▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PI – VERZENIO™ (ABEMACICLIB) TABLET

1 NAME OF THE MEDICINE

Abemaciclib

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Abemaciclib (VERZENIO) 50 mg film-coated tablets
Each film-coated tablet contains 50 mg abemaciclib.

Excipients with known effect
Each film-coated tablet contains 14 mg of lactose (as monohydrate).

Abemaciclib (VERZENIO) 100 mg film-coated tablets
Each film-coated tablet contains 100 mg abemaciclib.

Excipients with known effect
Each film-coated tablet contains 28 mg of lactose (as monohydrate).

Abemaciclib (VERZENIO) 150 mg film-coated tablets
Each film-coated tablet contains 150 mg abemaciclib.

Excipients with known effect
Each film-coated tablet contains 42 mg of lactose (as monohydrate).

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

VERZENIO 50 mg film-coated tablets
Beige, modified oval tablet debossed with “Lilly” on one side and “50” on the other.

VERZENIO 100 mg film-coated tablets
White, modified oval tablet debossed with “Lilly” on one side and “100” on the other.

VERZENIO 150 mg film-coated tablets
Yellow, modified oval tablet debossed with “Lilly” on one side and “150” on the other.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone (LHRH) agonist.

4.2 DOSE AND METHOD OF ADMINISTRATION

VERZENIO therapy should be initiated and supervised by physicians experienced in the use of anti-cancer therapies.

The recommended dose of VERZENIO is 150 mg orally, twice daily in combination with endocrine therapy. Administer the recommended dose of endocrine therapy when given with VERZENIO.

Women treated with the combination of VERZENIO plus endocrine therapy should be in a postmenopausal state prior to therapy.

It is recommended that treatment be continued until disease progression or unacceptable toxicity.

VERZENIO may be taken with or without food.

Dose Adjustments

Management of some adverse reactions may require dose interruption and/or dose reduction. If dose reduction is necessary, decrease the dose by 50 mg at a time. Discontinue VERZENIO for patients unable to tolerate 50 mg twice daily.

Table 1: Recommended Dose Modification for Adverse Reactions

Dose Level	VERZENIO dose combination therapy
Recommended starting dose	150 mg twice daily
First dose adjustment	100 mg twice daily
Second dose adjustment	50 mg twice daily

Table 2. Dose Modification and Management — Hematologic Toxicities including neutropenia

Monitor complete blood counts prior to the start of VERZENIO therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated.

CTCAE Grade	VERZENIO Dose Adjustments
Grade 1 or 2	No dose adjustment required.
Grade 3	Suspend dose until toxicity resolves to Grade 2 or less. Dose reduction is not required.
Grade 3, recurrent; or Grade 4	Suspend dose until toxicity resolves to Grade 2 or less. Resume at next lower dose.
Patient requires administration of blood cell growth factors	Suspend abemaciclib dose for at least 48 hours after the last dose of blood cell growth factors was administered and until toxicity resolves to Grade 2 or less. Resume at next lower dose unless the dose was already reduced for the toxicity that led to the use of the growth factor.

Table 3. Dose Modification and Management — Diarrhoea

At the first sign of loose stools, start treatment with antidiarrhoeal agents, such as loperamide.

CTCAE Grade	VERZENIO Dose Adjustments
Grade 1	No dose adjustment required.
Grade 2	If toxicity does not resolve within 24 hours to Grade 1 or less, suspend dose until resolution. Dose reduction is not required.
Grade 2 that persists or recurs after resuming the same dose despite maximal supportive measures	Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose.
Grade 3 or 4 or requires hospitalisation	

Table 4. Dose Modification and Management — Increased ALT

Monitor ALT prior to the start of VERZENIO therapy, every two weeks for the first two months, monthly for the next two months, and as clinically indicated.

CTCAE Grade	VERZENIO Dose Adjustments
Grade 1 (>ULN-3.0 x ULN) Grade 2 (>3.0-5.0 x ULN)	No dose adjustment required.
Persistent or Recurrent Grade 2, or Grade 3 (>5.0-20.0 x ULN)	Suspend dose until toxicity resolves to baseline or Grade 1. Resume at next lower dose.
Grade 4 (>20.0 x ULN)	Discontinue abemaciclib.

Table 5. Management recommendations for non-haematologic toxicities (excluding diarrhoea and ALT increased)

CTCAE Grade	VERZENIO Dose Adjustments
Grade 1 or 2	No dose adjustment required.
Persistent or recurrent Grade 2 toxicity that does not resolve with maximal supportive measures to baseline or Grade 1 within 7 days	Suspend dose until toxicity resolves to Grade 1 or less. Resume at next lower dose.
Grade 3 or 4	

CYP3A inhibitors

Avoid concomitant use of strong CYP3A inhibitors (for example, voriconazole) and use caution with coadministration of moderate (for example, ciprofloxacin) or weak (for example, ranitidine) CYP3A inhibitors (see Section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS). If coadministration with a CYP3A inhibitor is unavoidable, adjust the abemaciclib dose as described in Table 6.

Table 6. Dose modification in combination with CYP3A inhibitors[a]

CYP3A inhibitor	Expected increase in exposure	VERZENIO dose recommendation
Specific inhibitors[b]		
Ketoconazole	6.87 fold	50 mg once daily
Itraconazole	3.78 fold	50 mg twice daily
Clarithromycin	2.19 fold	100 mg twice daily
Diltiazem	2.41 fold	100 mg twice daily
Verapamil	1.63 fold	100 mg twice daily
For other inhibitors		
Strong inhibitor		50 mg twice daily

[a] Based on a 150 twice daily starting dose.

[b] Based on clinical results and physiologically-based pharmacokinetic simulations

With concomitant use of moderate CYP3A inhibitors, monitor for adverse reactions and consider reducing the VERZENIO dose in 50 mg decrements as demonstrated in Table 1, if necessary.

Avoid grapefruit or grapefruit juice. If a CYP3A inhibitor is discontinued, increase the VERZENIO dose (after 3-5 half-lives of the inhibitor) to the dose that was used before starting the inhibitor [see 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS].

CYP3A inducers

Avoid concomitant use of CYP3A inducers. Consider alternative agents without CYP3A induction [4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS].

Severe hepatic impairment

Decrease the dosing frequency to once daily [see 5.2 PHARMACOKINETIC PROPERTIES].

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified precautions

Neutropenia

Grade ≥3 neutropenia was reported in patients receiving abemaciclib in breast cancer studies. Monitor complete blood counts prior to starting abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Fatal events occurred in <1% of patients. Patients should be instructed to report any episode of fever to their healthcare provider. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia [see 4.2 DOSE AND METHOD OF ADMINISTRATION].

Infections/infestations

Infections were reported in patients receiving abemaciclib plus endocrine therapy at a higher rate than in patients treated with placebo plus endocrine therapy. Lung infection was reported in patients receiving abemaciclib without concurrent neutropenia. Fatal events occurred in <1% of patients. Patients should be monitored for signs and symptoms of infection and treated as medically appropriate.

Venous thromboembolism

Venous thromboembolic events were reported in 5.3% of patients treated with abemaciclib plus fulvestrant or aromatase inhibitors, compared to 0.8% of patients treated with placebo plus fulvestrant or aromatase inhibitors. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism and treated as medically appropriate.

Increased ALT

Grade ≥3 increased ALT was reported in patients receiving abemaciclib in breast cancer studies. Monitor ALT prior to the start of abemaciclib therapy, every 2 weeks for the first 2 months, monthly for the next 2 months, and as clinically indicated. Based on the level of ALT elevations, dose modification may be required [4.2 DOSE AND METHOD OF ADMINISTRATION].

Diarrhoea

Diarrhoea is the most common adverse reaction. Across clinical studies, median time to onset of the first diarrhoea event was approximately 6 to 8 days, and median duration of diarrhoea was 9 to 12 days (Grade 2) and 6 to 8 days (Grade 3). Diarrhoea can be associated with dehydration. Patients should start treatment with antidiarrhoeal agents such as loperamide at the first sign of loose stools, increase oral fluids and notify their healthcare provider. Dose modification is recommended for patients who develop ≥ Grade 2 diarrhoea (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Use in hepatic impairment

Abemaciclib is metabolised in the liver. In subjects with severe hepatic impairment, total abemaciclib unbound exposure increased 2.69-fold, and the abemaciclib half-life increased from 24 to 55 hours. Reduce the abemaciclib dosing frequency to once daily in patients with severe hepatic impairment.

Use in renal impairment

Abemaciclib and its metabolites are not significantly cleared renally. Dose adjustment is not necessary in patients with mild or moderate renal impairment. There are no data in patients with severe renal impairment, end stage renal disease, or in patients on dialysis.

Use in the elderly

Age had no effect on the exposure of abemaciclib in a population pharmacokinetic analysis in patients with cancer (135 males and 859 females; age range 24-91 years; and body weight range 36-175 kg).

Paediatric use

The safety and efficacy of abemaciclib in children aged less than 18 years has not been established. No data are available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicinal products on the pharmacokinetics of abemaciclib

Abemaciclib is primarily metabolised by CYP3A4.

CYP3A4 inhibitors

Co-administration of abemaciclib with CYP3A4 inhibitors can increase plasma concentrations of abemaciclib. In patients with advanced and/or metastatic cancer, co-administration of the CYP3A4 inhibitor clarithromycin resulted in a 3.4-fold increase in the plasma exposure of abemaciclib and a 2.5-fold increase in the combined unbound potency adjusted plasma exposure of abemaciclib and its active metabolites.

Use of strong CYP3A4 inhibitors together with abemaciclib should be avoided. If strong CYP3A4 inhibitors need to be co-administered, the dose of abemaciclib should be reduced (see section 4.2 DOSE AND METHOD OF ADMINISTRATION), followed by careful monitoring of toxicity. Examples of strong CYP3A4 inhibitors include, but not limited to: clarithromycin, itraconazole, ketoconazole, lopinavir/ritonavir, posaconazole or voriconazole. Avoid grapefruit or grapefruit juice.

No dose adjustment is necessary for patients treated with moderate or weak CYP3A4 inhibitors. There should, however, be close monitoring for signs of toxicity.

CYP3A4 inducers

Co-administration of abemaciclib with the strong CYP3A4 inducer rifampicin decreased the plasma concentration of abemaciclib by 95% and unbound potency adjusted plasma concentration of abemaciclib plus its active metabolites by 77% based on AUC0-∞. Concomitant use of strong CYP3A4 inducers (including, but not limited to: carbamazepine, phenytoin, rifampicin and St. John's wort) should be avoided due to the risk of decreased efficacy of abemaciclib.

Effects of abemaciclib on the pharmacokinetics of other medicinal products

Medicinal products that are substrates of transporters

Abemaciclib and its major active metabolites inhibit the renal transporters organic cation transporter 2 (OCT2), multidrug and extrusion toxin protein (MATE1), and MATE2-K. *In vivo* interactions of abemaciclib with clinically relevant substrates of these transporters, such as dofetilide or creatinine, may occur (see section 4.8). In a clinical drug interaction study with metformin (substrate of OCT2, MATE1 and 2) co-administered with 400 mg abemaciclib, a small but not clinically relevant increase (37%) in metformin plasma exposure was observed. This was found to be due to reduced renal secretion with unaffected glomerular filtration.

In healthy subjects, co-administration of abemaciclib and the P-glycoprotein (P-gp) substrate loperamide resulted in an increase in loperamide plasma exposure of 9% based on AUC0-∞ and 35% based on Cmax. This was not considered to be clinically relevant. However, based on the *in vitro* inhibition of P-gp and breast cancer resistance protein (BCRP) observed with abemaciclib, *in vivo* interactions of abemaciclib with narrow therapeutic index substrates of these transporters, such as digoxin or dabigatran etexilate, may occur.

In a clinical study in patients with breast cancer, there was no clinically-relevant pharmacokinetic drug interaction between abemaciclib and anastrozole, fulvestrant, exemestane, letrozole or tamoxifen.

It is currently unknown whether abemaciclib may reduce the effectiveness of systemically acting hormonal contraceptives, and therefore women using systemically acting hormonal contraceptives are advised to add a barrier method.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of abemaciclib on primary reproductive organs in rats and dogs have been assessed in repeat-dose toxicity studies. Cytotoxic effects to the male reproductive tract in rats and dogs indicate that abemaciclib may impair fertility in males. In toxicity studies in rats (≥10 mg/kg/day) and dogs (≥0.3 mg/kg/day), abemaciclib-related findings in the testis, epididymis, prostate, and seminal vesicle included decreased organ weights, intratubular cellular debris, hypospermia, tubular dilatation, atrophy, and degeneration/necrosis. These doses in rats and dogs are similar to or less than, respectively, the exposure (AUC) to pharmacologically-active material in humans at the maximum recommended human dose. Highly effective contraception is recommended for women with reproductive potential during treatment and for 3 weeks after the last dose of abemaciclib.

Use in pregnancy – Pregnancy Category D

There are no data on the use of VERZENIO in pregnant women. Based on findings in animals, and its mechanism of action, abemaciclib can cause fetal harm when administered to a pregnant woman. When pregnant rats were treated during the period of organogenesis (dose of ≥4 mg/kg/day; approximately equal to the human clinical exposure to abemaciclib based on AUC), reduced fetal weights were observed in the absence of maternal toxicity, accompanied by an increased incidence of cardiovascular and skeletal malformations and variations (absent innominate artery and aortic arch, malpositioned subclavian artery, unossified sternebra, bipartite ossification of thoracic centrum, and rudimentary or nodulated ribs).

VERZENIO is not recommended during pregnancy. Highly effective contraception is recommended (see **Effects on fertility**)."

Use in lactation

There are no data on the presence of abemaciclib in human milk, effects of abemaciclib on the breastfed child, or effects of abemaciclib on milk production. Breastfeeding is not recommended for patients receiving VERZENIO therapy as many drugs are excreted in human milk. There is a potential for serious adverse reactions in nursing infants from abemaciclib and nursing women are advised to discontinue breastfeeding during treatment.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of VERZENIO on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of the safety profile

The most commonly occurring adverse reactions are diarrhoea, infections, neutropenia, anaemia, fatigue, nausea, vomiting and decreased appetite.

Tabulated list of adverse reactions

In the following tables, adverse reactions are listed in order of MedDRA body system organ class and

frequency. Frequency gradings are: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 7. Adverse reactions reported in phase 3 studies of abemaciclib in combination with endocrine therapy (N=768)

System organ class *Frequency* Preferred term	Abemaciclib plus endocrine therapy[a] All Grades Toxicity (%)	Grade 3 Toxicity (%)	Grade 4 Toxicity (%)
Infections and infestations			
Very common			
Infections[b]	43.6	5.2	1.0
Blood and lymphatic system disorders			
Very common			
Neutropenia	45.1	22.9	2.5
Leukopenia	25.7	8.5	0.3
Anaemia	30.1	7.0	0.1
Thrombocytopenia	14.3	2.2	1.0
Common			
Lymphopenia	7.3	3.0	0.1
Uncommon			
Febrile neutropenia	0.9	0.7	0.1
Metabolism and nutrition disorders			
Very common			
Decreased appetite	26.4	1.3	0
Nervous system disorders			
Very common			
Dysgeusia	14.3	0	0
Dizziness	12.9	0.5	0
Eye disorders			
Common			
Lacrimation increased	6.8	0.1	0
Vascular disorders			
Common			
Venous thromboembolism[c]	5.3	1.7	0.3
Gastrointestinal disorders			
Very common			
Diarrhoea	84.6	11.7	0
Vomiting	27.7	1.2	0

Nausea	43.5	2.1	0
Skin and subcutaneous tissue disorders			
Very common			
Alopecia	20.7	0	0
Pruritus	13.5	0	0
Rash	12.9	1.0	0
Common			
Dry skin	9.0	0	0
Musculoskeletal and connective tissue disorders			
Common			
Muscular weakness	8.3	0.5	0
General disorders and administration site conditions			
Very common			
Fatigue	40.5	2.3	0
Pyrexia	10.7	0.1	0
Investigations			
Very common			
Alanine aminotransferase increased	15.1	4.8	0.3
Aspartate aminotransferase increased	14.2	2.9	0

[a] Abemaciclib in combination with letrozole, anastrozole, or fulvestrant.

[b] Infections includes all PTs that are part of the System Organ Class Infections and infestations.

[c] Venous thromboembolic events include DVT, pulmonary embolism, cerebral venous sinus thrombosis, subclavian, axillary vein thrombosis,DVT inferior vena cava and pelvic venous thrombosis

Description of selected adverse reactions

Neutropenia

Neutropenia was reported frequently (45.1%). and a Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 28.2% of patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant. The median time to onset of Grade 3 or 4 neutropenia was 29 to 33 days, and median time to resolution was 11 to 15 days. Febrile

neutropenia was reported in 0.9% patients. Dose modification is recommended for patients who develop Grade 3 or 4 neutropenia (see section 4.2).

Diarrhoea

Diarrhoea was the most commonly reported adverse reaction (see Table 7). Incidence was greatest during the first month of abemaciclib treatment and was lower subsequently. The median time to onset of the first diarrhoea event was approximately 6 to 8 days across studies, and the median duration of diarrhoea was 9 to 12 days (Grade 2) and 6 to 8 days (Grade 3) across studies. Diarrhoea returned to baseline or lesser grade with supportive treatment such as loperamide and/or dose adjustment (see section 4.2).

Increased aminotransferases

In patients receiving abemaciclib in combination with aromatase inhibitors or fulvestrant, ALT and AST elevations were reported frequently (15.1% and 14.2%, respectively). Grade 3 or 4 ALT or AST elevations (based on laboratory findings) were reported in 6.1% and 4.2% patients. The median time to onset of Grade 3 or 4 ALT elevation was 57 to 61 days, and median time to resolution was 14 days. The median time to onset of Grade 3 or 4 AST elevation was 71 to 185 days, and median time to resolution was 13 to 15 days. Dose modification is recommended for patients who develop Grade 3 or 4 ALT or AST increase (see section 4.2).

Creatinine

Although not an adverse reaction, abemaciclib has been shown to increase serum creatinine in 98.3% of patients (based on laboratory findings), 1.9% Grade 3 or 4 (based on laboratory findings). In patients receiving an aromatase inhibitor or fulvestrant alone, 78.4% reported an increase in serum creatinine (all laboratory grades). Abemaciclib has been shown to increase serum creatinine due to inhibition of renal tubular secretion transporters without affecting glomerular function (as measured by iohexol clearance) (see section 4.5). In clinical studies, increases in serum creatinine occurred within the first month of abemaciclib dosing, remained elevated but stable through the treatment period, were reversible upon treatment discontinuation, and were not accompanied by changes in markers of renal function, such as blood urea nitrogen (BUN), cystatin C, or calculated glomerular filtration rate based on cystatin C.

4.9 OVERDOSE

There is no known antidote for abemaciclib overdose. In case of overdose, use supportive therapy.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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. 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. The effect of abemaciclib on the QTcF interval was evaluated in 144 patients with advanced cancer. No large change (that is, >20 ms) in the QTcF interval was detected at the mean observed maximal steady state abemaciclib concentration following a therapeutic dosing schedule. In an exposure-response analysis in healthy subjects at the highest clinically relevant exposures, abemaciclib did not prolong the QTcF interval to any clinically relevant extent.

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. In breast cancer, cyclin D1/CDK4 has been shown to promote phosphorylation of the retinoblastoma protein (Rb), cell proliferation, and tumour growth. Abemaciclib prevents Rb phosphorylation, blocking progression from G1 into S phase of the cell cycle, leading to suppression of tumour growth in preclinical models following short duration target inhibition. In oestrogen 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 doses—as a single agent or in combination with antioestrogens—resulted in reduction of tumour size.

Clinical trials

Cardiac Electrophysiology

The effect of abemaciclib on the QTcF interval was evaluated in 144 patients with advanced cancer. No large change (that is, >20 ms) in the QTcF interval was detected at the mean observed maximal steady state abemaciclib concentration following a therapeutic dosing schedule.

In an exposure-response analysis in healthy subjects at exposures comparable to a 200 mg twice-daily dose, abemaciclib did not prolong the QTcF interval to any clinically relevant extent.

Randomised Phase 3 Study MONARCH 3: VERZENIO in combination with aromatase inhibitors

The efficacy and safety of VERZENIO was evaluated in MONARCH 3, a randomised, double-blind, placebo-controlled phase 3 study in women with HR positive, HER2 negative locally advanced or metastatic breast cancer who had not received prior systemic therapy in this disease setting. Patients were randomised in a 2:1 ratio to receive VERZENIO 150 mg twice daily plus a non-steroidal aromatase inhibitor given daily at the recommended dose. The primary endpoint was investigator-assessed progression-free survival (PFS) evaluated according to RECIST 1.1; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS).

Patients were well matched for baseline demographics and prognostic characteristics between the abemaciclib and aromatase inhibitor arm (AI) and the placebo plus AI arm. The median age of patients enrolled was 63 years (range 32-88). Approximately 39% of patients had received chemotherapy and 44% had received antihormonal therapy in the (neo)adjuvant setting prior to their diagnosis of advanced breast cancer. The majority of patients (96%) had metastatic disease at baseline. Approximately 22% of patients had bone-only disease, and 53% patients had visceral metastases.

At the pre-planned interim analysis, the study met the primary endpoint demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect. Primary efficacy results are summarised in Table 8 and Figure 1.

Table 8. MONARCH 3: Summary of efficacy data (Investigator assessment, intent-to-treat population)

	VERZENIO plus aromatase inhibitor	**Placebo plus aromatase inhibitor**
Progression-free survival	N=328	N=165
Investigator assessment, number of events (%)	138 (42.1)	108 (65.5)
Median [months] (95% CI)	28.18 (23.51, NR)	14.76 (11.24, 19.20)
Hazard ratio (95% CI) and p-value	0.540 (0.418, 0.698), p=0.000002	
Independent radiographic review, number of events (%)	91 (27.7)	73 (44.2)
Median [months] (95% CI)	NR (NR, NR)	19.36 (16.37, 27.91)
Hazard ratio (95% CI) and p-value	0.465 (0.339, 0.636); p < 0.000001	
Objective response rate[b] [%] (95% CI)	49.7 (44.3, 55.1)	37.0 (29.6, 44.3)
Duration of response [months] (95% CI)	27.39 (25.74, NR)	17.46 (11.21, 22.19)
Objective response for patients with measurable disease[a]	**N=267**	**N=132**
Objective response rate[b] [%] (95% CI)	61.0 (55.2, 66.9)	45.5 (37.0, 53.9)
Complete response, (%)	3.4	0
Partial response, (%)	57.7	45.5
Clinical benefit rate[c] **(measurable disease)** [%] (95% CI)	79.0 (74.1, 83.9)	69.7 (61.9, 77.5)

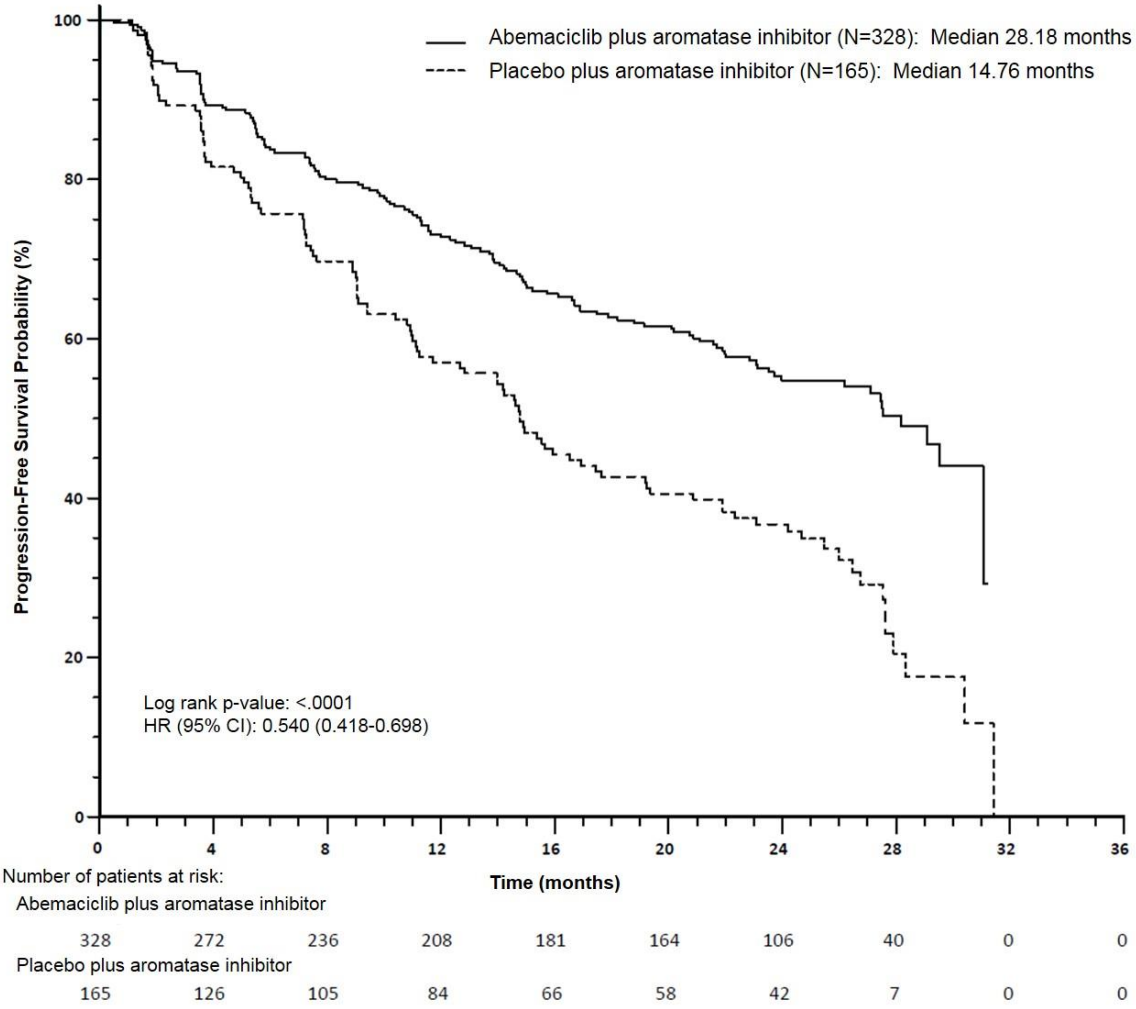
[a] Measurable disease defined per RECIST version 1.1

[b] Complete response + partial response

[c] Complete response + partial response + stable disease for ≥ 6 months

N=number of patients; CI=confidence interval; NR=not reached.

Figure 1. MONARCH 3: Kaplan-Meier plot of progression-free survival (Investigator assessment, intent-to-treat population)



Progression-free survival (PFS) was significantly prolonged in the VERZENIO plus aromatase inhibitor (AI) arm, (Hazard Ratio [HR] of 0.540 [95% CI, 0.418 to 0.698]); median PFS was 28.18 months in the VERZENIO plus AI arm and was 14.76 months in the placebo plus AI arm. These results correspond to a clinically meaningful reduction in the risk of disease progression or death of 46% for patients treated with abemaciclib plus an aromatase inhibitor.

Overall survival was not mature at the final PFS analysis (93 events observed across the two arms). The HR was 1.057 (95% CI: 0.683, 1.633), p=0.8017.

A series of prespecified subgroup PFS analyses showed consistent results across patient subgroups including age (<65 or ≥65 years), disease site, disease setting (de novo metastatic vs recurrent metastatic vs locally advanced recurrent), presence of measurable disease, progesterone receptor status, and baseline ECOG performance status. A reduction in the risk of disease progression or death was observed in patients with visceral disease, (HR of 0.567 [95% CI: 0.407, 0.789]), median PFS 21.6 months versus 14.0 months; in patients with bone-only disease (HR 0.565, [95% CI: 0.306, 1.044]); and in patients with measurable disease (HR 0.517, [95% CI: 0.392, 0.681]).

Randomised Phase 3 Study MONARCH 2: VERZENIO in combination with fulvestrant

The efficacy and safety of VERZENIO was evaluated in MONARCH 2, a randomised, double-blind, placebo-controlled phase 3 study in women with HR positive, HER2 negative locally advanced or metastatic breast cancer. Patients were randomised in a 2:1 ratio to receive VERZENIO 150 mg twice daily plus fulvestrant 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose, versus placebo plus fulvestrant alone according to the same schedule. The primary endpoint was investigator-assessed PFS evaluated according to RECIST 1.1; key secondary efficacy endpoints included objective response rate (ORR), clinical benefit rate (CBR) and overall survival (OS).

Patients were well matched for baseline demographics and prognostic characteristics between the abemaciclib plus fulvestrant arm and the placebo plus fulvestrant arm. The median age of patients enrolled was 60 years (range, 32-91 years). In each treatment arm the majority of patients were white and had not received chemotherapy or any prior endocrine therapy for metastatic disease. 17% of patients were pre/perimenopausal. Approximately 56% patients had visceral metastases. Approximately 25% patients had primary resistance to endocrine therapy as per ESMO International Consensus Guidelines for Advanced Breast Cancer, with the majority of patients having secondary resistance.

The study met the primary endpoint demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect. Primary efficacy results are summarised in Table 9 and Figure 2.

Table 9. MONARCH 2: Summary of efficacy data (Investigator assessment, intent-to-treat population)

	VERZENIO plus fulvestrant	**Placebo plus fulvestrant**
Progression-free survival	**N=446**	**N=223**
Investigator assessment, number of events (%)	222 (49.8)	157 (70.4)
Median [months] (95% CI)	16.4 (14.4, 19.3)	9.3 (7.4, 12.7)
Difference in PFS (months)	7.2	
Hazard ratio (95% CI) and p-value	0.553 (0.449, 0.681), p=0.0000001	
Independent radiographic review, number of events (%)	164 (36.8)	124 (55.6)
Median [months] (95% CI)	22.4 (18.3, NR)	10.2 (5.8, 14.0)
Hazard ratio (95% CI) and p-value	0.460 (0.363, 0.584); p <.000001	
Objective response rate[a] [%] (95% CI)	35.2 (30.8, 39.6)	16.1 **(**11.3, 21.0)
Duration of response [months] (95%CI)	NR (18.05, NR)	25.6 (11.9, 25.6)
Objective response for patients with measurable disease	**N=318**	**N=164**
Objective response rate[a] [%] (95% CI)	48.1 (42.6, 53.6)	21.3 (15.1, 27.6)
Complete response, (%)	3.5	0
Partial response, (%)	44.7	21.3
Disease control rate[b] **(measurable disease)** [%] (95% CI)	82.4 (78.2, 86.6)	72.6 (65.7, 79.4)
Clinical benefit rate[c] **(measurable disease)**	73.3 (68.4, 78.1)	51.8 (44.2, 59.5)

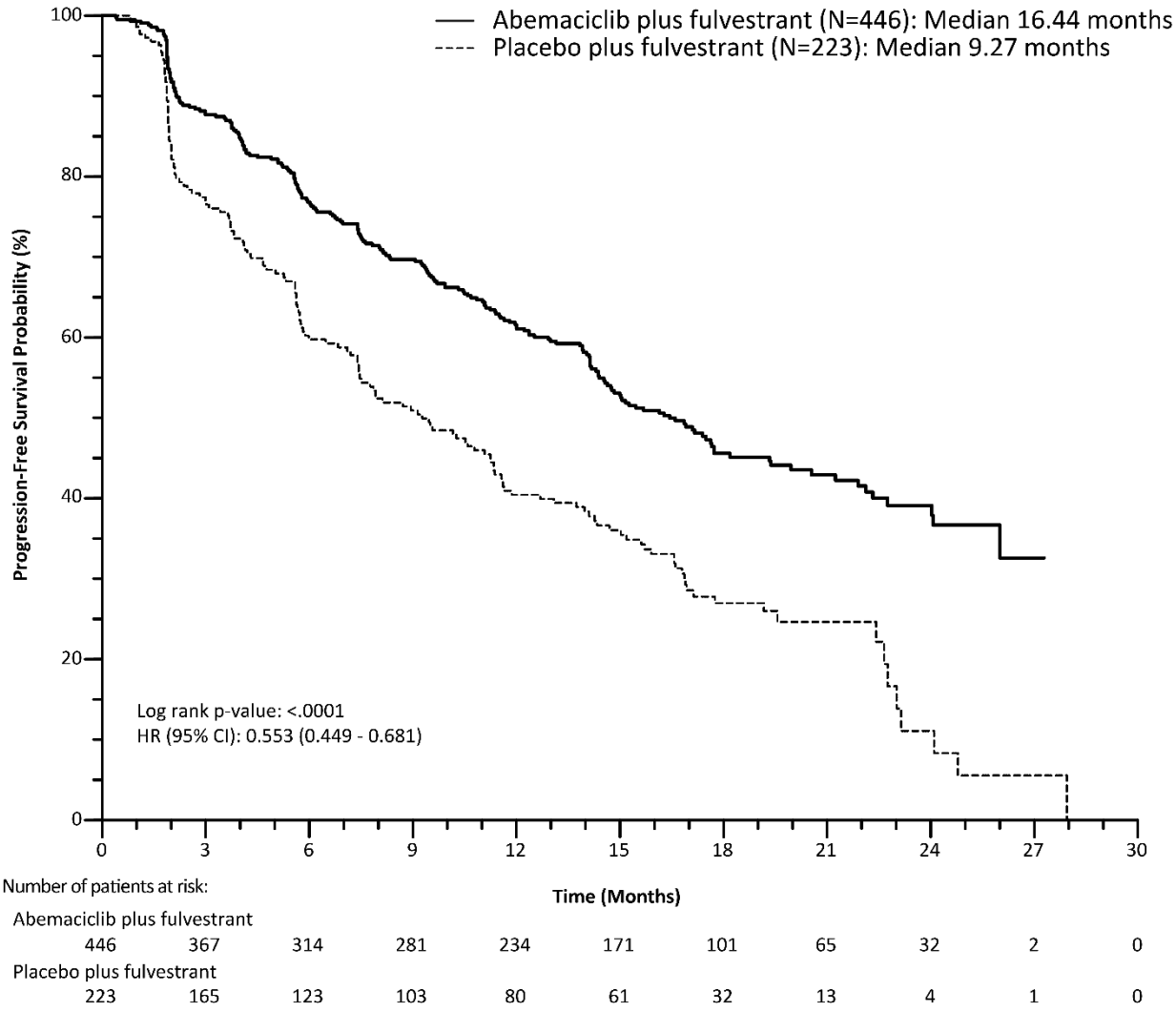
[a] Complete response + partial response

[b] Complete response + partial response + stable disease

[c] Complete response + partial response + stable disease for ≥ 6 months

N=number of patients; CI=confidence interval

Figure 2. MONARCH 2: Kaplan-Meier plot of progression-free survival (Investigator assessment, intent-to-treat population)



Median PFS was significantly prolonged in the VERZENIO plus fulvestrant arm (HR of 0.553 [95% CI 0.449, 0.681]); median PFS was 16.4 months versus 9.3 months in the placebo plus fulvestrant arm. These results correspond to a clinically meaningful reduction in the risk of disease progression or death of 44.7% and a 7.2 month improvement in median PFS for patients treated with VERZENIO plus fulvestrant. Early and sustained separation by treatment arm was apparent beginning at 8 weeks. VERZENIO plus fulvestrant prolonged progression-free survival with neither a clinically meaningful or significant detriment to health-related quality of life.

The addition of VERZENIO to fulvestrant significantly delayed the time to post-discontinuation chemotherapy, hazard ratio 0.651 (95% CI: 0.502, 0.845). The median time to chemotherapy for the abemaciclib arm was not yet reached and for the placebo plus fulvestrant arm was 26 months.

Overall survival was not mature at the final PFS analysis (133 events observed across the two arms). The HR was 0.854 (95% CI: 0.598, 1.221), p=0.3886.

A series of prespecified subgroup PFS analyses were performed based on prognostic factors and baseline characteristics to confirm consistency of the treatment effect. A reduction in the risk of disease progression or death in favour of the VERZENIO plus fulvestrant arm was observed in all patient subgroups. Consistent results were observed across patient subgroups including age (<65 or ≥65 years), race, geographic region, disease site, endocrine therapy resistance, presence of measurable disease, progesterone receptor status, and menopausal status. A reduction in the risk of disease progression or death was evident in patients with visceral disease, (HR of 0.481 (95% CI: 0.369, 0.627], median PFS 14.7 months versus 6.5 months); in patients with bone-only disease (HR of 0.543 [95% CI: 0.355, 0.833]); patients with measurable disease (HR of 0.523 [95% CI: 0.412, 0.644]). In patients who were pre/perimenopausal, the hazard ratio was 0.415 (95% CI: 0.246, 0.698); in patients who were progesterone receptor negative, the HR was 0.509 [95% CI: 0.325, 0.797]).

In the population of 44 patients who presented de novo with locally advanced or metastatic disease, and had not received any prior endocrine therapy, the addition of VERZENIO to fulvestrant reduced the risk of disease progression or death in this population by 54.6% (HR of 0.454 [95% CI: 0.179, 1.154]).

Phase 2 study MONARCH 1: VERZENIO monotherapy

The efficacy and safety of VERZENIO was evaluated in MONARCH 1, a single-arm, open-label trial in 132 women with HR positive, HER2 negative metastatic breast cancer who had failed prior endocrine therapies and had received one or 2 prior chemotherapy regimens in the metastatic setting. Patients received VERZENIO 200 mg twice daily. The primary endpoint was objective response rate (ORR). Efficacy results for MONARCH 1 are summarised in Table 10.

Table 10. MONARCH 1: Summary of efficacy data (Investigator assessment, intent-to-treat population)

	VERZENIO N=132
Objective response rate[a], [%] (95% CI**)**	19.7 (13.3, 27.5)
Median time to response (range)	3.7 months (1.1-14.2 months)
Median duration of response (95% CI)	8.6 months (5.8, 10.2 months)
Clinical benefit rate[b], [%] (95% CI**)**	42.4 (33.9, 51.3)

[a] All responses were partial responses.

[b] Clinical benefit rate includes all patients who achieved an objective response or who had stable disease for at least 6 months.

N=number of patient, CI=confidence interval.

At the time of the final analysis of survival (minimum of 18 months follow-up), 19 of the 26 responding patients had responses of 6 months or longer, and 6 patients were still on treatment with response durations ranging from 9.5+ to 20.5+ months.

Visceral crisis

There are no data on the efficacy and safety of abemaciclib in patients with visceral crisis.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Abemaciclib absorption is slow, with a median Tmax of 8.0 hours. The absolute bioavailability of abemaciclib is 45% (90% confidence interval: 40-51%). In the therapeutic dose range of 50-200 mg, the increase in plasma exposure (AUC) and Cmax 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 Cmax and AUC, respectively.

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, 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) 3A, with formation of N-desethyl abemaciclib (M2) representing the major metabolism pathway. Additional metabolites include hydroxyabemaciclib (M20), hydroxy-N-desethylabemaciclib (M18), and an oxidative metabolite (M1). Metabolites N-desethylabemaciclib (M2) and hydroxyabemaciclib (M20) are active with similar potency as abemaciclib.

Excretion

The geometric mean hepatic clearance (CL) of abemaciclib was 21.8 L/h (39.8% CV), and the mean plasma elimination half-life for abemaciclib in patients was 24.8 hours (52.1% CV). After a single oral dose of [14C]-abemaciclib, approximately 81% of the dose was excreted in faeces and 3.4% excreted in urine. The majority of the dose eliminated in faeces was metabolites.

Use in hepatic impairment

Abemaciclib is metabolised in the liver. In subjects with severe hepatic impairment, total abemaciclib unbound exposure increased 2.69-fold, and the abemaciclib half-life increased from 24 to 55 hours. Reduce the abemaciclib dosing frequency to once daily in patients with severe hepatic impairment.

Use in renal impairment

Abemaciclib and its metabolites are not significantly cleared renally. Dose adjustment is not necessary in patients with mild or moderate renal impairment. There are no data in patients with severe renal impairment, end stage renal disease, or in patients on dialysis.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Abemaciclib was not mutagenic in a bacterial reverse mutation (Ames) assay and did not induce structural chromosomal aberrations in the in vitro chromosome aberration assay with human lymphocytes, or the in vivo rat micronucleus test. Metabolites M2 and M20 were not mutagenic in the Ames assay and did not induce structural chromosomal aberrations in Chinese Hamster Ovary cells in the in vitro chromosome aberration assay.

Carcinogenicity

Long-term studies to assess the carcinogenic potential of abemaciclib have not been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet cores	Film coating
croscarmellose sodium	polyvinyl alcohol (E1203)
lactose monohydrate	titanium dioxide (E171)
microcrystalline cellulose	macrogol 3350 (E1521)
silicon dioxide	purified talc (E553b)
sodium stearyl fumarate	iron oxide yellow (E172) [50 mg and 150 mg tablets only]
	iron oxide red (E172) [50 mg tablets only]

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

The shelf life of VERZENIO tablets is 24 months.

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30 °C

6.5 NATURE AND CONTENTS OF CONTAINER

VERZENIO is available as a modified oval immediate-release film-coated tablet with "Lilly" debossed on one side and tablet strength in mg debossed on the other.

The 50 mg tablets are beige in colour, 100 mg is white and 150 mg tablets are yellow.

VERZENIO is supplied in PVC/PE/PCTFE blister packs sealed with aluminum foil lidding.

Pack sizes:

50 mg, 100 mg, 150 mg: 14 tablets*

50 mg, 100 mg, 150 mg: 42 tablets*

50 mg, 100 mg, 150 mg: 56 tablets*

50 mg, 100 mg, 150 mg: 70 tablets*.

**Not all pack sizes may be marketed.*

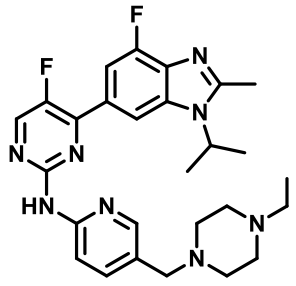
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The molecular formula for abemaciclib is C_{27} H_{32} F_2 N_8 and it has the following structural formula



CAS number

1231929-97-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

08-April-2019

10 DATE OF REVISION

N/A

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information