavoidable, adjust abemaciclib dose.[5]
  - Avoid concomitant use of strong and moderate CYP3A inducers. Consider alternative agents without CYP3A induction.[1]
- Based on exploratory analysis, the efficacy of adjuvant abemaciclib in monarchE was not compromised by dose reductions.[6]

RECOMMENDED DOSAGE IN EARLY BREAST CANCER

The recommended dose of abemaciclib is 150 mg orally, twice daily in combination with endocrine therapy (ET). Administer the recommended dose of ET when given with abemaciclib. It is recommended that abemaciclib treatment continue for 2 years. Treatment should be stopped if there is disease recurrence or unacceptable toxicity.[1,7]

Pre/perimenopausal women and men treated with the combination of abemaciclib plus an AI should be treated with a gonadotropin-releasing hormone agonist (GnRH) according to current clinical practice standards.[1]

Recommended Dosage in Metastatic Breast Cancer

The recommended dose of abemaciclib as a single agent is 200 mg orally, twice daily. It is recommended that treatment be continued until disease progression or unacceptable toxicity.[1,4]

The recommended dose of abemaciclib in combination with ET is 150 mg orally, twice daily. Administer the recommended dose of ET when given with abemaciclib.[1-3]

Pre/perimenopausal women treated with the combination of abemaciclib plus fulvestrant should be treated with a GnRH according to current clinical practice standards.[1]

Recommended Administration

Abemaciclib tablets should be swallowed whole. Abemaciclib tablets are not scored and are not designed to be split or divided into smaller doses.[5]

Patients should not

- chew
- crush, or
- split tablets before swallowing.[1]

No tablet should be ingested if

- broken
- cracked, or
- otherwise not intact.[1]

The patient may not get the full dose as prescribed if the tablet is crushed, broken, or split into smaller doses.[5]

Abemaciclib is for oral administration only. It is not available as a parenteral product for intravenous administration. The tablet cannot be dissolved/dispersed in an extemporaneous preparation for the purpose of intravenous administration.[5]

Non-Recommended Starting Doses

In the MONARCH 2 trial, patients were randomized in a 2:1 ratio to abemaciclib plus fulvestrant or placebo plus fulvestrant.

- Abemaciclib was administered at 150 mg orally twice daily on a continuous schedule.
- Fulvestrant was administered as a 500 mg intramuscular injection on
  - days 1 and 15 of the first cycle, and
  - day 1 of subsequent cycles (every 28 days).[3]

At study initiation, patients in the abemaciclib arm received 200 mg twice daily. Following a review of safety data and dose reduction rates, the protocol was amended to reduce the starting dose to 150 mg for new patients and all patients who were receiving 200 mg underwent a mandatory dose reduction to 150 mg.[3]

A blinded safety review revealed a high number of dose alterations for abemaciclib or placebo primarily due to diarrhea in the first treatment cycle. The starting abemaciclib dose was reduced to 150 mg twice daily to improve tolerability.[5]

Abemaciclib 150 mg twice daily is the recommended starting dose when used in combination with fulvestrant. The abemaciclib starting dose of 150 mg twice daily resulted in increased tolerability and fewer discontinuations, less diarrhea, and less severe neutropenia.[5]

There is no prospective information available on starting doses of less than 150 mg.

Details on a real-world retrospective analysis that evaluated demographic and clinical characteristics, dosing patterns, and incidence of pre-specified adverse events in patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) early breast cancer (EBC) initiating doses below 150 mg twice daily are available in a separate medical letter and available upon request.

A prospective, single-arm, open-label, phase 2 study (TRADE) is currently recruiting patients to assess whether a dose-increasing strategy for abemaciclib will have less side effects and better tolerability than the standard dosage approach in the high-risk, HR+, HER2- EBC setting.[8] Patients may receive up to 2 years of adjuvant abemaciclib plus ET. Intra-patient dose escalation for abemaciclib will be

- 50 mg twice daily on days 1 to 14
- 100 mg twice daily on days 15 to 28, and
- 150 mg twice daily on >day 28.[9]

A single-arm, open-label, phase 4 study (ADE-MI) is currently recruiting patients with high-risk, HR+, HER2- EBC to evaluate whether gradual up-titration of abemaciclib over 4 weeks will decrease the rate of grade 3 or worse diarrhea and allow more patients to stay at the intended dose. Patients will receive adjuvant abemaciclib plus ET, and after study intervention, may remain on therapy at the discretion of their treating providers. Dose escalation for abemaciclib will be

- Week 1: 50 mg twice daily
- Week 2: 100 mg twice daily
- Week 3: 150 mg in the morning and 100 mg in the evening, and
- Week 4+: 150 mg twice daily.[10,11]

Moore et al Retrospective Study on Abemaciclib Dose Escalation

A retrospective, single-center, cohort study was conducted to determine the optimal dosing for abemaciclib in patients 18 years and older with HR+, HER2- breast cancer who were treated with abemaciclib in combination with ET at the Duke Cancer Institute from October 1, 2015, to September 22, 2023. Patients were divided into three cohorts based on abemaciclib dosing strategy at initiation with

- Cohort A (n=36) receiving 50 mg
- Cohort B (n=12) receiving 100 mg, and
- Cohort C (n=80) receiving 150 mg.[12]

Patients in cohort A and B were dose escalated at varying intervals dependent on patient tolerance. The primary outcome was discontinuation rates (DCR) within 90 days due to adverse events (AEs). Secondary outcomes included

- DCR due to all causes within 90 days
- reason for DC
- grade of AE experienced
- percentage of patients on the standard regimen requiring a dose reduction (cohort C)
- highest dose maintained in the dose escalation group (cohort A), and
- time to progression (TTP) for advanced breast cancer (ABC) patients.[12]

A total of 128 female patients were included in the study, 43 (34%) with EBC and 85 (66%) with ABC. The number of post-menopausal patients was 103 (80.5%). Discontinuation rate at 90 days due to AEs was 5.6% in cohort A, 8.3% in cohort B, and 11.3% in cohort C (p=.801). Patients in Cohort A had an 81% lower chance of discontinuation of abemaciclib compared to cohort C (OR, 0.19; 95% CI, 0.02 to 1.04; p=.07).[12]

Overall, 90.6% of patients reported experiencing an AE. In cohort C, 54.5% of patients with EBC and 50.7% of patients with ABC required a dose reduction, with 43.9% of patients reducing to 50 mg. In cohort A, 37.9% and 14.3% of patients with EBC and ABC respectively, achieved a dose of 150 mg. In the ABC group, TTP was 278 days (IQR: 146.5-356) in cohort A and 287 days (IQR: 149-461) in cohort C.[12]

Dose escalation may be considered to reduce the AEs experienced in women with HR+, HER2- BC receiving abemaciclib.[12]

Administration for Patients Unable to Swallow

If a patient cannot swallow the abemaciclib tablet, the intact tablet may be placed in a glass with at least 10 mL of water. Allow the tablet to break apart (disperse) in the water. Please note that the tablet will not dissolve in the water to a clear solution. Once the tablet has dispersed the patient must drink all of the solution immediately (i.e., within 10 minutes of dispersing it in at least 10 mL of water).[5]

Make sure no residue of the tablet remained in the glass. If tablet residue remained rinse the glass with more water and let the patient drink the rinse solution. Repeat until no residue remains in the glass.[5]

The tablet may taste bitter if dispersed in water, but it is not expected that dispersing the tablet in water will alter its effectiveness.[5]

In a healthcare setting, open handling of abemaciclib powder is not recommended.[5]

Crushing or breaking the abemaciclib tablet may lead to accidental exposure to the active ingredient inside the tablet (i.e., powder containing the active ingredient) to patients not on abemaciclib therapy. Repeated exposure to the active ingredient may damage fertility, or in the case of pregnancy, the unborn child. Prolonged or repeated exposure may also cause specific target organ toxicity.[5]

Administration via Feeding Tube

Eli Lilly and Company has not performed specific studies to evaluate the impact of administering the tablets through a feeding tube such as a gastrostomy tube or jejunostomy tube. If possible, the tablets should be swallowed whole as directed in the prescribing information. Care must be taken not to expose other people to the tablet powder.[5]

If the patient cannot swallow the tablet, the intact tablet may be placed in a glass that contains at least 10 mL of water. Allow the tablet to break apart (disperse) in the water. Please note that the tablet will not dissolve in the water to a clear solution. Once the tablet has dispersed administer all of the solution with the dispersed tablet immediately (i.e., within 10 minutes of dispersing it in at least 10 mL of water).[5]

Make sure no residue of the tablet remained in the glass. If tablet residue remained behind rinse the glass with more water and administer the rinse solution. Repeat until no residue remains in the glass. Follow your standard procedure to rinse the feeding tube following the administration of the dose.[5]

It is not expected that dispersing the tablet in water for administration through a gastric tube, such as a G-tube or Y-tube, will impact the effectiveness of the tablet. The tablet contains no special coating (e.g., enteric coating), disintegrates readily in the stomach and is not impacted by the acidic environment of the stomach.[5]

Timing of Administration

- Patients should take the doses at approximately the same times every day.[1]
  - Preclinical results have also demonstrated that a chronic (or continuous) dosing strategy is important for achieving durable cell-cycle arrest.[13]
- If a patient vomits or misses a dose of abemaciclib, the patient should be instructed to take the next dose at its scheduled time.[1]

Food Effects

- Abemaciclib may be taken with or without food.[1]
- Patients should not consume grapefruit products while on treatment with abemaciclib.[1]

There is no information on the use of abemaciclib with other fruit or juices, including pomegranates or pomegranate juice.

Overdose

In case of overdose, use general supportive measures. There is no known antidote for abemaciclib overdose.[1]

DOSE MODIFICATIONS

Abemaciclib dose modification is recommended based on individual safety and tolerability. Management of some adverse reactions (eg, diarrhea, hematologic toxicities, or hepatotoxicity) may require dose interruption and/or dose reduction as shown in the following tables. If dose reduction is necessary, reduce dose by 50 mg as shown in Table 4. Discontinue abemaciclib for patients unable to tolerate 50 mg twice daily.[1,14]

Refer to the prescribing information for coadministered fulvestrant, tamoxifen, or an AI for dose modifications and other relevant safety information for those products.

Abemaciclib dose reductions were commonly and effectively implemented in monarchE to manage side effects and retain patients on treatment. Patients at high risk for toxicity requiring dose adjustment include those that are ≥65 years old or have ≥4 co-morbidities.[6]

Multiple analyses confirm that dose reductions did not compromise the efficacy of adjuvant abemaciclib in monarchE.[6]

All patients receiving adjuvant abemaciclib should be carefully monitored for toxicity, with dose adjustments as needed, with a goal of maximizing adherence to maintain benefit from adjuvant abemaciclib in combination with endocrine therapy.[6]

monarchE Dose Modifications

Detailed information provided in this section is from the most comprehensive safety analysis conducted at additional follow-up 1 (AFU1) after 27 months median follow-up, when most patients (90%) had completed 2 years of treatment and safety data were considered mature.[15] Safety findings at overall survival interim analysis 2 and overall survival interim analysis 3 remained consistent with prior monarchE analyses and the known safety profile of abemaciclib + ET.[16,17]

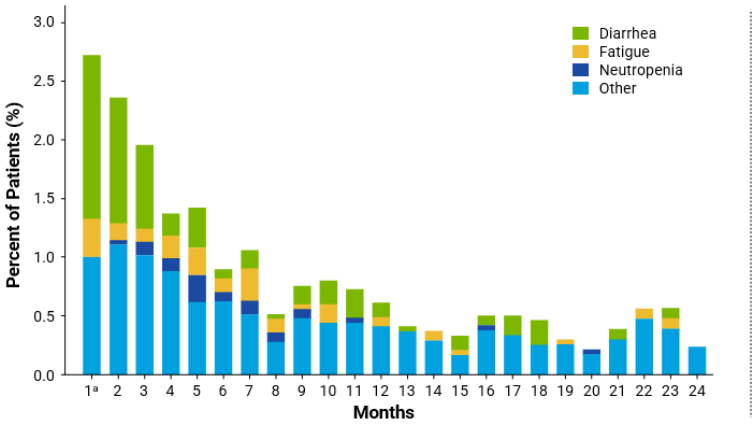
Results from exploratory analyses evaluating the impact of dose reductions on efficacy in monarchE have been published in NPJ Breast Cancer.[6]

Discontinuation of abemaciclib due to an AE was reported in 18.5% of patients in the abemaciclib arm, while 6.5% of patients in the abemaciclib arm (included in the 18.5%) discontinued both treatments. In the ET only arm, 1.1% discontinued ET due to AEs.[15]

The top 3 reasons for discontinuation of abemaciclib due to an AE in the abemaciclib arm were diarrhea (5.3%), fatigue (2.0%), and neutropenia (0.9%).[15]

While the abemaciclib discontinuation rate due to AEs was highest during the first month (2.7%), at the time of the AFU1 analysis, most discontinuations occurred in the first three months on treatment and stabilized beyond 6 months, as seen in Figure 1. Most AEs were manageable with dose adjustments and comedication, which allowed most patients to remain on treatment.[15]

Figure 1. Rates of Discontinuation of Abemaciclib due to AEs Were Highest the First Three Months[5,14,15]



Treatment Discontinuation*	Abemaciclib + ET N=2791, n (%)
For any reason	854 (30.6)
Due to AEs, including deaths due to AEs	515 (18.5)[b]
Diarrhea	147 (5.3)
Fatigue	56 (2.0)
Neutropenia	25 (0.9)[c]
Deaths due to AEs[d]	15 (0.5)

Figure 1 description: Data are from 24 months median treatment duration. The abemaciclib discontinuations were highest in the first month.

* In the by month analyses, number of patients at risk each month is used as the denominator to calculate % of events.

[a] Eighty-Eight percent of patients (67/76) discontinued treatment during the first month without prior dose reduction.

[b] Sixty-Six point Eight percent (344/515) and 52% (266/515) of abemaciclib discontinuations were due to grade 1/2 AEs (not protocol mandated) and without prior dose reduction, respectively.

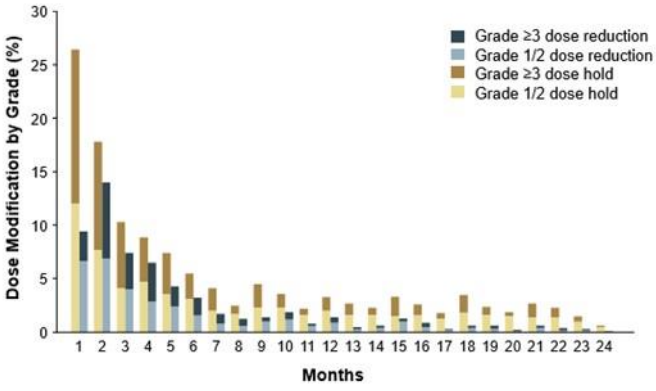
[c] One patient with neutropenia from PO analysis needed to be re-classified with different AE in the AFU1 data cut.

[d] On treatment or ≤30 days after discontinuing abemaciclib.

Abbreviations: AE = adverse event; AFU1 = additional follow-up 1; ET = endocrine therapy; N = number of patients in the safety population; n = number of patients within category; PO = primary outcome.

Most abemaciclib dose modifications due to AEs occurred early on treatment as seen in Figure 2.[15]

Figure 2. Abemaciclib Dose Modifications at AFU1 Analysis of monarchE[14,15]



Dose modifications due to AE, n (%)	Abemaciclib + ET (N=2791)[a]
Patients with dose reductions due to AE	1212 (43.4)
1 dose reduction	824 (29.5)[b]
2 dose reductions	388 (13.9)
AE leading to dose reductions	
Diarrhea	482 (17.3)
Neutropenia	226 (8.1)
Fatigue	125 (4.5)
Leukopenia	99 (3.5)
Patients with dose holds due to AE	1721 (61.7)
AE leading to dose holds	
Diarrhea	543 (19.5)
Neutropenia	440 (15.8)
Leukopenia	195 (7.0)
Fatigue	140 (5.0)

AE-related abemaciclib dose hold and reduction occurred in 61.7% and 43.4% of patients, respectively: primarily owing to diarrhea, neutropenia, or fatigue

Figure 2 description: Data are from 24 months median treatment duration. Most abemaciclib dose modifications occurred ≤6 months of therapy initiation and diminished over time.

[a] In the by month analyses, number of patients at risk each month is used as the denominator to calculate % of events.

[b] Patients who experienced 1 dose reduction at the Primary Outcome data cut but subsequently had another dose reduction before the AFU1 data cut were classified as patients with 2 dose reductions.

Abbreviations: AE = adverse events; AFU1 = additional follow-up 1; ET = endocrine therapy; N = number of patients in the safety arm; n = number of patients with dose modifications.

Less than half of the dose modifications were for grade ≥3 events.[15]

More than half (266 patients, 52%) of total discontinuations and 88% of discontinuations during the first month occurred without an attempt to address the AE via a dose modification.[15]

Abemaciclib dose adjustments due to AEs occurred in

- 1721 patients (61.7%) having held doses, and
- 1212 (43.4%) having dose reductions.[15]

Additional dose hold and reduction information is summarized in Table 1.

Table 1. Abemaciclib Dose Holds and Reductions at AFU1 Analysis of monarchE[15]

	Abemaciclib + ET (N=2791 [%])
Number (%) of patients with ≥1 dose hold due to AE	1721 (61.7)
Reasons leading to dose hold, n (%)	
Diarrhea	543 (19.5)
Neutropenia	440 (15.8)
Leukopenia	195 (7.0)
Fatigue	140 (5.0)
Number (%) of patients with ≥1 dose reduction due to an AE	1212 (43.4)

Reasons leading to dose reduction, n (%)	
Diarrhea	482 (17.3)
Neutropenia	226 (8.1)
Fatigue	125 (4.5)
Leukopenia	99 (3.5)

Abbreviation: AE = adverse event; ET = endocrine therapy.

monarchE Subgroup Analysis: Dose Modification by Age

Safety findings at a recent subgroup analysis by age inclusive of 4-year data (median follow-up, 42 months) with all treated patients off abemaciclib were consistent with previous analyses.[18]

As shown in Table 2, rates of dose modifications were higher in older patients.[18]

Table 2. Dose Modifications in monarchE by Age[18]

Abemaciclib dose adjustments due to AEs, %	Abemaciclib + ET		
	Overall Population (n=2791)	<65 years (n=2361)	≥65 years[a] (n=430)
Interruptions	62	60	68
Reductions	44	41	55
Discontinuations	18	15	38
Discontinuations without prior dose reductions	10	8	19

Abbreviations: AE = adverse event; ET = endocrine therapy.

[a] Patients ≥75 years have higher rates of abemaciclib dose adjustments and discontinuations due to AEs.

When all patients regardless of age were stratified by relative dose intensity (RDI) (Figure 3) 4-year invasive disease-free survival (IDFS) rates were generally consistent (87.1% vs 86.4% vs 83.7% from the lowest RDI group to the highest) suggesting maintenance of abemaciclib benefit upon dose modification to manage AEs.[18]

Figure 3. IDFS Stratified by RDI in Patients Treated with Abemaciclib (All Ages Included)[18]

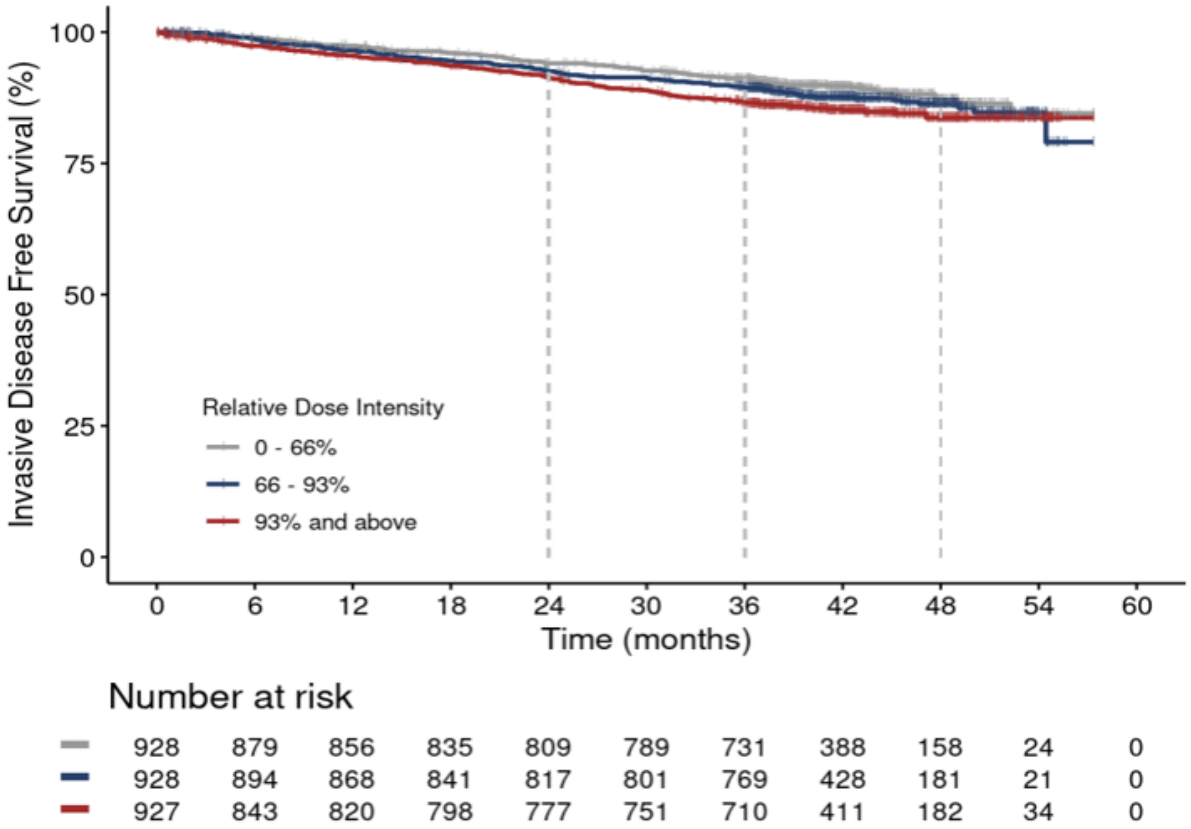


Figure 3 description: Kaplain-Meier survival curve stratified patients by RDI (defined as the average daily dose of abemaciclib received over the treatment duration, relative to the full dose [150mg twice a day]) into three equal sized subgroups (0-66%, 66-93%, and 93% and above). Patients stratified by RDI were found to have consistent 4-year IDFS rates (87.1% vs 86.4% vs 83.7% from the lowest RDI group to the highest) suggesting abemaciclib benefit is maintained when AEs are managed with dose modifications.

Abbreviations: AE = adverse event; IDFS = invasive disease-free survival; RDI = relative dose intensity.

monarchE Subgroup Analysis: Impact of Dose Reductions on Efficacy of Adjuvant Abemaciclib for Patients with High-Risk Early Breast Cancer

An exploratory analyses of 2791 patients treated with abemaciclib was conducted using data from a prespecified overall survival interim analysis (data cutoff: July 1, 2022) to investigate the impact of dose reductions on efficacy in the EBC setting. Since dose reductions were expected to be associated with lower RDI, efficacy assessment by RDI-defined patient subgroups was performed as an indirect evaluation of dose reduction impact on efficacy.[6] This method, however, does not account for the time and duration of dose adjustments. To incorporate the timing of the dose reduction and duration of treatment, a time-dependent Cox proportional hazard (PH) model was implemented to formally assess the impact of dose reductions on IDFS and DRFS.[5,6]

In monarchE, 1221 (43.7%) patients required dose reductions of abemaciclib to proactively manage adverse events. During the on-study treatment period, up to two 50 mg dose reductions were permitted prior to discontinuation. [6]

Patients treated with abemaciclib were classified into 3 equal-sized subgroups according to their RDI (≤66%, 66-93%, and ≥93%). RDI was defined as the average daily dose of abemaciclib over the actual treatment duration for each patient, relative to the full daily dose (150 mg twice daily). IDFS rates were estimated using the Kaplan-Meier method within each subgroup. [6]

Of the 2791 patients treated with abemaciclib

- 832 (29.8%) had one dose reduction, and
- 389 (13.9%) had two dose reductions.[6]

Patients ≥65 years old, or those with ≥4 co-morbidities were more likely to have dose reductions (55.8% in patients ≥65 years old and 49.9% in patients with ≥4 co-morbidities).[6]

Although patients with dose reductions had lower cumulative dose and smaller RDI, they were more likely to remain on abemaciclib treatment compared to patients without dose reductions.[6] The percentage of patients still on treatment >6 months by number of dose reductions was

- 81.3% (0 reductions, N=1570)
- 90.1% (1 reduction, N=832), and
- 85.6% (2 reductions, N=389).[6]

The IDFS rates were similar across RDI subgroups in the ITT population. The 4-year IDFS rates were generally constant (87.1% vs 86.4% vs 83.7% from the lowest RDI group to the highest) across the 3 RDI groups (0-66% vs 66%-93% vs ≥93%). Similar findings were observed in the abemaciclib-treated patients in Cohort 1.[6]

When considering the timing of dose reductions in the time-dependent Cox model, abemaciclib benefit was similar when staying at the full 150mg dose compared to being reduced to 100mg or 50mg (Table 3). These results were further supported by a time-dependent Cox PH model adjusted by baseline age, stratification factors, key disease characteristics, and pre-existing comorbidities.[6]

Table 3. Abemaciclib Efficacy with Dose Reductions in the ITT and Cohort 1 Populations[6]

Efficacy Endpoint	Staying at full dose versus Being reduced to lower doses	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
ITT		
IDFS	0.905 (0.727, 1.125)	0.922 (0.740, 1.148)
DRFS	0.942 (0.742, 1.195)	0.954 (0.751, 1.212)
Cohort 1		
IDFS	0.899 (0.718, 1.125)	0.918 (0.732, 1.150)

DRFS	0.958 (0.750, 1.223)	0.972 (0.76, 1.243)

Abbreviations: DRFS = distant relapse-free survival; HR = hazard ratio; IDFS = invasive disease-free survival; ITT = intent-to-treat.

Abemaciclib dose reductions were commonly and effectively implemented in monarchE to manage side effects and retain patients on treatment. Patients at high risk for toxicity requiring dose adjustment include those that are ≥65 years old or have ≥4 co-morbidities.[6]

Multiple analyses confirm that dose reductions did not compromise the efficacy of adjuvant abemaciclib in monarchE.[6]

All patients receiving adjuvant abemaciclib should be carefully monitored for toxicity, with dose adjustments as needed, with a goal of maximizing adherence to maintain benefit from adjuvant abemaciclib in combination with endocrine therapy.[6]

MONARCH 3 Dose Modifications

In MONARCH 3, an exploratory analysis was performed to examine the potential relationship between early toxicities associated with abemaciclib and PFS of patients. Compared to the placebo arm, patients treated with abemaciclib who had diarrhea within the first 7 days (hazard ratio [HR]=0.49; 95% confidence interval [CI]: 0.35-0.67) or who did not have diarrhea within the first 7 days (HR=0.58; 95% CI: 0.43-0.78) had an improvement in PFS.[19]

A time-dependent covariate analysis was performed to examine the association between current dose level (150 mg, 100 mg, 50 mg, and 0 mg) and PFS. Compared to being treated at the 150 mg dose level, there was no difference in PFS for patients reduced to

- 100 mg (HR=0.764; 95% CI: 0.467-1.251), or
- 50 mg (HR=0.985; 95% CI: 0.511-1.902).[20]

MONARCH 2 Dose Modifications

In MONARCH 2, the median time to dose reduction for patients started at 150 mg was 60.5 days, or approximately 2 cycles. There was no significant difference in PFS for those patients who had a dose reduction within the first 2 cycles compared to those who did not have a dose reduction within the first two cycles (HR=0.74; 95% CI: 0.47-1.17; p=.198). Results were similar for patients who had a dose reduction within the first 4 cycles compared to those who did not.[5]

However, the risk of disease progression was significantly higher following the discontinuation of abemaciclib completely (HR=2.520; 95% CI: 1.616-3.930; p<.0001).[5]

A time dependent covariate analysis was performed to evaluate the association between current dose level (150 mg, 100 mg, 50 mg, and 0 mg) and PFS. Compared to being treated at the 150 mg dose level, there was no difference in PFS for patients reduced to

- 100 mg (HR=1.033; 95% CI: 0.679-1.572; p=.8793), or
- 50 mg (HR=0.923; 95% CI: 0.499-1.706; p=.7973).[20]

Based on population pharmacokinetic/pharmacodynamic (PopPK/PD) modeling data, there is a positive linear relationship between abemaciclib exposure, tumor shrinkage, and PFS. Taking dose reductions into account, the average dose administered is similar between the patients who started at 200 mg and 150 mg twice daily, as is the observed efficacy. The totality of the

results of PopPK/PD modeling and exposure-response analysis also supports the starting dose of 150 mg twice daily in combination with fulvestrant, with dose reductions allowed in 50 mg decrements by taking into consideration the balance of risk and benefit.[5]

Dose Modification Tables

Table 4. Abemaciclib Dose Modification for Adverse Reactions[1]

Dose Level	Abemaciclib Dose in Combination With Endocrine Therapy	Abemaciclib Dose Single Agent
Recommended starting dose	150 mg twice daily	200 mg twice daily
First dose reduction	100 mg twice daily	150 mg twice daily
Second dose reduction	50 mg twice daily	100 mg twice daily
Third dose reduction	NA	50 mg twice daily

Abbreviation: NA = not applicable.

Note: Discontinue if unable to tolerate abemaciclib 50 mg twice daily.

Dose modification and management for hematologic toxicities are presented in Table 5.

Table 5. Abemaciclib Dose Modification and Management — Hematologic Toxicities[1,21]

Monitor complete blood counts prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.		
CTCAE Grade	**CTCAE Grade Definition[a]**	**Abemaciclib Dose Modifications**
Grade 1 or 2	Grade 1: <LLN - 1500/mm^3; <LLN - 1.5 x 10^9/L Grade 2: <1500 - 1000/mm^3; <1.5 - 1.0 x 10^9/L	No dose modification is required.
Grade 3	Grade 3: <1000 - 500/mm^3; <1.0 - 0.5 x 10^9/L	Suspend dose until toxicity resolves to ≤ grade 2. Dose reduction is not required.
Grade 3, recurrent, or grade 4	Grade 4: <500/mm^3; <0.5 x 10^9/L	Suspend dose until toxicity resolves to ≤ grade 2. Resume at next lower dose.
Patient requires administration of a blood cell growth factor[b]	NA	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factor and until toxicity resolves to ≤ grade 2. Resume at next lower dose unless already performed for the toxicity that led to the use of the growth factor.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; LLN = lower limit of normal; NA = not applicable.

[a] CTCAE grade definition shown for decreased neutrophil count as neutropenia was the most common hematologic toxicity

[b] Growth factor use as per current treatment guidelines.

Dose modification and management for diarrhea is presented in Table 6.

Table 6. Abemaciclib Dose Modification and Management — Diarrhea[1,5,21]

At the first sign of loose stools, start treatment with antidiarrheal agents and increase intake of oral fluids.		
CTCAE Grade	**CTCAE Grade Definition**	**Abemaciclib Dose Modifications**
Grade 1	Grade 1: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	No dose modification is required.
Grade 2	Grade 2: Increase of 4-6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	If toxicity does not resolve within 24 hours to ≤ grade 1, suspend dose until resolution. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures		Suspend dose until toxicity resolves to ≤ grade 1. Resume at next lower dose.
Grade 3 or 4 or requires hospitalization	Grade 3: Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL Grade 4: Life-threatening consequences; urgent intervention indicated	Suspend dose until toxicity resolves to ≤ grade 1. Resume at next lower dose.

Abbreviation: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events.

Dose modification and management for hepatotoxicity is presented in Table 7.

Table 7. Abemaciclib Dose Modification and Management — Hepatotoxicity[1]

Monitor ALT/AST prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	**Abemaciclib Dose Modifications**
Grade 1 (>ULN-3.0 x ULN) **Grade 2 (>3.0-5.0 x ULN)** **WITHOUT increase in total bilirubin above 2 x ULN**	No dose modification is required.
Persistent or recurrent grade 2, or grade 3 (>5.0-20.0 x ULN) **WITHOUT increase in total bilirubin above 2 x ULN**	Suspend dose until toxicity resolves to baseline or grade 1. Resume at next lower dose.
Elevation in AST and/or ALT >3 x ULN **WITH total bilirubin >2 x ULN, in the absence of cholestasis**	Discontinue abemaciclib.
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

Abbreviations: ALT = alanine transaminase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

Dose modification and management for interstitial lung disease (ILD)/pneumonitis is presented in Table 8.

Table 8. Abemaciclib Dose Modification and Management for Interstitial Lung Disease/Pneumonitis[1,21]

CTCAE Grade	CTCAE Grade Definition	Abemaciclib Dose Modifications
Grade 1 or 2	Grade 1: Asymptomatic; clinical or diagnostic observations only; intervention not indicated Grade 2: Symptomatic; medical intervention indicated; limiting instrumental ADL	No dose modification is required.
Grade 2 that persists or recurs despite maximal supportive measures and does not return to baseline or grade 1 within 7 days		Suspend dose until toxicity resolves to baseline or ≤ grade 1. Resume at next lower dose.
Grade 3 or 4	Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated Grade 4: Life-threatening respiratory compromise; urgent intervention indicated (eg. tracheotomy or intubation)	Discontinue abemaciclib.

Abbreviation: ADL = activities of daily living; CTCAE = Common Terminology Criteria for Adverse Events.

Dose modification and management for venous thromboembolic events (VTE) is presented in Table 9.

Table 9. Abemaciclib Dose Modifications and Management - VTEs[1]

CTCAE Grade	Abemaciclib Dose Modifications
Early Breast Cancer	
Any Grade	Suspend dose and treat as clinically indicated. Resume abemaciclib when the patient is clinically stable.
Advanced or Metastatic Breast Cancer	
Grade 1 or 2	No dose modification is required.
Grade 3 or 4	Suspend dose and treat as clinically indicated. Resume abemaciclib when the patient is clinically stable.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; VTE = venous thromboembolic event.

Dose modification and management for nonhematologic toxicities (excluding diarrhea, alanine transaminase/aspartate aminotransferase increased, ILD/pneumonitis and VTEs) are presented in Table 10.

Table 10. Abemaciclib Dose Modification and Management - Other Toxicities[a1]

CTCAE Grade	Abemaciclib Dose Modifications
Grade 1 or 2	No dose modification is required.

Persistent or recurrent grade 2 toxicity that does not resolve with maximal supportive measures within 7 days to baseline or grade 1	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 3 or 4	

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events; ILD = interstitial lung disease; VTE = venous thromboembolic events.

[a] Excluding diarrhea, hematologic toxicity, hepatotoxicity, ILD/pneumonitis, and VTEs.

Hepatic Impairment

For patients with severe hepatic impairment (Child-Pugh C), decrease the abemaciclib dosing frequency to once daily. No dosage adjustments are necessary in patients with mild or moderate hepatic impairment (Child-Pugh A or B).[1]

Effect of Other Drugs on Abemaciclib

Abemaciclib is primarily metabolized by cytochrome P450 (CYP) 3A4.[1] If coadministration with a strong CYP3A inhibitor is unavoidable, adjust the abemaciclib dose as described.[1]

Strong CYP3A Inhibitors

Strong and moderate CYP3A4 inhibitors increased the exposure of abemaciclib plus its active metabolites to a clinically meaningful extent and may lead to increased toxicity.[1] Strong CYP3A inhibitors include:

- **Ketoconazole**: Predicted to increase the area under the curve (AUC) of abemaciclib by up to 16-fold. Avoid concomitant use of ketoconazole.[1]
- **Clarithromycin**: Coadministration of clarithromycin 500 mg twice daily with a single 50 mg dose of abemaciclib (0.3 times the approved recommended 150 mg dosage), increased the relative potency adjusted unbound area under the curve from time zero to infinity ($AUC_{0\text{-}INF}$) of abemaciclib plus its active metabolites by 2.5-fold relative to abemaciclib alone in cancer patients.[1]

In patients with recommended starting doses of 200 mg twice daily or 150 mg twice daily, reduce the abemaciclib dose to 100 mg twice daily with concomitant use of strong CYP3A inhibitors other than ketoconazole. In patients who have had a dose reduction to 100 mg twice daily due to adverse reactions, further reduce the abemaciclib dose to 50 mg twice daily with concomitant use of strong CYP3A inhibitors.[1,5]

If a patient taking abemaciclib discontinues a CYP3A inhibitor, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the strong inhibitor.[1]

Avoid grapefruit or grapefruit products.[1]

Grapefruit and its juice contain furanocoumarins, such as bergamottin, epoxybergamottin, and 6′,7′-dihydroxybergamottin, that inhibit the CYP3A4 enzyme.[22]

Other citrus fruits like Seville oranges, pomelos, and limes may also contain relatively high levels of furanocoumarins.[23-25]

Lilly has not systematically evaluated the pharmacokinetic interactions of abemaciclib with citrus fruits.

Moderate CYP3A Inhibitors

Verapamil and diltiazem are moderate CYP3A inhibitors which are predicted to increase the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites by approximately 1.6-fold and 2.4-fold, respectively.[1]

Strong and Moderate CYP3A Inducers

Coadministration of strong or moderate CYP3A inducers decreased the plasma concentrations of abemaciclib plus its active metabolites and may lead to reduced activity. Avoid concomitant use of strong or moderate CYP3A inducers and consider alternative agents.[1,5]

Strong CYP3A Inducers

Coadministration of 600 mg daily doses of rifampin (a strong CYP3A inducer) with a single 200 mg dose of abemaciclib decreased the relative potency adjusted unbound AUC0-INF of abemaciclib plus its active metabolites (M2, M18, and M20) by approximately 70% in healthy subjects.[1]

Moderate CYP3A Inducers

Efavirenz, bosentan, and modafinil (moderate CYP3A inducers) are predicted to decrease the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by 53%, 41%, and 29%, respectively.[1]

Loperamide

Coadministration of a single 8 mg dose of loperamide with a single 400 mg dose of abemaciclib in healthy subjects increased the relative potency adjusted unbound $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites by 12%, which is not considered clinically relevant.[1]

Endocrine Therapies

In clinical studies in patients with breast cancer, there was no clinically relevant effect of fulvestrant, anastrozole, letrozole, exemestane, or tamoxifen on the pharmacokinetic (PK) of abemaciclib.[1]

Effect of Abemaciclib on Other Drugs

Loperamide

In a clinical drug interaction study in healthy subjects, coadministration of a single 8 mg dose of loperamide with a single 400 mg dose of abemaciclib in healthy subjects (2.7 times the approved recommended 150 mg dosage) increased the relative potency $AUC_{0\text{-}INF}$ of abemaciclib plus its active metabolites by 12%, and increased loperamide $AUC_{0\text{-}INF}$ by 9% and maximum

concentration (C_{max}) by 35% relative to loperamide alone. These effects are not considered clinically relevant.[1,5]

Metformin

In a clinical drug interaction study in healthy subjects, coadministration of a single 1000 mg dose of metformin, a clinically relevant substrate of renal organic cation transporter (OCT)2, and multidrug and toxin extrusion protein (MATE)1 and 2-K transporters, with a single 400 mg dose of abemaciclib (2.7 times the approved recommended 150 mg dosage) increased metformin $AUC_{0\text{-}INF}$ by 37% and C_{max} by 22% relative to metformin alone. Abemaciclib reduced the renal clearance and renal secretion of metformin by 45% and 62%, respectively, relative to metformin alone, without any effect on glomerular filtration rate as measured by iohexol clearance and serum cystatin C.[1,5]

Endocrine Therapies

In clinical studies in patients with breast cancer, there was no clinically relevant effect of abemaciclib on the PK of fulvestrant, anastrozole, letrozole, exemestane, or tamoxifen.[1]

CYP Metabolic Pathways

In a clinical drug interaction study in patients with cancer, multiple doses of abemaciclib (200 mg twice daily for 7 days) did not result in clinically meaningful changes in the pharmacokinetics of CYP1A2, CYP2C9, CYP2D6 and CYP3A4 substrates. Abemaciclib is a substrate of CYP3A4, and time-dependent changes in pharmacokinetics of abemaciclib as a result of autoinhibition of its metabolism were not observed.[1]

ENCLOSED PRESCRIBING INFORMATION

VERZENIO® (abemaciclib) tablets, for oral use, Lilly

REFERENCES

The published references below are available by contacting 1-800-LillyRx (1-800-545-5979).

1. Verzenio [package insert]. Indianapolis, IN: Eli Lilly and Company; 2025.

2. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638-3646. https://doi.org/10.1200/jco.2017.75.6155

3. Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2− advanced breast cancer who had progressed while receiving endocrine therapy. *J Clin Oncol*. 2017;35(25):2875-2884. https://doi.org/10.1200/JCO.2017.73.7585

4. Dickler MN, Tolaney SM, Rugo HS, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory $HR^+/HER2^-$ metastatic breast cancer. *Clin Cancer Res*. 2017;23(17):5218-5224. http://dx.doi.org/10.1158/1078-0432.CCR-17-0754

5. Data on file, Eli Lilly and Company and/or one of its subsidiaries.

6. 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(1):34. https://doi.org/10.1038/s41523-024-00639-1

7. Johnston SRD, Harbeck N, Hegg R, et al; monarchE Committee Members and Investigators. Abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER2−, node-positive, high-risk, early breast cancer (monarchE). *J Clin Oncol.* 2020;38(34):3987-3998. https://doi.org/10.1200/JCO.20.02514

8. TRADE: dose escalation tolerability of abemaciclib in HR+ HER2- early stage breast cancer. ClinicalTrials.gov identifier: NCT06001762. Updated March 26, 2024. Accessed May 9, 2024. https://www.clinicaltrials.gov/study/NCT06001762

9. Mayer EL. Next generation therapeutics in hormone positive breast cancer: balancing efficacy and tolerability. Oral presentation at: 46th Annual San Antonio Breast Cancer Symposium; December 5-9, 2023; San Antonio, TX. Accessed May 9, 2024. https://youtu.be/8_hSfZVDGFA

10. Abemaciclib dose escalation to maintain intensity (ADE-MI) (BRE-09). ClinicalTrials.gov identifier: NCT06169371. Updated January 26, 2024. Accessed May 9, 2024. https://www.clinicaltrials.gov/study/NCT06169371

11. Prescott K, Gadi VK, Danciu OC, et al. Abemaciclib dose escalation to maintain intensity (ADE-MI). Poster presented at: 60th Annual Meeting of the American Society of Clinical Oncology (ASCO); May 31-June 4, 2024; Chicago, IL. Accessed June 18, 2024. https://meetings.asco.org/abstracts-presentations/238252

12. Moore H, Erner E, Dent S, et al. Impact of abemaciclib dose escalation on compliance and safety in hormone receptor positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) breast cancer. Poster presented at: 47th Annual San Antonio Breast Cancer Symposium (SABCS); December 10-13, 2024; San Antonio, TX. Accessed February 14, 2025. https://sabcs.org/Portals/0/Documents/SABCS24%20-%20Formatted%20Abstracts%20Feb%2025%20update.pdf?ver=V0iZJzNQY-DH8euAlPEzNg%3d%3d

13. Tate SC, Cai S, Ajamie RT, et al. Semi-mechanistic pharmacokinetic/pharmacodynamic modeling of the antitumor activity of LY2835219, a new cyclin-dependent kinase 4/6 inhibitor, in mice bearing human tumor xenografts. *Clin Cancer Res.* 2014;20(14):3763-3774. http://dx.doi.org/10.1158/1078-0432.CCR-13-2846

14. Rugo H, O'Shaughnessy J, Song C, et al. Safety outcomes from monarchE: phase 3 study of abemaciclib combined with endocrine therapy for the adjuvant treatment of HR+, HER-2-, node-positive, high risk, early breast cancer. *The Breast.* 2021;56(suppl 1):S23-S24. St. Gallen International Breast Cancer Conference abstract P013. https://doi.org/10.1016/S0960-9776(21)00101-6

15. Rugo HS, O'Shaughnessy J, Boyle F, et al; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: safety and

patient-reported outcomes from the monarchE study. *Ann Oncol*. 2022;33(6):616-627. https://doi.org/10.1016/j.annonc.2022.03.006

16. Johnston SRD, Toi M, O'Shaughnessy J, et al; monarchE Committee Members. 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(1):77-90. https://doi.org/10.1016/S1470-2045(22)00694-5

17. Rastogi P, O'Shaughnessy J, Martin M, et al. Adjuvant abemaciclib plus endocrine therapy for hormone receptor-positive, human epidermal growth factor receptor 2-negative, high-risk early breast cancer: results from a preplanned monarchE overall survival interim analysis, including 5-year efficacy outcomes. *J Clin Oncol*. 2024;42(9):987-993. https://doi.org/10.1200/jco.23.01994

18. Hamilton EP, Kim JH, Eigeliene N, et al. Efficacy and safety results by age in monarchE: adjuvant abemaciclib combined with endocrine therapy (ET) in patients with HR+, HER2-, node-positive, high-risk early breast cancer (EBC). Poster presented at: 59th Annual Meeting of the American Society of Clinical Oncology (ASCO); June 2-6, 2023; Chicago, IL. Accessed May 22, 2023. https://meetings.asco.org/abstracts-presentations/218406

19. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer.* 2019;5:5. http://dx.doi.org/10.1038/s41523-018-0097-z

20. Rugo HS, Sledge GW Jr, Johnston S, et al. The association of early toxicity and outcomes for patients treated with abemaciclib. *J Clinical Oncol.* 2018;36(15 suppl):1053. https://doi.org/10.1200/JCO.2018.36.15_suppl.1053

21. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE) November 27, 2017. Accessed October 10, 2022. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

22. Hung WL, Suh JH, Wang Y. Chemistry and health effects of furanocoumarins in grapefruit. *J Food Drug Anal*. 2017;25(1):71-83. https://doi.org/10.1016/j.jfda.2016.11.008

23. Malhotra S, Bailey DG, Paine MF, Watkins PB. Seville orange juice-felodipine interaction: comparison with dilute grapefruit juice and involvement of furocoumarins. *Clin Pharmacol Ther*. 2001;69(1):14-23. https://doi.org/10.1067/mcp.2001.113185

24. Guo LQ, Chen QY, Wang X, et al. Different roles of pummelo furanocoumarin and cytochrome P450 3A5*3 polymorphism in the fate and action of felodipine. *Curr Drug Metab*. 2007;8(6):623-630. https://doi.org/10.2174/138920007781368917

25. Masuda M, Watanabe S, Tanaka M, et al. Screening of furanocoumarin derivatives as cytochrome P450 3A4 inhibitors in citrus. *J Clin Pharm Ther*. 2018;43(1):15-20. https://doi.org/10.1111/jcpt.12595