

**Product Monograph
Including Patient Medication Information**

PrVERZENIO®

Abemaciclib tablets

For oral use

50 mg, 100 mg, 150 mg, 200 mg of abemaciclib

Protein Kinase Inhibitor

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Part 1: Healthcare Professional Information

1 Indications

Early Breast Cancer

VERZENIO® (abemaciclib tablets) is indicated in combination with endocrine therapy 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 disease recurrence based on clinicopathological features.

Advanced or Metastatic Breast Cancer

VERZENIO (abemaciclib tablets) is indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer.

- In combination with an aromatase inhibitor in postmenopausal women as initial endocrine-based therapy.-
- In combination with fulvestrant in women with disease progression following endocrine therapy. Pre- or perimenopausal women must also be treated with a gonadotropin-releasing hormone (GnRH) agonist.
- As a single agent in women with disease progression following endocrine therapy and at least 2 prior chemotherapy regimens. At least one chemotherapy regimen should have been administered in the metastatic setting, and at least one should have contained a taxane.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years of age): Evidence from clinical trials showed no differences in safety or effectiveness of VERZENIO between patients ≥65 years and < 65 years of age with early breast cancer or metastatic breast cancer.

2 Contraindications

VERZENIO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, (see [6 Dosage Forms, Strengths, Composition and Packaging](#)).

3 Serious Warnings and Precautions Box

The following are significant adverse drug reactions identified in clinical trials conducted with VERZENIO:

- Venous thromboembolism, including deaths (see [4.2 Recommended Dose and Dosage Adjustment](#), and [7 Warnings and Precautions, Hematologic](#))

4 Dosage and Administration

4.1 Dosing Considerations

Pre/perimenopausal women and men treated with the combination of VERZENIO plus an aromatase inhibitor should be treated with a gonadotropin releasing hormone (GnRH) agonist according to local clinical practice.

Patients with severe hepatic impairment require dose adjustment (see [4.2 Recommended Dose and Dosage Adjustment](#), and [10 Clinical Pharmacology](#)).

Health Canada has not authorized an indication for pediatric use (see [1.1 Pediatrics](#)).

4.2 Recommended Dose and Dosage Adjustment

For early breast cancer in combination with Endocrine Therapy:

The recommended dose of VERZENIO is 150 mg taken orally, twice daily. For early breast cancer (EBC) continue VERZENIO until completion of either 2 years of treatment or until disease recurrence or unacceptable toxicity.

For advanced or metastatic breast cancer:

When used in combination with endocrine therapy, the recommended dose of VERZENIO is 150 mg taken orally, twice daily. When used as a single agent, the recommended dose of VERZENIO is 200 mg taken orally, twice daily. For advanced or metastatic breast cancer (MBC), continue treatment until disease progression or unacceptable toxicity.

For full dosing instructions of the coadministered endocrine therapy, refer to the corresponding Product Monograph.

For All Indications:

Management of some adverse reactions may require dose interruptions, dose reductions and/or permanent discontinuation of VERZENIO. The recommended VERZENIO dose modifications for adverse reactions are provided in Tables 1-7.

For dose modifications and other relevant safety information of the coadministered endocrine therapy, refer to the corresponding Product Monograph.

Discontinue VERZENIO for patients unable to tolerate 50 mg twice daily.

Table 1 - VERZENIO Dose Modifications for Adverse Reactions

Dose Level	VERZENIO Dose Combination with Endocrine Therapy	VERZENIO Dose for 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	not applicable	50 mg twice daily

Table 2 - VERZENIO Dose Modification and Management for Hematologic Toxicities^a

Monitor complete blood counts prior to the start of VERZENIO therapy, every two weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade	VERZENIO 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 <i>next lower dose</i> .

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events.

^a If blood cell growth factors are required, suspend VERZENIO 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 dose already reduced for the toxicity that led to the use of the growth factor. Use growth factor as per current treatment guidelines.

Table 3 - VERZENIO Dose Modification and Management for Diarrhea

At the first sign of loose stools, start treatment with antidiarrheal agents, such as loperamide, and increase intake of oral fluids.	
CTCAE Grade	VERZENIO 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. No dose reduction is 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 <i>next lower dose</i> .
Grade 3 or 4 or requires hospitalization	

Table 4 - VERZENIO Dose Modification and Management for Hepatotoxicity

Monitor ALT, AST, and serum bilirubin prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated.	
CTCAE Grade for ALT and AST	VERZENIO 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 <i>next lower dose</i> .
Elevation in AST and/or ALT >3 x ULN WITH total bilirubin >2 x ULN, in the absence of cholestasis	Discontinue VERZENIO.
Grade 4 (>20.0 x ULN)	Discontinue VERZENIO.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal.

Table 5 - VERZENIO Dose Modification and Management for Interstitial Lung Disease (ILD)/Pneumonitis

CTCAE Grade	VERZENIO 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 <i>next lower dose</i> .
Grade 3 or 4	Discontinue VERZENIO.

Table 6 - VERZENIO Dose Modification and Management for Venous Thromboembolic Events (VTEs)

CTCAE Grade	VERZENIO Dose Modifications
Early Breast Cancer	
Any Grade	Suspend dose and treat as clinically indicated. Resume VERZENIO 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 VERZENIO when the patient is clinically stable.

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate (see [7 Warnings and Precautions](#)).

Table 7 - VERZENIO Dose Modification and Management for Other Toxicities^a

CTCAE Grade	VERZENIO 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 <i>next lower dose</i> .
Grade 3 or 4	Suspend dose until toxicity resolves to baseline or ≤Grade 1. Resume at <i>next lower dose</i> .

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

CYP3A inhibitors

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministered moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors. If coadministration with a CYP3A inhibitor is unavoidable, adjust the abemaciclib dose as described in Table 21 (see [9 Drug Interactions](#)).

If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor (see [9 Drug Interactions](#), and [10 Clinical Pharmacology](#)).

Avoid grapefruit, grapefruit juice, or grapefruit products.

Severe hepatic impairment (Child-Pugh Class C)

Decrease the dosing frequency to once daily (see [7 Warnings and Precautions](#), and [10 Clinical Pharmacology](#)).

CYP3A inducers

Avoid concomitant use of strong CYP3A inducers (for example, rifampin). Consider alternative agents with less CYP3A induction (see [10 Clinical Pharmacology](#)).

4.4 Administration

VERZENIO tablets should be swallowed whole (do not to chew, crush, or split tablets before swallowing). No tablet should be ingested if it is not intact.

VERZENIO may be taken with or without food (see [10 Clinical Pharmacology](#)). Patients should be instructed to take their doses of VERZENIO at approximately the same times every day.

4.5 Missed Dose

If the patient vomits or misses a dose of VERZENIO, the patient should take the prescribed dose at the next scheduled time. The patient should not take 2 doses at the same time to make up for the missed dose.

5 Overdose

There is no known antidote for VERZENIO. The treatment of overdose of VERZENIO should consist of general supportive measures.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition and Packaging

Table 8 - Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength	Non-medicinal Ingredients (Tablet Core)	Non-medicinal Ingredients (Tablet Film Coating)
Oral	Tablet / 50 mg	croscarmellose sodium, lactose monohydrate, microcrystalline cellulose 101, microcrystalline cellulose 102, silicon dioxide, sodium stearyl fumarate	<u>Beige:</u> iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide
Oral	Tablet / 100 mg		<u>White:</u> polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide
Oral	Tablet / 150 mg		<u>Yellow:</u> iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide
Oral	Tablet / 200 mg		<u>Beige:</u> iron oxide red, iron oxide yellow, polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide

Description

VERZENIO is supplied in packages of 28 tablets (two blister packs of 14 tablets) in dose strengths of 50 mg, 100 mg, 150 mg, or 200 mg.

VERZENIO 50 mg tablets are a modified oval beige tablet with “Lilly” debossed on one side and “50” on the other side.

VERZENIO 100 mg tablets are a modified oval white to practically white tablet with “Lilly” debossed on one side and “100” on the other side.

VERZENIO 150 mg tablets are a modified oval yellow tablet with “Lilly” debossed on one side and “150” on the other side.

VERZENIO 200 mg tablets are a modified oval beige tablet with “Lilly” debossed on one side and “200” on the other side.

7 Warnings and Precautions

Please see [3 Serious Warnings and Precautions Box](#).

Driving and Operating Machinery

No studies on the effects of VERZENIO (abemaciclib) on the ability to drive or operate machinery have been conducted. However, since fatigue and dizziness have been reported with the use of VERZENIO, patients should exercise caution when driving or operating machinery while taking VERZENIO.

Gastrointestinal

Diarrhea

Diarrhea was the most frequently reported adverse reaction in EBC patients treated with VERZENIO plus endocrine therapy (All Grade: 83%, Grade 3: 8%) and MBC patients treated with VERZENIO plus letrozole or anastrozole (All Grade: 82%, Grade 3: 10%), VERZENIO plus fulvestrant (All Grade: 86%, Grade 3: 13%), or VERZENIO as a single agent (All Grade: 90%, Grade 3: 20%). There were no reports of Grade 4 diarrhea (see [8 Adverse Reactions](#)).

Diarrhea incidence was greatest during the first month of VERZENIO dosing. The time to onset and resolution for diarrhea were similar across monarchE, MONARCH 3, MONARCH 2, and MONARCH 1 (see [8 Adverse Reactions](#)). The median time to onset of the first diarrhea event ranged from 6 to 8 days; and the median duration of Grade 2 and Grade 3 diarrhea ranged from 6 to 11 days and 5 to 8 days, respectively. Across studies, 19% to 26% of patients with diarrhea required a VERZENIO dose omission and 17% to 23% required a dose reduction.

At the first sign of loose stools, patients should start antidiarrheal therapy such as loperamide, increase oral fluids, and notify their healthcare professional for further instructions and appropriate follow-up. For Grade 3 or 4 diarrhea, or diarrhea that requires hospitalization, discontinue VERZENIO until toxicity resolves to ≤Grade 1, and then resume VERZENIO at the next lower dose (see [4 Dosage and Administration](#)).

Hematologic

Neutropenia

Grade ≥3 neutropenia was reported in patients receiving abemaciclib in EBC and MBC studies.

The occurrence of any grade neutropenia in VERZENIO-treated patients ranged from 37% to 46% (monarchE, MONARCH 1, MONARCH 2, MONARCH 3). Grade ≥3 neutropenia (based on laboratory findings) occurred in VERZENIO-treated patients and ranged from 19% to 32%. Across studies, the median time to the first episode of Grade ≥3 neutropenia ranged from 29 days to 37 days, and the median duration of Grade ≥3 neutropenia ranged from 12 days to 16 days. (see [8 Adverse Reactions](#)).

Febrile neutropenia was reported in ≤1% of patients exposed to VERZENIO in the MONARCH studies. Two deaths due to neutropenic sepsis were observed in MONARCH 2. Inform patients to promptly report any episodes of fever to their healthcare professional (see [Patient Medication Information](#)).

Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see

[4 Dosage and Administration](#), and [7 Warnings and Precautions, Monitoring and Laboratory Tests](#)).

Venous Thromboembolism

The occurrence of any grade venous thromboembolic events in VERZENIO-treated patients (monarchE, MONARCH 2, MONARCH 3) ranged from 2% to 6%. Venous thromboembolic events included deep vein thrombosis (DVT), pulmonary embolism, pelvic venous thrombosis, cerebral venous thrombosis, subclavian and axillary vein thrombosis, and inferior vena cava thrombosis. Across the clinical development program, deaths due to venous thromboembolism have been reported (see [8 Adverse Reactions](#)).

Dose interruption is recommended for EBC patients with any grade venous thromboembolic event and for MBC patients with a Grade 3 or 4 venous thromboembolic event (see [4 Dosage and Administration](#)).

Arterial Thromboembolic Events

In metastatic breast cancer studies, serious arterial thromboembolic events (ATEs), including ischemic stroke and myocardial infarction, have been reported more frequently in the VERZENIO treatment arms when administered in combination with endocrine therapies. A causal association has not been established between VERZENIO treatment and an increased risk of ATEs. The benefits and risks of continuing VERZENIO in patients who experience a severe ATE should be considered.

Hepatic/Biliary/Pancreatic

Hepatotoxicity

Grade ≥ 3 increased ALT and AST was reported in patients receiving abemaciclib in EBC and MBC studies.

The occurrence of Grade ≥ 3 ALT and AST increases in VERZENIO-treated patients (monarchE, MONARCH 2, MONARCH 3) ranged from 2% to 6% and from 2% to 4%, respectively (see [8 Adverse Reactions](#)). Across studies, the median time to onset of Grade ≥ 3 ALT increases ranged from 57 days to 87 days and the median time to resolution to Grade < 3 was 13 days to 14 days. The median time to onset of Grade ≥ 3 AST increases ranged from 83 days to 185 days and the median time to resolution to Grade < 3 ranged from 11 days to 15 days.

Dose interruption, dose reduction, or dose discontinuation is recommended for patients who develop persistent or recurrent Grade 2, or Grade 3 or 4, hepatic transaminase elevation (see [4 Dosage and Administration](#), and [7 Warnings and Precautions, Monitoring and Laboratory Tests](#)).

Immune

Infections

Infections were reported in patients receiving abemaciclib plus endocrine therapy at a higher rate than in patients treated with placebo plus endocrine therapy and were also reported in patients treated with single-agent abemaciclib. Fatal events of infection occurred in approximately 1% of patients across the MONARCH 1, MONARCH 2 and MONARCH 3 studies.

Monitoring and Laboratory Tests

Monitor complete blood counts prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see [4 Dosage and Administration](#), and [7 Warnings and Precautions](#)).

Monitor liver function tests prior to the start of VERZENIO therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated (see [4 Dosage and Administration](#), and [7 Warnings and Precautions](#)).

Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate (see [4 Dosage and Administration](#), and [7 Warnings and Precautions](#)).

Monitor patients for signs and symptoms of infection and treat as medically appropriate (see [7 Warnings and Precautions](#)).

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (see [4 Dosage and Administration](#), and [7 Warnings and Precautions](#)).

Reproductive Health

Women with reproductive potential should be advised to use highly effective contraception during treatment with VERZENIO and for at least 3 weeks after the last dose (see [7.1.1 Pregnant Women](#) and [16 Non-Clinical Toxicology](#)).

Pregnancy testing is recommended for women of reproductive potential prior to initiating treatment with VERZENIO.

- **Fertility**

Cytotoxic effects to the male reproductive tract in rodents and dogs indicate that abemaciclib may impair fertility in males (see [16 Non-Clinical Toxicology](#)).

- **Teratogenic Risk**

Abemaciclib was teratogenic in rats (see [16 Non-Clinical Toxicology](#)).

Respiratory

Severe, life threatening, or fatal interstitial lung disease (ILD)/pneumonitis can occur in patients treated with VERZENIO. In VERZENIO-treated patients in EBC (monarchE: n=2791), 3% of patients experienced ILD/pneumonitis of any grade: 0.4% had Grade 3 or 4 ILD and there was one fatality due to ILD/pneumonitis (<0.1%). In VERZENIO-treated patients in MBC (MONARCH 1, MONARCH 2, MONARCH 3: n=900), 3.2% of VERZENIO-treated patients had ILD/pneumonitis of any grade, 0.4% had Grade 3 or 4 ILD, and 0.4% had fatal ILD/pneumonitis. The median time to onset of ILD/pneumonitis was 6.3 months for VERZENIO-treated patients in EBC and 8.2 months for VERZENIO-treated patients in MBC after the initiation of VERZENIO.

Other potential causes of ILD/pneumonitis should be excluded. Dose interruptions or dose reduction is recommended for patients who develop persistent or recurrent Grade 2 ILD/pneumonitis. Permanently discontinue VERZENIO in all patients with Grade 3 or 4

ILD/pneumonitis (see [4 Dosage and Administration](#)).

7.1 Special Populations

7.1.1 Pregnancy

There are no available human data on VERZENIO use in pregnant women to inform any drug-associated risks. In animal studies, abemaciclib was teratogenic and caused decreased fetal weight at maternal exposures similar to the exposure in humans at the recommended clinical dose (see [16 Non-Clinical Toxicology](#)). Based on findings in animals and its mechanism of action, VERZENIO can cause fetal harm when administered to a pregnant woman.

Pregnant women or women who become pregnant while taking the drug should be apprised of the potential hazard to the fetus (see [16 Non-Clinical Toxicology](#)).

7.1.2 Breastfeeding

It is unknown if abemaciclib or its metabolites are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfed infants from VERZENIO, advise lactating women not to breastfeed during VERZENIO treatment and for at least 3 weeks after the last dose.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorised an indication for pediatric use.

8 Adverse Reactions

8.1 Adverse Reaction Overview

The safety of VERZENIO has been assessed in patients from three randomized Phase 3 studies and one single-arm Phase 2 study of patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

The most common adverse reactions reported in $\geq 20\%$ of patients in any study receiving abemaciclib in combination with endocrine treatment or as a single agent were diarrhea, neutropenia, fatigue, infections, nausea, vomiting, abdominal pain, decreased appetite, anemia, alopecia, leukopenia, headache, and thrombocytopenia.

The most common serious adverse reactions reported in patients in any study receiving abemaciclib in combination with endocrine treatment or as a single agent were pneumonia, sepsis, pulmonary embolism, deep venous thrombosis, diarrhea, neutropenia, anemia, and pneumonitis; the frequency of these events varied across studies and ranged from 0.1% to 2.1% of patients.

Of the 2791 VERZENIO-treated patients in monarchE (early breast cancer trial), 15.4% were 65 years of age or older. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients.

Of the 900 patients who received VERZENIO in MONARCH 1, MONARCH 2, and MONARCH 3 (metastatic breast cancer trials), 38% were 65 years of age or older. No overall differences in safety or effectiveness of VERZENIO were observed between these patients and younger patients; however, subgroup analyses from clinical studies demonstrated that patients ≥ 65 years of age reported more hematologic adverse events, hypokalemia (including Grade 3), hypocalcemia, Grade ≥ 3 infections, decreased appetite, and increased blood creatinine compared to younger patients.

Population pharmacokinetic analyses of combined data from monarchE, MONARCH 2 and MONARCH 3 demonstrated that East Asian patients do not have significantly different abemaciclib exposure compared to patients of other races; however, higher frequencies of adverse events (any grade and Grade ≥ 3) of ALT increased, AST increased, and neutropenia were reported in East Asian patients compared to Caucasian patients in subgroup analyses of data for monarchE, MONARCH 2 and MONARCH 3. No dose adjustment based on race is required for abemaciclib.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect the rates observed in clinical practice and should not be compared to the frequencies reported in clinical trials of another drug.

Early Breast Cancer – Combination with Endocrine Therapy

The safety of VERZENIO (150 mg twice daily) plus endocrine therapy was evaluated in monarchE, a Phase 3 randomized (1:1) open-label trial (see [14 Clinical Trials](#)). The data described below reflect exposure to VERZENIO in 2791 out of 5591 adult women and men with HR-positive, HER2-negative, node-positive, early breast cancer at high risk of recurrence who received at least 1 dose of VERZENIO plus endocrine therapy. Choice of standard endocrine therapy such as tamoxifen or an aromatase inhibitor, with or without ovarian function suppression or androgen suppression per standard practice was as determined by the investigator. Patients who had a history of VTE were not eligible for the study.

At the time of the final overall survival analysis, in the VERZENIO plus endocrine therapy arm the median follow-up was 76 months for VERZENIO and for the endocrine-treatment. Median dose compliance was 98% for VERZENIO.

Dose reductions of VERZENIO due to an adverse reaction occurred in 44% of patients receiving VERZENIO plus endocrine therapy, most commonly due to diarrhea (17%) and neutropenia (8%).

In the VERZENIO plus endocrine therapy arm, permanent discontinuation of VERZENIO due to an adverse event was reported in 19% of patients, including 6% of patients who discontinued both study drugs. In the endocrine therapy only arm, 1.1% of patients permanently discontinued endocrine therapy due to an adverse event. The most common adverse reactions leading to VERZENIO discontinuations were diarrhea (5%), fatigue (2%), and neutropenia (0.9%).

Deaths during treatment or during the 30-day follow up, regardless of causality, were reported in 21 cases (0.8%) of VERZENIO plus endocrine therapy treated patients versus 20 cases (0.7%)

of endocrine therapy alone treated patients. The causes of death during treatment and during the 30-day follow up in patients receiving VERZENIO plus endocrine therapy were: cardiac arrest (n=1), cardiac failure (n=2), myocardial infarction (n=1), ventricular fibrillation (n=1), cerebral hemorrhage (n=1), cerebrovascular accident (n=1), pneumonitis (n=1), hypoxia (n=1), diarrhea (n=1), mesenteric artery thrombosis (1), general physical health deterioration (n=1), pneumonia (1), COVID-19 pneumonia (1), suspected COVID-19 (1), and study disease (6).

The safety profile for men treated with VERZENIO in combination with endocrine therapy is consistent with that observed in women.

Adverse reactions reported in $\geq 10\%$ and at a higher frequency in patients who received VERZENIO plus endocrine therapy than in patients who received endocrine therapy alone in monarchE are listed in Table 9.

Table 9 - Adverse Reactions ($\geq 10\%$ and at a Higher Frequency in Patients Receiving VERZENIO Plus Endocrine Therapy Versus Patients Receiving Endocrine Therapy Alone) in monarchE

Adverse Reaction	VERZENIO Plus Endocrine Therapy N=2791			Endocrine Therapy Alone N=2800		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood and Lymphatic System Disorders						
Neutropenia	46	19	<1	6	<1	<1
Leukopenia	38	11	<1	7	<1	0
Anemia	25	2	<1	4	<1	<1
Lymphopenia	14	5	<1	3	<1	0
Thrombocytopenia	13	1	<1	2	<1	<1
Gastrointestinal Disorders						
Diarrhea ^a	84	8	0	9	<1	0
Nausea	30	<1	0	9	<1	0
Vomiting	18	<1	0	5	<1	0
Stomatitis	16	<1	0	6	0	0
General Disorders and Administration Site Conditions						
Fatigue	41	3	0	18	<1	0
Infections and Infestations						
Infections ^{b,c}	52	5	<1	39	3	<1
Investigations						

Alanine aminotransferase increased	13	3	<1	6	<1	0
Aspartate aminotransferase increased	12	2	<1	5	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	12	<1	0	3	<1	0
Nervous System Disorders						
Headache	20	<1	0	15	<1	0
Dizziness	11	<1	0	7	<1	0
Skin and Subcutaneous Tissue Disorders						
Rash	11	<1	0	5	0	0
Alopecia	11	0	0	3	0	0

^a One Grade 5 event was reported in the VERZENIO plus endocrine therapy arm.

^b Eight Grade 5 events were reported; 3 in the Verzenio plus endocrine arm and 5 in the endocrine therapy alone arm.

^c Includes all reported preferred terms that are part of the Infections and Infestations system organ class. Most common infections (>5%) include upper respiratory tract infection, urinary tract infection, and nasopharyngitis.

Additional adverse reactions in monarchE reported in VERZENIO-treated patients include:

- Pruritus-9%
- Dyspepsia-8%
- Nail disorder-6%
- Lacrimation increased-6%
- Dysgeusia-5%
- Venous thromboembolic events (including pulmonary embolism)-3%

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, leukopenia, diarrhea, infections, and lymphopenia.

Diarrhea incidence was greatest during the first month of VERZENIO dosing and was lower during subsequent months. The median time to onset of the first diarrhea event was 8 days, and the median durations of diarrhea for Grade 2 and Grade 3 were 6 days and 5 days, respectively. Most diarrhea events recovered or resolved (96%) with supportive treatment alone or together with VERZENIO dose modifications (see [4 Dosage and Administration](#), and [Patient Medication Information](#)). The median time to the first dose reduction due to diarrhea was 55 days. Twenty-three percent (23%) of patients with diarrhea required a dose omission.

Metastatic Breast Cancer – VERZENIO in combination with an Aromatase Inhibitor

The safety of VERZENIO (150 mg twice daily) plus anastrozole (1 mg/day) or letrozole (2.5 mg/day) was evaluated in MONARCH 3, a Phase 3 randomized (2:1), double-blinded,

placebo-controlled trial (see [14 Clinical Trials](#)). The data described below reflect exposure to VERZENIO in 327 out of 488 patients with HR-positive, HER2-negative metastatic breast cancer who received at least 1 dose of VERZENIO plus anastrozole or letrozole. Patients were randomly assigned to receive the combination of VERZENIO plus anastrozole or letrozole versus placebo plus anastrozole or letrozole. The median duration of treatment was 15.3 months for the VERZENIO arm and 13.9 months for the placebo arm.

Dose reductions due to an adverse reaction occurred in 47% of patients receiving VERZENIO plus a non-steroidal aromatase inhibitor (NSAI), most commonly due to diarrhea (14%) and neutropenia (13%), compared to 2% and 0.6%, respectively, for patients treated with placebo plus an NSAI.

Permanent study treatment discontinuation due to an adverse event was reported in 17% of patients receiving VERZENIO plus an aromatase inhibitor and in 3% of the patients receiving placebo plus an aromatase inhibitor. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus an aromatase inhibitor included alanine aminotransferase (ALT) increased (1.8%), lung infection (1.8%), diarrhea (1.2%), and venous thromboembolic events (VTEs) (1.2%).

Deaths on therapy or within 30 days of treatment discontinuation were reported for 15 patients (4.6%) treated with VERZENIO plus NSAI (including 11 [3.4%] due to adverse events and 4 [1.2%] due to study disease) and 3 patients (2%) treated with placebo plus NSAI (including 2 [1.2%] due to adverse events and 1 [0.6%] due to study disease). Causes of death for patients receiving VERZENIO plus an aromatase inhibitor included: 4 (1.2%) due to underlying disease, 4 (1.2%) due to lung infection, 2 (0.6%) due to VTE, 2 (0.6%) due to respiratory failure, 1 (0.3%) due to cerebral ischemia, 1 (0.3%) due to cerebrovascular accident, and 1 (0.3%) due to pneumonitis.

Treatment-emergent adverse events reported in $\geq 5\%$ and at a higher frequency in patients who received VERZENIO plus anastrozole or letrozole than in patients who received placebo plus anastrozole or letrozole in MONARCH 3 are listed in Table 10.

Table 10 - Treatment-Emergent Adverse Events ($\geq 5\%$ and at a Higher Frequency in Patients Receiving VERZENIO Plus Anastrozole or Letrozole Versus Patients Receiving Placebo Plus Anastrozole or Letrozole) in MONARCH 3

Treatment-Emergent Adverse Event	VERZENIO + anastrozole or letrozole N=327			Placebo + anastrozole or letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood and Lymphatic System Disorders						
Neutropenia	44	22	2	2	<1	<1
Anemia	32	7	0	8	1	0
Leukopenia	22	8	<1	3	0	<1
Thrombocytopenia	13	2	<1	3	<1	0

Lymphopenia	7	3	0	4	0	0
Eye Disorders						
Lacrimation increased	7	0	0	<1	0	0
Dry eye	5	0	0	<1	0	0
Gastrointestinal Disorders						
Diarrhea	82	10	0	32	1	0
Nausea	41	1	0	21	1	0
Abdominal pain	31	2	0	13	1	0
Vomiting	30	2	0	13	3	0
Constipation	17	<1	0	14	0	0
Stomatitis	13	0	0	11	0	0
Dyspepsia	8	0	0	3	0	0
Dry mouth	5	0	0	3	0	0
General Disorders and Administration Site Conditions						
Fatigue	41	2	0	34	0	0
Influenza like illness	12	0	0	9	0	0
Peripheral edema	10	0	0	6	0	0
Pain	8	<1	0	7	0	0
Infections and Infestations						
Upper respiratory tract infection	10	0	0	6	0	0
Lung infection	7	2	<1	3	0	0
Injury, Poisoning and Procedural Complications						
Fall	6	<1	0	3	<1	0
Investigations						
Blood creatinine increased	21	2	<1	4	0	0
Alanine aminotransferase increased	17	6	<1	8	2	0
Aspartate aminotransferase increased	17	4	0	8	1	0
Weight decreased	11	<1	0	3	<1	0

Blood alkaline phosphatase increased	6	<1	0	4	<1	0
Metabolism and Nutrition Disorders						
Decreased appetite	26	2	0	11	<1	0
Hypokalemia	9	3	<1	1	0	0
Musculoskeletal and Connective Tissue Disorders						
Bone pain	10	0	0	9	0	0
Muscular weakness	5	0	0	4	<1	0
Nervous System Disorders						
Headache	20	<1	0	16	0	0
Dizziness	14	<1	0	11	0	0
Neuropathy	11	<1	0	10	0	0
Dysgeusia	10	0	0	3	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	15	0	0	12	0	0
Dyspnea	12	<1	<1	7	<1	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	28	0	0	11	0	0
Rash	15	<1	0	5	0	0
Pruritus	14	0	0	9	0	0
Dry skin	10	0	0	3	0	0
Nail ridging	5	0	0	1	0	0
Vascular Disorders						
Hypertension	7	3	0	6	<1	0
Venous thromboembolic events ^a	6	2	<1	<1	0	<1

^a Venous thromboembolic events included deep vein thrombosis (DVT), pulmonary embolism, and pelvic venous thrombosis.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, increased ALT, and anemia.

Diarrhea incidence was greatest during the first month of VERZENIO dosing and was lower during subsequent months. The median time to onset of the first diarrhea event was 8 days, and the median durations of diarrhea for Grade 2 and Grade 3 were 12 days and 8 days, respectively. Most diarrhea events recovered or resolved (89%) with supportive treatment alone or together with VERZENIO dose modifications (see [4 Dosage and Administration](#), and [Patient Medication Information](#)). The median time to the first dose reduction due to diarrhea was 41 days. Nineteen percent (19%) of patients with diarrhea required a dose omission.

Metastatic Breast Cancer – Combination with Fulvestrant

The safety of VERZENIO (150 mg twice daily) plus fulvestrant (500 mg) was evaluated in MONARCH 2, a Phase 3 randomized (2:1), double-blinded, placebo-controlled trial (see [14 Clinical Trials](#)). The data described below reflect exposure to VERZENIO in 441 out of 664 patients with HR-positive, HER2-negative metastatic breast cancer who received at least 1 dose of VERZENIO plus fulvestrant in MONARCH 2. Patients were randomly assigned to receive the combination VERZENIO plus fulvestrant, versus placebo plus fulvestrant.

Median duration of treatment was 12 months for patients receiving VERZENIO plus fulvestrant and 8 months for patients receiving placebo plus fulvestrant.

Dose reductions due to an adverse reaction occurred in 43% of patients receiving VERZENIO plus fulvestrant. The most frequently reported adverse events that led to dose reduction were diarrhea (19%) and neutropenia (10%).

Permanent study treatment discontinuation due to an adverse event was reported in 9% of patients receiving VERZENIO plus fulvestrant and in 3% of patients receiving placebo plus fulvestrant. Adverse reactions leading to permanent discontinuation for patients receiving VERZENIO plus fulvestrant which occurred at $\geq 1\%$ were infection (1.6%), diarrhea (1.4%), and hepatotoxicity (0.9%).

Deaths on therapy or within 30 days of treatment discontinuation were reported for 14 patients (3.2%) treated with VERZENIO plus fulvestrant and for 10 patients (4.5%) treated with placebo plus fulvestrant. Causes of death for patients receiving VERZENIO plus fulvestrant included: 5 (1.1%) due to underlying disease, 3 (0.7%) due to sepsis, 1 (0.2%) due to cerebral infarction, 1 (0.2%) due to hepatic failure, 1 (0.2%) due to hepatotoxicity, 1 (0.2%) due to lung infection, 1 (0.2%) due to multiple organ dysfunction syndrome, and 1 (0.2%) due to pneumonitis.

Treatment-emergent adverse events reported in $\geq 5\%$ and at a higher frequency in patients who received VERZENIO plus fulvestrant than in patients who received placebo plus fulvestrant in MONARCH 2 are listed in Table 11.

Table 11 - Treatment-Emergent Adverse Events ($\geq 5\%$ and at a Higher Frequency in Patients Receiving VERZENIO Plus Fulvestrant Versus Patients Receiving Placebo Plus Fulvestrant) in MONARCH 2

Treatment-Emergent Adverse Event	VERZENIO + Fulvestrant N=441			Placebo + Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood and Lymphatic System Disorders						
Neutropenia	46	24	3	4	1	<1
Anemia	29	7	<1	4	<1	0
Leukopenia	28	9	<1	2	0	0
Thrombocytopenia	16	2	1	3	0	<1

Lymphopenia	7	3	<1	<1	0	0
Eye Disorders						
Lacrimation increased	7	<1	0	1	0	0
Gastrointestinal Disorders						
Diarrhea	86	13	0	25	<1	0
Nausea	45	3	0	23	<1	0
Abdominal pain	35	3	0	16	<1	0
Vomiting	26	<1	0	10	2	0
Stomatitis	15	<1	0	10	0	0
Dry mouth	7	0	0	6	0	0
Dyspepsia	6	0	0	5	0	0
General Disorders and Administration Site Conditions						
Fatigue	40	3	0	27	<1	0
Peripheral edema	12	0	0	7	0	0
Pyrexia	11	<1	<1	6	<1	0
Influenza like illness	8	0	0	7	0	0
Chills	6	0	0	<1	0	0
Pain	5	0	0	4	0	0
Infections and Infestations						
Upper respiratory tract infection	11	0	0	8	<1	0
Urinary tract infection	9	<1	0	3	0	0
Investigations						
Alanine aminotransferase increased	13	4	<1	5	2	0
Aspartate aminotransferase increased	12	2	0	7	3	0
Blood creatinine increased	12	<1	0	<1	0	0
Weight decreased	10	<1	0	2	<1	0
Blood alkaline phosphatase increased	5	1	0	3	0	0

Metabolism and Nutrition Disorders						
Decreased appetite	27	1	0	12	<1	0
Hypokalemia	7	3	<1	2	<1	0
Musculoskeletal and Connective Tissue Disorders						
Muscular weakness	11	<1	0	6	0	0
Pain in extremity	8	<1	0	3	<1	0
Myalgia	8	0	0	6	0	0
Nervous System Disorders						
Headache	20	<1	0	15	<1	0
Dysgeusia	18	0	0	3	0	0
Dizziness	13	<1	0	6	0	0
Psychiatric Disorders						
Depression	5	0	0	4	<1	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	13	0	0	11	0	0
Skin and Subcutaneous Tissue Disorders						
Alopecia	16	0	0	2	0	0
Pruritus	13	0	0	6	0	0
Rash	11	1	0	5	0	0
Dry Skin	9	0	0	1	0	0
Dermatitis acneiform	5	<1	0	2	0	0
Nail ridging	5	0	0	0	0	0
Vascular Disorders						
Venous thromboembolic events ^a	5	2	<1	<1	<1	0

^a Venous thromboembolic events include deep vein thrombosis (DVT), pulmonary embolism, cerebral venous sinus thrombosis, subclavian and axillary vein thrombosis, and DVT inferior vena cava.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, leukopenia, anemia, and infections.

Diarrhea incidence was greatest during the first month of VERZENIO dosing and was lower during subsequent months. The median time to onset of the first diarrhea event was 6 days, and the median durations of diarrhea for Grade 2 and Grade 3 were 9 days and 6 days, respectively. Most diarrhea events recovered or resolved (85%) with supportive treatment alone or together with VERZENIO dose modifications (see [4 Dosage and Administration](#), and [Patient Medication](#)

[Information](#)). The median time to the first dose reduction due to diarrhea was 29 days. Twenty-two percent (22%) of patients with diarrhea required a dose omission.

Metastatic Breast Cancer – Used as a Single Agent

The safety of VERZENIO (200 mg twice daily) was evaluated in MONARCH 1, a Phase 2 single-arm, open-label, multicenter trial (see [14 Clinical Trials](#)). The data described below reflect exposure to VERZENIO in 132 patients with measurable HR-positive, HER2-negative metastatic breast cancer. The median duration of treatment was 4.6 months.

Dose reductions due to an adverse reaction occurred in 49% of patients receiving VERZENIO as a single agent. The most frequent adverse reactions resulting in a dose reduction were diarrhea (20%), neutropenia (11%), and fatigue (9%).

Deaths during treatment or within 30 days of treatment discontinuation due to adverse events were reported in 3 patients (2%). The cause of death in these patients was due to pneumonitis, sepsis, and lung infection.

Treatment-emergent adverse events (≥5%) reported in patients who received VERZENIO as a single agent in MONARCH 1 are listed in Table 12.

Table 12 - Treatment-Emergent Adverse Events (with a Frequency of ≥5% in Patients Receiving VERZENIO as a Single Agent) in MONARCH 1

Treatment-Emergent Adverse Event	Single Agent VERZENIO N=132				
	All Grades ^a %	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4 %
Blood and Lymphatic System Disorders					
Neutropenia	37	2	11	19	5
Anemia	25	8	12	5	0
Thrombocytopenia	21	10	7	4	0
Leukopenia	17	2	9	5	<1
Eye Disorders					
Lacrimation increased	8	7	<1	0	0
Dry eye	5	5	0	0	0
Gastrointestinal Disorders					
Diarrhea	90	42	29	20	0
Nausea	64	39	21	5	0
Abdominal pain	39	22	14	2	0
Vomiting	35	23	11	2	0
Constipation	17	13	4	<1	0
Dry mouth	14	12	2	0	0

Stomatitis	14	11	2	0	0
Dyspepsia	8	7	2	0	0
Flatulence	5	5	<1	0	0
Gastroesophageal reflux disease	5	5	0	0	0
General Disorders and Administration Site Conditions					
Fatigue	65	21	31	13	0
Pain	20	11	7	2	0
Pyrexia	11	10	<1	0	0
Peripheral edema	8	5	2	0	0
Chills	6	5	<1	0	0
Infections and Infestations					
Upper respiratory tract infection	8	<1	6	<1	0
Urinary tract infection	8	0	8	0	0
Investigations					
Weight decreased	14	10	4	0	0
Blood creatinine increased	13	5	8	<1	0
Aspartate aminotransferase increased	8	5	<1	2	0
Alanine aminotransferase increased	7	4	2	<1	0
Metabolism and Nutrition Disorders					
Decreased appetite	46	28	14	3	0
Dehydration	10	2	5	2	0
Hypokalemia	5	2	2	2	0
Musculoskeletal and Connective Tissue Disorders					
Back pain	11	7	4	<1	0
Arthralgia	8	6	2	0	0
Bone pain	7	5	<1	<1	0
Muscular weakness	7	2	3	2	0
Myalgia	5	4	2	0	0
Pain in extremity	5	4	<1	0	0

Nervous System Disorders					
Headache	21	14	7	0	0
Dysgeusia	12	11	2	0	0
Dizziness	11	10	2	0	0
Neuropathy	8	5	2	0	0
Psychiatric Disorders					
Anxiety	5	4	2	0	0
Insomnia	5	3	2	0	0
Respiratory, Thoracic and Mediastinal Disorders					
Cough	19	15	4	0	0
Dyspnea	14	5	5	3	<1
Oropharyngeal pain	6	5	<1	0	0
Upper-airway cough syndrome	5	5	0	0	0
Rhinitis allergic	5	5	0	0	0
Skin and Subcutaneous Tissue Disorders					
Alopecia	12	10	2	0	0
Dry skin	9	8	<1	0	0
Rash	8	7	0	2	0
Pruritus	8	6	<1	<1	0

^a Refer to NCI CTCAE Criteria Version 4.03 for each Grade of toxicity.

The most frequently reported (≥5%) Grade 3 or 4 adverse reactions were neutropenia, diarrhea, fatigue, leukopenia, anemia, and nausea.

Diarrhea incidence was greatest during the first month of VERZENIO dosing and was lower during subsequent months. The median time to onset of the first diarrhea event was 7 days, and the median durations of diarrhea for Grade 2 and Grade 3 were 8 days and 5 days, respectively. Most diarrhea events recovered or resolved (93%) with supportive treatment alone or together with VERZENIO dose modifications (see [4 Dosage and Administration](#), and [Patient Medication Information](#)). Twenty-six percent (26%) of patients with diarrhea required a dose omission and 23% required a dose reduction. The median time to the first dose reduction due to diarrhea was 28 days.

Clinical trials have not been conducted in a pediatric population.

8.3 Less Common Clinical Trial Adverse Reactions

Additional less common adverse events (all grades) included:

Blood and lymphatic system disorders: febrile neutropenia.

Cardiac disorders: atrial fibrillation, cardiac failure, palpitations, sinus tachycardia.

Ear and labyrinth disorders: vertigo.

Eye disorders: eye pain, vision blurred.

Gastrointestinal disorders: abdominal distension, anal hemorrhage, colitis, dental caries, dysphagia, enterocolitis, gastritis, gastroesophageal reflux disease, gingival pain, hemorrhoids, mouth ulceration, oral pain, periodontal disease, rectal hemorrhage, toothache.

General disorders and administration site conditions: chest pain, chills, edema, face edema, localized edema, malaise, mucosal inflammation, non-cardiac chest pain.

Hepatic disorders: hepatic steatosis

Immune system disorders: hypersensitivity.

Infections and infestations: bronchitis, cellulitis, conjunctivitis, gastroenteritis, gingivitis, influenza, oral herpes, pharyngitis, rash pustular, sepsis, sinusitis, skin infection, tooth infection, vaginal infection, viral infection, vulvovaginal candidiasis, wound infection.

Injury, poisoning and procedural complications: contusion, fracture, procedural pain, seroma.

Investigations: blood bilirubin increased, gamma-glutamyltransferase increased.

Metabolism and nutrition disorders: dehydration, hypercalcemia, hypercholesterolemia, hyperkalemia, hypertriglyceridemia, hyperuricemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia, vitamin B12 deficiency.

Musculoskeletal and connective tissue disorders: arthritis, flank pain, osteonecrosis of jaw.

Nervous system disorders: amnesia, cerebrovascular accident, lethargy, syncope.

Psychiatric disorders: confusional state.

Renal and urinary disorders: acute kidney injury, chronic kidney disease, cystitis noninfective, dysuria, memory impairment, pollakiuria, taste disorder, urinary tract pain.

Reproductive system and breast disorders: pelvis pain, vulvovaginal dryness.

Respiratory, thoracic and mediastinal disorders: dysphonia, epistaxis, nasal congestion, nasal dryness, pneumonitis, productive cough, pulmonary fibrosis, rhinorrhea. ILD/pneumonitis (monarchE: 2.9%, MONARCH 2: 2.0%; MONARCH 3, 5.2%).

Skin and subcutaneous tissue disorders: dermatitis, eczema, erythema, night sweats, pain of skin, palmar-plantar erythrodysesthesia syndrome, skin hyperpigmentation, urticaria.

Vascular disorders: hematoma, hypotension, lymphoedema.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Creatinine Increased

VERZENIO has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters, without affecting glomerular function (see [10 Clinical Pharmacology](#)). In clinical studies, increases in serum creatinine (mean increase, 0.2-0.3 mg/dL) occurred within the first month of VERZENIO dosing, remained elevated but stable through the treatment period, and were reversible upon treatment discontinuation. Alternative markers such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate (GFR), which are not based on creatinine, may be considered to determine whether renal function is impaired.

Table 13 - Laboratory Findings – Hematologic Abnormalities in monarchE

Hematologic Abnormality	VERZENIO Plus Endocrine Therapy N=2791			Endocrine Therapy Alone N=2800		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
White blood cell decreased	89	19	<1	29	1	0
Neutrophil count decreased	84	19	<1	23	2	<1
Anemia	68	1	0	17	<1	0
Lymphocyte count decreased	59	13	<1	24	2	<1
Platelet count decreased	37	<1	<1	10	<1	<1

Table 14 - Laboratory Findings – Clinical Chemistry Abnormalities in monarchE

Clinical Chemistry Abnormality	VERZENIO Plus Endocrine Therapy N=2791			Endocrine Therapy Alone N=2800		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	99	<1	0	91	<1	0
Alanine aminotransferase increased	39	3	<1	24	1	0

Aspartate aminotransferase increased	33	2	<1	18	<1	0
Hypokalemia	11	1	<1	4	<1	<1

Table 15 - Laboratory Findings – Hematologic Abnormalities in MONARCH 3

Hematologic Abnormality	VERZENIO + anastrozole or letrozole N=327			Placebo + anastrozole or letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
White blood cell decreased	83	15	0	31	<1	0
Anemia	84	2	0	33	0	0
Neutrophil count decreased	81	20	3	22	3	0
Lymphocyte count decreased	58	9	<1	27	2	0
Platelet count decreased	40	1	<1	14	<1	0

Table 16 - Laboratory Findings – Clinical Chemistry Abnormalities in MONARCH 3

Clinical Chemistry Abnormality	VERZENIO + anastrozole or letrozole N=327			Placebo + anastrozole or letrozole N=161		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	3	0	85	0	0
Alanine aminotransferase increased	53	7	<1	28	2	0
Aspartate aminotransferase increased	44	5	0	26	<1	0

Table 17 - Laboratory Findings – Hematologic Abnormalities in MONARCH 2

Hematologic Abnormality	VERZENIO + Fulvestrant N=441			Placebo + Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
White blood cell decreased	90	23	<1	33	<1	0
Neutrophil count decreased	87	29	4	30	4	<1
Anemia	84	3	0	34	<1	0
Lymphocyte count decreased	63	12	<1	32	2	0
Platelet count decreased	53	<1	1	15	0	0

Table 18 - Laboratory Findings – Clinical Chemistry Abnormalities in MONARCH 2

Clinical Chemistry Abnormality	VERZENIO + Fulvestrant N=441			Placebo + Fulvestrant N=223		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Creatinine increased	98	1	0	74	0	0
Alanine aminotransferase increased	41	4	<1	32	1	0
Aspartate aminotransferase increased	37	4	0	25	4	<1

Table 19 - Laboratory Findings – Hematologic Abnormalities for Patients Receiving VERZENIO as a Single Agent in MONARCH 1

Hematologic Abnormality	Single Agent VERZENIO N=132				
	All Grades %	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4 %
White blood cell decreased	91	19	45	28	0
Neutrophil count decreased	88	18	43	22	5

Anemia	69	30	39	0	0
Lymphocyte count decreased	42	5	24	13	<1
Platelet count decreased	41	29	10	2	0

Table 20 - Laboratory Findings – Clinical Chemistry Abnormalities for Patients Receiving VERZENIO as a Single Agent in MONARCH 1

Clinical Chemistry Abnormality	Single Agent VERZENIO N=132				
	All Grades %	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4 %
Creatinine increased	99	47	51	<1	0

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of VERZENIO. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency.

Respiratory, thoracic, and mediastinal disorders: Interstitial lung disease (ILD)/pneumonitis

9 Drug Interactions

9.2 Drug Interactions Overview

Abemaciclib is primarily metabolized by CYP3A4 to several active metabolites.

Coadministration of abemaciclib with some CYP3A inhibitors can increase plasma concentrations of abemaciclib and active metabolites. The concomitant use of strong CYP3A inhibitors should be avoided.

Coadministration of abemaciclib with strong CYP3A inducers may decrease the plasma concentrations of abemaciclib and its active metabolites. The concomitant use of strong CYP3A inducers should be avoided.

9.4 Drug-Drug Interactions

The drugs listed in this table are based on either drug interaction clinical trials or predicted interactions due to the expected magnitude and seriousness of the interaction.

Table 21 - Established or Potential Drug-Drug Interactions

Common Name	Source of Evidence	Effect	Clinical Comment ^a
Drugs that may increase abemaciclib concentrations			
Strong CYP3A Inhibitor	CT, P	- In a clinical study of 26 patients, coadministration of a CYP3A inhibitor clarithromycin resulted in a 3.4-fold increase in the plasma exposure of abemaciclib and a 2.2-fold increase in the combined plasma exposure of abemaciclib and its active metabolites. - The strong CYP3A inhibitors ketoconazole and itraconazole are predicted to increase the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by 7.2-fold and 3.8-fold, respectively.	- Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole). If coadministration with a strong CYP3A inhibitor is unavoidable, adjust the abemaciclib dose to 50 mg twice daily. For ketoconazole the abemaciclib dose should be reduced to 50 mg once daily. For clarithromycin, the abemaciclib dose should be reduced to 100 mg twice daily. - If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.
Moderate CYP3A Inhibitor	P	The moderate CYP3A inhibitors diltiazem and verapamil are predicted to increase the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by 2.4-fold and 1.6-fold, respectively.	- Use caution with coadministered moderate CYP3A inhibitors (for example, ciprofloxacin). If coadministration with a moderate CYP3A inhibitor is unavoidable, adjust the abemaciclib dose to 50 mg twice daily. For diltiazem and verapamil the abemaciclib dose should be reduced to 100 mg twice daily. - If a CYP3A inhibitor is discontinued, increase

			the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.
Weak CYP3A Inhibitor	T		• Use caution with coadministered weak CYP3A inhibitors (for example, ranitidine). If coadministration with a weak CYP3A inhibitor is unavoidable, adjust the abemaciclib dose to 100 mg twice daily. • If a CYP3A inhibitor is discontinued, increase the abemaciclib dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor.
Drugs that may decrease abemaciclib concentrations			
Strong CYP3A Inducers	CT, P	• Data from a study in 24 healthy subjects indicated that coadministration of abemaciclib with the strong CYP3A inducer rifampin decreased the plasma exposure of abemaciclib plus its active metabolites by 77% based on AUC_{0-INF} and 45% based on C_{max}. • Carbamazepine (strong CYP3A inducer) is predicted to decrease the relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by 54%.	• Avoid concomitant use of strong CYP3A inducers (for example, rifampin, phenytoin, carbamazepine, and St. John's wort). Consider alternative agents with less CYP3A induction.
Moderate CYP3A Inducers	P	• Efavirenz, bosentan, and modafinil (moderate CYP3A inducers) are predicted to decrease the	• No abemaciclib dose adjustment is required for patients who must use concomitant

		relative potency adjusted unbound AUC of abemaciclib plus its active metabolites (M2, M18, and M20) by 52%, 42%, and 29% respectively.	moderate CYP3A inducers.
Weak CYP3A Inducers	T		No Abemaciclib dose adjustment is required for patients who must use concomitant weak CYP3 inducers.
Drugs which may alter the concentrations of abemaciclib			
Loperamide	CT	In a clinical drug interaction study in healthy subjects, coadministration of a single 8 mg dose of loperamide with 400 mg abemaciclib had no statistically significant effect on Abemaciclib pharmacokinetics.	No dose adjustment is required when abemaciclib is coadministered with loperamide.
Endocrine Therapies	CT	In clinical studies in patients with breast cancer, there was no clinically relevant effect of fulvestrant, anastrozole, letrozole, or exemestane on abemaciclib pharmacokinetics.	No dose adjustment is required when abemaciclib is coadministered with endocrine therapies.
Effect of abemaciclib on other drugs			
CYP1A2, CYP2C9, CYP2D6 and CYP3A4 Substrates	CT	- 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	No dose adjustment is required when abemaciclib is coadministered with CYP substrates.

		abemaciclib as a result of autoinhibition of its metabolism were not observed.	
Loperamide	CT	In a clinical drug interaction study in healthy subjects, coadministration of a single 8 mg dose of loperamide with a single 400 mg abemaciclib dose increased loperamide AUC_{0-1NF} by 9% and C_{max} by 35% relative to loperamide alone.	No dose adjustment is required when abemaciclib is coadministered with loperamide.
OCT2, MATE1, and MATE2 Substrates	CT	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 2 (OCT2), multidrug and toxin extrusion protein 1 (MATE1), and MATE2-K transporters, with a single 400 mg dose of abemaciclib increased metformin AUC_{0-1NF} 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 (GFR) as measured by iothexol clearance and serum cystatin C.	Concurrent administration of abemaciclib with other clinically relevant substrates of OCT2, MATE1, and MATE2 should be done with caution.
Endocrine Therapies	CT	In clinical studies in patients with breast cancer, there was no clinically relevant effect of abemaciclib on the pharmacokinetics of	No dose adjustment is required when abemaciclib is coadministered with endocrine therapies.

		fulvestrant, anastrozole, letrozole, or exemestane.	
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^a For concomitant medications where a dose reduction or caution is recommended, close clinical monitoring is recommended for the duration of administration of the concomitant medication.

Legend: CT = Clinical Trial; P = Predicted; T = Theoretical.

In Vitro Studies

Transporters: Abemaciclib and its major active metabolites inhibit the renal transporters OCT2, MATE1, and MATE2-K at concentrations achievable at the approved recommended dosage. The observed serum creatinine increase in clinical studies with abemaciclib is likely due to inhibition of tubular secretion of creatinine via OCT2, MATE1, and MATE2-K (see [8 Adverse Reactions](#)). Abemaciclib and its major metabolites at clinically relevant concentrations do not inhibit the hepatic uptake transporters OCT1, OATP1B1, and OATP1B3 or the renal uptake transporters OAT1 and OAT3. Abemaciclib and its major active metabolites, M2 and M20, are not substrates of hepatic uptake transporters OCT1, organic anion transporting polypeptide 1B1 (OATP1B1), or OATP1B3.

P-gp and BCRP Transporters: In vitro, abemaciclib is a substrate of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). The effect of P-gp or BCRP inhibitors on the pharmacokinetics of abemaciclib has not been studied. Based on the in vitro inhibition of P-gp and BCRP observed with abemaciclib, in vivo interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin, may occur.

Statins (Rosuvastatin and Atorvastatin)

Co-administration of abemaciclib with rosuvastatin and atorvastatin, which are substrates of BCRP or P-gp, may increase the risk of rhabdomyolysis due to increased statin plasma concentration. Close monitoring is recommended.

9.5 Drug-Food Interactions

Abemaciclib may be taken with or without food. A food effect study demonstrated a 26% increase in C_{max} of abemaciclib and its active metabolites following a high fat breakfast compared with fasted dosing (see [10 Clinical Pharmacology](#)). Although significant, this increase is within observed variability.

Grapefruit, grapefruit juice, and products containing grapefruit extract may increase abemaciclib plasma concentrations and should be avoided (see [4 Dosage and Administration](#), and [10 Clinical Pharmacology](#)).

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established. St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A4/5 that may decrease abemaciclib plasma concentrations and should be avoided (see [9.4 Drug-Drug Interactions](#), [CYP3A Inducers](#)).

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Abemaciclib is an inhibitor of cyclin D-dependent kinases 4 and 6 (CDK4 and CDK6) and was most active against cyclin D1/CDK4 in enzymatic assays. Abemaciclib prevents retinoblastoma protein (Rb) phosphorylation, blocking progression from G1 into S phase of the cell cycle, leading to suppression of tumor growth in preclinical models following short duration target inhibition. In estrogen receptor–positive breast cancer cell lines, sustained target inhibition by abemaciclib prevents rebound of Rb phosphorylation and cell cycle reentry, resulting in senescence and apoptosis. In breast cancer xenograft models, abemaciclib dosed daily without interruption at clinically relevant concentrations—as a single agent or in combination with antiestrogens—resulted in reduction of tumor size.

10.2 Pharmacodynamics

In cancer patients, abemaciclib inhibits CDK4 and CDK6 as indicated by inhibition of phosphorylation of Rb and topoisomerase II alpha, which results in cell cycle inhibition upstream of the G1 restriction point at doses of 50 mg to 200 mg twice daily. monarchE, MONARCH 2, and MONARCH 3 exposure-response analyses support the 150 mg twice daily starting dose in combination with endocrine therapy and support dose reductions as needed for tolerability to a dose as low as 50 mg twice daily. MONARCH 1 exposure-response analysis supports the 200 mg twice daily starting dose when used as a single agent.

Cardiac Electrophysiology

Based on evaluation of the QTc interval in patients and in a healthy volunteer study, abemaciclib did not cause large mean increases (i.e., 20 ms) in the QTc interval.

10.3 Pharmacokinetics

The pharmacokinetics of abemaciclib were characterized in patients with cancer following oral doses ranging from 50 mg to 225 mg once daily and 75 mg to 275 mg twice daily. Healthy subjects received single oral doses ranging from 150 mg to 600 mg.

Table 22 - Summary of Abemaciclib Pharmacokinetic Parameters

$C_{\max,ss}$ (ng/mL)	$T_{\max}$ (hours)	$t_{1/2}$ (hours)	$AUC_{\tau,ss}$ (ng*h/mL)	CL (L/h)	Vd (L)
249 (35%) ^a	8.0 (4.1, 24)	24.8 (52%)	2520 (35%)	21.8 (40%)	747 L (69%)

Abbreviations: $AUC_{\tau,ss}$ = area under the concentration versus time curve during one dosing interval at steady state; $C_{\max,ss}$ = maximum plasma concentration after multiple dosing at steady-state; CL = hepatic clearance; $t_{1/2}$ = half-life; $T_{\max}$ = time of observed maximum plasma concentration after a single dose; Vd = systemic volume of distribution.

Data are presented as geometric mean (CV%) for all parameters except $T_{\max}$ which is presented as median (range).

^a Patients in MONARCH 2 who started at an abemaciclib dose of 150 mg twice daily.

Absorption

The absolute bioavailability of abemaciclib after a single oral dose of 200 mg is 45% (19% CV) (90% confidence interval: 40-51%). In the therapeutic dose range of 50-200 mg, the increase in plasma exposure (AUC) and C_{max} is dose proportional. Steady state was achieved within 5 days following repeated twice daily dosing, and abemaciclib accumulated with a geometric mean accumulation ratio of 3.7 (58% CV) and 5.8 (65% CV) based on C_{max} and AUC, respectively. Abemaciclib absorption is slow, with a median T_{max} of 8.0 hours (range: 4.1-24.0 hours). A high-fat, high-calorie meal (approximately 800 to 1000 calories with 150 calories from protein, 250 calories from carbohydrate, and 500 to 600 calories from fat) administered to healthy subjects increased the AUC_{0-INF} of abemaciclib plus its active metabolites by 9% and increased C_{max} by 26%.

Distribution

Abemaciclib was highly bound to plasma proteins in humans (mean bound fraction was approximately 96-98%), and the binding was independent of concentration from 152 ng/mL to 5066 ng/mL. Abemaciclib binds to both human serum albumin and alpha-1-acid glycoprotein. The geometric mean systemic volume of distribution is approximately 747 L (68.6% CV).

In patients with advanced cancer, including breast cancer, concentrations of abemaciclib and its active metabolites M2 and M20 in cerebrospinal fluid are comparable to unbound plasma concentrations.

Metabolism

Hepatic metabolism is the main route of clearance for abemaciclib. Abemaciclib is metabolized to several metabolites primarily by cytochrome P450 (CYP) 3A4, with formation of N-desethylabemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxy-N-desethylabemaciclib (M18), and an oxidative metabolite (M1). M2, M18, and M20 are equipotent to abemaciclib and their AUCs accounted for 25%, 13%, and 26% of the total circulating analytes in plasma, respectively.

Elimination

The geometric mean hepatic clearance (CL) of abemaciclib in patients was 21.8 L/h (40% CV), and the mean plasma elimination half-life for abemaciclib in patients was 24.8 hours (52% CV).

Excretion

After a single 150 mg oral dose of radiolabeled abemaciclib, approximately 81% of the dose was recovered in feces and approximately 3% recovered in urine. The majority of the dose eliminated in feces was metabolites.

Special Populations and Conditions

- **Pediatrics** Pharmacokinetics of abemaciclib have not been evaluated in children and adolescents <18 years of age.
- **Geriatrics** Age (range, 24-91 years of age) does not alter abemaciclib pharmacokinetics.
- **Sex** Gender does not alter abemaciclib pharmacokinetics.
- **Ethnic Origin** Race was not identified as a significant covariate for abemaciclib

pharmacokinetics in patients with cancer.

- **Hepatic Insufficiency** Abemaciclib is metabolized in the liver. Following a single 200 mg oral dose of abemaciclib, the relative potency adjusted unbound $AUC_{0-\infty}$ of abemaciclib plus its active metabolites (M2, M18, M20) in plasma increased 1.2-fold in subjects with mild hepatic impairment (Child-Pugh A, n=9), 1.1-fold in subjects with moderate hepatic impairment (Child-Pugh B, n=10), and 2.7 in subjects with severe hepatic impairment (Child-Pugh C, n=6) relative to subjects with normal hepatic function (n=10). In addition, in subjects with severe hepatic impairment, the mean plasma elimination half-life of abemaciclib increased to 55 hours compared to 24 hours in subjects with normal hepatic function; therefore, a dose reduction is required in patients with severe hepatic impairment (see [4 Dosage and Administration](#)).
- **Renal Insufficiency** Renal clearance of abemaciclib and its metabolites is minor, with appropriately 3.4% of the dose recovered in urine. In a population pharmacokinetic analysis that included baseline Cockcroft-Gault creatinine clearance (CrCl) information for 989 individuals, in which 383 individuals had mild renal impairment ($60 \text{ mL/min} \leq \text{CrCl} < 90 \text{ mL/min}$) and 127 individuals had moderate renal impairment ($30 \text{ mL/min} \leq \text{CrCl} < 60 \text{ mL/min}$), mild and moderate renal impairment had no effect on the exposure of abemaciclib; therefore, no dose adjustment is needed based on the above-mentioned patient factors for abemaciclib. The effect of severe renal impairment ($\text{CrCl} < 30 \text{ mL/min}$) on pharmacokinetics of abemaciclib is unknown. There are no data in patients with severe renal impairment, end stage renal disease, or in patients on dialysis. Caution should be used in patients with severe renal impairment.
- **Obesity** Body weight (range 36-175 kg) had no effect on the exposure of abemaciclib.

11 Storage, Stability And Disposal

Store at room temperature (15°C to 30°C). Keep out of reach and sight of children.

Any unused product or waste material should be disposed of in accordance with local requirements.

Part 2: Scientific Information

13 Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance: abemaciclib

Chemical name: 2-Pyrimidinamine, *N*-[5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl]-5-fluoro-4-[4-fluoro-2-methyl-1-(1-methylethyl)-1*H*-benzimidazol-6-yl]-

Molecular formula and molecular mass: The empirical formula is C₂₇H₃₂F₂N₈ with a molecular weight of 506.59.

Structural formula:



Physicochemical properties: Abemaciclib is a practically white to yellow powder. Abemaciclib has pH dependent solubility and is considered highly soluble, with solubility ≥ 5 mg/mL up to pH 6.0 and 1.577 mg/mL at pH 6.8 in aqueous media.

14 Clinical Trials

14.1 Clinical Trials by Indication

Early Breast Cancer-Combination with Endocrine Therapy

Table 23 - Summary of Trial Design and Patient Demographics –monarchE- Early Breast Cancer combination with Endocrine Therapy

Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)
Randomized (1:1), Phase III, open label, multicenter study	Patients (adult women and men) received 2 years of VERZENIO (150 mg orally twice daily on a continuous schedule) plus physician's choice of standard endocrine therapy or choice of standard endocrine therapy alone. After the end of the study treatment period, standard adjuvant endocrine therapy continued for a duration of at least 5 years if deemed medically appropriate	VERZENIO + standard endocrine therapy (N=2808) standard endocrine therapy alone (N=2829) (5637 total)	VERZENIO + standard endocrine therapy = 51 (23-89) years standard endocrine therapy alone = 51 (22-86) years

The efficacy of VERZENIO plus physician's choice of standard endocrine therapy was evaluated in monarchE, a randomized (1:1), open-label, multicenter study in adult women and men with HR-positive, HER2-negative, node-positive, resected, early breast cancer (EBC) with clinical and pathological features consistent with a high risk of disease recurrence. To be enrolled, all patients had to have HR positive, HER2-negative EBC with tumor involvement in at least 1 axillary lymph node (pALN). Two cohorts of patients were enrolled. To be enrolled in cohort 1, patients needed to have either ≥ 4 pALN, or pALN 1-3 and tumor grade 3 and/or tumor size ≥ 50 mm. To be enrolled in cohort 2, patients were required to have pALN 1-3 and Ki-67 score of $\geq 20\%$ as measured in untreated breast tumor tissue, using a clinical trial assay at a central laboratory. For patients in cohort 1 with available untreated breast tissue samples, retrospective central testing of tissue was conducted to establish if the Ki-67 score was $\geq 20\%$ or $< 20\%$ (specified in the protocol as "Ki-67 high" or "Ki-67 low", respectively). The intent to treat (ITT) population included patients from both cohort 1 (n=5120) and cohort 2 (n=517). Randomization to treatment was stratified by prior treatment (neoadjuvant chemotherapy versus adjuvant chemotherapy versus no chemotherapy); menopausal status (premenopausal versus postmenopausal); and region (North America/Europe versus Asia versus other). Men were stratified as postmenopausal.

Patients were randomly assigned to receive 150 mg of VERZENIO orally, twice daily, plus endocrine therapy or endocrine therapy alone, VERZENIO was given orally, without regard to

food, with at least 6 hours separating doses on a continuous schedule. Patients received VERZENIO for up to 2 years or until disease recurrence, or unacceptable toxicity. After the end of the study treatment period, standard adjuvant endocrine therapy continued for a duration of at least 5 years if deemed medically appropriate.

Initial endocrine therapy received by patients included letrozole (39%), tamoxifen (31%), anastrozole (22%), or exemestane (8%), and 22% of patients received ovarian suppression at any time.

Demographics and baseline characteristics are outlined in Table 24.

Table 24 - Baseline Demographic and Disease Characteristics for the Intent to Treat (ITT) Population – monarchE – Early Breast Cancer combination with Endocrine Therapy

	Demographic Parameter	VERZENIO + Endocrine Therapy N=2808	Endocrine Therapy Alone N=2829	Total (N=5637)
Age (years)	Median age (range)	51 (23-89)	51 (22-86)	51 (22-89)
Age group, n (%)	Age <65 years	2371 (84.4)	2416 (85.4)	4787 (84.9)
	Age ≥65 years	437 (15.6)	413 (14.6)	850 (15.1)
Gender, n (%)	Women	2787 (99.3)	2814 (99.5)	5601 (99.4)
	Men	21 (0.7)	15 (0.5)	36 (0.6)
Race, n (%) ^a	White	1947 (70.3)	1978 (71.0)	3925 (70.7)
	Asian	675 (24.4)	669 (24.0)	1344 (24.2)
	American Indian/Alaska Native	64 (2.3)	58 (2.1)	122 (2.2)
	Black	57 (2.1)	53 (1.9)	110 (2.0)
	Multiple	22 (0.8)	25 (0.9)	47 (0.8)
	Native Hawaiian or Other Pacific Islander	3 (0.1)	4 (0.1)	7 (0.1)
Menopausal status, n (%)	Premenopausal	1225 (43.7)	1224 (43.3)	2449 (43.5)
	Postmenopausal	1578 (56.3)	1605 (56.7)	3183 (56.5)
Number of positive lymph nodes, n (%)	0	7 (0.2)	7 (0.2)	14 (0.2)
	1-3	1119 (39.9)	1143 (40.4)	2262 (40.1)
	≥4	1680 (59.8)	1679 (59.3)	3359 (59.6)
Prior systemic therapy, n (%)	(Neo)adjuvant	1056 (37.6)	1070 (37.8)	2126 (37.7)
	Chemotherapy	1026 (36.5)	1029 (36.4)	2055 (36.5)
	Endocrine therapy	86 (3.1)	97 (3.4)	183 (3.2)
	Adjuvant	2447 (87.1)	2471 (87.3)	4918 (87.2)
	Chemotherapy	1734 (61.8)	1731 (61.2)	3465 (61.5)

	Endocrine therapy	1764 (62.8)	1795 (63.4)	3559 (63.1)
	Radiotherapy	2680 (95.4)	2700 (95.4)	5380 (95.4)
Histological grade of tumor, n (%)	Grade 1	209 (7.4)	215 (7.6)	424 (7.5)
	Grade 2	1373 (48.9)	1395 (49.3)	2768 (49.1)
	Grade 3	1090 (38.8)	1066 (37.7)	2156 (38.2)
	Grade cannot be assessed	126 (4.5)	140 (4.9)	266 (4.7)
Primary tumor size by pathology following definitive surgery	<20 mm	780 (27.8)	765 (27.0)	1545 (27.4)
	≥20 mm but <50 mm	1369 (48.8)	1419 (50.2)	2788 (49.5)
	≥50 mm	610 (21.7)	612 (21.6)	1222 (21.7)
Progesterone Receptor status, n (%)	Positive	2421 (86.2)	2453 (86.7)	4874 (86.5)
	Negative	298 (10.6)	294 (10.4)	592 (10.5)
Estrogen receptor status, n (%)	Positive	2782 (99.1)	2807 (99.2)	5589 (99.1)
	Negative	16 (0.6)	17 (0.6)	33 (0.6)
Disease stage at initial diagnosis, n (%)	Stage IA	2 (0.1)	1 (0.04)	3 (0.1)
	Stage IIA	323 (11.5)	353 (12.5)	676 (12.0)
	Stage IIB	389 (13.9)	387 (13.7)	776 (13.8)
	Stage IIIA	1027 (36.6)	1024 (36.2)	2051 (36.4)
	Stage IIIB	104 (3.7)	91 (3.2)	195 (3.5)
	Stage IIIC	950 (33.8)	962 (34.0)	1912 (33.9)
Central lab Ki-67 results from untreated tumor, n (%)	<20%	953 (33.3)	973 (34.4)	1926 (34.2)
	≥20%	1262 (44.9)	1233 (43.6)	2495 (44.3)

^a Race not reported for 1.5%.

MonarchE – Study Results

The primary end point was invasive disease-free survival (IDFS). IDFS was defined as the time from randomization to the first occurrence of ipsilateral invasive breast tumor recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary non-breast invasive cancer, or death attributable to any cause. At the second interim efficacy analysis, with a median follow-up of 15.5 months, a statistically

significant improvement in IDFS was observed in patients who received VERZENIO plus endocrine therapy versus those who received endocrine therapy alone. Patients treated with VERZENIO plus endocrine therapy had a 25.3% reduction in risk of recurrence or death compared to patients treated with endocrine therapy alone.

At the time of the second overall survival interim analysis (OS IA2), with median follow up of 42 months, efficacy results were updated for the ITT population. All patients were off study treatment with approximately 82% of patients completing the 2-year on-study treatment period.

Patients treated with VERZENIO plus endocrine therapy had a clinically meaningful reduction of 33.6% in risk of recurrence or death compared to patients treated with endocrine therapy alone. The Kaplan-Meier curves continue to separate over time beyond the 2-year treatment period of VERZENIO, demonstrating a clinically meaningful absolute improvement in 4-year IDFS rate of 6.4%. Consistent benefit was observed across patient stratification subgroups of geographic region, prior chemotherapy, and menopausal status. Also, patients treated with VERZENIO plus endocrine therapy had a 34.1% reduction in risk of distant recurrence or death [distant relapse free survival (DRFS), a secondary endpoint], compared to patients treated with endocrine therapy alone and a clinically meaningful absolute improvement in 4 year DRFS rate, of 5.9%. The most common sites of distant recurrence were bone, liver, and lung.

At the final OS analysis with median follow up of 76 months, patients treated with VERZENIO plus endocrine therapy had a statistically significant improvement in overall survival, with a reduction in the risk of death of 15.8% compared to patients treated with endocrine therapy alone.

Efficacy results from the monarchE study are summarized in Table 25. The Kaplan-Meier curve for IDFS is shown in Figure 1.

Table 25 - Efficacy Results of monarchE– Intent-to-Treat Population – Early Breast Cancer combination with Endocrine Therapy

	VERZENIO + Endocrine Therapy N=2808	Endocrine Therapy Alone N=2829
Primary endpoint		
Invasive Disease–Free Survival (IDFS)		
Number of patients with an event (n, %)	336 (12.0)	499 (17.6)
Hazard ratio (95% CI)	0.664 (0.578, 0.762)	
p-value	0.0096 ^a	
IDFS at 48 months (95% CI)	85.8 (84.2, 87.3)	79.4 (77.5, 81.1)
Key secondary endpoints		
Distant Relapse Free Survival (DRFS)^b		
Number of patients with an event (n, %)	281 (10.0)	421 (14.9)
Hazard ratio (95% CI)	0.659 (0.567, 0.767)	
DRFS at 48 months (95% CI)	88.4 (86.9, 89.7)	82.5 (80.7, 84.1)

	VERZENIO + Endocrine Therapy N=2808	Endocrine Therapy Alone N=2829
Overall Survival (OS)^c		
Number of patients with an event (n, %)	301 (10.7)	360 (12.7)
Hazard ratio (95% CI)	0.842 (0.722, 0.981)	
p-value	0.0273	
OS at 84 months (% , 95% CI)	86.8 (85.1, 88.3)	85.0 (83.3, 86.4)

Abbreviation: CI = confidence interval.

^a This p-value is from the pre-specified interim IDFS analysis. IDFS data from OS Interim Analysis 2 (OS IA2)

^b Distant relapse free survival is defined as the time from randomization to distant recurrence or death from any cause, whichever occurs first. DRFS data from the OS IA2

^c OS data from the final OS analysis

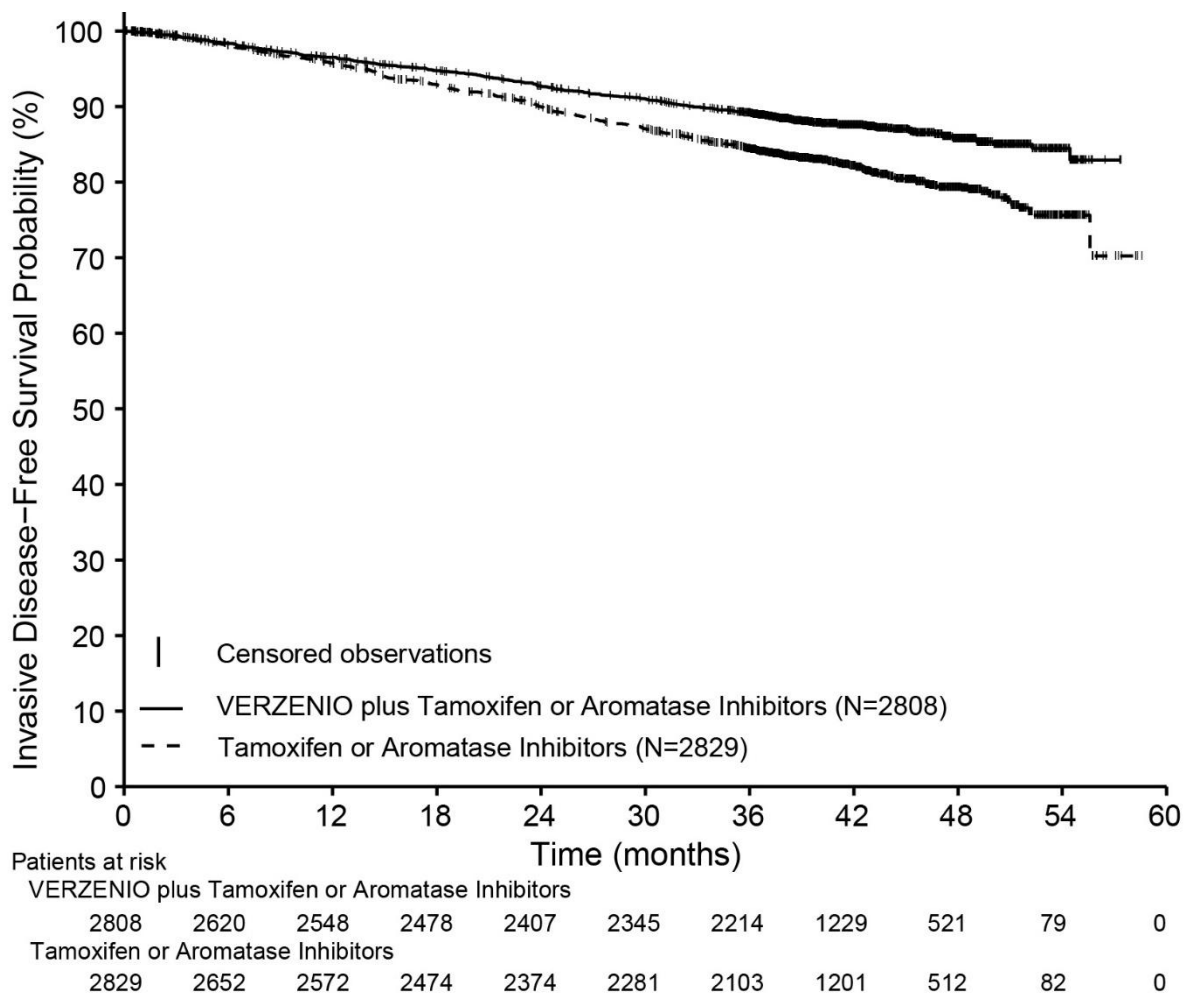


Figure 1: Kaplan-Meier Curves of IDFS : VERZENIO plus Endocrine Therapy versus Endocrine Therapy Alone for the Intent-to-Treat Population – monarchE

Metastatic Breast Cancer

Combination with an Aromatase Inhibitor

VERZENIO (abemaciclib) for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor in postmenopausal women as initial endocrine based therapy.

Table 26 - Summary of Trial Design and Patient Demographics in MONARCH 3 - Metastatic Breast Cancer combination with an Aromatase Inhibitor

Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)
Randomized (2:1), Phase III, double-blinded, placebo-controlled, multicenter study	Patients received VERZENIO (150 mg orally twice daily on a continuous schedule) or placebo, plus physician's choice of a NSAI (letrozole 2.5 mg or anastrozole 1 mg, orally once daily) on a 28 day cycle.	VERZENIO + NSAI (N=328) Placebo + NSAI (N=165) (493 total)	VERZENIO + NSAI = 63 (38-87) years Placebo + NSAI = 63 (32-88) years

The efficacy of VERZENIO in combination with a non-steroidal aromatase inhibitor (NSAI) was evaluated in MONARCH 3, a randomized, placebo-controlled multicenter study in postmenopausal women with hormone receptor positive (HR-positive), human epidermal growth factor receptor 2 (HER2)-negative advanced (not amenable to curative therapy) or metastatic breast cancer who had not received prior systemic therapy in this disease setting. Patients could have received (neo)adjuvant endocrine therapy if they were at least 12 months from end of therapy. A total of 493 patients were randomized to receive VERZENIO or placebo orally twice daily in combination with physician's choice of letrozole (80% of patients) or anastrozole (20% of patients). Randomization was stratified by metastatic disease site (visceral, bone only, or other) and by prior (neo)adjuvant endocrine therapy (aromatase inhibitor versus other versus no prior endocrine therapy).

VERZENIO or placebo was given orally, without regard to food, every 12 ($\pm$ 2) hours on Days 1 through 28 of a 28 day cycle. Patients received study treatment until objective disease progression or unacceptable toxicity. Crossover between treatment arms was not allowed.

Demographics and baseline characteristics are outlined in Table 27.

Table 27 - Baseline Demographic and Disease Characteristics for the Intent to Treat (ITT) Population – MONARCH 3- Metastatic Breast Cancer combination with an Aromatase Inhibitor

	Demographic Parameter	VERZENIO + anastrozole or letrozole (N=328)	Placebo + anastrozole or letrozole (N=165)	Total (N=493)
Age (years)	Median age (range)	63.0 (38.0-87.0)	63.0 (32.0-88.0)	63.0 (32.0-88.0)
Age group n (%)	Age <65 years	180 (54.9)	91 (55.2)	271 (55.0)
	Age ≥65 years	148 (45.1)	74 (44.8)	222 (45.0)
Race, n (%) ^a	White	186 (56.7)	102 (61.8)	288 (58.4)
	Asian	103 (31.4)	45 (27.3)	148 (30.0)
	Black	5 (1.5)	3 (1.8)	8 (1.6)
	Other	6 (1.8)	4 (2.4)	10 (2.0)
ECOG performance status (PS), n (%)	0	192 (58.5)	104 (63.0)	296 (60.0)
	1	136 (41.5)	61 (37.0)	197 (40.0)
Stage of disease at initial diagnosis, n (%)	Stage III	62 (18.9)	24 (14.5)	86 (17.4)
	Stage IV	132 (40.2)	61 (37.0)	193 (39.1)
Disease Setting at Study Entry, n (%)	De novo metastatic	135 (41.2)	61 (37.0)	196 (39.8)
	Metastatic recurrent	182 (55.5)	99 (60.0)	281 (57.0)
	Locoregionally recurrent	11 (3.4)	5 (3.0)	16 (3.2)
Progesterone Receptor (PgR) status, n (%)	Positive	255 (77.7)	127 (77.0)	382 (77.5)
	Negative	70 (21.3)	36 (21.8)	106 (21.5)
Disease site, n (%)	Visceral	172 (52.4)	89 (53.9)	261 (52.9)
	Non-visceral			
	Bone only	70 (21.3)	39 (23.6)	109 (22.1)
	Other	86 (26.2)	37 (22.4)	123 (24.9)
	Number of organ sites			
	1	96 (29.3)	47 (28.5)	143 (29.0)
	2	76 (23.2)	42 (25.5)	118 (23.9)
	≥3	154 (47.0)	75 (45.5)	229 (46.5)

Treatment-free interval, n (%)	Patients with adjuvant therapy, n (%)	137 (97.9)	72 (100.0)	209 (98.6)
	≤24 months	22 (15.7)	19 (26.4)	41 (19.3)
	>24 months	115 (82.1)	53 (73.6)	168 (79.2)
Prior systemic therapy, n (%)	(Neo)adjuvant and/or adjuvant ^b	166 (50.6)	85 (51.5)	251 (50.9)
	Endocrine	141 (43.0)	78 (47.3)	219 (44.4)
	Aromatase inhibitor ^c	85 (25.9)	50 (30.3)	135 (27.4)
	Chemotherapy	125 (38.1)	66 (40.0)	191 (38.7)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

^a Race not reported for 8.5%.

^b Patients may have received treatment in more than 1 setting.

^c Patient reported.

MONARCH 3 – Study Results

The primary efficacy objective was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1. Secondary efficacy endpoints included overall survival (OS) and objective response rate (ORR).

The final analysis, performed at a median follow-up time of 26.7 months for both treatment arms, indicated that patients who received VERZENIO with a NSAI had a statistically significant 46% reduction in the risk of disease progression or death compared to those treated with placebo plus a NSAI. Data from an independent radiographic review was supportive of this treatment effect. Efficacy results from the MONARCH 3 study are summarized in Table 28 and the Kaplan-Meier curve for PFS is shown in Figure 3.

Table 28 - Efficacy Results of MONARCH 3 (Investigator Assessment) – Intent-to-Treat (ITT) Population - Metastatic Breast Cancer combination with an Aromatase Inhibitor

	VERZENIO + anastrozole or letrozole	Placebo + anastrozole or letrozole
Progression-Free Survival^a	N=328	N=165
Median, months (95% CI)	28.18 (23.51, NR)	14.76 (11.24, 19.20)
Hazard ratio (95% CI)	0.540 (0.418, 0.698)	
p-value (2-sided) log-rank stratified	p<.0001	
Objective Response Rate for Patients with Measurable Disease	N=267	N=132

Objective response rate ^{a,b} , n (%)	163 (61.0)	60 (45.5)
95% CI	55.2, 66.9	37.0, 53.9
Complete response, n (%)	9 (3.4)	0
Partial response, n (%)	154 (57.7)	60 (45.5)

Abbreviation: CI = confidence interval, RECIST = Response Evaluation Criteria in Solid Tumors.

^a Evaluated according to RECIST version 1.1.

^b Complete response + partial response.

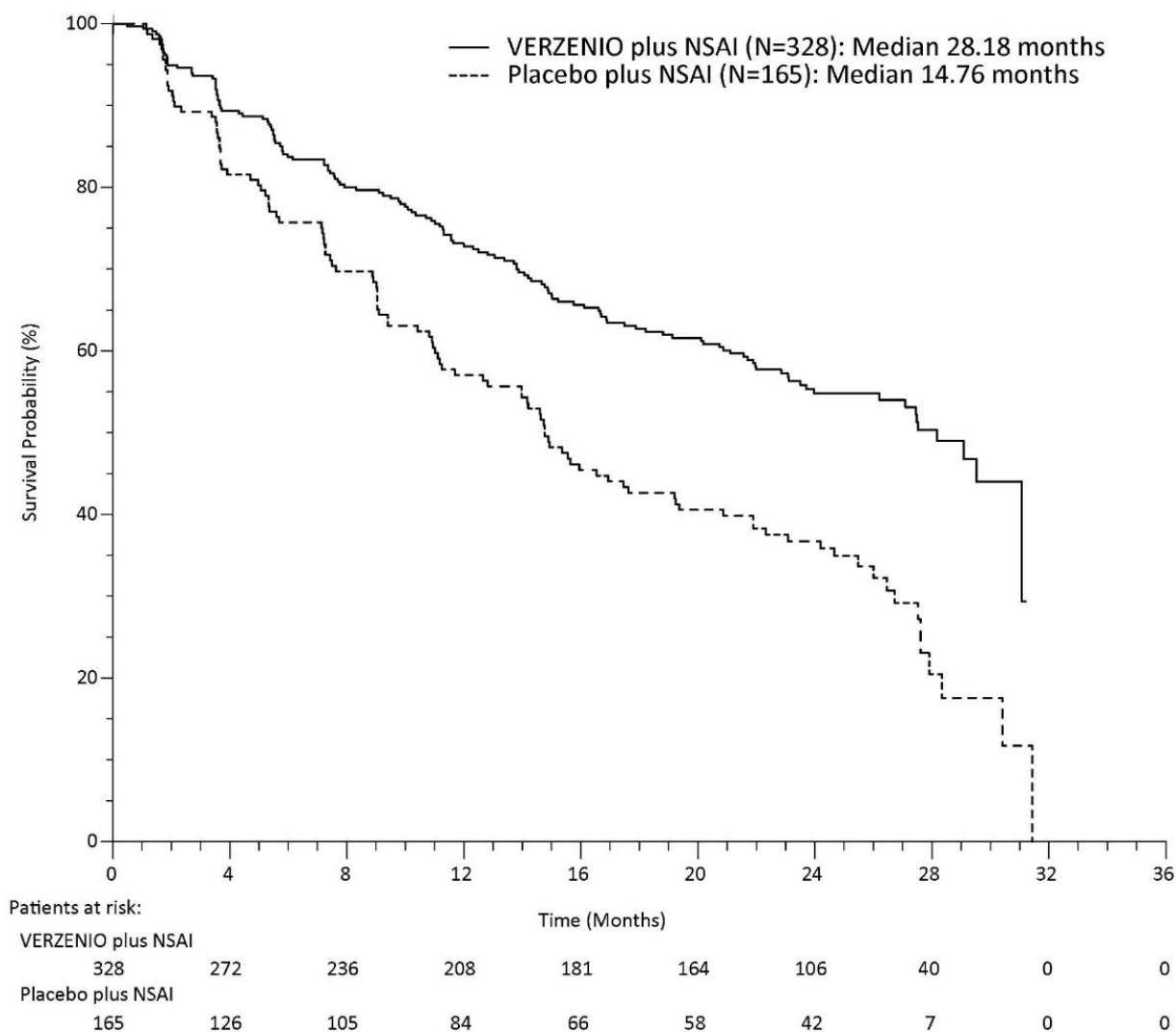


Figure 3. Kaplan-Meier Curves of Progression-Free Survival: VERZENIO plus NSAID versus Placebo plus NSAID – MONARCH 3

A series of prespecified subgroup PFS analyses were performed based on prognostic factors and baseline characteristics. Consistent benefit was observed across predefined patient subgroups (Figure 4).

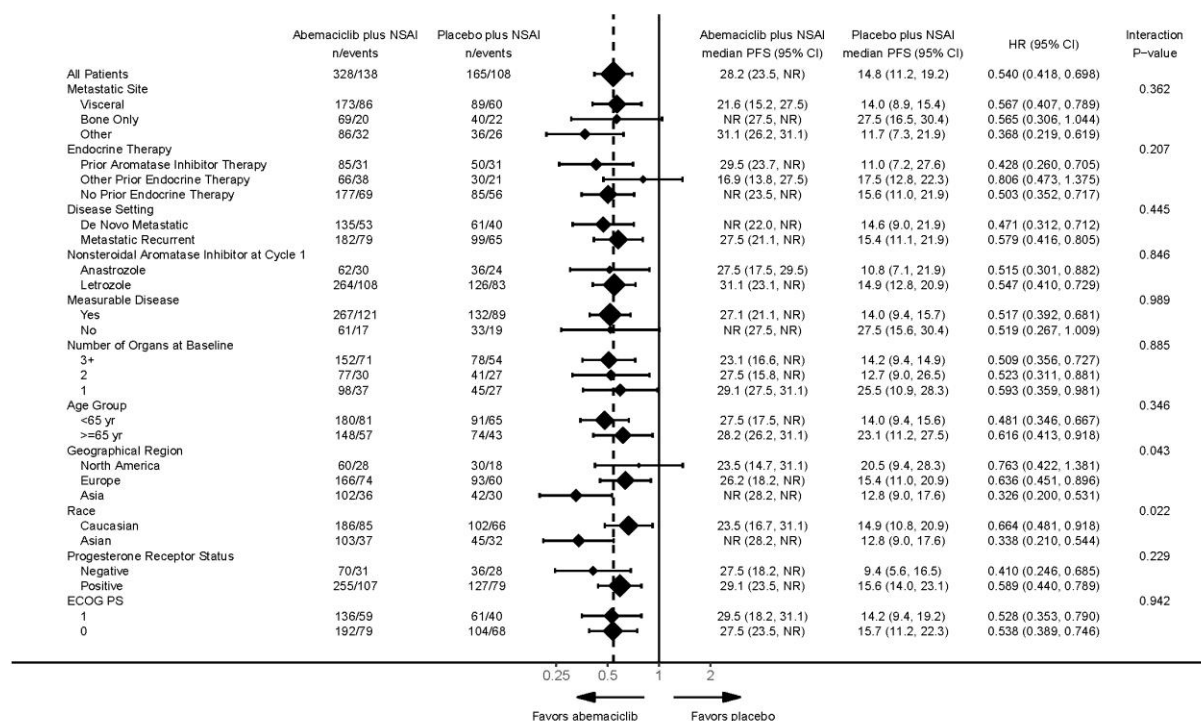


Figure 4. Forest Plot of Subgroup Analyses of Progression-Free Survival by Investigator Assessment, Intent-to-Treat Population – MONARCH 3

Overall survival data were not mature at the time of the final PFS analysis. With a total of 93 events observed (63 events in the VERZENIO plus NSAI arm and 30 events in the placebo plus NSAI arm), the hazard ratio (HR) was 1.057.

Metastatic Breast Cancer

Combination with Fulvestrant

VERZENIO (abemaciclib) for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with fulvestrant in women with disease progression following endocrine therapy

Table 29 - Summary of Trial Design and Patient Demographics in MONARCH 2- Metastatic Breast Cancer combination with Fulvestrant

Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)
Randomized (2:1), Phase III, placebo-controlled, multicenter study	Patients received VERZENIO (150 mg orally twice daily on a continuous schedule), or placebo, plus intramuscular injection of 500 mg fulvestrant on day 1 and 15 of cycle 1 and day 1 of cycle 2 and beyond.	VERZENIO + fulvestrant (N=446) Placebo + Fulvestrant (N=223) (669 total)	VERZENIO + Fulvestrant = 59 (32-91) Placebo + Fulvestrant = 62 (32-87)

The efficacy of VERZENIO in combination with fulvestrant was evaluated in MONARCH 2, a randomized, placebo-controlled, multicenter study in women with HR-positive, HER2-negative advanced or metastatic breast cancer who had disease progression following endocrine therapy and who had not received chemotherapy in the metastatic setting. Randomization was stratified by metastatic disease site (visceral, bone only, or other) and by sensitivity to prior endocrine therapy (primary or secondary resistance).

VERZENIO or placebo was given orally, without regard to food, every 12 ($\pm$ 2) hours on Days 1 through 28 of a 28-day cycle. Patients received study treatment until disease progression or unacceptable toxicity. Pre-/perimenopausal women enrolled in the study received a gonadotropin-releasing hormone agonist (e.g., goserelin) for at least 4 weeks prior to and for the duration of treatment. Crossover between treatment arms was not allowed.

Demographics and baseline characteristics are outlined in Table 30.

Table 30 - Baseline Demographic and Disease Characteristics for the Intent to Treat (ITT) Population – MONARCH 2 - Metastatic Breast Cancer combination with Fulvestrant

	Demographic Parameter	VERZENIO + Fulvestrant (N=446)	Placebo + Fulvestrant (N=223)	Total (N=669)
Age (years)	Median age (range)	59.0 (32.0-91.0)	62.0 (32.0-87.0)	60.0 (32.0-91.0)
Age group n (%)	Age <65 years	291 (65.3)	133 (59.6)	424 (63.4)
	Age $\geq$ 65 years	155 (34.8)	90 (40.4)	245 (36.6)
Menopausal status, n (%)	Pre-/perimenopausal	72 (16.1)	42 (18.8)	114 (17.0)
	Postmenopausal	371 (83.2)	180 (80.7)	551 (82.4)
Race, n (%) ^a	White	237 (53.1)	136 (61.0)	373 (55.8)
	Asian	149 (33.4)	65 (29.1)	214 (32.0)

	Black	9 (2.0)	5 (2.2)	14 (2.1)
	Other	18 (4.0)	8 (3.6)	26 (3.9)
ECOG performance status (PS), n (%)	0	264 (59.2)	136 (61.0)	400 (59.8)
	1	176 (39.5)	87 (39.0)	263 (39.3)
Stage of disease at initial diagnosis, n (%)	Stage III	113 (25.4)	51 (22.9)	164 (24.5)
	Stage IV	86 (19.3)	45 (20.2)	131 (19.6)
Progesterone receptor (PgR) status, n (%)	Positive	339 (76.0)	171 (76.7)	510 (76.2)
	Negative	96 (21.5)	44 (19.7)	140 (20.9)
Endocrine therapy resistance, n (%)	Primary resistance	111 (24.9)	58 (26.0)	169 (25.3)
	Secondary resistance	326 (73.1)	163 (73.1)	489 (73.1)
Metastatic disease site, n (%)	Visceral	245 (54.9)	128 (57.4)	373 (55.8)
	Non-visceral			
	Bone only	123 (27.6)	57 (25.6)	180 (26.9)
	Other	75 (16.8)	38 (17.0)	113 (16.9)
Treatment in locally advanced/metastatic setting, n (%)	Endocrine	173 (38.8)	86 (38.6)	259 (38.7)
	Letrozole	95 (21.3)	41 (18.4)	136 (20.3)
	Anastrozole	28 (6.3)	15 (6.7)	43 (6.4)
	Exemestane	14 (3.1)	9 (4.0)	23 (3.4)
	Tamoxifen	48 (10.8)	24 (10.8)	72 (10.8)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

^a Race not reported for 4.2%.

MONARCH 2 – Study Results

The primary efficacy outcome measure was investigator-assessed progression-free survival (PFS) evaluated according to RECIST v1.1. Secondary efficacy endpoints included OS and ORR.

The efficacy analyses, performed at a median follow-up time of 20 months for both treatment arms, indicated that patients who received VERZENIO with fulvestrant had a statistically significant 44.7% reduction in the risk of disease progression or death compared to those treated with placebo plus fulvestrant (Table 31 and Figure 5). Data from an independent

radiographic review was supportive of this treatment effect. Consistent benefit was observed across predefined patient subgroups and menopausal status (Figure 6).

A preplanned overall survival (OS) analysis was performed after 338 events (211 in the VERZENIO with fulvestrant arm and 127 in the placebo with fulvestrant arm). Based on a pre-specified interim analysis on OS, a statistically significant increase in survival was observed in the VERZENIO plus fulvestrant arm compared to the placebo plus fulvestrant arm, with a hazard ratio of 0.757 (95% confidence interval: 0.606 to 0.945, 2-sided $p=.0137$). The median OS was 46.7 months in the VERZENIO plus fulvestrant arm versus 37.3 months in the placebo plus fulvestrant arm (Table 31 and Figure 7). Consistent benefit was observed across the predefined patient subgroups.

Efficacy results from the MONARCH 2 study are summarized in Table 31 and the Kaplan-Meier curves for PFS and OS are shown in Figure 5, and Figure 7, respectfully.

Table 31 - Efficacy Results of MONARCH 2– Intent-to-Treat (ITT) Population - Metastatic Breast Cancer combination with Fulvestrant

	VERZENIO + Fulvestrant	Placebo + Fulvestrant
Progression-Free Survival^a (Investigator Assessment)	N=446	N=223
Median, months (95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 11.4)
Hazard ratio (95% CI)	0.553 (0.449, 0.681)	
p-value (2-sided) log-rank stratified	$p<.0001$	
Overall Survival^b		
Number of deaths (%)	211 (47.3)	127 (57.0)
Median – months (95% CI)	46.7 (39.2, 52.2)	37.3 (34.4, 43.2)
Hazard ratio (95% CI)	0.757 (0.606, 0.945)	
p-value (2-sided) log-rank stratified	$p=.0137$	
Objective Response Rate for Patients with Measurable Disease	N=318	N=164
Objective response rate ^{a,c} , n (%)	153 (48.1)	35 (21.3)
95% CI	42.6, 53.6	15.1, 27.6
Complete response, n (%)	11 (3.5)	0 (0.0)
Partial response, n (%)	142 (44.7)	35 (21.3)

Abbreviation: CI = confidence interval, RECIST = Response Evaluation Criteria in Solid Tumors.

^a Evaluated according to RECIST version 1.1.

^b The interim analysis for OS data was conducted after 338 events.

^c Complete response + partial response.

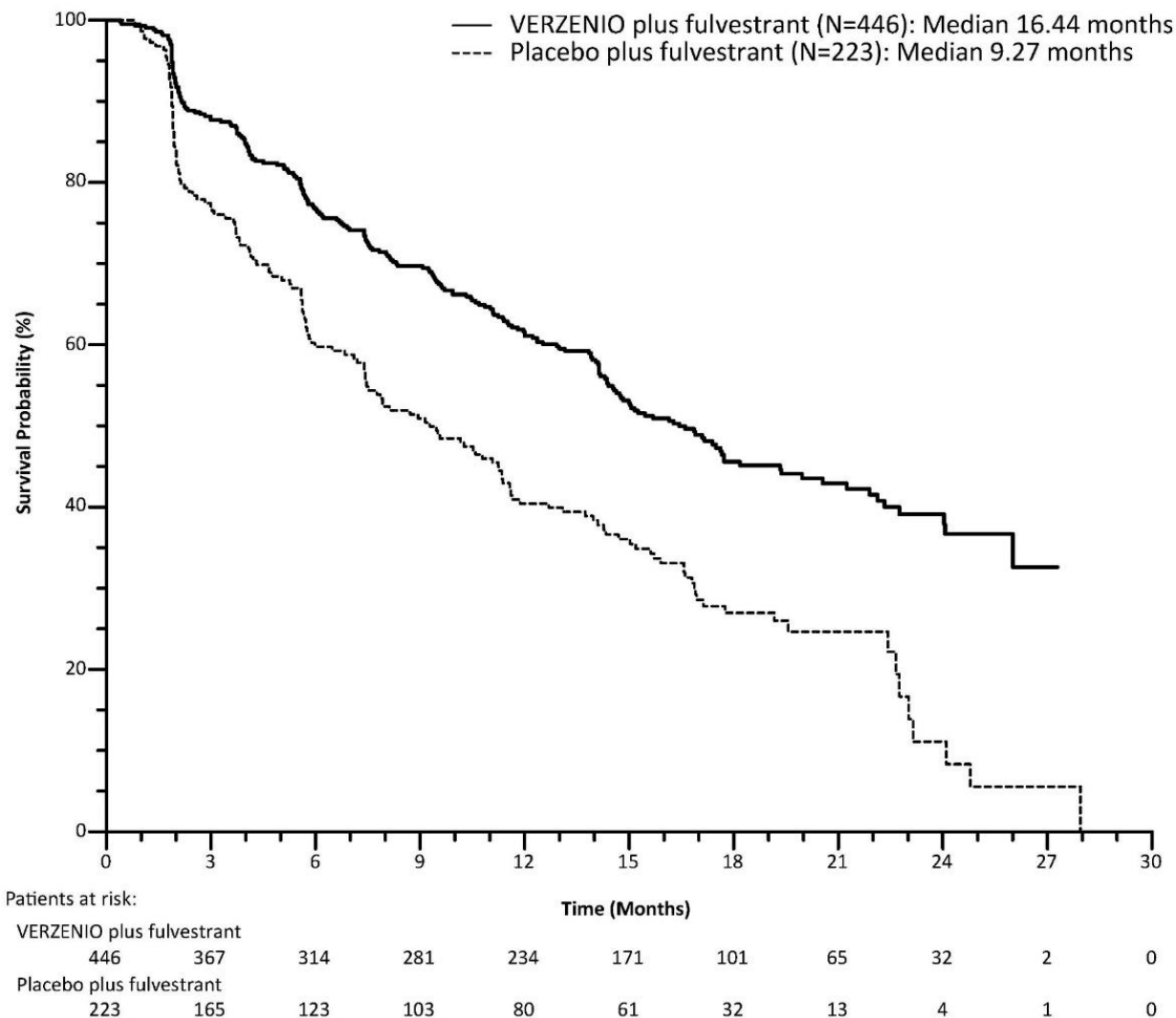


Figure 5. Kaplan-Meier Curves of Progression-Free Survival: VERZENIO plus Fulvestrant versus Placebo plus Fulvestrant – MONARCH 2

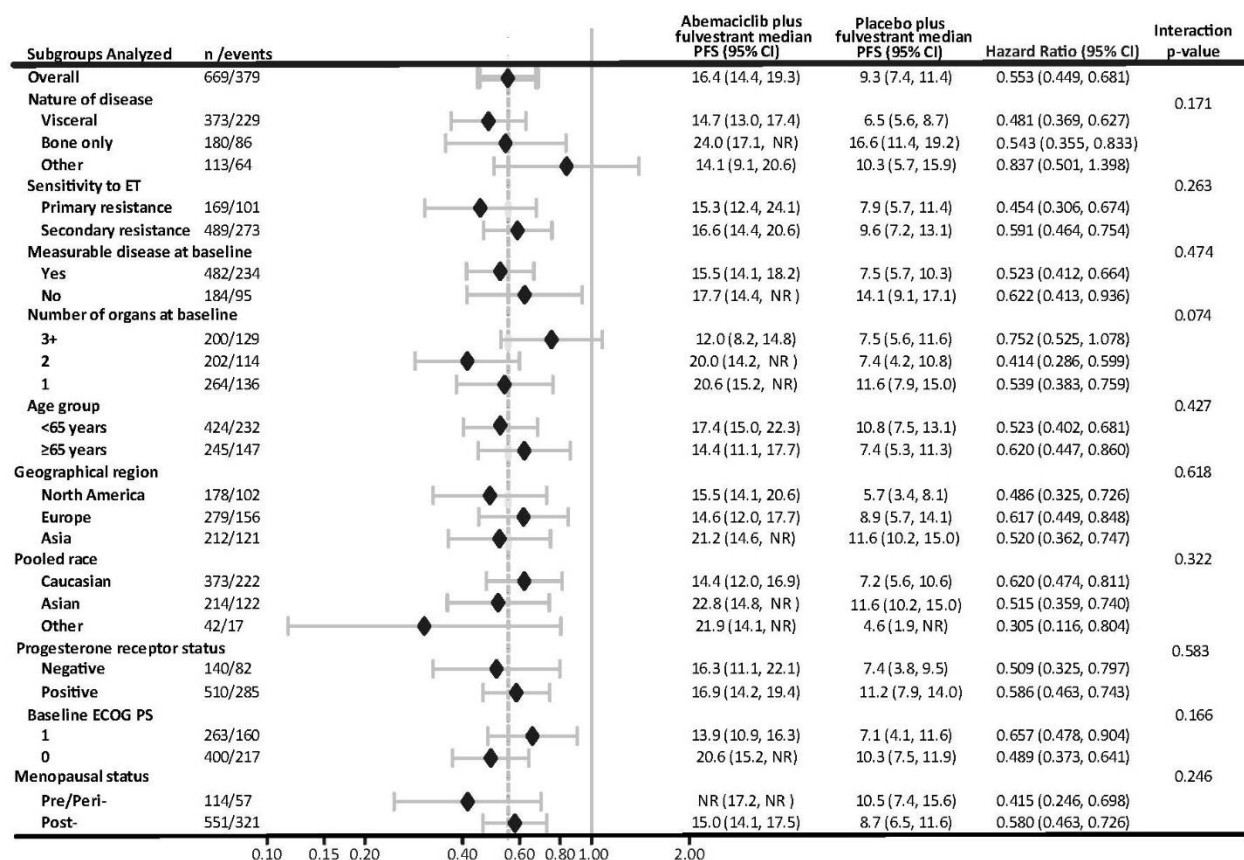


Figure 6. Forest Plot of Summary of Progression-Free Survival by Select Subgroups, Intent-to-Treat Population – MONARCH 2

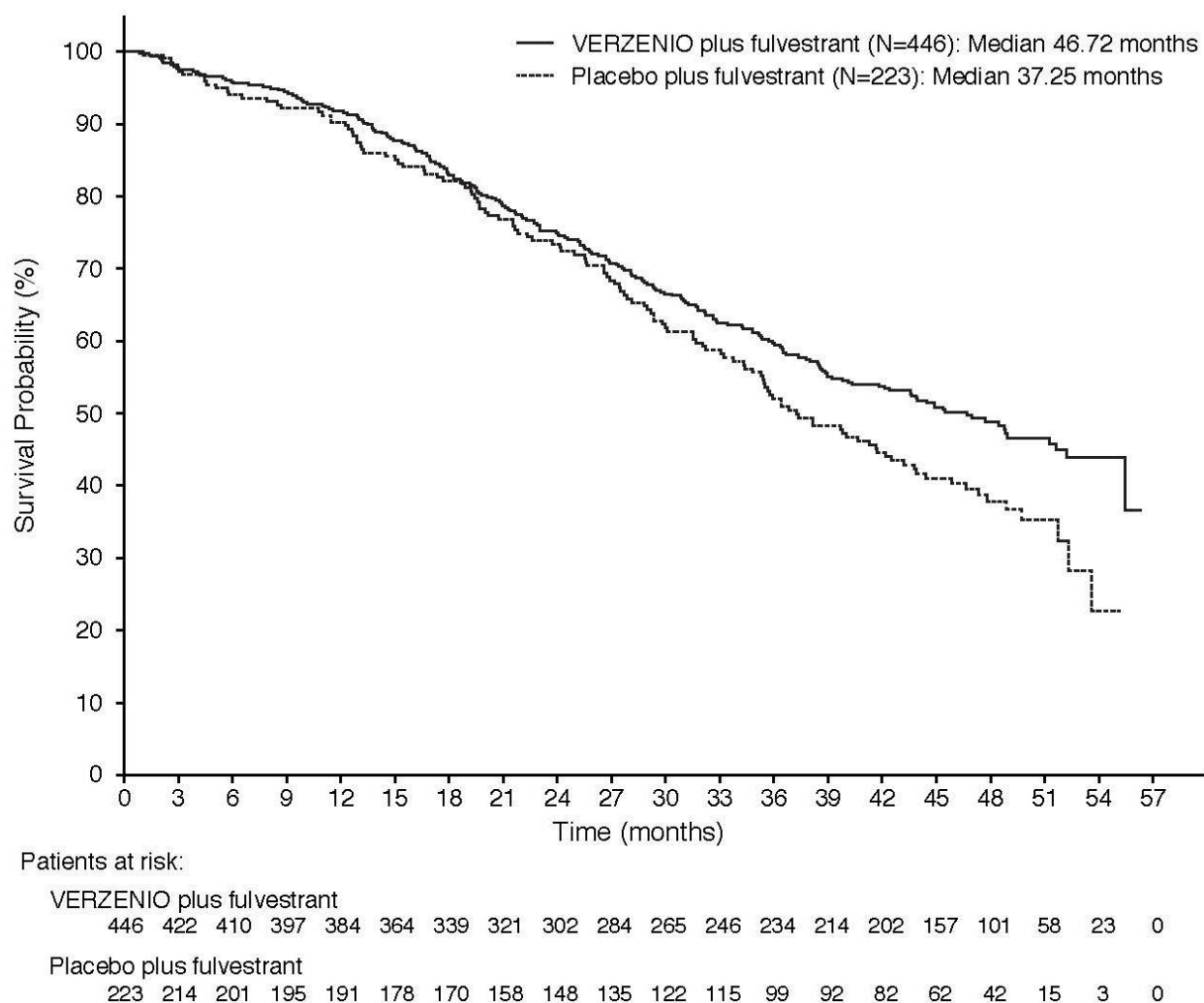


Figure 7. Kaplan-Meier Curves of Overall Survival: VERZENIO plus Fulvestrant versus Placebo plus Fulvestrant – MONARCH 2

Metastatic Breast Cancer

Used as a Single Agent

VERZENIO (abemaciclib) for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer as a single agent in women with disease progression following endocrine therapy and at least 2 prior chemotherapy regimens. At least one chemotherapy regimen should have been administered in the metastatic setting, and at least one should have contained a taxane

Table 32 - Summary of Trial Design and Patient Demographics in MONARCH 1 - Metastatic Breast Cancer used as a Single Agent

Trial design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)
Single arm, Phase II, open-label, multicenter study	Patients received VERZENIO 200 mg orally twice daily on a continuous schedule.	Single-agent VERZENIO (N=132)	Single-agent VERZENIO = 58 (36-89) years

The efficacy of single agent VERZENIO was evaluated in MONARCH 1, a single-arm, open-label, multicenter study in women with previously treated HR-positive, HER2-negative metastatic breast cancer with disease progression on or following prior endocrine therapy and at least 2 chemotherapy regimens (including a taxane in any setting and no more than 2 regimens in the metastatic setting). All patients had measurable disease at study entry. VERZENIO was given orally (with no food 1 hour before or 1 hour after drug administration) every 12 ($\pm$ 2) hours on Days 1 through 28 of a 28-day cycle. Study treatment continued until disease progression or unacceptable toxicity. The median number of cycles received per patient was 5, with a median duration of therapy of 138.5 days.

In the metastatic setting, patients had received a median of 3 (range, 1-8) prior lines of systemic therapy and 2 (range, 1-6) lines of endocrine therapy. In the metastatic setting, chemotherapy regimens (no more than 2) included taxane-based (68.9%) capecitabine (55.3%), gemcitabine (7.6%), vinorelbine (6.8%), and eribulin (4.5%), and targeted therapies (everolimus, 28.0%).

The duration of metastatic disease (date of Stage IV disease diagnosis to date of first dose of study drug) was 27.6 months (range 0.1 to 228.9).

Demographics and baseline characteristics are outlined in Table 33.

Table 33 - Baseline Demographic and Pre-Treatment Disease Characteristics for the Intent to Treat (ITT) Population – MONARCH 1 - Metastatic Breast Cancer used as a Single Agent

	Demographic Parameter	Single Agent VERZENIO (N=132)
Age (years)	Median age (range)	58.0 (36.0-89.0)
Age group n (%)	Age <65 years	90 (68.2)
	Age $\geq$ 65 years	42 (31.8)
Race, n (%) ^a	White	112 (84.8)
	Black	6 (4.5)
	Asian	2 (1.5)
ECOG performance status (PS), n (%)	0	73 (55.3)
	1	59 (44.7)

Disease site, n (%)	Visceral	119 (90.2)
	Liver	93 (70.5)
	Lung	31 (23.5)
	Bone	82 (62.1)
	Bone Only	3 (2.3)
Number of Metastatic Sites, n (%)	1	19 (14.4)
	2	46 (34.8)
	≥3	67 (50.8)
Prior Therapy Regimens in Metastatic Setting, n (%)	Prior Endocrine Therapy	
	1 regimen	48 (36.4)
	2 regimens	25 (18.9)
	3 regimens	24 (18.2)
	≥4 regimens	18 (13.6)
	Prior Chemotherapy	
	1 regimen	67 (50.8)
	2 regimens	64 (48.5)
	3 regimens	1 (0.8)

Abbreviation: ECOG = Eastern Cooperative Oncology Group.

^a Race not reported for 9.1%.

MONARCH 1 – Study Results

The primary efficacy outcome measure was confirmed objective response rate (ORR) by investigator assessment as defined by RECIST V1.1. Secondary efficacy endpoints included Duration of Response (DoR). An independent radiographic review of scans was also performed for efficacy assessment.

Efficacy results from the MONARCH 1 study are summarized in Table 34.

Table 34 - Efficacy Results of MONARCH 1– Intent-to-Treat (ITT) Population- Metastatic Breast Cancer used as a Single Agent

	Single Agent VERZENIO N=132	
	Investigator Assessed	Independent Review
Objective Response Rate^a, n (%)	26 (19.7)	23 (17.4)
95% CI	13.3, 27.5	11.4, 25.0

Best Overall Response^a		
Partial response, n (%)	26 (19.7)	23 (17.4)
Complete response, n (%)	0	0
Duration of Response^a		
Duration of response, median, months	8.6	7.2
95% CI	5.8, 10.2	5.6, NR

Abbreviations: CI = confidence interval, NR = not reached, RECIST = Response Evaluation Criteria in Solid Tumors.

^a Evaluated according to RECIST version 1.1.

16 Non-Clinical Toxicology

General Toxicology: Repeat-dose oral toxicity studies were conducted in mice and dogs for up to 3 months and in rats for up to 6 months. The primary target organs associated with daily dosing of abemaciclib in rodents and dogs were the bone marrow, gastrointestinal tract, lymphoid tissues, and male reproductive tract. Morphologic changes in these organs were consistent with antiproliferative effects in rapidly dividing cells, including peripheral blood cytopenias and bone marrow hypocellularity; crypt necrosis/hyperplasia and villous atrophy in the intestines; lymphoid depletion; and hypospermatogenesis and atrophy in the testis. Effects in lung (alveolar macrophage accumulation and bronchoalveolar inflammation) were observed in dogs and mice treated for 3 months at exposure levels approximately 0.1 and 11 times the exposure (AUC) in humans at the recommended dose, respectively and at approximately 2.9 times human exposure in rats. Effects in lung occurred at the lowest dose tested in rats, 10 mg/kg/day.

Effects in eyes (retinal atrophy, cataracts) occurred only in rodents. Eye effects occurred at exposure levels lower than human exposure levels. Effects in kidney (tubular degeneration/regeneration, vacuolation, dilatation) and minor effects in pancreas (vacuolation, atrophy) occurred in mice treated for 3 months and rats treated for 6 months at exposure levels approximately 1.8 and 2.9 times higher than human exposure levels, respectively. Effects in kidney occurred at the lowest dose tested in rats, 10 mg/kg/day. Effects in skeletal muscles (myofiber degeneration) only occurred in rats at exposure levels approximately 6 times higher than the human exposure levels.

Complete or partial recovery was observed for all target organs at the end of the 28-day recovery period, with the exception of the effects on the male reproductive tract. Recovery of eye effects has not been assessed.

Carcinogenicity: Abemaciclib was assessed for carcinogenicity in a 2-year rat study. In 12% of male rats, daily oral administration of abemaciclib resulted in benign testicular interstitial cell adenomas at the highest dose tested, 3 mg/kg/day (approximately 1.5 times the human clinical exposure at 150 mg BID based on AUC). This finding was preceded by interstitial cell hyperplasia. At dose levels greater than or equal to 0.3 mg/kg/day (approximately 0.1 times the human clinical exposure at 150 mg BID based on AUC) interstitial cell hyperplasia was observed. It is unknown if these effects will translate to humans. There were no neoplastic findings in female rats.

Genotoxicity: Abemaciclib and its active human metabolites M2 and M20 were not mutagenic

in a bacterial reverse mutation (Ames) assay or clastogenic in an in vitro chromosomal aberration assay in Chinese hamster ovary cells or human peripheral blood lymphocytes. Abemaciclib was not clastogenic in an in vivo rat bone marrow micronucleus assay.

Reproductive and Developmental Toxicology:

Fertility Studies

Abemaciclib may impair fertility in males of reproductive potential. In repeat-dose toxicity studies up to 3-months duration, abemaciclib-related findings in the testis, epididymis, prostate, and seminal vesicle at doses ≥ 10 mg/kg/day in rodents and ≥ 0.3 mg/kg/day in dogs included decreased organ weights, intratubular cellular debris, hypospermia, tubular dilatation, atrophy, and degeneration/necrosis. These doses in rats and dogs resulted in approximately 2 and 0.02 times, respectively, the exposure (AUC) in humans at the maximum recommended human dose. No effects on female reproductive organs were observed in repeat-dose toxicity studies. In a rat male fertility study, abemaciclib had no effects on reproductive performance. In a rat female fertility and early embryonic development study and in repeat-dose toxicity studies, abemaciclib did not have any effect on reproductive performance or any important effects on the female reproductive tract indicative of a risk of impaired fertility.

Embryo-Fetal Development Studies

In an embryo-fetal development study, pregnant rats received oral doses of abemaciclib up to 15 mg/kg/day during the period of organogenesis; abemaciclib was teratogenic. Doses ≥ 4 mg/kg/day caused decreased fetal body weights and increased incidence of cardiovascular and skeletal malformations and variations. These findings included absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs. At 4 mg/kg/day in rats, the maternal systemic exposures were approximately equal to the human exposure (AUC) at the recommended dose.

Special Toxicology: Abemaciclib was not phototoxic in a rat phototoxicity study at oral dose levels up to 40 mg/kg. Abemaciclib did not cause dermal toxicity in a rat study in which abemaciclib was applied to the skin at dose levels up to 2000 mg/kg. Abemaciclib was not an irritant in a bovine corneal opacity and permeability test.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrVERZENIO®

Abemaciclib tablets

This Patient Medication Information is written for the person who will be taking **VERZENIO**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **VERZENIO**, talk to a healthcare professional.

Your early or advanced breast cancer may be treated with VERZENIO in combination with another drug. Read the patient leaflet for the other drug as well as this one.

Serious warnings and precautions box

Venous Thromboembolism:

Venous thromboembolism refers to a blood clot. Blood clots can happen in any vein. Together they are called **Venous Thromboembolism**. In some patients it can lead to death.

Venous thromboembolism includes:

- deep vein thrombosis (DVT): blood clot in a large vein
- pulmonary embolism: blood clot in the lung
- pelvic venous thrombosis: blood clot in the pelvis
- cerebral venous thrombosis: blood clot in the brain
- blood clots in other veins such as in the abdomen, armpit, or on the way to the heart

Your healthcare professional might temporarily stop your dose of VERZENIO if you develop blood clots during treatment. The symptoms are listed in the table “Serious side effects and what to do about them”. It is found later in this leaflet.

What VERZENIO is used for:

VERZENIO is used to treat the different types of breast cancer in adults. The breast cancer has to be hormone receptor (HR)-positive and human epidermal growth factor receptor 2 (HER2)-negative. The types of breast cancer that VERZENIO treats are:

- Early breast cancer in adult women and men after completion of breast cancer surgery and related treatments. The cancer is lymph node positive and has a high chance of coming back. VERZENIO is taken:
 - with another treatment for breast cancer called hormone therapy.
- Advanced breast cancer in adult women, when it has spread to other parts of the body (metastatic). VERZENIO is taken:

- with another drug for breast cancer called an aromatase inhibitor. You must have already gone through menopause to take VERZENIO with an aromatase inhibitor. This is an initial therapy.
- Or
- with another drug for breast cancer called fulvestrant. This is used when the cancer gets worse after initial therapy. If you have not yet gone through menopause, you must also take a medicine that will stop your ovaries from making estrogen.
- Or
- by itself. You must have breast cancer that came back after having had hormone therapy and at least two kinds of prior chemotherapy treatment.

How VERZENIO works:

Abemaciclib is a type of drug called a kinase inhibitor. It works by stopping cancer cells from dividing and growing. This may slow the growth and spread of breast cancer cells. It is given by itself, or together with other drugs (aromatase inhibitor, tamoxifen, or fulvestrant).

The ingredients in VERZENIO are:

Medicinal ingredients: abemaciclib

Non-medicinal ingredients: croscarmellose sodium, lactose monohydrate, microcrystalline cellulose 101, microcrystalline cellulose 102, polyethylene glycol, polyvinyl alcohol, silicon dioxide, sodium stearyl fumarate, talc, titanium dioxide

Also contains:

50 mg and 200 mg tablets: iron oxide red, iron oxide yellow

150 mg tablet: iron oxide yellow

VERZENIO comes in the following dosage forms:

Tablets: 50 mg, 100 mg, 150 mg, and 200 mg

Do not use VERZENIO if:

- You are allergic to abemaciclib or any of the other ingredients of VERZENIO.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VERZENIO. Talk about any health conditions or problems you may have, including if you:

- Have fever, chills, or any other signs of an infection
- Have liver or kidney problems
- Are over 65 years old

Other warnings you should know about:

- **Pregnancy and breast-feeding**
 - VERZENIO may cause harm to your unborn child. Avoid getting pregnant while receiving this medicine and for at least 3 weeks after the last dose of VERZENIO.
 - If you have not gone through menopause, you should have a pregnancy test done before you start treatment with VERZENIO.

- Talk to your healthcare professional about the best birth control for you.
- If you become pregnant during treatment with VERZENIO, inform your healthcare professional right away.
- Do not breast-feed your baby during treatment with VERZENIO and for at least 3 weeks after the last dose.
- **Fertility in male patients**
Before starting on VERZENIO you should know that it may affect your fertility. This may affect your ability to father a child. Talk to your healthcare professional if this is a concern for you.
- **Low white blood cell counts (neutropenia)**
Low white blood cell counts are common while taking VERZENIO. They may cause serious infections that can cause death.
- **Infections**
Serious infections can occur while taking VERZENIO. They may cause death.
- **Liver problems**
VERZENIO can cause serious liver problems.
- **Diarrhea**
 - VERZENIO can cause diarrhea. It may be severe at times.
 - The most common time to start having diarrhea is during the first month of treatment.
 - If you start having diarrhea, your healthcare professional may tell you to stop taking VERZENIO for a short time, decrease your dose, or stop your treatment. Cases of diarrhea have occurred with dehydration or an infection.
 - **If you have any loose or liquid stools**, tell your healthcare professional right away. Start taking an antidiarrheal medicine (such as loperamide) and drink more fluids.
- **Blood clots in your arteries**
Taking VERZENIO in combination with endocrine therapies for treatment of metastatic breast cancer may lead to serious blood clots. These blood clots can cause heart attack or stroke. It is not known if these blood clots occurred due to VERZENIO alone.
- **Lung problems (pneumonitis)**
 - VERZENIO can cause severe inflammation of the lungs during treatment that can lead to death.
 - Tell your healthcare professional right away if you have any new or worsening symptoms, including trouble breathing or shortness of breath, cough with or without mucus, or chest pain.
 - If you develop lung problems during treatment with VERZENIO, your healthcare professional may tell you to temporarily stop taking VERZENIO, decrease your dose, or stop your treatment.
- **Children and adolescents (under 18 years of age)**
VERZENIO should not be given to patients under the age of 18 years.

- **Driving and Using Machines**

Fatigue and dizziness can occur with VERZENIO. Before you do this wait until you know how you respond.

- **Check-ups and testing**

You will have regular visits with your healthcare professional, before, during, or at the end of your treatment. They will check for signs and symptoms of:

- Lung problems
- Blood clots
- Infections
- Blood and liver problems by doing blood tests

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with VERZENIO:

- Some medicines for fungal infections, such as ketoconazole, itraconazole, posaconazole, and voriconazole
- Some medicines for infections (antibiotics), such as clarithromycin, ciprofloxacin, and rifampin
- Some medicines for high blood pressure, such as verapamil and diltiazem
- HIV medicines, such as saquinavir, ritonavir, and nelfinavir
- Medicines to treat epilepsy, such as carbamazepine and phenytoin
- The diabetes medicine metformin
- Some medicines for acid reflux such as ranitidine
- Medicines used to treat congestive heart failure and abnormal heart rhythms, such as digoxin
- St. John's wort, an herbal product used to treat depression and other conditions (also known as *hypericum perforatum*)
- Do not eat grapefruit or drink grapefruit juice while on VERZENIO. This includes any products with grapefruit. Grapefruit may increase the amount of VERZENIO in your blood.
- Rosuvastatin and atorvastatin, which are medicines (statins) to treat high cholesterol.

Other medicines not listed here may also interact.

How to take VERZENIO:

- Take exactly as your healthcare professional tells you.
- Take with or without food.
- Swallow tablets whole.
 - Do NOT chew, crush, or split the tablets.
 - Do NOT take damaged tablets.
- Take doses at approximately the same time every day.
- If you vomit after taking a dose, take your next dose at your regular time.
- Your healthcare professional may decide to delay, stop, interrupt, decrease, or reduce your dose. This may occur if you get side effects.
- Take VERZENIO for as long as your healthcare professional recommends.

Usual dose:

Early Breast Cancer

Adult dose for women and men:

- When VERZENIO is taken with another drug or treatment for breast cancer: 150 mg two times a day (total of 300 mg a day).
- The smallest dose is: 50 mg two times a day.

Advanced or Metastatic Breast Cancer**Adult dose for women:**

- When VERZENIO is taken with another drug or treatment for breast cancer: 150 mg two times a day (total of 300 mg a day).
- When VERZENIO is taken by itself: 200 mg two times a day (total of 400 mg a day).
- The smallest dose is: 50 mg two times a day.

Your healthcare professional will monitor your health. If you start having side effects, you may be told to delay or stop taking VERZENIO for a short time. Or, you may need to decrease your dose, or stop your treatment.

Overdose:

If you think you, or a person you are caring for, have taken too much VERZENIO, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms

Missed dose:

- If you miss a dose of VERZENIO, take your next dose at your regular time.
- Do not take 2 doses of VERZENIO at the same time.

Possible side effects from using VERZENIO:

These are not all the possible side effects you may have when taking VERZENIO. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Diarrhea, nausea, vomiting, decreased appetite, bloating, abdominal pain
- Headache, dizziness, sense of spinning
- Hair loss or thinning
- Feel faint or light-headed
- Tiredness, fatigue, muscle weakness
- Fracture or break a bone
- Rash, dry, itchy, infected or darkened or painful skin, bruising
- Ongoing itchy inflammation of the skin, inflamed fat layer below the skin
- Palmar-plantar erythrodysesthesia syndrome: pain, swelling, numbness, tingling, redness, and sometimes flaking or blistering of the palms or soles
- Increased tears
- Eye pain and blurred vision
- Changes to your sense of taste, dry mouth, sores in mouth, difficulty swallowing

VERZENIO can cause abnormal blood test results. This includes increased creatinine and liver enzymes. Your healthcare professional will test your blood before you start on VERZENIO.

They will then test it every 2 weeks for the first two months. Then once a month for two months and whenever they think it is needed. Your healthcare professional will tell you if your test results are abnormal and if you need treatment to correct these side effects.

Serious side effects and what to do about them

Frequency / Side Effect / Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Very Common			
Leukopenia, neutropenia, lymphopenia (Low white blood cells): Chills, fever, infection. Fatigue, aches and pains, and flulike symptoms.		✓	
Anemia (Low red blood cells): Being short of breath, feeling very tired, loss of energy, weakness.		✓	
Thrombocytopenia (Low blood platelets): Bruising or bleeding for longer than usual if you hurt yourself. Fatigue, weakness.		✓	
Liver Problems: Feeling very tired with loss of appetite, pain on the upper right side of your stomach area (abdomen).		✓	
Diarrhea: At the first sign of loose or liquid stools.		✓	
Common			
Venous Thromboembolism (Blood clots in veins): Swelling, redness and pain in one part of the body, arms, or legs. This can be warm to touch. Sudden chest pain, rapid breathing and heart rate, shortness of breath. (Blood clots in the brain): Severe headache, feel numb, weak or cannot move arms, legs, or face, difficulty talking or seeing, fainting, or passing out, confusion, dizziness, blurred vision, or seizure (fit).		✓	
Infections: Upper Respiratory Tract (a cold): Chills, cough, fever, runny nose, shortness of breath, or sore throat. Urinary Tract: pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		✓	

Hypokalemia (Decreased potassium in the blood): Irregular heartbeats, muscle weakness and generally feeling unwell.		✓	
Hypocalcemia (Low Level of Calcium in the Blood): Muscle cramps in the back and legs. Dry skin. Confusion and memory loss.		✓	
Pneumonia (Infection in the lungs), Pneumonitis (Lung inflammation), or Pulmonary Fibrosis : New or worsening shortness of breath, cough, wheezing or fever. Difficult and painful breathing. Feel tired.		✓	
Heart Problems (Tachycardia, atrial fibrillation, palpitations, heart failure) : Fast or irregular heartbeat, chest pain, heart racing or skips a beat, short of breath, fatigue, inability to exercise, and fluid in the legs.		✓	
Kidney Problems (Inability of the kidneys to properly clean the blood): A change in the amount of urine you pass. Water retention with weight gain swelling of legs and ankles, puffy face or hands. Lack of appetite, nausea, vomiting, weakness. Itchy skin. Decreased concentration. Flank or lower back pain.		✓	
Sepsis (Blood infection that is body wide): High fever, fast heart rate, and breathing.		✓	
Unknown			
Allergic Reactions : Itch, rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature between 15°C to 30°C.

- Keep out of reach and sight of children.

If you want more information about VERZENIO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website www.lilly.ca, or by calling 1-888-545-5972.

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