Horizon Scanning in Oncology

Palbociclib (Ibrance®) in combination with fulvestrant for the treatment of hormone-receptor-positive, HER2-negative advanced or metastatic breast cancer

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The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunethta.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model

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1 Research questions

EUnetHTA HTA Core Model®

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

Element ID	Research question
Description of the technology	
B0001	What is palbociclib?
A0022	Who manufactures palbociclib?
A0007	What is the target population in this assessment?
A0020	For which indications has palbociclib received marketing authorisation?
Health problem and current use	
A0002	What is breast cancer?
A0004	What is the natural course of breast cancer?
A0006	What are the consequences of breast cancer for the society?
A0023	How many people belong to the target population?
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A0003	What are the known risk factors for breast cancer?
A0024	How is breast cancer currently diagnosed according to published guidelines and in practice?
A0025	How is breast cancer currently managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of palbociclib on mortality?
D0005	How does palbociclib affect symptoms and findings (severity, frequency) of breast cancer?
D0006	How does palbociclib affect progression (or recurrence) of breast cancer?
D0011	What is the effect of palbociclib on patients' body functions?
D0012	What is the effect of palbociclib on generic health-related quality of life?
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Safety	
C0008	How safe is the palbociclib in relation to the comparator(s)?
C0002	Are there harms related to dosage or frequency of applying palbociclib?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of palbociclib?
A0021	What is the reimbursement status of palbociclib?

2 Drug description

Generic/Brand name/ATC code:

Palbociclib/Ibrance®/PD0332991

B0001: What is palbociclib?

first-in-class CDK4/6 inhibitor

Cell cycle progression is highly regulated from quiescence (G_0), pre-DNA synthesis (G_1), DNA synthesis (S), pre-division (G_2), to mitosis (M). As key cell cycle regulators, cyclin-dependent kinases 4 and 6 (CDK4/6) interact with cyclin D_1 to hyperphosphorylate retinoblastoma (Rb), causing the release of transcription factors that allow cell progression from G1 to S phase. Dysregulation of the cell cycle during cancer may occur through loss of Rb function, or amplification of cyclin D_1 or CDK. Palbociclib, a first-in-class, reversible, small molecule inhibitor of CDK4/6, blocks Rb phosphorylation and prevents cell cycle progression from G_1 to S phase [2].

125 mg/day for 3 weeks, 1 week off

Palbociclib is administered as a 125 mg oral capsule taken once daily for three weeks followed by one week off, comprising a 28-day cycle, repeated until disease progression. Fulvestrant is co-administered intramuscularly (IM) at a dose of 500 mg on days 1, 15, 29, and once every 28 days thereafter. Pre- and perimenopausal women are also treated with luteinizing hormone-releasing hormone (LHRH) agonists such as goserelin according to clinical practice [3].

monitor CBC, reduce/interrupt dose for safety/tolerability

Complete blood counts (CBC) are monitored prior to starting palbociclib, every two weeks for the first two cycles, and monthly thereafter. Dose interruption, reduction (to 100 mg or 75 mg), or delay in starting a treatment cycle is recommended for patients who develop grade 3 (absolute neutrophil count (ANC) 500 - < 1000/mm^3) or 4 neutropenia (ANC < 5000/mm^3), or grade ≥ 3 non-hematologic toxicity. Patients should avoid concomitant use of strong CYP3A inhibitors or have their dose reduced to 75 mg once daily. If a dose reduction below 75 mg/day is required treatment should be discontinued [3].

A0022: Who manufactures palbociclib?

Pfizer Inc.

3 Indication

A0007: What is the target population in this assessment?

HR-positive, HER2-negative advanced or MBC

Palbociclib is indicated as treatment for hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer (MBC) in combination with fulvestrant in women with disease progression during or following endocrine therapy (ET) [3].

Palbociclib (Ibrance®) in combination with fulvestrant for the treatment of hormone-receptor-positive, HER2-negative advanced or metastatic breast cancer

4 Current regulatory status

A0020: For which indications has palbociclib received marketing authorisation?

In February 2015, the US Food and Drug Administration (FDA) granted accelerated approval of palbociclib for the treatment of postmenopausal women with HR-positive, HER2-negative advanced breast cancer as first-line treatment in combination with letrozole. Initial approval was based on the results of a phase II study (PALOMA-1) and confirmed in a phase III study (PALOMA-2) [4].

FDA: licensed as 1st-line with letrozole in February 2015

In February 2016, the FDA expanded the licensing indication to include palbociclib in combination with fulvestrant for women with HR-positive, HER2-negative advanced or MBC with disease progression during or following ET. Expanded approval was based on the results of the phase III PALOMA-3 trial [5].

FDA: licensed as 2nd-line with fulvestrant in February 2016

Palbociclib has received marketing authorisation by the European Medicines Agency (EMA) in November 2016 for the treatment of HR-positive, HER2-negative locally advanced breast cancer (LABC) or MBC in combination with an aromatase inhibitor (AI), or in combination with fulvestrant in women who have received prior ET [6].

EMA: marketing authorisation for LABC/MBC in November 2016

5 Burden of disease

A0002: What is breast cancer?

Breast cancer commonly develops from an uncontrolled growth of epithelial cells lining the milk ducts and/or lobules caused by dysregulation of the cell cycle. In the early stages, atypical cells confined to the milk ducts are termed stage 0, ductal carcinoma in situ (DCIS). Stage I breast cancer is invasive, but is restricted to the area where the first abnormal cells arose. Most (70%–80% of) breast cancers are diagnosed as stage I (localized to one area) or stage II (early locally advanced), invasive ductal carcinoma (IDC) or invasive lobular carcinoma (ILC), where abnormal cells have spread beyond the ducts or glands into breast tissue.

HR-positive, HER2-negative is the most common type of breast cancer

Stage III, LABC includes tumours larger than 5 cm in diameter that involve the skin, underlying muscle, lymph nodes or inflammatory breast cancer (IBC). All primary invasive cancers are evaluated for HR status and HER2 expression. HR-positive cancers account for approximately 65% and 80% of breast cancers in pre- and postmenopausal women, respectively [7]. HER2 is overexpressed in approximately 15%–23% of patients [7]. HR-positive, HER2-negative is the most common type of breast cancer, accounting for approximately 70% of cases. Between 5% and 10% of patients are diagnosed with stage IV MBC that has spread beyond the breast and lymph nodes [7-

9]. MBC that can no longer be controlled is considered advanced or palliative [10].

A0004: What is the natural course of breast cancer?

metastasize to bone, liver, lungs, brain; 5 years survival < 25%

Breast cancer cells commonly travel through the lymphatic system and blood stream forming metastatic tumours in bone, liver, lungs and brain. Stage IV breast cancers that have spread to distant parts of the body have a poor prognosis with five-year survival rates of less than 25% [7].

A0006: What are the consequences of breast cancer for the society?

metastasize; leading cause of cancer death in women worldwide

Globally, breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death in women worldwide [9]. Approximately 30% of women diagnosed with early stage breast cancer develop advanced or MBC despite treatment [7]. Patients may progress or further metastasize, causing significant cancer specific morbidity and mortality. In Austria, breast cancer is the 19th leading cause of disability adjusted life years and accounts for approximately 28,000 (2.6% of total) years of life lost due to premature mortality [11].

A0023: How many people belong to the target population?

5,521 new cases of breast cancer in Austria in 2012, 1,548 deaths

In Austria, 5,521 new cases of breast cancer were diagnosed in 2012, with a corresponding incidence rate of 40.3 per 1,000,000 persons; 1.1 per 100,000 men and 76.1 per 100,000 women (based on the WHO-world population 2011). Accounting for 30% of all cancers, breast cancer is the most frequently diagnosed cancer among Austrian women and the leading cause of death due to cancer. Breast cancer attributed to 1,548 deaths with an overall mortality of 8.9 per 100,000 persons; 0.3 per 100,000 men and 16.0 per 100,000 women (based on the WHO-world population 2011) [12].

A0005: What are the symptoms and the burden of breast cancer?

main symptoms: breast lump, thickening, pain

Signs of breast cancer may include a hard, immovable, lump in the breast with irregular borders. Patients with LABC may experience dimpling or thickening of the skin, a change in shape or colour, nipple inversion or discharge, and pain in the breast or armpit. Patients with MBC may experience bone pain, fractures, headaches, seizures, swollen lymph nodes, shortness of breath or jaundice depending on the organs involved [10, 13].

A0003: What are the known risk factors for breast cancer?

main risk factors: increasing age, female gender, Caucasian race

Risk factors for developing breast cancer include increasing age, female gender, a personal or family history of breast cancer, Caucasian race, obesity, early menarche, nulliparity or older age at first birth, late menopause, hormone replacement therapy, increased breast density, alcohol consumption and cigarette smoking [10]. According to data from the Surveillance Epidemiology, and End Results (SEER) database, the probability of developing breast cancer in the United States between 2006 and 2008 was 2.3 (1 in 44 women) for women aged 50 to 59 years of age, 3.5 (1 in 29 women) for those

aged 60 to 69 years, and 6.7 (1 in 15 women) for women above the age of 70 years [9, 10].

A0024: How is breast cancer currently diagnosed according to published guidelines and in practice?

diagnostics: mammography, biopsy, HR status, bone, CT, PET scans

A mammogram of both breasts is performed to define tumour size and assess whether the contralateral breast is affected. Breast magnetic resonance imaging (MRI) or ultrasound may also be performed to estimate tumour size and distinguish a fluid-filled or a solid mass. During a biopsy, a sample of breast cells or tissue from the lump is examined to determine the presence of cancer cells, and HR or HER2 protein expression. HR status is an important factor in planning clinical management. Bone scans, blood tests, x-rays, CT and PET scans may be conducted to determine whether breast cancer has spread to bone, liver, lungs or brain [9, 14].

6 Current treatment

A0025: How is breast cancer currently managed according to published guidelines and in practice?

1st-line: ET involving tamoxifen with LHRH agonists; AIs +/- CDK inhibitor

Previously untreated, advanced and MBC that is HR-positive and HER2-negative is treated using ET and/or chemotherapy and/or surgery and/or radiation therapy and/or targeted therapy.

First-line ET involves:

- a third generation aromatase inhibitor (AI) (anastrozole, letrozole, or exemestane) for postmenopausal patients;
- tamoxifen and ovarian suppression with LHRH agonists or tamoxifen alone for premenopausal patients; and

2nd-line: fulvestrant or exemestane with everolimus

Patients who progress on ET may undergo second-line treatment involving:

- a non-cross-resistant AI, tamoxifen, the selective estrogen down-regulator (SERD) fulvestrant, fulvestrant plus an AI, an AI plus a CDK 4/6 inhibitor, any ET in combination with the rapamycin inhibitor everolimus [8, 15, 16].

advanced: continue treatment or undergo palliative care

If advanced or MBC can no longer be controlled, treatment to slow tumour growth or palliative care to manage cancer symptoms and side effects of therapies can be applied[10].

7 Evidence

278 citations; phase III RCT, PALOMA-3

A literature search was conducted on 25 October 2016 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms included “Palbociclib”, “PD-0332991”, “breast cancer”

and "breast neoplasms". The manufacturer was also contacted and submitted five studies, all of which were identified through the literature search. Manual searching yielded an FDA approval document [3], EMA initial authorisation [6], two clinical guidance documents [9, 15], two clinical study reports [17, 18], an economic guidance report [19], a press release [20], and statistical information [12].

Overall, 278 citations were identified; a multicentre, randomized, phase III trial (PALOMA-3) contributed to the evidence regarding the efficacy and safety of palbociclib in combination with fulvestrant for the treatment of HR-positive, HER2-negative MBC [21-25].

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

The methodological quality of the evidence was conducted to assess the risk of bias at the study level based on EUnetHTA internal validity for RCTs [26]. Evidence was assessed based on adequate generation of randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Details of study quality are reported in Table 5 of the appendix.

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

To evaluate the magnitude of clinically meaningful benefit that can be expected from a new anti-cancer treatment the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [27]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [28]. Details of the magnitude of clinically meaningful benefit scale are reported in Table 3.

7.1 Clinical efficacy and safety – Phase III studies

PALOMA-3: efficacy and safety of palbociclib + fulvestrant (n=521)

PALOMA-3, a global multicentre, randomised, double-blind, placebo-controlled, phase III study assessed the safety and efficacy of palbociclib in combination with fulvestrant as second-line treatment for HR-positive, HER2-negative advanced or MBC in women with disease progression during or following ET. Eligible patients were 18 years and older, with confirmed HR-positive, HER2-negative MBC, Eastern Co-operative Oncology Group (ECOG) performance status 0–1, bone disease or measurable disease defined by Response Evaluation Criteria In Solid Tumours version 1.1 (RECIST v1.1), with relapse or progression following previous ET. Patients that received one prior line of chemotherapy for advanced disease were also eligible for study. Pre- and perimenopausal women received LHRH agonist treatment with goserelin 4 weeks prior to randomisation. Patients previously treated with fulvestrant, everolimus or a CDK or PI3K/mTOR inhibitor; and those with extensive metastasis were excluded [21].

primary endpoint: investigator-assessed PFS; secondary endpoints: OS, ORR, DOR, PROs

Patients were stratified by sensitivity to ET, menopausal status, and presence of visceral metastasis. A centralised interactive system block randomised 521 women to receive palbociclib plus fulvestrant (n = 347) or placebo plus fulvestrant (n = 174) in a 2:1 ratio. Fulvestrant 500 mg was administered by intramuscular (IM) injection on days 1, 15, 29, and once every 28 days thereafter. Patients received 125 mg oral palbociclib or matching placebo once daily for 3 weeks, followed by a week off, comprising a 28-day cycle that repeated until disease progression or unacceptable toxicity. A dose modification strategy was adopted for patients who experienced investigational drug toxicity. The primary endpoint was investigator-assessed PFS

defined as the time from randomisation to radiological disease progression or death. Secondary endpoints included overall survival (OS), confirmed objective response rate (ORR), duration of response (DOR); patient-reported outcomes (PROs) and safety [23, 25]. The mutation statuses of PIK3CA, and the estrogen receptor gene ESR1 were assessed at baseline [21, 24].

trial stopped early due to significant efficacy results

Interim analysis at a cut-off of 195 PFS events on Dec 5, 2014 resulted in stopping the trial early in April 2015, because significant efficacy was reached having crossed the pre-specified Haybittle-Peto efficacy-stopping boundary ($\alpha = 0.00135$). Later statistical analyses at a cut-off of 259 PFS events on March 16, 2015 supported the results of the interim analysis. Median follow-up was 8.9 months (IQR 8.7–9.2); 191 (55% of) patients receiving palbociclib plus fulvestrant and 51 (29% of) placebo plus fulvestrant patients remained on treatment [21]. Approximately 128 (37% of 347) patients discontinued treatment due to disease progression in the palbociclib plus fulvestrant group compared to 107 (61% of 174) patients in the placebo plus fulvestrant group.

median age of 57 years, randomisation stratified by ET sensitivity, menopausal status, and visceral metastasis

Patients had a median age of 57 years, 74% were Caucasian, 80% were postmenopausal, and all had an ECOG PS of 0–1 and prior systemic therapy; 75% had received prior chemotherapy. Approximately 25% of patients had received no prior therapy in the metastatic setting, 60% had visceral metastases, and 23% had bone disease [3]. PIK3CA mutations were detected in 129 (33% of 395) of available samples and baseline demographics and clinical characteristics did not differ by PIK3CA status [3]. ESR1 mutations were found in 25% (91 of 360) of patients, of whom 29% (26 of 91) had mutations conferring acquired resistance to prior AI [24]. Detailed patient characteristics, including inclusion and exclusion criteria, are reported in Table 4 of the appendix.

7.1.1 Clinical efficacy

D0001: What is the expected beneficial effect of palbociclib on mortality?

OS: not mature; only 29% of 197 events had occurred by the time of final analysis of PFS

At the time of final analysis of PFS, OS data were not mature with only 29% of events. By the time of analysis, 57 deaths had occurred in the palbociclib plus fulvestrant group and 21 occurred in the placebo plus fulvestrant group, accounting for only 29% of the 197 events needed for an OS analysis [21]. The efficacy of palbociclib is reported in Table 1.

D0006: How does palbociclib affect progression (or recurrence) of advanced or MBC?

palbociclib extended median PFS from 4.6 months to 9.5 months

Median PFS was 9.5 months (95% CI 9.2–11.0) in the palbociclib plus fulvestrant group compared with 4.6 months (95% CI 3.5–5.6) in the placebo plus fulvestrant group (HR 0.46, 95% CI 0.36–0.59; two-sided $p < 0.0001$) in the intention to treat analysis [21]. Response to treatment was not significantly affected by the PIK3A status or the level of expression of HR [21]. Palbociclib plus fulvestrant significantly improved PFS compared to placebo plus fulvestrant in both patients with ESR1 mutations (HR 0.43, 95% CI 0.25–0.74; $p = 0.0021$) and those without (HR 0.48, 95% CI 0.35–0.70; $p < 0.001$) [24]. Palbociclib plus fulvestrant resulted in longer PFS than fulvestrant alone [21, 22].

D0005: How does palbociclib affect symptoms and findings (severity, frequency) of advanced and MBC?

significant improvement in ORR, and pain compared to placebo; DOR was 9.3 months

Of patients with measurable disease at baseline, 66 (24.6%, 95% CI 19.6-30.2) in the palbociclib plus fulvestrant group showed an objective response versus 15 (10.9%, 95% CI 6.2–17.3) in the placebo plus fulvestrant group (OR 2.69, 95% CI 1.43–5.26; two-sided p = 0.0012) [21]. Significantly greater improvement from baseline in pain was also observed (-3.3 [95% CI -5.1 – -1.5] versus 2.0 [95% CI -0.6–4.6; p = 0.0011]) [23]. Duration of response was 9.3 months in the palbociclib plus fulvestrant group compared with 7.6 months in the placebo plus fulvestrant group [3]. The median time to response was 112 days (IQR 58–160) for the palbociclib plus fulvestrant group and 57 days (52–106) for the placebo plus fulvestrant group [21]. The efficacy of palbociclib plus fulvestrant and the probability of disease progression after 6 months were not significantly associated with the level of HR expression [21].

D0011: What is the effect of palbociclib on patients' body functions?

mild/ moderate hepatic impairment: no effects on efficacy

Palbociclib undergoes hepatic metabolism by CYP3A and SULT2A1 enzymes. Mild or moderate hepatic or renal impairment did not affect the safety or efficacy of palbociclib according to a pharmacokinetic analysis involving 183 patients [3].

D0012: What is the effect of palbociclib on generic health-related quality of life?

difference on QoL scale: 66.1 vs. 63.0 in favour of palbociclib

delayed deterioration in QoL

Results of the global QoL scale using the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30) were in favour of palbociclib, with estimated QoL scores 66.1 (95% CI 64.5–67.7) versus 63.0 (95% CI 60.6–65.3; p = 0.0313) [23]. The overall change from baseline was -0.9 (95% CI -2.5–0.7) in the palbociclib plus fulvestrant group and -4.0 (95% CI -6.3–1.7) in the placebo plus fulvestrant group [23]. From the five functional scales of the EORTC QLQ-C30, only the emotional functioning scale differed, also favouring palbociclib [29]. Treatment with palbociclib plus fulvestrant significantly delayed deterioration in global QoL ($p < 0.025$) and pain ($p < 0.001$) compared to placebo and fulvestrant. Palbociclib plus fulvestrant allowed patients to maintain their QoL [23].

D0013: What is the effect of palbociclib on disease-specific quality of life?

delayed deterioration in pain

Results of the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Breast Cancer Module (EORTC QLQ-BR23) suggest favour towards placebo regarding being upset about the loss of one's hair. There was an improvement in the median time to deterioration in pain from 3.5 months (95% CI 2.5–5.4) in the placebo plus fulvestrant group to 7.2 months in the palbociclib plus fulvestrant group (95% CI 5.6–NE; HR 0.66, 95% CI 0.51–0.88).

Table 1: Efficacy results of the phase III PALOMA-3 phase trial [3, 21, 23]

Descriptive statistics and estimate variability (data cut-off of March 16, 2016)	**Treatment group**	**Palbociclib + fulvestrant**	**Placebo + fulvestrant**
	Number of subjects	n = 347	n = 174
	Median PFS, months	9.5 (95% CI 9.2–11.0)	4.6 (95% CI 3.5–5.6)
	Number of PFS events, n (%)	145 (41.8)	114 (65)
	OS	NR	NR
	ORR, n (%) of patients	66 (24.6%, 95% CI 19.6–30.2)	15 (10.9%, 95% CI 6.2–17.3)
	DOR, months [3]	9.3	7.6
	PROs[23, 29] Overall global QoL EORTC QLQ-C30 (pain) EORTC QLQ-C30[1] EORTC QLQ-BR23[2]	66.1 (95% CI 64.5–67.7) -3.3 (CI -5.1 – -1.5) -0.9 (95% CI -2.5–0.7) 3.5 (95% CI 2.5–5.4)	63.0 (95% CI 60.6–65.3) 2.0 (95% CI -0.6–4.6) -4.0 (95% CI -6.3–1.7) 7.2 (95% CI 5.6, NE)
Effect estimate per comparison	Comparison groups		Palbociclib + fulvestrant versus Placebo + fulvestrant
	Median PFS, months	HR	0.46
		95% CI	0.36–0.59
		Two-sided log-rank	p < 0.0001
	Number of PFS events	HR	0.46
		95% CI	0.36–0.59
		Two-sided log-rank	p < 0.0001
	OS	NR	NR
	ORR, n (%) of patients	OR	2.69
		95% CI	1.43–5.26
		Two-sided log-rank	p = 0.0012
	DOR	NR	NR
	PROs[23, 29] EORTC QLQ-BR23	HR	0.66
		95%	0.51–0.88
		NR	NR
Notes	NSD in PFS between patients with (n = 129) and without (n = 266) PIK3CA mutations. Median PFS was 5.8 months (95% CI 5.3–9.5) in patients with PIK3CA mutations and 9.2 months (95% CI 7.5–10.8) in patients without mutations (HR 1.26, 95% CI 0.94–1.68; one-sided log-rank p = 0.94). In patients with a PIK3CA mutation, median PFS was 9.5 months (95% CI 4.7–11.2) in palbociclib plus fulvestrant group and 3.6 months (95% CI 1.9–5.6) in the placebo plus fulvestrant group (HR 0.48, 95% CI 0.30–0.78; two-sided log-rank p = 0.002). NSD in the magnitude of benefit associated with palbociclib plus fulvestrant (two-sided $p_{intervention}$ = 0.83) or HR status (0.77). At the time of final analysis of PFS, OS data were not mature with 29% of events.		

Abbreviations: CI = confidence interval; DOR = duration of response; EORTC QLQ-C30 = European Organisation for Research and treatment of Cancer Quality-of-Life Questionnaire; EORTIC QLQ-BR23 = European Organisation for Research and treatment of Cancer Quality-of-Life Questionnaire Breast Cancer Module; HR = hazard ratio; OR: odds ratio; NE = not estimable; NR = not reported; NSD = no significant difference; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PROs = patient reported outcomes

[1] global QoL scale (EORTC QLQ-C30) → overall change from baseline

[2] median time to deterioration in pain (EORTC QLQ-BR23)

7.1.2 Safety

C0008: How safe is palbociclib in relation to the comparator(s)?

SAE: I 13 % vs. C 17%

Neutropenia: I 83% vs. C 4%
Neutropenia grade ≥3: I 66% vs. 1%

Leukopenia: I 53% vs C 5%

Serious adverse events (SAEs) occurred in 44 (13%) of 345 palbociclib plus fulvestrant recipients and 30 (17%) of 172 placebo plus fulvestrant recipients [21]. Neutropenia, of all grades, was substantially more frequent in the palbociclib plus fulvestrant group than in the placebo plus fulvestrant group (286 [83%] of 345 palbociclib recipients versus 7 [4%] of 172 placebo recipients) [3]. Grade 3 or 4 neutropenia was reported in 228 (66%) of 345 patients receiving palbociclib plus fulvestrant and 2 (1%) patients receiving placebo plus fulvestrant [3]. The median time to first episode of neutropenia was 15 days; the median duration of grade ≥3 neutropenia was 7 days [3, 25]. Palbociclib plus fulvestrant resulted in one death due to neutropenic sepsis [3].

most common AEs: neutropenia, leukopenia, infection, fatigue, nausea, anaemia, stomatitis, headache, diarrhoea, thrombocytopenia, constipation, vomiting, alopecia, rash, decreased appetite, pyrexia

Leukopenia, of all grades, was also significantly more common in the palbociclib plus fulvestrant group than in the placebo plus fulvestrant group (183 [53%] of 345 versus 9 [5%] of 172) [3]. Grade 3 or 4 leukopenia was reported in 108 (31%) of 345 palbociclib recipients versus 4 (2%) of patients receiving placebo [3]. Pulmonary embolism was reported at a higher rate in palbociclib plus fulvestrant- treated patients (1%) compared with no cases in those treated with placebo plus fulvestrant [3]. Anaemia was reported in 104 (30%) of palbociclib plus fulvestrant recipients versus 22 (13%) of patients receiving placebo [3].

The most common adverse events (AEs) occurring in ≥10% of palbociclib plus fulvestrant recipients were neutropenia, leukopenia, infections, fatigue, nausea, anaemia, stomatitis, headache, diarrhoea, thrombocytopenia, constipation, vomiting, alopecia, rash, decreased appetite, and pyrexia, Table 2 [3, 29].

C0002: Are there harms related to dosage or frequency of applying palbociclib?

54% of patients dose interruption

36% cycle delay
34% dose reduction

6% discontinued due to AE

Investigators reported that palbociclib plus fulvestrant was well tolerated; neutropenia was effectively managed by dose modification without loss of efficacy [25]. In the palbociclib plus fulvestrant group, 187 (54%) patients experienced a dose interrruption due to an AE, 123 (36%) patients had a cycle delay, and 117 (34%) patients had at least one dose reduction during the study compared to 10 (6%), three (2%), and three (2%), respectively, in the placebo plus fulvestrant group [21]. AEs accounted for permanent discontinued treatment in 19 (6% of 345) palbociclib plus fulvestrant recipients and six (3% of 172) placebo plus fulvestrant recipients [3]. AEs causing discontinuation in palbociclib plus fulvestrant recipients included fatigue (0.6%), infections (0.6%), and thrombocytopenia (0.6%).

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of palbociclib?

pregnant or lactating women
concomitant CYP3A inhibitors or inducers

Palbociclib is not recommended for use in pregnant or lactating women due to potential risk of miscarriage, birth defects and AEs in infants. Women are advised to use effective contraception during treatment and at least 3 weeks following the last dose. Concomitant use of strong CYP3A inhibitors or inducers should be avoided [3].

Table 2: Most frequent adverse events [3]

Adverse Event (according to CTCAE C version4.0)	**Palbociclib + fulvestrant** (n = 345)			**Placebo + fulvestrant** (n = 172)		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Infections	162 (47)	10 (3)	4 (1)	53 (31)	5 (3)	0 (0%)
Blood and lymph disorders						
Febrile neutropenia	4 (1)	4 (1)	0 (0)	2 (1)	0 (0)	2 (1)
Neutropenia	286 (83)	190 (55)	38 (11)	7 (4)	2 (1)	0 (0)
Leukopenia	183 (53)	104 (30)	4 (1)	9 (5)	2 (1)	2 (1)
Anaemia	104 (30)	10 (3)	0 (0)	22 (13)	7 (2)	0 (0)
Thrombocytopenia	79 (23)	7 (2)	4 (1)	0 (0)	0 (0)	0 (0)
Decreased appetite	55 (16)	4 (1)	0 (0)	14 (8)	2 (1)	0 (0)
Headache	90 (26)	4 (1)	0 (0)	34 (20)	0 (0)	0 (0)
Gastrointestinal disorders						
Nausea	117 (34)	0 (0)	0 (0)	48 (28)	2 (1)	0 (0)
Stomatitis	97 (28)	4 (1)	0 (0)	22 (13)	0 (0)	0 (0)
Diarrhoea	83 (24)	0 (0)	0 (0)	33 (19)	2 (1)	0 (0)
Constipation	69 (20)	0 (0)	0 (0)	28 (16)	0 (0)	0 (0)
Vomiting	66 (19)	4 (1)	0 (0)	26 (15)	2 (1)	0 (0)
Skin disorders						
Alopecia	62 (18)	N/A	N/A	10 (6)	N/A	N/A
Rash	59 (17)	4 (1)	0 (0)	10 (6)	0 (0)	0 (0)
General disorders						
Fatigue	141 (41)	7 (2)	0 (0)	50 (29)	2 (1)	0 (0)
Asthenia	28 (8)	0 (0)	0 (0)	9 (5)	2 (1)	0 (0)
Pyrexia	49 (13)	1 (<1)	0 (0)	9 (5)	0 (0)	0 (0)
Laboratory abnormalities						
WBC decreased	342 (99)	155 (45)	4 (1)	45 (26)	0 (0)	2 (1)
Neutrophils decreased	331 (96)	193 (56)	38 (11)	24 (14)	0 (0)	2 (1)
Anaemia	269 (78)	10 (3)	0 (0)	69 (40)	7 (2)	0 (0)
Platelets decreased	214 (62)	7 (2)	4 (1)	17 (10)	0 (0)	0 (0)

Abbreviations: CTCAE = common terminology criteria for adverse events

7.2 Clinical effectiveness and safety – further studies

PALOMA-1: Phase II palbociclib + letrozole

The US FDA granted accelerated approval of palbociclib in combination with letrozole as first-line treatment for postmenopausal women with HR-positive, HER2-negative MBC based on results of the phase II PALOMA-1 trial (TRIO-18; Study 1003; A5481003; and NCT00721409) [30]. Patients were randomised to receive letrozole alone or in combination with palbociclib 125 mg daily for three weeks followed by one week off. Palbociclib plus letrozole increased median PFS from 10.2 months to 20.2 months compared to letrozole alone (HR 0.488; 95% CI 0.319–0.748; one-sided p = 0.0004). Palbociclib increased the median DOR from 7.6 months to 13.8 months.

increased median PFS 10.2 months to 20.2 months compared to letrozole-alone

dose reductions: 36% of patients discontinuation: 8%

Dose reduction due to an AE occurred in 36% of palbociclib plus letrozole recipients, while no reductions were observed in letrozole-treated patients. Approximately 8% of palbociclib plus letrozole recipients permanently dis-

continued treatment due to neutropenia, asthenia and fatigue. The most common AEs occurring in ≥ 10% of patients, included neutropenia, leukopenia, fatigue, anaemia, infections, nausea, stomatitis, alopecia, diarrhoea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. SAEs reported in palbociclib plus letrozole treated patients included pulmonary embolism (3 of 83, 4%) and diarrhoea (2 of 83, 2%) [3]. The study was limited in that it was of open-label design, had insufficient power to detect OS, the endpoint was investigator assessed with lack of central radiology review, and modifications were made to the statistical analysis that could increase type 1 error [2].

palbociclib monotherapy as 3rd line for Rb-positive MBC: benefit in 19%

The safety and efficacy of palbociclib plus letrozole as first-line treatment for HR-positive, HER-2-negative advanced breast cancer was confirmed in a multicentre, double-blind, phase III study, PALOMA-2 [4] involving 666 patients. Postmenopausal patients were randomly assigned to receive 125 mg of palbociclib per day, or matching placebo for three weeks followed by one week off. All patients received 2.5 mg of letrozole per day. Palbociclib plus letrozole increased the median PFS from 14.5 months to 24.8 months (HR 0.58; 95% CI, 0.46–0.72; $p < 0.001$). The most common grade 3 or 4 AEs were neutropenia, leukopenia, anaemia and fatigue. AEs resulting in discontinuation of treatment occurred in 43 (9.7%) palbociclib plus letrozole patients and in 13 (5.9%) of placebo plus letrozole recipients. The study was limited due to immature OS data at the time of analysis. An OS analysis will be conducted when a total number of 390 death have occurred per protocol [4].

8 Estimated costs

A0021: What is the reimbursement status of the technology?

€ 4,582.55 per 28-day cycle

Palbociclib is available as 75, 100, and 125 mg capsules. At the recommended dose of 125 mg once daily for three weeks, followed by one week off, palbociclib costs approximately € 4,582.55 per 28-day cycle [31]. Additional costs will incur due to the combination of palbociclib with fulvestrant.

9 Ongoing research

5 phase III studies are ongoing, investigating palbociclib in MBC patients

In November 2016, a search in databases http://clinicaltrials.gov/ and https://www.clinicaltrialsregister.eu/ctr-search/ was conducted. The following ongoing phase III trials are investigating palbociclib in HR-positive MBC:

- **NCT02028507:** Phase III study of palbociclib (PD-0332991) in combination with ET (exemestane or fulvestrant) versus chemotherapy (capecitabine) in HR- positive, HER2-negative MBC patients with resistance to non-steroidal AIs. Estimated study completion date is July 2020.

Palbociclib (Ibrance®) in combination with fulvestrant for the treatment of hormone-receptor-positive, HER2-negative advanced or metastatic breast cancer

- **NCT02297438:** A multicentre, randomized, double-blind phase III study Of palbociclib (oral Cdk 4/6 inhibitor) plus letrozole versus placebo plus letrozole for the treatment of previously untreated Asian postmenopausal women with HR-positive, HER2-negative advanced breast cancer. Estimated study completion date is April 2018.
- **NCT02513394:** Palbociclib collaborative adjuvant study: a randomized phase III trial of palbociclib with standard adjuvant ET Versus Standard adjuvant ET alone for HR-positive, HER2-negative early breast cancer. Estimated study completion date is September 2025.
- **NCT01864746:** Phase III study evaluating palbociclib (PD-0332991), a cyclin-dependent kinase (CDK) 4/6 inhibitor in patients with HR-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy "PENELOPE-B". Estimated study completion date is November 2023.
- **NCT02600923:** Phase III, open label study of palbociclib in combination with letrozole as treatment for postmenopausal women with HR-positive, HER2-negative advanced breast cancer for whom letrozole is deemed appropriate. Estimated study completion date is October 2018.

Various phase I and II trials are currently ongoing that are investigating palbociclib in different treatment regimens and combinations in HR-positive MBC (NCT02592746, NCT02668666, NCT02599714, NCT02448420, NCT02605486, NCT02491983, NCT02592083, NCT02549430).

various ongoing phase I and II trials for the treatment of HR-positive MBC

10 Discussion

In February 2015, the US FDA issued a first-in-class, accelerated approval for the CDK4/6 inhibitor palbociclib, plus letrozole, as first-line treatment for postmenopausal women with HR-positive, HER2-negative advanced breast cancer. Initial approval was based on the phase II PALOMA-1 trial demonstrating palbociclib plus letrozole increased median PFS by 10 months compared to letrozole alone. The safety and efficacy was confirmed in a phase III trial (PALOMA-2) [4]. In February 2016, licensing was expanded to include palbociclib plus fulvestrant, for women with HR-positive, HER2-negative advanced or MBC with disease progression during or following ET. Expanded approval was based the phase III PALOMA-3 trial showing palbociclib plus fulvestrant increased median PFS by 4.9 months compared to palbociclib plus placebo [3, 29]. In November 2016, palbociclib was approved by the EMA for treatment of HR-positive, HER2-negative advanced or MBC in combination with an aromatase inhibitor (AI) or with fulvestrant in women who progress during or following ET [6].

marketing authorisation in the US since February 2015

indication approved by the FDA in 2016

approved by the EMA in November 2016

PALOMA-3: palbociclib increased median PFS +4.9 months compared to control

data based on interim-analysis

OS data incomplete

OS data were not mature. According to protocols, 197 and 390 events would be needed for an OS analysis in PALOMA-3 and PALOMA-2, respectively [4, 21]. Palbociclib plus fulvestrant recipients showed an improvement in objective response, response duration, global QOL and time to deterioration in pain compared to placebo recipients. Uncertainty exists regarding whether the pre-specified definition for deterioration in pain (≥ 10 point change) would be considered clinically meaningful. Evidence suggests that while a statistically significant change may be observed using the EORTC QLQ-C30, changes of 23.5 units and 7.2 units, are required to gain clinically important differences in pain and function, respectively [32]. By administering the questionnaires querying symptoms over the off-treatment week, the impact of the side effects of palbociclib combination therapy on QoL may be attenuated. Timing of the questionnaire is critical to assessing treatment-related outcomes. The PROs data without a prospectively specified statistical analysis plan were considered exploratory and descriptive in this study [29].

most common AEs: neutropenia, leukopenia, infections, fatigue, nausea and anaemia

The most common AEs occurring in ≥10% of palbociclib plus fulvestrant-treated patients included neutropenia, leukopenia, infections, fatigue, nausea, and anaemia. Grade 3 or 4 neutropenia and leukopenia were reported in 66% and 31% of palbociclib plus fulvestrant recipients. While neutropenia was managed by dose modification, one death resulted from neutropenic sepsis. In the palbociclib combination therapy group, 54% of patients required a dose interruption due to an AE, 36% had a cycle delay, 34% had a dose reduction, and 6% discontinued therapy due to fatigue, infections and thrombocytopenia.

palbociclib consistently punctuated by dose interruption, reduction, cycle delay or discontinuation due to AEs

While investigators suggest that primary neutropenia can be effectively managed by dose modification without affecting efficacy, existing studies suggest treatment with palbociclib is consistently punctuated by dose interruption, reduction, cycle delay or discontinuation due to AEs [3, 21]. Complete blood counts are monitored at baseline and every two weeks during the first two cycles to identify when a dose reduction may be needed to reduce the effects of drug toxicity. Long-term data regarding toxicity and compliance, correlated with clinically meaningful measures of QoL, will better inform decision makers regarding the tolerability and patient acceptability of palbociclib [2].

role in treatment regimens unclear

Selective CDK4/6 inhibitors ribociclib and abemaciclib are also currently under development for the treatment of breast cancer [33]. Currently, palbociclib-based therapies are being studied as first- and second-line treatments for advanced breast cancer, as well as adjuvant and neoadjuvant therapy for early-stage breast cancer [34]. Palbociclib plus fulvestrant may be used following failure of prior ET and/or one line of chemotherapy for advanced disease. Physician and patient preference contribute to palbociclib's place in treatment as there are no head-to-head comparisons of first-line versus subsequent-line use and OS data are lacking to support PFS as a relevant endpoint [2].

lack of comparison trials

€ 4,582.55 per 28-day cycle

Efficacy, cost, AEs, and patient acceptance are important factors for decisions regarding clinical management and reimbursement. However, there is no evidence regarding the comparative OS advantage of palbociclib combination therapy with letrozole or fulvestrant or an AI alone, fulvestrant alone or in combination with an AI, or everolimus plus exemestane at this time [2]. Palbociclib costs approximately € 4,582.55 per 28-day cycle [31].

Palbociclib (Ibrance®) in combination with fulvestrant for the treatment of hormone-receptor-positive, HER2-negative advanced or metastatic breast cancer

Palbociclib is a first-in-class CDK4/6 inhibitor for use in combination with fulvestrant as treatment for HR-positive, HER2-negative advanced or MBC with disease progression during or following ET [3]. While palbociclib increased median PFS by 4.9 months, this endpoint is not currently supported by OS data or clinically important differences in QoL. While Rb protein is the only reliable indicator for palbociclib activity until now, one may need to find further indicators and biomarkers to assess the efficacy of palbociclib for future use [34].

first-in-class CDK4/6 inhibitor

improved PFS, but no OS data available

additional costs and toxicity

Table 3: Benefit assessment based on ESMO-MCBS[3] [27] and adapted benefit assessment based on ESMO-MCBS[3] [28]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
							MG (months)	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
adapted ESMO-MCBS	Palbociclib	locally advanced or metastatic breast cancer	Not curative	PFS	2b	≤ 6 m	+4.9	0.46 (0.36–0.59)	HR ≤ 0.65 AND PFS gain ≥ 1.5 m	3	+51% grade ≥3 AEs (-1)[4]	ND	-1	**2**
ESMO-MCBS	Palbociclib	locally advanced or metastatic breast cancer	Not curative	PFS	2b	≤ 6 m	+4.9	0.46 (0.36–0.59)	HR ≤ 0.65 AND PFS gain ≥ 1.5 m	3	-	ND	-1 (AJ: d)[5]	**2**

Abbrevations: AJ = Adjustments, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, ND = no difference, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulted by the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut off values and outcomes that lead to an up- or downgrading seem to be arbitrary. Additionally, they are independent of the primary outcome and therefore a reason for confounding. Hence, we report the adjustments separately.

[3] European Society for Medical Oncology- Magnitude of Clinical Benefit Scale

[4] 1 level downgrade, because >10% grade ≥3 adverse events.

[5] 1 level downgrade, because the drug ONLY leads to improved PFS and QOL assessment does not demonstrate improved QoL

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12 Appendix

Table 4: Characteristics of the phase III PALOMA-3 trial

Title: Palbociclib (PD-0332991) combined with fulvestrant in HR-positive HER2-negative MBC after endocrine failure (PALOMA-3) [3, 17, 18, 21]			
Study identifier	NCT01942135, EudraCT 2013-002580-26		
Design	PALOMA-3, an international (17 countries), MC (144 centres), DB phase III RCT designed to demonstrate the superiority and safety of palbociclib in combination with fulvestrant (Faslodex®) over fulvestrant alone in prolonging PFS in women with HR-positive, HER2-negative MBC with disease progression following ET. Pre-/perimenopausal women received LHRH agonist therapy with goserlin (Zoladex® or generic).		
	Duration of main phase:		Enrolment: Oct 2013 to Aug 2014; interim analysis cut-off of Dec 2014; IDMC stopped study early in April 2015 after 195 PFS events because efficacy was reached having crossed pre-specified Haybittle-Peto efficacy-stopping boundary (α = 0.00135)
	Duration of Run-in phase:		Pre/perimenopausal women commenced LHRH agonist 4 weeks before randomisation
	Duration of Extension phase:		Latter statistical analyses at cut-off of 259 PFS events March 16, Median follow-up was 8.9 months.
Hypothesis	Exploratory (statistical analyses are after predefined stopping point): study designed to assess efficacy and safety of palbociclib + fulvestrant versus fulvestrant alone. Assuming a 6 month median PFS for control, 238 events were needed in the treatment groups for the study to have 90% power to detect clinically meaningful improvement in median PFS from 6.0 to 9.38 months [HR: 0.64, one-sided significance α=0.025].		
Funding	Sponsored by Pfizer in collaboration with AstraZeneca		
Treatment groups	Palbociclib + fulvestrant (n=347)		Palbociclib 125 mg/day orally for 3 weeks followed by 1 week off; repeated until disease progression; dose modification allowed in patients experiencing toxicity. Fulvestrant 500 mg intramuscularly on days 1, 15, 29, and once monthly thereafter.
	Placebo + fulvestrant (n=174)		Placebo orally for 3 weeks followed by 1 week off; repeated until disease progression. Fulvestrant 500 mg intramuscularly on days 1, 15, 29, and once monthly thereafter.
Endpoints and definitions	Progression-free survival	PFS	Time from date of randomisation to radiological disease progression according to RECIST v1.1 assessed up to 12 months by the investigator.
	Overall survival	OS	Time from date of randomisation to date of death by any cause assessed up to 36 months.
	Objective response rate	ORR	OR is defined as overall CR or PR according to RECIST v1.1. Proportion of participants with CR or PR relative to all randomised participants and randomised participants with measurable disease at baseline, assessed up to 12 months.
	Duration of response	DOR	Time from OR (CR or PR) to disease progression or death due to any cause.
	Patient reported outcome measures	PROs	PROs were assessed on Day 1 of cycles 1-4 and every other subsequent cycle starting with cycle 6 using EORTC QLQ-C30, and its breast cancer module EORTC QLQ BR23 where higher scores (range 1-100) may indicate better functioning and QoL or worse symptom severity.
Database lock	Last verified: July 2016		
Results and Analysis			

<table>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis
Interim analysis after 195 PFS events Dec 5, 2014 resulted in stopping trial early in April 2015; reached pre-specified Haybittle-Peto efficacy-stopping boundary (α=0.00135).
Latter statistical analyses after 259 PFS events March 16, 2015 supported interim results.
Efficacy analyses were intent to treat for all data up to data cut-off of March 16, 2015.
Safety population includes patients who received at least one does of study drug. No analyses were done in the pre-protocol population, Patients whose treatment deviated from protocol were not excluded.
For PROs, repeated measures mixed-effects analyses were performed to compare on-treatment overall scores and changes from baseline between groups while controlling for baseline. Between group, comparisons of time to deterioration in global QoL and pain were made using an un-stratified log-rank test and Cox proportional hazards model.</td></tr>
<tr><td rowspan="3">Analysis population</td><td>Inclusion</td><td colspan="2">❁ Women > 18 years, of any menopausal status, with non-curable locally advanced or MBC
❁ Confirmed HR-positive, HER2-negative
❁ Progressed within 12 months of prior adjuvant or within 1 month from prior advanced/metastatic ET
❁ On LHRH agonist at least 28 days, willing to switch to goserlin (Zoladex®) at randomisation
❁ Measurable disease defined by RECIST v1.1, or bone-only disease with ECOG PS0-1
❁ Adequate organ and marrow function, resolved of prior therapy
❁ Patient agrees to provide metastatic tumour tissue at baseline</td></tr>
<tr><td>Exclusion</td><td colspan="2">❁ Prior treatment with fulvestrant, everolimus, or CDK or PI3K-mTOR inhibitor
❁ Extensive advanced/metastatic, symptomatic visceral disease, or uncontrolled or symptomatic CNS metastases
❁ Major surgery or anti-cancer therapy within 2 weeks of randomisation
❁ Prior stem cell or bone marrow transplant
❁ Use of potent CYP3A4 inhibitors or inducers</td></tr>
<tr><td colspan="3"><table>
<tr><th>Characteristics</th><th>Palbociclib + fulvestrant (n=347)</th><th>Placebo + fulvestrant (n=174)</th></tr>
<tr><td>Median age (range), years</td><td>57 (30–88)</td><td>56 (29–80)</td></tr>
<tr><td>Race, n (%)
White
Asian
Black and others</td><td>
252 (73)
74 (21)
21 (6)</td><td>
133 (76)
31 (18)
10 (6)</td></tr>
<tr><td>ECOG status, n (%)
0
1</td><td>
206 (59)
141 (41)</td><td>
116 (67)
58 (33)</td></tr>
<tr><td>Menopausal status, n (%)
Premenopausal
Postmenopausal</td><td>
72 (21)
275 (79)</td><td>
36 (21)
138 (79)</td></tr>
<tr><td>Non-measurable disease, n (%)
Bone
Others</td><td>
75 (22)
4 (1)</td><td>
36 (21)
0 (0)</td></tr>
<tr><td>Measurable disease, n (%)
Any measurable disease
Visceral disease
Lung involvement
Liver involvement
Peritoneal involvement
Brain or pleural involvement</td><td>
268 (77)
206 (59)
100 (29)
127 (37)
2 (1)
4 (1)</td><td>
138 (79)
105 (60)
45 (26)
81 (47)
1 (1)
2 (1)</td></tr>
<tr><td>Number of previous lines of ET, n (%)
1
2
≥3</td><td>
160 (46)
140 (40)
47 (14)</td><td>
91 (52)
61 (35)
22 (13)</td></tr>
<tr><td>Purpose of recent therapy, n (%)
Adjuvant therapy
Treatment of advanced or MBC</td><td>
74 (21)
273 (79)</td><td>
40 (23)
133 (76)</td></tr>
<tr><td>Disease-free interval, n (%)
Data available
> 24 months
12–24 months
< 12 months</td><td>
233 (67)
192 (82)
30 (13)
11 (5)</td><td>
123 (71)
101 (82)
19 (15)
3 (2)</td></tr>
</table></td></tr>
</table>

	Previous ET, n (%) Sensitive to previous ET AI Tamoxifen AI and tamoxifen	 274 (79) 137 (39) 51 (15) 159 (46)	 136 (78) 70 (40) 23 (13) 81 (47)
	Previous chemotherapy, n (%) Neoadjuvant or adjuvant Treatment of metastatic	 139 (40) 113 (33)	 74 (43) 64 (37)
	Estrogen or progesterone-receptor status, n (%) Estrogen and progesterone-receptor positive ≥ median of distribution < median of distribution Estrogen and progesterone-receptor positive ≥ median of distribution < median of distribution	 81 (23) 71 (20) 179 (52) 165 (48)	 40 (23) 29 (17) 100 (57) 90 (52)
	Central lab median H-score (IQR); mean (SD) Estrogen receptor Progesterone receptor	 110 (40–160); 107 (74) 10 (0–100); 53 (68)	 114 (23–150); 99 (72) 20 (0–100); 51 (62)

Abbreviations: AI: aromatase inhibitor; CR = complete response; DB = double blind; EORTC QLQ BR23 = European Organization for Research and Treatment of Cancer Breast Cancer Module; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D = EuroQol-5D; ET = endocrine therapy; HER2 = human epidermal growth factor receptor 2; HR = hormone receptor; IDMC: independent data monitoring committee; LHRH = luteinizing hormone releasing hormone; MBC = metastatic breast cancer; MC = multicentre; OR = objective response ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; QoL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumours; RCT = randomised controlled trial

Table 5: risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomized controlled trials) [26]

Criteria for judging risk of bias		risk of bias
Adequate generation of randomisation sequence: 2:1 block size of 6, via centralised interactive web-based and voice-based randomisation system		yes
Adequate allocation concealment: via centralised interactive web-based and voice-based randomisation system		yes
Blinding	**Patient:** masked to treatment group assignment, matching placebo	yes
	Treating Physician: masked to treatment group assignment	yes
	Outcome assessment: masked to treatment group assignment until IDMC recommended stopping at pre-planned interim analysis	yes
Selective outcome reporting unlikely: outcomes reported as specified in protocol		yes
No other aspects which increase the risk of bias: consistency in reporting, planned interim analyses that led to premature study termination; industry funded, study database held by industry who designed, conducted, administered treatment, collected and analysed data		no (low)
Risk of bias – study level		low

Abbreviations: IDMC = independent data monitoring committee