AUSTRALIAN PRODUCT INFORMATION – IBRANCE® (PALBOCICLIB)

1. NAME OF THE MEDICINE

Palbociclib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each IBRANCE tablet contains palbociclib 75 mg, 100 mg or 125 mg.

Each IBRANCE capsule contains palbociclib 75 mg, 100 mg or 125 mg.

Excipients with known effect

IBRANCE capsules contain lactose monohydrate.

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

3. PHARMACEUTICAL FORM

IBRANCE is supplied as hard capsules or a film-coated tablets for oral administration.

75 mg strength: Opaque, hard capsule with a light orange body (printed “PBC 75” in white) and a light orange cap (printed “Pfizer” in white). Round, light purple, film-coated tablet debossed with “Pfizer” on one side and “PBC 75” on the other side.

100 mg strength: Opaque, hard capsule with a light orange body (printed “PBC 100” in white) and a caramel cap (printed “Pfizer” in white). Oval, green, film-coated tablet debossed with “Pfizer” on one side and “PBC 100” on the other side.

125 mg strength: Opaque, hard capsule with a caramel body (printed “PBC 125” in white) and a caramel cap (printed “Pfizer” in white). Oval, light purple, film-coated tablet debossed with “Pfizer” on one side and “PBC 125” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IBRANCE 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 as initial endocrine-based therapy
- fulvestrant in patients who have received prior therapy.

4.2 Dose and method of administration

Dosage

The recommended dose of IBRANCE is a 125 mg capsule or tablet taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days.

When coadministered with palbociclib, an aromatase inhibitor should be administered according to the dose schedule reported in the Product Information for that aromatase inhibitor.

When coadministered with palbociclib, the recommended dose of fulvestrant is 500 mg administered intramuscularly on Days 1, 15, 29 and once monthly thereafter. Please refer to the Product Information for fulvestrant.

Method of administration

IBRANCE *capsules* should be taken with food. IBRANCE *tablets* may be taken with or without food.

Patients should be encouraged to take their dose at approximately the same time each day. Continue the treatment as long as the patient is deriving clinical benefit from therapy.

If the patient vomits or misses a dose, an additional dose should not be taken. The next prescribed dose should be taken at the usual time. IBRANCE capsules or tablets should be swallowed whole (do not chew, crush, open the capsules or split the tablets prior to swallowing). No capsule or tablet should be ingested if it is broken, cracked or otherwise not intact.

Prior to the start of, and throughout treatment, pre/perimenopausal women treated with the combination of IBRANCE plus aromatase inhibitor/fulvestrant should also be treated with a luteinising hormone-releasing hormone (LHRH) agonist according to local clinical practice. Pre- and perimenopausal women were not enrolled in PALOMA-1 and PALOMA-2.

For men treated with the combination of IBRANCE plus aromatase inhibitor therapy, consider treatment with an LHRH agonist according to current clinical practice standards.

Dosage adjustments

Dose modification of IBRANCE is recommended based on individual safety and tolerability.

Management of some adverse reactions may require temporary dose interruptions/delays and/or dose reductions or permanent discontinuation as per dose reduction schedules provided in Tables 1, 2 and 3 (see Section 4.4 Special warnings and precautions for use and Section 4.8 Adverse effects (undesirable effects)).

Table 1. IBRANCE recommended dose modifications for adverse events

Dose Level	Dose
Recommended dose	125 mg/day
First dose reduction	100 mg/day
Second dose reduction	75 mg/day*

*If further dose reduction below 75 mg/day is required, discontinue the treatment.

Table 2. IBRANCE dose modification and management – haematological toxicities[a]

Monitor full blood count prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated. After the first 6 cycles, if neutropenia of grade 3 or higher has not occurred, frequency of full blood count monitoring can be decreased to every 3 months (prior to the beginning of a cycle) and as clinically indicated.	
CTCAE Grade	**Dose modification and management**
Grade 1 or 2	No dose adjustment is required.
Grade 3	Day 1 of any cycle: If Grade 3 on day 1 of any cycle, withhold IBRANCE until recovery to Grade ≤2, and repeat full blood count within 1 week. When recovered to Grade ≤2, start the next cycle at that time at the *same dose.* Day 15 of first 2 cycles: If Grade 3 on Day 15, continue IBRANCE at the current dose to complete cycle and repeat full blood count on Day 22. If Grade 4 on Day 22, see Grade 4 dose modification guidelines below. In cases of prolonged (>1 week) recovery from Grade 3 events, or in cases of recurrent Grade 3 neutropenia, anaemia or thrombocytopenia on Day 1 of subsequent cycles, consider dose reduction.
Grade 3 neutropenia[b] with fever ≥38.5ºC and/or infection	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.
Grade 4	At any time: Withhold IBRANCE until recovery to Grade ≤2. Resume at the *next lower dose*.

Grading according to CTCAE 4.0
ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events; LLN-lower limit of normal.

[a] Table applies to all haematological adverse reactions except lymphopenia (unless associated with clinical events, e.g., opportunistic infections).

[b] ANC: Grade 1: ANC <LLN - 1500/mm^3; Grade 2: ANC 1000 - <1500/mm^3; Grade 3: ANC 500 - <1000/mm^3; Grade 4: ANC <500/mm^3.

Table 3. IBRANCE dose modification and management – non-haematological Toxicities

CTCAE Grade	**Dose Modifications**
Grade 1 or 2	No dose adjustment is required.
Grade ≥3 non-haematological toxicity (if persisting despite medical treatment)	Withhold until symptoms resolve to: Grade ≤1; Grade ≤2 (if not considered a safety risk for the patient) Resume at the *next lower dose*.

Grading according to CTCAE 4.0
CTCAE=Common Terminology Criteria for Adverse Events.

Permanently discontinue IBRANCE in patients with severe interstitial lung disease (ILD)/pneumonitis (see Section 4.4 Special warnings and precautions for use, Interstitial lung disease (ILD)/pneumonitis).

No dose modifications are required on the basis of patient's age, sex or body weight (see Section 5.2 Pharmacokinetic properties).

Dosage adjustment in renal impairment

No dose adjustment is required for patients with mild, moderate or severe renal impairment (creatinine clearance [CrCl] ≥15 mL/min). Insufficient data are available in patients requiring haemodialysis to provide any dosing recommendation in this patient population (see Section 5.2 Pharmacokinetic properties, Special populations, Renal impairment).

Dosage adjustment in hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment (Child-Pugh classes A and B). For patients with severe hepatic impairment (Child-Pugh class C), the recommended dose of IBRANCE is 75 mg once daily for 21 consecutive days followed by 7 days off treatment (see Section 5.2 Pharmacokinetic properties, Special populations, Hepatic impairment).

Dosage adjustment in the elderly

No dose adjustment is necessary in patients ≥65 years of age (see Section 5.2 Pharmacokinetic properties, Special populations, Elderly ≥65 years).

Children and adolescents

The safety and efficacy of IBRANCE in children and adolescents <18 years of age have not been established.

4.3 Contraindications

Use of IBRANCE is contraindicated in patients with hypersensitivity to palbociclib or to any of the excipients.

4.4 Special warnings and precautions for use

Identified precautions

Myelosuppression

Neutropenia

Decreased neutrophil counts have been observed very commonly in clinical studies with IBRANCE. In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), Grade 3 (ANC 500---<1000/mm^3) and Grade 4 (ANC <500/mm^3) decreased neutrophil counts were reported in 56.1% and 10.6% of patients respectively (see Section 4.8 Adverse effects (undesirable effects)).

In PALOMA-1 and PALOMA-2 the median time to first episode of any grade neutropenia was 15 days (range 12-700 days) and 28 days (range 12-854) for Grade ≥3 neutropenia. The median duration of Grade ≥3 neutropenia was 33 days (range 1-534).

In PALOMA-3 the median time to first episode of neutropenia was 15 days (13-317 days) for any grade and 16 days (range 13-587) for Grade ≥3 neutropenia. The median duration for Grade ≥3 neutropenia was 21 days (range 1-167).

An increase in palbociclib exposure has been associated with more severe neutropenia; in Asian subjects, frequency of grade ≥3 neutropenia is higher than in White subjects (see Section 5.2 Pharmacokinetic properties, Special populations, Asian race).

Febrile neutropenia has been reported in 2.3% of patients receiving palbociclib in combination with letrozole in PALOMA-2 and in 1.2% of patients receiving palbociclib in combination with fulvestrant in PALOMA-3. One death due to neutropenic sepsis was reported in PALOMA-3.

Febrile neutropenia has not been reported in PALOMA-1. Febrile neutropenia has been reported in about 2% of patients exposed to IBRANCE across the overall clinical program (see Section 4.4 Special warnings and precautions for use, Identified precautions, Infections).

Monitor full blood count prior to the start of IBRANCE therapy and at the beginning of each cycle, as well as on Day 15 of the first 2 cycles, and as clinically indicated.

Dosing interruption, dose reduction or delay in starting treatment cycles is recommended for patients who develop Grade 3 or 4 neutropenia. Appropriate monitoring should be performed (see Section 4.2 Dose and method of administration).

Anaemia

Anaemia has been observed very commonly in clinical studies with IBRANCE. In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), Grade 3 and Grade 4 anaemia was observed in 7.0% and 4.3% of patients respectively (see Section 4.8 Adverse effects (undesirable effects)).

In PALOMA-1 and PALOMA-2 the median time to first episode of any grade anaemia was 29 days (range 1-777 days) and 195 days (range 14-760) for Grade ≥3 anaemia. The median duration of Grade ≥3 anaemia was 7 days (range 1-125). In PALOMA-3 the median time to first episode of anaemia was 25 days (12-378 days) for any grade and 52 days (range 15-363) for Grade ≥3 anaemia. The median duration for Grade ≥3 anaemia was 7 days (range 1-125). Across both studies, supportive treatment with red blood cell growth factors and transfusions was administered in 2.4% and 1.7%, respectively, on the palbociclib arms, and in 0.4% and 0%, respectively on the comparator arms.

Thrombocytopenia

Thrombocytopenia has been observed very commonly in clinical studies with IBRANCE. In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), Grade 3 and Grade 4 thrombocytopenia was observed in 2.1% and 3.2% of patients, respectively (see Section 4.8 Adverse effects (undesirable effects)).

In PALOMA-1 and PALOMA-2 the median time to first episode of any grade thrombocytopenia was 27 days (range 2-875 days) and 256 days (range 21-652 days) for Grade ≥3 thrombocytopenia. The median duration of Grade ≥3 thrombocytopenia was 7 days (range 1-28 days). In PALOMA-3 the median time to first episode of thrombocytopenia was 15 days (13-422 days) for any grade and 23 days (range 15-57) for Grade ≥3 thrombocytopenia. The median duration for Grade ≥3 thrombocytopenia was 7 days (range 1-9 days).

Interstitial lung disease (ILD)/pneumonitis

Severe, life-threatening, or fatal ILD and/or pneumonitis can occur in patients treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, including IBRANCE when taken in combination with endocrine therapy.

In patients receiving IBRANCE in combination with letrozole (PALOMA-1 and PALOMA-2) and in combination with fulvestrant (PALOMA-3), ILD was reported in 1.7% and 1.4% of patients, respectively. Across PALOMA-1, PALOMA-2 and PALOMA-3 0.1% had Grade 3, and no Grade 4 or no fatal cases were reported (see Section 4.8 Adverse effects (undesirable effects)). Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis (e.g. hypoxia, cough, dyspneoa). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, interrupt IBRANCE immediately and evaluate the patient. Permanently discontinue IBRANCE in patients with severe ILD or pneumonitis (see Section 4.2 Dose and method of administration).

Infections

Since IBRANCE has myelosuppressive properties, it may predispose to infections.

Infections of any grade have been reported at a higher rate in patients treated with IBRANCE. Infections of any grade occurred in 63.6% of patients treated with IBRANCE and letrozole in PALOMA-1 and PALOMA-2 compared to 42.8% of patients treated in the comparator arm. Infections of any grade occurred in 55.1% of patients treated with IBRANCE and fulvestrant in PALOMA-3, compared to 36.0% of patients treated in the comparator arm.

Grade 3 and 4 infections occurred in 8.7% of patients treated with IBRANCE and letrozole in PALOMA-1 and PALOMA-2 compared to 2.3% of patients treated in the comparator arm. Grade 3 and 4 infections occurred in 6.1% of patients treated with IBRANCE in PALOMA-3 compared to 3.5% of patients treated in the comparator arm.

Monitor patients for signs and symptoms of infection and treat as medically appropriate (see Section 4.8 Adverse effects (undesirable effects)).

Physicians should inform patients to immediately report any episodes of fever.

Venous thromboembolism

Venous thromboembolic events were reported in patients treated with IBRANCE. Patients should be monitored for signs and symptoms of deep vein thrombosis and pulmonary embolism, and treated as medically appropriate.

Use in hepatic impairment

See Section 4.2 Dose and method of administration, Dosage adjustment in hepatic impairment and Section 5.2 Pharmacokinetic properties, Special populations, Hepatic impairment.

Use in renal impairment

See Section 4.2 Dose and method of administration, Dosage adjustment in renal impairment and Section 5.2 Pharmacokinetic properties, Special populations, Renal impairment.

Use in the elderly

See Section 4.2 Dose and method of administration, Dosage adjustment in the elderly and Section 5.2 Pharmacokinetic properties, Special populations, Elderly (≥65 years).

Paediatric use

The safety and efficacy of IBRANCE in paediatric patients have not been studied.

Effects on laboratory tests

See Section 4.4 Special warnings and precautions for use, Identified precautions, Myelosuppression.

4.5 Interactions with other medicines and other forms of interactions

Palbociclib is primarily metabolised by CYP3A and sulfotransferase (SULT) enzyme SULT2A1. *In vivo*, palbociclib is a time-dependent inhibitor of CYP3A.

Agents that may increase palbociclib plasma concentrations

Effect of CYP3A inhibitors

Data from a drug-drug interaction (DDI) study in healthy subjects indicate that coadministration of multiple 200 mg doses of itraconazole with a single 125 mg dose of IBRANCE increased palbociclib total exposure (area under the curve, AUC_{inf}) and the maximum observed plasma concentration (C_{max}) by approximately 87% and 34%, respectively, relative to a single 125 mg dose of IBRANCE given alone. The concomitant use of strong CYP3A inhibitors including, but not limited to, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telithromycin, voriconazole and grapefruit or grapefruit juice should be avoided.

Agents that may decrease palbociclib plasma concentrations

Effect of CYP3A inducers

Data from a DDI study in healthy subjects indicate that coadministration of multiple 600 mg doses of rifampin, a strong CYP3A inducer, with a single 125 mg dose of IBRANCE decreased palbociclib AUC_{inf} and C_{max} by 85% and 70%, respectively, relative to a single 125 mg dose of IBRANCE given alone. Data from a DDI study in healthy subjects indicate that coadministration of multiple 400 mg daily doses of modafinil, a moderate CYP3A inducer, with a single 125 mg IBRANCE dose decreased palbociclib AUC_{inf} and C_{max} by 32% and 11%, respectively, relative to a single 125 mg dose of given alone.

The concomitant use of strong CYP3A inducers including, but not limited to, carbamazepine, enzalutamide, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin and St. John's wort should be avoided.

Coadministration of a moderate CYP3A inducer (modafinil) decreased the plasma exposure of palbociclib in healthy subjects by 32%. Moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil and nafcillin) can be used concurrently with IBRANCE when unavoidable. No dosing adjustments are required.

Effect of acid reducing agents

IBRANCE capsules

Data from a DDI study in healthy subjects indicated that coadministration of a single 125 mg dose of IBRANCE capsules with multiple doses of the proton pump inhibitor (PPI) rabeprazole under fed conditions decreased palbociclib C_{max} by 41%, but had limited impact on AUC_{inf} (13% decrease) compared with a single 125 mg IBRANCE capsule administered alone.

Given the reduced effect on gastric pH of H2-receptor antagonists and local antacids compared to PPIs under fed conditions, there is no clinically relevant effect of PPIs, H2-receptor antagonists or local antacids on palbociclib exposure.

Data from another DDI study in healthy subjects indicated that coadministration of a single IBRANCE capsule with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively, when compared with a single 125 mg IBRANCE capsule administered alone.

Therefore, IBRANCE capsules should be taken with food (see Section 4.2 Dose and method of administration).

IBRANCE film-coated tablets

Coadministration of multiple doses of the PPI rabeprazole with a single 125 mg IBRANCE tablet under fasted conditions had no effect on the rate and extent of absorption of palbociclib when compared to a single 125 mg IBRANCE tablet administered alone (see Section 4.2 Dose and method of administration).

Effects of IBRANCE on other drugs

Palbociclib is a weak time-dependent inhibitor of CYP3A following daily 125 mg dosing at steady state in humans. In a DDI study in healthy subjects, coadministration of midazolam with multiple doses of palbociclib increased the midazolam AUC_{inf} and C_{max} values by 61% and 37%, respectively, as compared with administration of midazolam alone.

The dose of sensitive CYP3A substrates, particularly those with a narrow therapeutic index (e.g., alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), may need to be reduced when coadministered with IBRANCE as IBRANCE may increase their exposure.

In vitro, palbociclib is not an inhibitor of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19 or 2D6 and is not an inducer of CYP1A2, 2B6, 2C8 or 3A4 at clinically relevant concentrations.

Letrozole

Data from a clinical study in patients with breast cancer showed that there was no drug interaction between palbociclib and letrozole when the 2 drugs were coadministered.

Fulvestrant

Data from a clinical study in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and fulvestrant when the 2 drugs were coadministered.

Goserelin

Data from a clinical study in patients with breast cancer showed that there was no clinically relevant drug interaction between palbociclib and goserelin when the 2 drugs were coadministered.

***In vitro* studies with transporters**

In vitro evaluations indicate that palbociclib has a low potential to inhibit the activities of drug transporters P-glycoprotein (P-gp, systemically), breast cancer resistance protein (BCRP, systemically), organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transporting polypeptide (OATP)1B1, OATP1B3 and bile salt export pump (BSEP) at clinically relevant concentrations. Based on *in vitro* data, palbociclib has the potential to inhibit OCT1 at clinically relevant concentrations, as well as the potential to inhibit P-gp or BCRP in the gastrointestinal tract at the proposed clinical dose. Based on *in vitro* data, palbociclib was a weak substrate for P-gp and a moderate substrate for BCRP; however, P-gp and BCRP mediated transport are unlikely to significantly affect the extent of oral absorption of palbociclib at therapeutic doses.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Palbociclib did not affect oestrous cycling, mating or fertility in female rats at any dose tested up to 300 mg/kg/day (approximately 3 times human clinical exposure based on AUC). However, no clinical data have been obtained on fertility in human females. Based on nonclinical safety findings, male fertility may be compromised by treatment with IBRANCE. Men should consider sperm preservation prior to beginning therapy with IBRANCE.

Palbociclib is considered to have the potential to impair reproductive function and fertility in male humans based on nonclinical findings in rats and dogs. Palbociclib-related findings in the testis, epididymis, prostate and seminal vesicle included decreased organ weight, atrophy or degeneration, hypospermia, intratubular cellular debris, lower sperm motility and density, and decreased secretion. These findings were observed in rats and/or dogs at exposures ≥6 times or subtherapeutic compared to human clinical exposure based on AUC, respectively. The effects appeared to be reversible.

Use in pregnancy – Pregnancy Category D

There are no adequate and well-controlled studies in pregnant women receiving IBRANCE. Based on findings in animals and mechanism of action, palbociclib can cause fetal harm when administered to a pregnant woman.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving IBRANCE. Women of childbearing potential who are receiving this drug should use adequate contraceptive methods during therapy and for at least a month after completing therapy. Partners of females of childbearing potential receiving this drug should use adequate contraception methods during therapy and for at least 14 weeks after completing therapy.

Palbociclib was fetotoxic in pregnant rats and rabbits. Reduced fetal body weights were observed at a maternally toxic dose of 300 mg/kg/day in rats (3 times human clinical exposure based on AUC) and an increased incidence of skeletal variations, including small phalanges in the forelimb, was observed at a maternally toxic dose of 20 mg/kg/day in rabbits (6 times human clinical exposure based on AUC). An increased incidence of a skeletal variation (increased incidence of a rib present at the seventh cervical vertebra) at ≥100 mg/kg/day (equivalent to human clinical exposure based on AUC) was seen in rats while other skeletal variations and skeletal ossification were seen in rabbits at ≥10 mg/kg/day (3 times human clinical exposure based on AUC). Actual fetal exposure and cross-placenta transfer have not been examined.

CDK4/6 double knockout mice have been reported to die in late stages of fetal development due to severe anaemia. However, knockout mouse data may not be predictive of effects in humans due to differences in degree of target inhibition.

Female patients taking palbociclib during pregnancy or who become pregnant while taking palbociclib should be apprised of the potential hazard to the fetus.

Use in lactation

No studies have been conducted in humans to assess the effect of IBRANCE on milk production, its presence in breast milk or its effects on the breast-fed child. It is unknown whether palbociclib is excreted in human milk. Patients receiving IBRANCE should not breast-feed.

4.7 Effects on ability to drive and use machines

No studies on the effects of IBRANCE on the ability to drive or operate machinery have been conducted. However, patients experiencing fatigue while taking IBRANCE should exercise caution when driving or operating machinery.

4.8 Adverse effects (undesirable effects)

The overall safety profile of IBRANCE is based on pooled data from 872 patients who received palbociclib in combination with endocrine therapy (N=527 in combination with letrozole and N=345 in combination with fulvestrant) in randomised clinical studies in HR-positive, HER2-negative advanced or metastatic breast cancer.

PALOMA-1 and PALOMA-2: Patients treated with the combination IBRANCE plus letrozole

The safety profile of IBRANCE (125 mg/day) in combination with letrozole (2.5 mg/day) versus the comparator arm is based on data from PALOMA-1 and PALOMA-2. Table 4 below shows the adverse reactions observed in 527 patients with HR-positive, HER2-negative advanced breast cancer who received at least 1 dose of IBRANCE plus letrozole in PALOMA-1 and PALOMA-2.

Table 4. Adverse Drug Reactions Reported for Patients Who Received Palbociclib Plus Letrozole or Letrozole Alone or Placebo Plus Letrozole in PALOMA-1 ***(Dec-2017 Cutoff)*** **and PALOMA-2** ***(Nov-2021 Cutoff)***

System Organ Class	Palbociclib Plus Letrozole (N=527)			Letrozole Alone or Placebo plus Letrozole (N=299)		
Preferred Term[a]	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[b]	63.9[c]	7.2	1.5	42.8	2.3	0
Blood and lymphatic system disorders						
Neutropenia[d]	81.2	56.2	12.1	6.0	1.0	0.3
Leukopenia[e]	43.3	25.4	0.8	3.0	0	0
Anaemia[f]	30.0	6.6	0.4	10.0	0	0
Thrombocytopenia[g]	21.4	1.9	0.2	2.3	0.3	0
Febrile neutropenia	1.9	1.5	0.4	0	0	0
Eye disorders						
Vision blurred	4.9	0.2	0	2.3	0	0
Increased lacrimation	6.8	0.2	0	0.7	0	0
Dry eye	4.9	0	0	3.7	0	0
Metabolism and nutrition disorders						
Decreased appetite	19.7	0.8	0	8.7	0	0
Nervous system disorders						
Dysgeusia	7.6	0	0	2.3	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	9.9	0	0	5.7	0	0
Gastrointestinal disorders						
Stomatitis[h]	32.4	0.9	0	14.0	0.3	0
Nausea	36.3	0.6	0	23.7	1.7	0
Diarrhoea	29.0	1.9	0	20.1	1.0	0
Vomiting	18.0	0.8	0	14.0	1.3	0
Skin and subcutaneous tissue disorders						
Alopecia	31.9	0	0	12.7	0	0
Rash[i]	19.7	1.1	0	11.4	0.3	0
Dry skin	13.7	0	0	6.7	0	0
General disorders and administration site conditions						
Fatigue	40.8	3.2	0.4	27.4	1.3	0
Asthenia	18.0	2.7	0	10.4	0	0
Pyrexia	14.2	0	0	7.4	0	0
Investigations						
ALT increased	13.5	2.3	0.4	4.7	0	0
AST increased	13.3	2.7	0	5.0	0.7	0

N=number of patients; ILD=Interstitial lung disease; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase.

Grades determined by National Cancer Institute Common Terminology Criteria for Adverse Events 4.0.

* Adverse Drug Reaction (ADR) identified post-marketing

a. Preferred Terms (PTs) are listed according to MedDRA 25.1.
b. INFECTIONS include all reported PTs that are part of the System Organ Class Infections and infestations.
c. Most common infections (≥1%) include: Nasopharyngitis, Upper respiratory tract infection, Urinary tract infection, Oral herpes, Sinusitis, Rhinitis, Bronchitis, Influenza, Pneumonia, Gastroenteritis, Conjunctivitis, Herpes zoster, Pharyngitis, Cellulitis, Cystitis, Lower respiratory tract infection, Tooth infection, Gingivitis, Skin infection, Gastroenteritis viral, Respiratory tract infection, Respiratory tract infection viral, Folliculitis.
d. NEUTROPENIA includes the following PTs: Neutropenia, Neutrophil count decreased.
e. LEUKOPENIA includes the following PTs: Leukopenia, White blood cell count decreased.
f. ANAEMIA includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.
g. THROMBOCYTOPENIA includes the following PTs: Thrombocytopenia, Platelet count decreased.
h. STOMATITIS includes the following PTs: Aphthous ulcer, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.
i. RASH includes the following: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.

Table 5. Laboratory Abnormalities in PALOMA-2 Study *(26-Feb-2016 Cutoff)*

	IBRANCE plus Letrozole (N=444)			**Placebo plus Letrozole (N=222)**		
Laboratory Abnormality	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
WBC decreased	97	35	1	25	1	0
Neutrophils decreased	95	56	12	20	1	1
Anaemia	78	6	0	42	2	0
Platelets decreased	63	1	1	14	0	0
ALT increased	43	2	<1	30	0	0
AST increased	52	3	0	34	1	0

N=number of patients; WBC=white blood cells; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase.

The most common adverse reactions (≥20%) of any grade reported in patients in the IBRANCE plus letrozole arm by descending frequency were neutropenia, infections, leukopenia, nausea, fatigue, alopecia, stomatitis, anaemia, diarrhoea and thrombocytopenia.

Dose reductions due to an adverse event of any grade occurred in 36.2% of patients receiving IBRANCE plus letrozole in PALOMA-1 and PALOMA-2. No dose reductions were allowed for the comparator arm. Permanent treatment discontinuation associated with an adverse event occurred in 10.6% patients receiving IBRANCE plus letrozole in PALOMA-1 and PALOMA-2 and in 5.0% of patients in the comparator arm.

In PALOMA-2 patients receiving IBRANCE plus letrozole, the starting dose of IBRANCE was 125 mg once daily. Dose reductions to 100 mg occurred in 36% of patients and dose reductions to 75 mg occurred in 14% of patients due to adverse events.

Neutropenia of any grade was reported in 81.2% of patients receiving IBRANCE plus letrozole in PALOMA-1 and PALOMA-2, with Grade 3 neutropenia reported in 56.2% of patients and Grade 4 neutropenia reported in 12.1% of patients (see Section 4.4 Special warnings and precautions for use).

The most frequently reported Grade >3 adverse reactions (≥5%) in patients receiving IBRANCE plus letrozole by descending frequency were neutropenia, leukopenia, infections and anaemia.

The most frequently (≥1%) reported serious adverse drug reactions in patients receiving palbociclib plus letrozole (PALOMA-1 and PALOMA-2) were infections (4.6%) and febrile neutropenia (1.3%).

Cataract was reported in 3.2% of patients receiving IBRANCE plus letrozole and in 0.5% of patients receiving placebo plus letrozole in PALOMA-2.

PALOMA-3: Patients treated with the combination IBRANCE plus fulvestrant

The safety of IBRANCE (125 mg/day) plus fulvestrant (500 mg) versus placebo plus fulvestrant was evaluated in PALOMA-3. Table 6 below shows the adverse reaction in patients with HR-positive, HER2-negative advanced or metastatic breast cancer who received at least 1 dose of IBRANCE plus fulvestrant.

Table 6. Adverse Drug Reactions Reported for Patients Who Received Palbociclib Plus Fulvestrant or Placebo Plus Fulvestrant in PALOMA-3 Study *(Sept-2022 Cutoff)*

System Organ Class	Palbociclib Plus Fulvestrant (N=345)			Placebo Plus Fulvestrant (N=172)		
Preferred Term[a]	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Infections and infestations						
Infections[b]	55.1[c]	4.9	1.2	36.0	3.5	0
Blood and lymphatic system disorders						
Febrile neutropenia	1.2	1.2	0	0	0	0
Neutropenia[d]	84.3	57.7	11.9	3.5	0	0
Leukopenia[e]	60.3	37.7	0.9	5.2	0.6	0
Anaemia[f]	32.2	4.3	0	13.4	2.3	0
Thrombocytopenia[g]	25.8	2.3	0.9	0	0	0
Eye disorders						
Blurred vision	6.7	0	0	1.7	0	0
Increased lacrimation	7.8	0	0	1.2	0	0
Dry eye	4.3	0	0	1.7	0	0
Metabolism and nutrition disorders						
Decreased appetite	17.7	1.4	0	10.5	0.6	0
Nervous system disorders						
Dysgeusia	5.2	0	0	2.9	0	0
Respiratory, thoracic and mediastinal disorders						
Epistaxis	7.2	0	0	2.3	0	0
Gastrointestinal disorders						
Stomatitis[h]	31.0	0.9	0	14.5	0	0
Nausea	36.5	0.6	0	30.2	0.6	0
Diarrhoea	27.5	0	0	20.3	1.2	0
Vomiting	22.0	0.6	0	16.3	0.6	0
Skin and subcutaneous tissue disorders						
Alopecia	19.7	0	0	6.4	0	0
Rash[i]	18.8	0.9	0	5.8	0	0
Dry skin	8.4	0	0	1.7	0	0
General disorders and administration site conditions						
Fatigue	43.8	3.2	0	32.6	1.2	0
Asthenia	8.1	0	0.3	8.1	1.2	0
Pyrexia	13.6	0.3	0	5.8	0	0
Investigations						
ALT increased	9.3	2.0	0	5.2	0.6	0
AST increased	12.2	3.2	0	7.6	2.3	0

N=number of patients; ILD=Interstitial lung disease; ALT= Alanine aminotransferase; AST= Aspartate aminotransferase.
Grades determined by National Cancer Institute Common Terminology Criteria for Adverse Events 4.0.
* Adverse Drug Reaction (ADR) identified post-marketing
a. Preferred Terms (PTs) are listed according to MedDRA 25.1.
b. INFECTIONS includes all reported PTs that are part of the System Organ Class Infections and infestations.
c. Most common infections (≥1%) include: Nasopharyngitis, Upper respiratory tract infection, Urinary tract infection, Bronchitis, Rhinitis, Influenza, Conjunctivitis, Sinusitis, Pneumonia, Cystitis, Oral herpes, Respiratory tract infection, Gastroenteritis, Tooth infection, Pharyngitis, Eye infection, Herpes simplex, Paronychia.
d. NEUTROPENIA includes the following PTs: Neutropenia, Neutrophil count decreased.
e. LEUKOPENIA includes the following PTs: Leukopenia, White blood cell count decreased.
f. ANAEMIA includes the following PTs: Anaemia, Haemoglobin decreased, Haematocrit decreased.
g. THROMBOCYTOPENIA includes the following PTs: Thrombocytopenia, Platelet count decreased.
h. STOMATITIS includes the following PTs: Aphthous ulcer, Cheilitis, Glossitis, Glossodynia, Mouth ulceration, Mucosal inflammation, Oral pain, Oropharyngeal discomfort, Oropharyngeal pain, Stomatitis.
i. RASH includes the following PTs: Rash, Rash maculo-papular, Rash pruritic, Rash erythematous, Rash papular, Dermatitis, Dermatitis acneiform, Toxic skin eruption.

Table 7. Laboratory Abnormalities in PALOMA-3 Study *(31-Jul-2015 Cutoff)*

Laboratory Abnormality	IBRANCE plus Fulvestrant (N=345)			Placebo plus Fulvestrant (N=172)		
	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
WBC decreased	99	45	1	26	0	1
Neutrophils decreased	96	56	11	14	0	1
Anaemia	78	3	0	40	2	0
Platelets decreased	62	2	1	10	0	0
ALT increased	36	2	0	34	0	0
AST increased	43	4	0	48	4	0

N=number of patients; WBC=white blood cells; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase.

The most common adverse drug reactions of any grade reported in >20% of patients receiving palbociclib in combination with fulvestrant were neutropenia, leukopenia, infections, fatigue, nausea, anaemia, stomatitis, diarrhoea, thrombocytopenia and vomiting.

Dose reductions due to an adverse event of any grade occurred in 35.9% of patients receiving IBRANCE plus fulvestrant. No dose reduction was allowed for fulvestrant in PALOMA-3. Permanent treatment discontinuation associated with an adverse event occurred in 5.5% of patients receiving IBRANCE plus fulvestrant and in 3.5% of patients receiving placebo plus fulvestrant.

In PALOMA-3 patients receiving IBRANCE plus fulvestrant, the starting dose of IBRANCE was 125 mg once daily. Dose reductions to 100 mg occurred in 34% of patients and dose reductions to 75 mg occurred in 12% of patients due to adverse events.

Neutropenia of any grade was reported in 84.3% of patients receiving IBRANCE in combination with fulvestrant in PALOMA-3, with Grade 3 neutropenia being reported in 57.7% of patients and Grade 4 neutropenia being reported in 11.9% of patients (see Section 4.4 Special warnings and precautions for use).

The most frequently (≥1%) reported serious adverse drug reactions in patients receiving palbociclib plus fulvestrant (PALOMA-3) were infections (4.1%), pyrexia (1.4%) and neutropenia (1.2%).

Postmarketing experience

The following adverse reactions have been identified during post-approval use of IBRANCE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Vascular disorders: Venous thromboembolism.
Respiratory disorders: Interstitial lung disease (ILD)/pneumonitis.
Skin and subcutaneous tissue disorders: Palmar-plantar erythrodysesthesia syndrome (PPES), erythema multiforme.
Investigations: Blood creatinine increased.

Reporting suspected adverse 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/safety/reporting-problems.

4.9 Overdose

There is no known antidote for palbociclib. The treatment of IBRANCE overdose should consist of general supportive measures. For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Through inhibition of CDK4/6, palbociclib reduced cellular proliferation by blocking progression of the cell from G1 into S phase of the cell cycle. Testing of palbociclib in a panel of molecularly profiled breast cancer cell lines revealed high efficacy against luminal breast cancers, particularly oestrogen receptor (ER)-positive breast cancers. Mechanistic analyses revealed that the combination of palbociclib with anti-oestrogen agents enhanced the re-activation of retinoblastoma (Rb) through inhibition of Rb phosphorylation resulting in reduced E2F signalling and growth arrest.

The enhanced growth arrest of the ER-positive breast cancer cell lines treated with palbociclib and anti-oestrogen agents is accompanied by increased cell senescence resulting in a sustained cell cycle arrest following drug removal and increased cell size associated with a senescent phenotype. *In vivo* studies using a patient-derived ER-positive breast cancer xenograft model (HBCx-34) demonstrated that the combination of palbociclib and letrozole further enhanced inhibition of Rb phosphorylation, downstream signalling and dose-dependent tumour growth. This supports the contribution of senescence-associated growth arrest as a mechanism

associated with the antitumour efficacy of combined palbociclib/ER antagonist in ER-positive breast cancer models.

In the presence or absence of an anti-oestrogen, palbociclib-treated bone marrow cells did not become senescent and resumed proliferation following palbociclib withdrawal, consistent with pharmacologic quiescence. The *in vitro* breast cancer cells, conversely, became senescent following palbociclib or anti-oestrogen treatment with additive effects in combination and remained arrested in the presence of anti-oestrogen.

Mechanism of action

Palbociclib is a small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of multiple signalling pathways which lead to cellular proliferation.

Clinical trials

Study A5481003: Randomised Phase 1/2 study of IBRANCE in combination with letrozole (PALOMA-1)

The efficacy of palbociclib was evaluated in a randomised, open-label, multicentre study of palbociclib plus letrozole versus letrozole alone conducted in postmenopausal women with ER-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer who did not receive previous systemic treatment for their advanced disease.

The study was comprised of a limited Phase 1 portion (N=12), designed to confirm the safety and tolerability of the combination palbociclib plus letrozole, followed by a randomised Phase 2 portion (N=165), designed to evaluate the efficacy and safety of palbociclib in combination with letrozole compared with letrozole alone in the first-line treatment of postmenopausal women with ER-positive, HER2-negative advanced breast cancer.

Randomisation was stratified by disease site (visceral versus bone only versus other) and by disease-free interval (>12 months from the end of adjuvant treatment to disease recurrence versus ≤12 months from the end of adjuvant treatment to disease recurrence or *de novo* advanced disease).

The patient demographic and baseline characteristics were generally balanced between the study arms in terms of age, race, disease sites, stage and prior therapies.

The primary endpoint of the study was investigator-assessed progression-free survival (PFS) evaluated according to Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0. The median PFS (mPFS) for patients in the palbociclib plus letrozole arm was 20.2 months (95% confidence interval [CI]: 13.8, 27.5) and 10.2 months (95% CI: 5.7, 12.6) for patients in the letrozole-alone arm. The observed hazard ratio (HR) was 0.488 (95% CI: 0.319, 0.748) in favour of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of 0.0004.

At the final overall survival (OS) analysis, the observed HR was 0.897 (95% CI: 0.623, 1.294) with a stratified 1-sided p-value of 0.2812. The median OS in the palbociclib plus letrozole arm was 37.5 months (95% CI: 31.4, 47.8) and in the letrozole alone arm was 34.5 months (95% CI: 27.4, 42.6).

The estimated survival probabilities at 12, 24, and 36 months between the 2 treatment arms were 89.0% versus 87.0%, 77.9% versus 71.1%, and 50.8% versus 47.4%, in favor of palbociclib plus letrozole, respectively.

Study A5481008: Randomised, Phase 3 study of IBRANCE in combination with letrozole (PALOMA-2)

The efficacy of palbociclib in combination with letrozole versus letrozole plus placebo was evaluated in an international, randomised, double-blind, placebo-controlled, parallel-group, multicentre study conducted in women with ER-positive, HER2-negative locally advanced or metastatic breast cancer who had not received prior systemic treatment for their advanced disease, whose disease was not amenable to resection or radiation therapy with curative intent, and for whom chemotherapy was not clinically indicated based on investigator's best medical judgement.

A total of 666 postmenopausal women were randomised 2:1 to either the palbociclib plus letrozole arm or to the placebo plus letrozole arm and were stratified by site of disease (visceral, non-visceral), disease-free interval from the end of (neo)adjuvant treatment to disease recurrence (de novo metastatic, ≤12 months from the end of adjuvant treatment to disease recurrence, >12 months from the end of adjuvant treatment to disease recurrence) and by the type of prior (neo)adjuvant anticancer therapies (prior hormonal therapy, no prior hormonal therapy).

Patients continued to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death or withdrawal of consent, whichever occurred first. Crossover between treatment arms was not allowed.

Patients were well matched for baseline demographics and disease characteristics between the palbociclib plus letrozole arm and the placebo plus letrozole arm. The median age of patients enrolled in this study was 62 years (range 28-89). A detailed summary of the demographics and baseline characteristics are presented in Table 8.

Table 8. Summary of Demographics and Baseline Disease Characteristics – PALOMA-2 Study (Intent-to-Treat Population)

Parameter	IBRANCE plus Letrozole (N=444)	Placebo plus Letrozole (N=222)
Age (years)		
Median (Min, Max)	62 (30, 89)	61 (28, 88)
<65 [n (%)]	263 (59.2)	141 (63.5)
≥65 [n (%)]	181 (40.8)	81 (36.5)
Race [n (%)]		
White	344 (77.5)	172 (77.5)
Black	8 (1.8)	3 (1.4)
Asian	65 (14.6)	30 (13.5)
ECOG Performance Status [n (%)]		
0	257 (57.9)	102 (45.9)
1	178 (40.1)	117 (52.7)
2	9 (2.0)	3 (1.4)
Disease site [n (%)]		
Visceral	214 (48.2)	110 (49.5)
Non-visceral	230 (51.8)	112 (50.5)
Measurable disease at baseline [n (%)]		
Yes	338 (76.1)	171 (77.0)
No	106 (23.9)	51 (23.0)
Disease-Free Interval [n (%)]		
>12 months since completion of prior (neo)adjuvant therapy	178 (40.1)	93 (41.9)
≤12 months since completion of prior (neo)adjuvant therapy	99 (22.3)	48 (21.6)
De novo advanced disease	167 (37.6)	81 (36.5)
Prior hormonal therapy use in (neo)adjuvant treatment [n (%)]		
Yes	249 (56.1)	126 (56.8)
No	195 (43.9)	96 (43.2)
Prior chemotherapy for primary diagnosis in (neo)adjuvant treatment [n (%)]		
Yes	213 (48.0)	109 (49.1)
No	231 (52.0)	113 (50.9)
Most recent hormonal therapy[b]		
Aromatase inhibitors	91 (36.5)	44 (34.9)
Anti-oestrogens	154 (61.8)	75 (59.5)
Other	4 (1.6)	7 (5.6)

Abbreviations: ECOG=Eastern Cooperative Oncology Group; Max=maximum; Min=minimum; N=number of patients; N / n=number of patients.

a: Race also includes 'Other: not reported/missing subjects'.

b: Aromatase inhibitors=anastrozole, letrozole or exemestane, Anti-oestrogens=tamoxifen, tamoxifen citrate, toremifene, toremifene citrate or fulvestrant; Other=not aromatase inhibitor and not anti-oestrogen.

The primary endpoint of the study was PFS evaluated according to RECIST version 1.1 as assessed by investigator. Secondary efficacy endpoints included objective response (OR), duration of response (DOR), clinical benefit response (CBR), overall survival (OS), safety, EQ-5D scores and health-related quality of life (QoL) assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire.

At the data cutoff date of 26-February-2016, the study met its primary objective of improving PFS. The HR was 0.576 (95% CI: 0.463, 0.718) in favour of palbociclib plus letrozole, with a stratified log-rank test 1-sided p-value of <0.000001. An updated analysis of the primary and

secondary endpoints was performed after an additional 15 months of follow up (data cutoff date: 31-May-2017). A total of 405 PFS events were observed; 245 events (55.2%) in the palbociclib plus letrozole arm and 160 (72.1%) in the comparator arm.

Table 9 shows the efficacy results based on the primary and the updated analyses from the PALOMA-2 study, as assessed by the investigator and by the independent review.

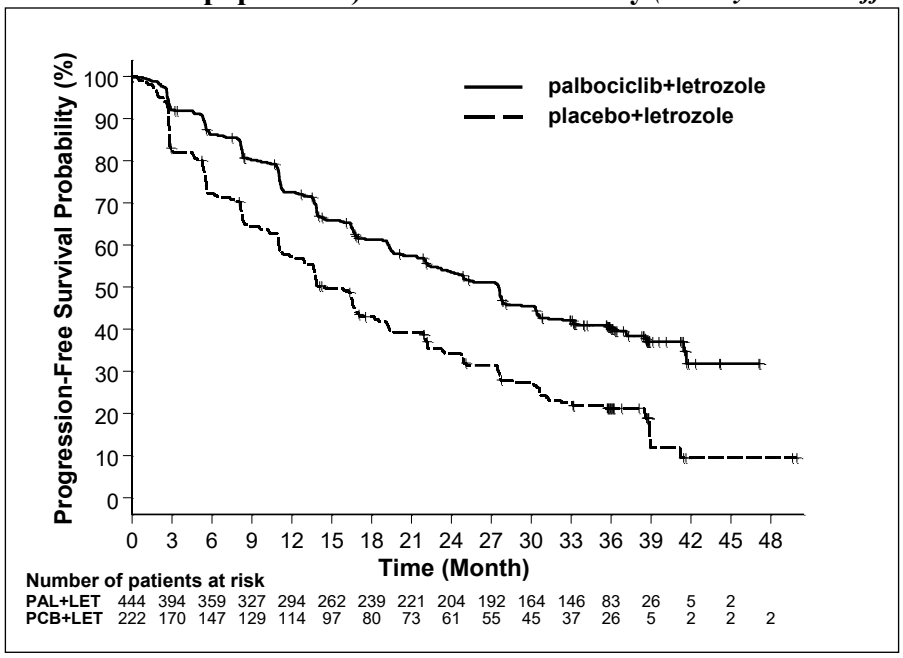
Table 9. PALOMA-2 (intent-to-treat population) - efficacy results based on primary and updated cutoff dates

	Primary Analysis (26 February 2016 Cutoff)		**Updated Analysis (31 May 2017 Cutoff)**	
	IBRANCE plus Letrozole (N=444)	**Placebo plus Letrozole (N=222)**	**IBRANCE plus Letrozole (N=444)**	**Placebo plus Letrozole (N=222)**
Progression-Free Survival by Investigator Assessment				
Number of events (%)	194 (43.7)	137 (61.7)	245 (55.2)	160 (72.1)
Median PFS [months (95% CI)]	24.8 (22.1, NE)	14.5 (12.9, 17.1)	27.6 (22.4 30.3)	14.5 (12.3, 17.1)
Hazard ratio [(95% CI) and p-value]	0.576 (0.463, 0.718), p<0.000001		0.563 (0.461, 0.687), p<0.000001	
Progression-Free Survival by Independent Assessment				
Number of events (%)	152 (34.2)	96 (43.2)	193 (43.5)	118 (53.2)
Median PFS [months (95% CI)]	30.5 (27.4, NE)	19.3 (16.4, 30.6)	35.7 (27.7, 38.9)	19.5 (16.6, 26.6)
Hazard ratio [(95% CI) and 1-sided p-value]	0.653 (0.505, 0.844), p=0.000532		0.611 (0.485, 0.769), p=0.000012	
ORR* [% (95% CI)]	46.4 (41.7, 51.2)	38.3 (31.9, 45.0)	47.5 (42.8, 52.3)	38.7 (32.3, 45.5)
ORR* measurable disease [% (95% CI)]	60.7 (55.2, 65.9)	49.1 (41.4, 56.9)	62.4 (57.0, 67.6)	49.7 (42.0, 57.4)
DOR* [months (95% CI)]	20.1 (19.3, 28.0)	16.7 (13.8, 22.5)	25.3 (22.1, 34.5)	16.8 (14.2, 25.3)
CBRR* [% (95% CI)]	85.8 (82.2, 88.9)	71.2 (64.7, 77.0)	85.6 (82.0, 88.7)	71.2 (64.7, 77.0)

N=number of patients; CI=confidence interval; NE=not estimable; ORR=objective response rate; CBRR=clinical benefit response rate; DOR=duration of response; PFS=progression-free-survival.
*Secondary endpoints results are based on confirmed and unconfirmed responses according to RECIST 1.1.

The Kaplan-Meier curves for PFS based on the updated cutoff date of 31 May 2017 are displayed in Figure 1 below.

Figure 1. Kaplan-Meier plot of progression-free survival (investigator assessment, intent-to-treat population) – PALOMA-2 study ***(31-May-2017 cutoff date)***



PAL=palbociclib; LET=letrozole; PCB=placebo.

Prespecified subgroup analyses indicated that the treatment effect (by median PFS) was consistent in all subgroups defined by stratification factors and baseline characteristics, including presence/absence of visceral metastases at baseline and presence of bone-only disease at baseline. An exploratory analysis showed that median PFS was longer in the palbociclib plus letrozole arm for 512 patients whose tumour tested positive for Rb protein expression by immunohistochemistry (IHC) (HR 0.543 [95% CI: 0.433, 0.681], mPFS 27.4 months versus 13.7 months). For the 51 patients whose tumours tested negative for Rb protein expression by IHC, the difference between treatment arms was not statistically significant.

Patients with advanced, symptomatic visceral spread at risk of life-threatening complications in the short term were not included in PALOMA-2.

At the time of the updated analyses for PFS, time to initiation of subsequent anticancer therapies was also assessed. The results from these analyses are shown in Table 10.

Table 10. PALOMA-2 study: Time to initiation of subsequent anticancer therapies ***(31-May-2017 cutoff date)***

	IBRANCE plus letrozole (N=444)	**Placebo plus letrozole (N=222)**
Median (95% CI) time to first subsequent therapy	28.0 (23.6, 29.6)	17.7 (14.3, 21.5)
Median (95% CI) time to second subsequent therapy	38.8 (34.4, NE)	28.8 (25.7, 33.5)

N=number of patients; CI=confidence interval

An analysis of time-to-deterioration composite endpoint (TTD) in Functional Assessment of Cancer Therapy-Breast (FACT-B), defined as the time between baseline and first occurrence of decrease of ≥7 points in FACT-B scores, was carried out based on survival analysis methods

using a Cox proportional hazards model and log-rank test. No statistically significant difference was observed in TTD in FACT-B total scores between the palbociclib plus letrozole arm and the placebo plus letrozole arm (HR of 1.042 [95% CI: 0.838, 1.295]; 1-sided p-value=0.663.

Pre- and perimenopausal women were not enrolled in PALOMA-1 or PALOMA-2.

The results from the final OS analysis from the PALOMA-2 study are presented in Table 11. After a median follow-up time of 90 months, the final OS results were not statistically significant. The Kaplan-Meier plot of OS is shown in Figure 2.

Table 11. PALOMA-2 (Intent-to-Treat Population) – Final Overall Survival Results

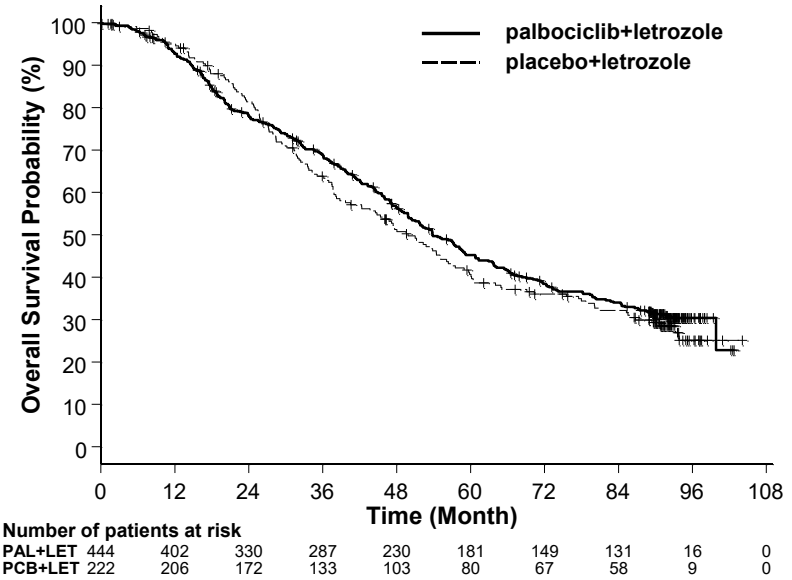
Final Overall Survival (OS) (15 November 2021 Cutoff)		
	Palbociclib plus letrozole (N=444)	**Placebo plus letrozole (N=222)**
Number of OS events (%)	287 (64.6)	148 (66.7)
Number of subjects remaining in follow-up (%)	116 (26.1)	48 (21.6)
Median OS (months, 95% CI)	53.8 (49.8, 59.2)	49.8 (42.3, 56.4)
Hazard ratio (95% CI) and p-value[†]	0.921 (0.755, 1.124), p=0.2087[†*]	

CI=confidence interval.

[*] Not statistically significant.

[†] 1-sided p-value from the log-rank test stratified by disease site (visceral vs. non-visceral) per randomisation.

Figure 2. Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) – PALOMA-2



PAL=palbociclib; LET=letrozole; PCB=placebo.

Study A5481023: Randomised, Phase 3 study of IBRANCE in combination with fulvestrant (PALOMA-3)

The efficacy of palbociclib in combination with fulvestrant versus placebo plus fulvestrant was evaluated in an international, randomised, double-blind, parallel-group, multicentre study conducted in women with HR-positive, HER2-negative locally advanced or metastatic breast cancer, regardless of their menopausal status, whose disease progressed after prior endocrine therapy and was not amenable to resection or radiation therapy with curative intent based on investigator's best medical judgement.

A total of 521 pre/postmenopausal women whose disease had progressed on or within 12 months after completion of adjuvant endocrine therapy, or on or within 1 month from prior endocrine therapy for advanced disease, were randomised 2:1 to the palbociclib plus fulvestrant arm or the placebo plus fulvestrant arm and stratified by: documented sensitivity to prior hormonal therapy, menopausal status at study entry (pre/peri versus postmenopausal) and presence of visceral metastases. Crossover between treatment arms was not allowed.

Patients were balanced for baseline demographics and prognostic characteristics between the palbociclib plus fulvestrant arm and the placebo plus fulvestrant arm. The median age of patients enrolled in this study was 57 years (range 29, 88). The majority of patients in each treatment arm were White, had documented sensitivity to prior hormonal therapy and were postmenopausal. All patients had received prior systemic therapy and most patients in each treatment arm had received a previous chemotherapy regimen. More than half (62%) had an ECOG performance status of 0, 60% had visceral metastases and 60% had received more than 1 prior hormonal regimen for their primary diagnosis.

Table 12. Summary of Demographic and Baseline Characteristics by Treatment – PALOMA-3 Study (Intent-to-Treat Population)

Parameter	IBRANCE Plus Fulvestrant (N=347)	Placebo Plus Fulvestrant (N=174)
Age (years)		
Median (Min, Max)	57 (30, 88)	56 (29, 80)
<65 [n (%)]	261 (75.2)	131 (75.3)
≥65 [n (%)]	86 (24.8)	43 (24.7)
Race[a]		
White	252 (72.6)	133 (76.4)
Asian	74 (21.3)	31 (17.8)
Black	12 (3.5)	8 (4.6)
ECOG performance status [n (%)]		
0	207 (59.7)	115 (66.1)
1	140 (40.3)	59 (33.9)
Documented sensitivity to prior hormonal therapy[b] [n (%)]		
Yes	274 (79.0)	136 (78.2)
No	73 (21.0)	38 (21.8)
Visceral metastases[a] [n (%)]		
Yes	206 (59.4)	105 (60.3)
No	141 (40.6)	69 (39.7)
Menopausal status[b,c] [n (%)]		
Pre/Peri[d]	72 (20.7)	36 (20.7)
Post	275 (79.3)	138 (79.3)
Prior systemic therapies [n (%)]		
No	0	0
Yes	347 (100)	174 (100)
Number of regimens		
1	71 (20.5)	39 (22.4)
2	106 (30.5)	56 (32.2)
3	98 (28.2)	35 (20.1)
>3	72 (20.7)	44 (25.3)
Previous chemotherapy regimen for primary diagnosis		
No	96 (27.7)	36 (20.7)
Yes	251 (72.3)	138 (79.3)
Prior hormonal regimen for primary diagnosis		
1	133 (38.3)	77 (44.3)
>1	214 (61.7)	97 (55.7)

Abbreviations: ECOG=Eastern Cooperative Oncology Group; Max=maximum; Min=minimum; N / n=number of patients.

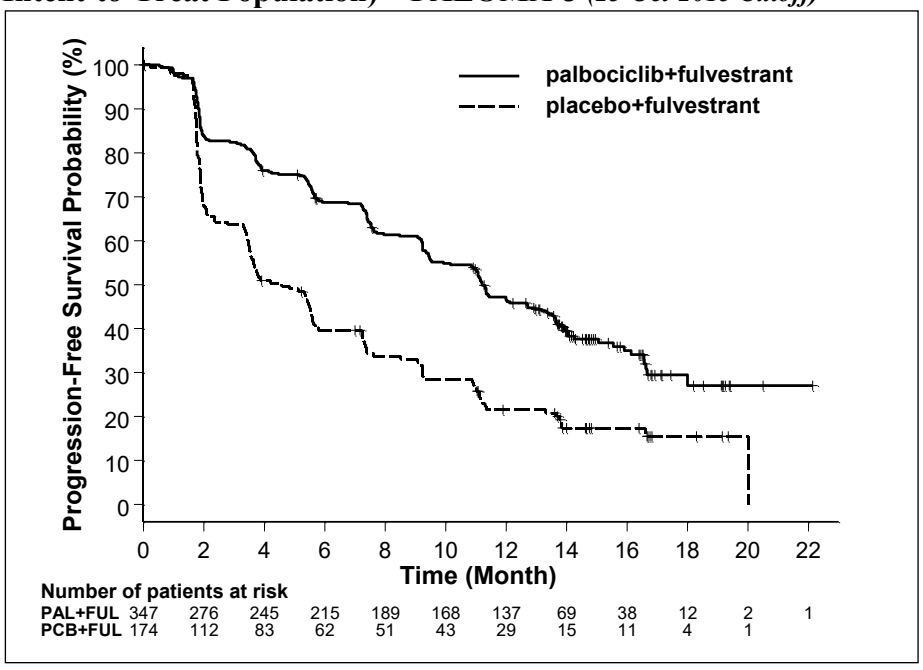
a. Race also included Other (9/521) and Unspecified (2/521)
b. Based on the randomisation.
c. Postmenopausal defined by at least 1 of the following criteria: 1) ≥60 years of age, 2) <60 years of age and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause, and serum estradiol and follicle stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal females; 3) documented bilateral oophorectomy; or 4) medically confirmed ovarian failure. Pre/perimenopausal defined as not meeting the criteria for being postmenopausal.
d. Of the 72 pre/peri menopausal patients, 1 patient was never treated and 1 patient incorrectly randomised (postmenopausal as per investigator).

The primary endpoint of the study was investigator-assessed PFS evaluated according to RECIST version 1.1. Secondary PFS analyses were based on a random sample Blinded Independent Central Radiology Review (BICR) of 40.5% of the ITT population. Secondary endpoints included OR, DOR, CBR, OS, safety, change in QoL and TTD. Patient-reported outcomes including Global QoL and pain were measured using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire (QLQ-C30) and the Breast Cancer Module (BR23) questionnaire.

The study met its primary endpoint of prolonging investigator-assessed PFS at the interim analysis conducted on 82% of the planned PFS events at final analysis; the results crossed the prespecified Haybittle-Peto efficacy boundary (α=0.00135), demonstrating a statistically significant prolongation in PFS and a clinically meaningful treatment effect. The estimated HR from the stratified analysis was 0.422 (95% CI: 0.318, 0.560; 1-sided p<0.000001) in favour of palbociclib plus fulvestrant. The mPFS was 9.2 months (95% CI: 7.5, not estimable [NE]) in the palbociclib plus fulvestrant arm and 3.8 months (95% CI: 3.5, 5.5) in the placebo plus fulvestrant arm.

A more mature update of efficacy data is reported in Figure 3 and Table 13.

Figure 3. Kaplan-Meier Plot of Progression-Free Survival (Investigator Assessment, Intent-to-Treat Population) – PALOMA-3 ***(23-Oct-2015 Cutoff)***



CI=confidence interval; FUL=fulvestrant; N=number of patients; NE=not estimable; PAL=palbociclib; PCB=placebo; PFS=progression-free survival.

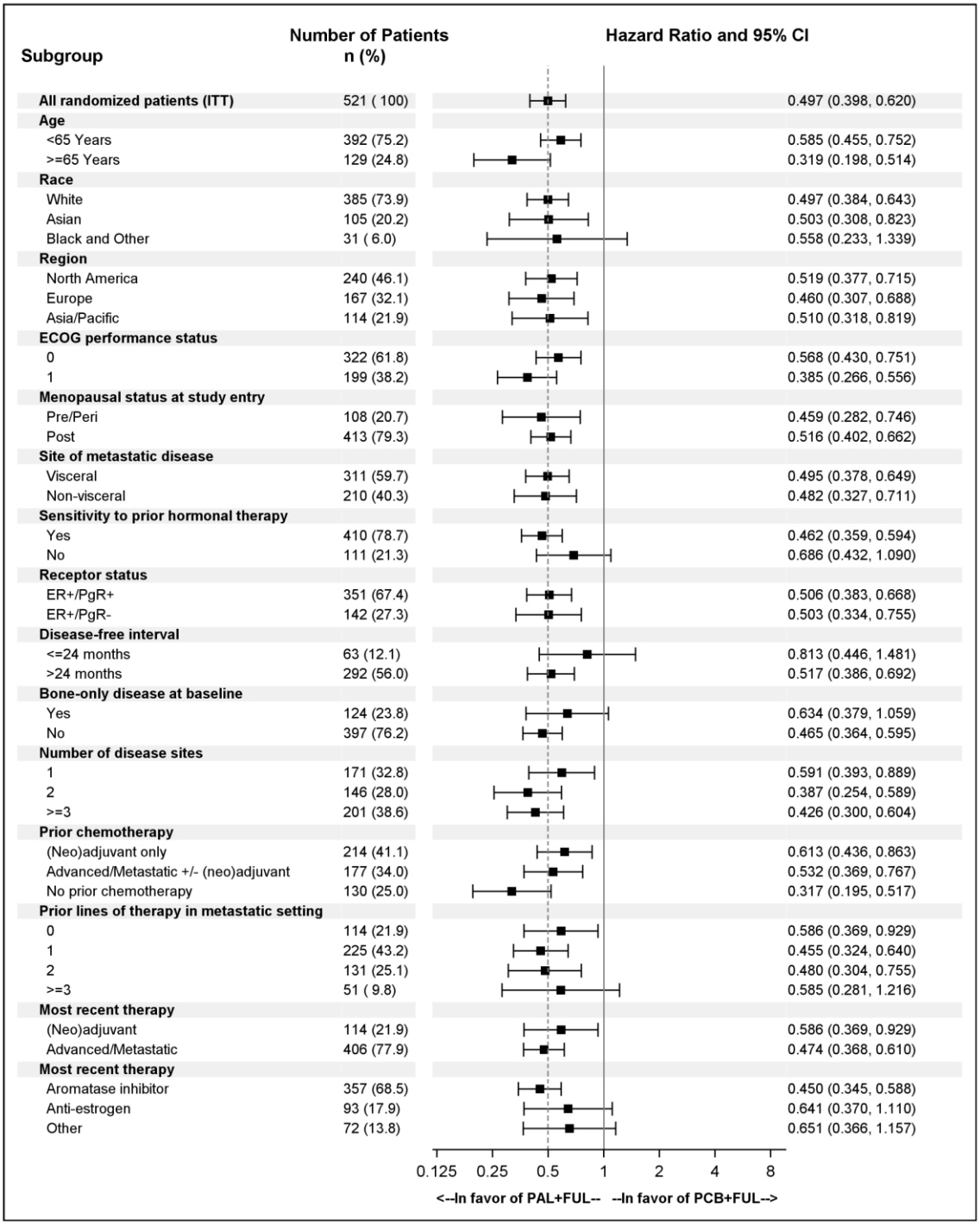
Table 13. Efficacy Results – PALOMA-3 Study (Investigator Assessment, Intent-to-Treat Population)

	Final Analysis (05-Dec-2014 Cutoff)		Updated Analysis (23-Oct-2015 Cutoff)	
	IBRANCE plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**	**IBRANCE plus Fulvestrant (N=347)**	**Placebo plus Fulvestrant (N=174)**
Progression-Free Survival				
Median PFS [months (95% CI)]	9.2 (7.5, NE)	3.8 (3.5, 5.5)	11.2 (9.5, 12.9)	4.6 (3.5, 5.6)
Hazard ratio [(95% CI) and p-value]	0.422 (0.318, 0.560), p<0.000001		0.497 (0.398, 0.620), p<0.000001	
ORR [% (95% CI)][a]	10.4 (7.4, 14.1)	6.3 (3.2, 11.0)	21.0 (16.9, 25.7)	8.6 (4.9, 13.8)
ORR measurable disease [% (95% CI)][a]	13.4 (9.6, 18.1)	8.0 (4.0, 13.8)	27.3 (22.1, 33.1)	10.9 (6.2, 17.3)
DOR [months (95% CI)][a]	9.3 (4.0, NE)	5.7 (3.7, 5.7)	10.4 (8.3, NE)	9.0 (5.6, NE)
CBRR [% (95% CI)][a]*	34.0 (29.0, 39.3)	19.0 (13.4, 25.6)	66.3 (61.0, 71.2)	39.7 (32.3, 47.3)

CBRR=clinical benefit response rate; CI=confidence interval; DOR=duration of response; N=number of patients; NE=not estimable; PFS=progression-free survival; ORR=objective response rate.
[a] Based on confirmed responses.
*CBR includes complete response (CR), partial response (PR) and stable disease (SD) ≥24 weeks. Of note, no CRs were reported in the palbociclib plus fulvestrant arm.

Prolongation of PFS in the palbociclib plus fulvestrant arm was also demonstrated in most individual patient subgroups supporting internal consistency of PFS benefit findings within the study and was supported by the secondary PFS random sample BICR audit.

Figure 4. Forest Plot of Subgroup Analyses of Progression-Free Survival PALOMA-3 Study (Investigator Assessment, Intent-to-Treat Population) ***(23-Oct-2015 Cutoff)***



CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ER=oestrogen receptor; FUL=fulvestrant; ITT=intent-to-treat; n=number of patients meeting prespecified criteria; PAL=palbociclib; PCB=placebo; PgR=progesterone receptor.

As per inclusion criteria, pre/perimenopausal women were enrolled in the study if already treated with an LHRH agonist from at least 4 weeks. If they were not treated with goserelin prior to study entry, they were switched to goserelin when they started the study treatment. In the palbociclib plus fulvestrant arm 70 pre/perimenopausal women received goserelin for the duration of the study and in the placebo plus fulvestrant arm 36 pre/perimenopausal women received goserelin.

The palbociclib plus fulvestrant arm demonstrated similar clinical benefit in the pre/perimenopausal patient population (HR=0.494 [95% CI: 0.300, 0.813]) and postmenopausal population (HR=0.508 [95% CI: 0.395, 0.652]). Similarly, the mPFS for the palbociclib plus fulvestrant arm was 11.3 months (95% CI: 7.5, 15.0) in the pre/perimenopausal setting versus 11.2 months (95% CI: 9.5, 12.7) in the postmenopausal setting; while the mPFS in the placebo plus fulvestrant arm was 5.6 months (95% CI: 1.7, 9.2) in the pre/perimenopausal setting versus 3.9 months (95% CI: 3.5, 5.5) in the postmenopausal setting.

The overall survival (OS) data were not mature at the time of the final PFS analysis (11% of patients had died). Patients will continue to be followed for the final analysis.

Patient-reported symptoms were assessed using the EORTC QLQ-C30 and EORTC QLQ-BR23. A total of 335 patients in the palbociclib plus fulvestrant arm and 166 patients in the placebo plus fulvestrant arm completed the questionnaire at baseline and at least 1 postbaseline visit.

Time to Deterioration (TTD) was prespecified as time between baseline and first occurrence of ≥10-point increase from baseline in pain symptom scores. Addition of palbociclib to fulvestrant resulted in a symptom benefit by significantly delaying TTD in pain symptom scores compared with placebo plus fulvestrant (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; p<0.001).

After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (59.5% of randomised patients). A clinically meaningful 6.9-month improvement in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed, although this result was not statistically significant at the prespecified significance level of 0.0235. A higher proportion of patients in the placebo plus fulvestrant arm received post-progression systemic treatments overall in comparison with the patients in the palbociclib plus fulvestrant arm (80.5% versus 71.8%) respectively. Also, in placebo plus fulvestrant arm, 15.5% of randomised patients received palbociclib and other CDK inhibitors as post progression subsequent treatments.

The results from the final OS data from PALOMA-3 Study are presented in Table 14. The relevant Kaplan-Meier plots are shown in Figures 3 and 5.

Table 14. Efficacy Results – PALOMA-3 (Investigator Assessment, Intent-to-Treat Population) ***(13 April 2018 Cutoff)***

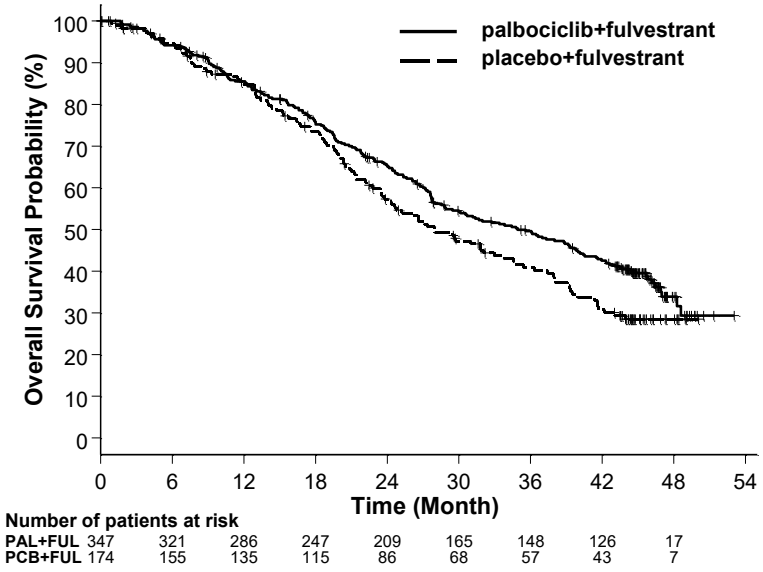
Final Overall Survival (OS)		
	IBRANCE plus Fulvestrant (N=347)	**Placebo plus Fulvestrant (N=174)**
Number of events (%)	201 (57.9)	109 (62.6)
Median (months [95% CI])	34.9 (28.8, 40.0)	28.0 (23.6, 34.6)
Hazard ratio (95% CI) and p-value†	0.814 (0.644, 1.029) p=0.0429†*	

CI=confidence interval.

* Not statistically significant.

† 1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior endocrine therapy per randomisation.

Figure 5. Kaplan-Meier Plot of Overall Survival (Intent-to-Treat Population) – PALOMA-3



FUL=fulvestrant; PAL=palbociclib; PCB=placebo.

A positive treatment effect of palbociclib plus fulvestrant versus placebo plus fulvestrant on OS was observed in the majority of the prespecified subgroups. Due to the low event number and smaller sample size in some of the prespecified subgroups, the magnitude of estimated effect of palbociclib added to fulvestrant could not always be determined. The OS results from patients subgroups defined by stratification factors at randomisation are reported in Table 15 below.

Table 15. Overall Survival in Patients Subgroups Defined by Stratification Factors

	IBRANCE plus Fulvestrant	**Placebo plus Fulvestrant**	**HR (95% CI)**	**p-value***
ITT Sub-group	ne/N	ne/N		
Menopausal Status at Study Entry				
Postmenopausal	161/275	91/138	0.73 (0.57, 0.95)	p=0.009
Peri/premenopausal	40/72	18/36	1.07 (0.61, 1.86)	p=0.41
Documented Sensitivity to Prior Hormonal Therapy				
Yes	150/274	84/136	0.72 (0.55, 0.94)	p=0.008
No	51/73	25/38	1.14 (0.70, 1.84)	p=0.297
Site of Metastatic Disease				
Visceral	138/206	72/105	0.85 (0.64, 1.13)	p=0.132
Non-visceral	63/141	37/69	0.69 (0.46, 1.04)	p=0.036

CI=confidence interval; FUL=fulvestrant; HR=Hazard Ratio; ITT=Intent-to-Treat; ne=number of events; N=number of patients; PAL=palbociclib; PCB=placebo.

[*] One sided p-value. No multiplicity adjustments were made for the subgroup analyses.

The estimated survival probabilities for palbociclib plus fulvestrant versus placebo plus fulvestrant were respectively: 65.3% (95% CI: 59.9, 70.2) vs. 57.3% (95% CI: 49.2, 64.6) at 2 years and 49.6% (95% CI: 44.0, 54.9) vs. 40.8% (95% CI: 32.9, 48.5) at 3 years.

Men were not enrolled in PALOMA-1, PALOMA-2 and PALOMA-3.

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of palbociclib were characterised in patients with solid tumours including advanced breast cancer and in healthy volunteers.

Absorption

The time to C_{max} (T_{max}) of palbociclib is generally between 6 to 12 hours following oral administration of IBRANCE capsules. The T_{max} of palbociclib is generally observed between 4 to 12 hours following oral administration of IBRANCE tablets. The mean absolute bioavailability of palbociclib after an oral 125 mg dose is 46%. In the dosing range of 25 mg to 225 mg, the AUC and C_{max} increase proportionally with dose in general. Steady state was achieved within 8 days following repeated once daily dosing. With repeated once daily administration, palbociclib accumulates with a median accumulation ratio of 2.4 (range 1.5-4.2).

Food effect

IBRANCE capsules

Palbociclib absorption and exposure were very low in approximately 13% of the population under the fasted condition. Food intake increased the palbociclib exposure in this small subset of the population, but did not alter palbociclib exposure in the rest of the population to a clinically relevant extent. Therefore, food intake reduced the intersubject variability of palbociclib exposure, which supports administration of IBRANCE capsules with food.

Compared to palbociclib given under overnight fasted conditions, the AUC_{inf} and C_{max} of palbociclib increased by 21% and 38% when given with high-fat food, by 12% and 27% when given with low-fat food and by 13% and 24% when moderate-fat food was given 1 hour before and 2 hours after palbociclib dosing. In addition, food intake significantly reduced the intersubject and intrasubject variability of palbociclib exposure. Based on these results, IBRANCE capsules should be taken with food.

IBRANCE film-coated tablets

The AUC_{inf} and C_{max} of palbociclib increased by 22% and 26%, respectively, when IBRANCE tablets were given with a high-fat, high-calorie meal (approximately 800 to 1000 calories with 150, 250, and 500 to 600 calories from protein, carbohydrate, and fat, respectively), and by 9% and 10%, respectively, when IBRANCE tablets were given with a moderate fat, standard-calorie meal (approximately 500 to 700 calories with 75 to 105, 250 to 350, and 175 to 245 calories from protein, carbohydrate, and fat, respectively), compared to IBRANCE tablets given under overnight fasted conditions. Based on these results, IBRANCE tablets may be taken with or without food.

Gastric pH elevating medication effect

IBRANCE capsules

In a healthy subject study, coadministration of a single 125 mg IBRANCE capsule with multiple doses of the PPI rabeprazole under fed conditions decreased palbociclib C_{max} by 41%, but had limited impact on AUC_{inf} (13% decrease), when compared to a single 125 mg IBRANCE capsule administered alone. Given the reduced effect on gastric pH of H2 receptor antagonists and local antacids compared to PPIs, the effect of these classes of acid-reducing agents on palbociclib exposure under fed conditions is expected to be minimal. Under fed conditions there is no clinically relevant effect of PPIs, H2-receptor antagonists or local antacids on palbociclib exposure. In another healthy subject study, coadministration of a single 125 mg IBRANCE capsule with multiple doses of the PPI rabeprazole under fasted conditions decreased palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively, when compared with a single 125 mg IBRANCE capsule administered alone.

IBRANCE film-coated tablets

Coadministration of multiple doses of the PPI rabeprazole with a single 125 mg IBRANCE tablet under fasted conditions had no effect on the rate and extent of absorption of palbociclib when compared to a single 125 mg IBRANCE tablet administered alone.

Distribution

Binding of palbociclib to human plasma proteins *in vitro* was ~85%, with no concentration dependence over the concentration range of 500 ng/mL to 5000 ng/mL. The mean fraction unbound (f_u) of palbociclib in human plasma *in vivo* increased incrementally with worsening hepatic function. There was no obvious trend in the mean palbociclib f_u in human plasma *in vivo* with worsening renal function. The geometric mean apparent volume of distribution (V_z/F) was 2583 (26%) L.

Metabolism

In vitro and *in vivo* studies indicate that palbociclib undergoes extensive hepatic metabolism in humans. Following oral administration of a single 125 mg dose of [^{14}C]palbociclib to humans, the major primary metabolic pathways for palbociclib involved oxidation and sulfonation, with acylation and glucuronidation contributing as minor pathways. Palbociclib was the major circulating drug-derived entity in plasma. The major circulating metabolite was a glucuronide conjugate of palbociclib, although it only represented 1.5% of the administered dose in the excreta. The glucuronide metabolite is primarily formed by UGT1A1 and to a lesser extent, by UGT1A4. The majority of the material was excreted as metabolites. In faeces, the sulfamic acid conjugate of palbociclib was the major drug-related component, accounting for 25.8% of the administered dose. *In vitro* studies with human hepatocytes, liver cytosolic and S9 fractions and recombinant sulfotransferase (SULT) enzymes indicated that CYP3A and SULT2A1 are mainly involved in the metabolism of palbociclib.

Excretion

The geometric mean apparent oral clearance (CL/F) of palbociclib was 63.08 L/h and the mean plasma elimination half-life was 28.8 hours in patients with advanced breast cancer. In 6 healthy male subjects given a single oral dose of [^{14}C]palbociclib, a median of 91.6% of the total administered radioactive dose was recovered in 15 days; faeces (74.1% of dose) was the

major route of excretion, with 17.5% of the dose recovered in urine. Excretion of unchanged palbociclib in faeces and urine was 2.3% and 6.9% of the administered dose, respectively.

Special populations

Based on a population pharmacokinetic analysis in 183 patients with cancer (50 male and 133 female patients, age ranging from 22 to 89 years and body weight ranging from 37.9 to 123 kg), gender had no effect on the exposure of palbociclib and age and body weight had no clinically important effect on the exposure of palbociclib.

Elderly (≥65 years)

Of 444 patients who received palbociclib in Study A5481008 (PALOMA-2), 181 patients (41%) were ≥65 years of age with 133 (30%) patients between the age of 65 and 74, and 48 (11%) patients ≥75 years of age. Of 347 patients who received palbociclib in Study A5481023 (PALOMA-3), 86 patients (25%) were ≥65 years of age with 59 (17%) patients between the age of 65 and 74, and 27 (8%) patients ≥75 years of age. No overall differences in safety were observed across all age groups and elderly age groups. Neutropenia was the most common adverse event with palbociclib across all age groups; however, the incidence of febrile neutropenia was low in all age groups. No overall differences effectiveness of palbociclib were observed between these patients and younger patients.

Children and adolescents

Pharmacokinetics of palbociclib have not been evaluated in patients ≤18 years of age.

Renal impairment

Data from a pharmacokinetic trial in subjects with varying degrees of renal function indicate that total palbociclib exposure (AUC_{inf}) was increased by 39%, 42%, and 31% with mild (60 mL/min ≤ CrCl <90 mL/min), moderate (30 mL/min ≤ CrCl <60 mL/min), and severe (CrCl <30 mL/min) renal impairment, respectively, relative to subjects with normal (CrCl ≥90 mL/min) renal function. Peak palbociclib exposure (C_{max}) was increased by 17%, 12%, and 15% for mild, moderate, and severe renal impairment, respectively, relative to subjects with normal renal function. This study included a small number of patients with severe renal impairment (n=6) and palbociclib use in this population is considered largely uncharacterised.

In addition, based on a population pharmacokinetic analysis that included 183 patients with advanced cancer where 73 patients had mild renal impairment and 29 patients had moderate renal impairment, mild and moderate renal impairment had no effect on the PK of palbociclib. The pharmacokinetics of palbociclib have not been studied in patients requiring haemodialysis.

Hepatic impairment

Data from a pharmacokinetic trial in subjects with varying degrees of hepatic function indicate that palbociclib unbound exposure (unbound AUC_{inf}) decreased by 17% in subjects with mild hepatic impairment (Child-Pugh class A), and increased by 34% and 77% in subjects with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C), respectively, relative to subjects with normal hepatic function. This study included a small number of patients with severe hepatic impairment (n=7) and palbociclib use in this population is considered largely uncharacterised.

Peak palbociclib unbound exposure (unbound C_{max}) was increased by 7%, 38% and 72% for mild, moderate and severe hepatic impairment, respectively, relative to subjects with normal hepatic function. In addition, based on a population pharmacokinetic analysis that included 183 patients with advanced cancer where 40 patients had mild hepatic impairment based on National Cancer Institute (NCI) classification (total bilirubin ≤ Upper Limit of Normal (ULN) and Aspartate Aminotransferase (AST) >ULN, or total bilirubin >1.0 to 1.5 × ULN and any AST), mild hepatic impairment had no effect on the PK of palbociclib.

Asian race

In a dedicated PK study in healthy volunteers, palbociclib geometric mean AUC_{inf} and C_{max} values were 30% and 35% higher, respectively, in Japanese subjects compared with non-Asian subjects after a single oral dose. However, this finding was not reproduced consistently in subsequent studies in breast cancer patients after multiple dosing. Based on an analysis of the cumulative pharmacokinetic, safety and efficacy data, no dose adjustment based on Asian race is considered necessary.

Cardiac electrophysiology

The effect of palbociclib on the QT interval corrected for heart rate (QTc) was evaluated using time-matched electrocardiograms (ECGs) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with breast cancer. Palbociclib did not prolong QTc to any clinically relevant extent at the recommended dose of 125 mg daily for 21 consecutive days followed by 7 days off treatment.

5.3 Preclinical safety data

The primary target organ findings following single and/or repeat dosing included haematolymphopoietic and male reproductive organ effects in rats and dogs, and effects on bone and actively growing incisors in rats only. These systemic toxicities were generally observed at clinically relevant exposures based on AUC. Partial to full reversal of effects on the haematolymphopoietic, male reproductive systems and incisor teeth were established, whereas the bone effect was not reversed following a 12-week nondosing period. The effect on bone indicate a potential risk for children and adolescents. In addition, cardiovascular effects (QTc prolongation, decreased heart rate and increased RR interval and systolic blood pressure) were identified in telemetered dogs at ≥4 times human clinical exposure based on C_{max}.

Genotoxicity

Palbociclib was not mutagenic in a bacterial reverse mutation (*Ames*) assay and did not induce structural chromosomal aberrations in the *in vitro* human lymphocyte chromosome aberration assay.

Palbociclib induced micronuclei via an aneugenic mechanism in Chinese Hamster Ovary cells *in vitro* and in the bone marrow of rats.

Carcinogenicity

Palbociclib was assessed for carcinogenicity in a 6-month transgenic mouse study and in a 2-year rat study. Palbociclib was negative for carcinogenicity in transgenic mice at doses up to 60 mg/kg/day (No Observed Effect Level [NOEL] approximately 7 times human clinical

exposure based on AUC). Palbociclib was carcinogenic in rats. Palbociclib-related neoplastic finding in rats included an increased incidence of microglial cell tumors in the central nervous system of males at 30 mg/kg/day (5 times human clinical exposure based on AUC). There were no neoplastic findings in female rats at any dose up to 200 mg/kg/day. The NOEL for palbociclib-related carcinogenicity effects was 10 mg/kg/day (approximately 2 times the human clinical exposure based on AUC) and 200 mg/kg/day (approximately 4 times the human clinical exposure based on AUC) in males and females, respectively. The relevance of the male rat neoplastic finding to humans is unknown.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

IBRANCE capsules

Microcrystalline cellulose, lactose monohydrate, sodium starch glycollate, silicon dioxide and magnesium stearate.

The capsules are opaque and are differentiated by size, colour and printing. The capsule shells contain gelatin, iron oxide red, iron oxide yellow and titanium dioxide and are printed with Opacode S-1-7085 white printing ink. The capsule shells consist of a light orange body/light orange cap (75 mg), a light orange body/caramel cap (100 mg) and a caramel body/caramel cap (125 mg).

IBRANCE film-coated tablets

Tablet core: Microcrystalline cellulose, silicon dioxide, crospovidone, magnesium stearate and succinic acid.

Film coating: Hypromellose, titanium dioxide, triacetin, indigo carmine aluminium lake, iron oxide red (75 mg and 125 mg tablets only), and iron oxide yellow (100 mg tablets only).

The tablets are differentiated by shape, colour and embossing. The 75 mg tablet is round shaped and light purple, the 100 mg tablet is oval shaped and green, the 125 mg tablet is oval shaped and light purple.

6.2 Incompatibilities

See Section 4.5 Interactions with other medicines and other forms of interactions.

6.3 Shelf life

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.

IBRANCE tablets: store in the original blister package to protect from moisture.

6.5 Nature and contents of container

IBRANCE 75 mg, 100 mg and 125 mg capsules are supplied in HDPE bottles or PVC/PCFTE/PVC Al blister packs containing 21 capsules.

IBRANCE 75 mg, 100 mg and 125 mg film-coated tablets are supplied in PVC/OPA/Al/PVC Al blister packs containing 21 tablets.

Not all pack sizes may be available.

6.6 Special precautions for disposal

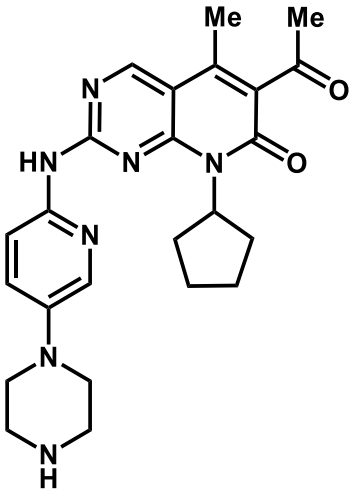
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 Physicochemical properties

The chemical name of palbociclib is 6-acetyl-8-cyclopentyl-5-methyl-2-{[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-d]pyrimidin-7(8H)-one.

Its molecular formula is $C_{24}H_{29}N_7O_2$ which corresponds to a molecular weight of 447.54 Daltons.

Chemical structure



Palbociclib is a yellow to orange powder with a pKa of 7.4 (secondary piperazine nitrogen) and 3.9 (pyridine nitrogen). The solubility of palbociclib in aqueous media decreases over the range pH 4.3 to pH 9.0 from greater than 0.7 mg/mL to less than 0.002 mg/mL. At or below pH 4, palbociclib behaves like a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly. The partition coefficient (1-octanol/water) at pH 7.4 is 0.99.

CAS number

571190-30-2

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedicalinformation.com.au

9. DATE OF FIRST APPROVAL

03 May 2017

10. DATE OF REVISION

09 April 2026

® Registered trademark

Summary Table of Changes

Section changed	Summary of new information
4.4, 4.8	Update for the risk of VTE per TGA PB request