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Abemaciclib (Verzenio®) in combination with a nonsteroidal aromatase inhibitor (NSAI) as initial therapy for advanced breast cancer (ABC)

Ludwig Boltzmann Institut
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Ludwig Boltzmann Institut
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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 A working version (unpublished) of V3.0 of the Model was used.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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Abstract

Introduction

As key cell cycle regulators, cyclin-dependent kinases 4 and 6 (CDK4/6) interact with cyclin D to hyperphosphorylate retinoblastoma (Rb), releasing transcription factors that allow cell proliferation. During oestrogen receptor (ER)-positive luminal breast cancer, dysregulation of the cell cycle occurs through loss of Rb function, or amplification of cyclin D1 or CDK. Abemaciclib, the third small molecule CDK4/6 inhibitor to be developed, blocks phosphorylation and prevents cell cycle progression. By targeting the ER and cyclin D-CDK4/6 pathways in combination, it is thought that this may lead to extensive inhibition of tumour growth and prevent endocrine therapy (ET) resistance.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer. Quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomized controlled trials. Furthermore, the magnitude of clinically meaningful benefit that can be expected from abemaciclib was evaluated based on, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology.

Results of the MONARCH 3 trial

In the phase III, MONARCH 3 study, 493 postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced breast cancer (ABC), without prior systemic treatment for advanced disease, were randomised 2:1 to abemaciclib or placebo plus a non-steroidal aromatase inhibitor until disease progression or unacceptable toxicity. At interim analysis, while overall survival (OS) data were not mature, there were 32 (9.8%) deaths in the abemaciclib group and 17 (10.3%) in the placebo group. At a median follow-up of 17.8 months, median progression-free survival (PFS) was 14.7 months in the placebo group but had not yet been reached in the abemaciclib group. While a consistent PFS benefit was observed across subgroups, patients with indicators of poor prognosis, such as short treatment-free interval or liver metastases, derived greater benefit from abemaciclib than those with longer treatment-free intervals or bone-only disease. Abemaciclib also increased the overall response rate (ORR) by 13.7% and the clinical benefit rate by 6.5%. Grade ≥3 adverse events were more common in abemaciclib recipients compared to placebo (55.0% versus 21.7%); notably neutropenia (21.1%), diarrhoea (9.5%), leukopenia (7.6%), increased alanine aminotransferase (6.1%), and anaemia (5.8%).

Conclusion

Overall, abemaciclib with endocrine therapy substantially reduces the risk of disease progression and increases ORR versus ET alone as initial therapy for HR-positive, HER2-negative ABC in postmenopausal women. OS and quality of life data are needed to confirm patients achieve a clinically relevant benefit over time in the context of increasing toxicity. Biomarker trials that track cellular proliferation and evaluate Rb protein and ER activity may help to identify which patients benefit most from adding abemaciclib as initial treatment. As there are no comparative trials, differences in the safety profiles of CDK4/6 inhibitors may assist physicians in selecting the most appropriate CDK4/6 inhibitor to meet individual patient needs.

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1 Research questions

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.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is abemaciclib?
A0022	Who manufactures abemaciclib?
A0007	What is the target population in this assessment?
A0020	For which indications has abemaciclib 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 cancerfor the society?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of breast cancer?
A0003	What are the known risk factors for breast cancer?
A0024	How is breast cancer currently diagnosed according to published guidelines and in practice?
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Clinical effectiveness	
D0001	What is the expected beneficial effect of abemaciclib on mortality?
D0005	How does abemaciclib affect symptoms and findings (severity, frequency) of breast cancer?
D0006	How does abemaciclib affect progression (or recurrence) of breast cancer?
D0011	What is the effect of abemaciclib on patients' body functions?
D0012	What is the effect of abemaciclib on generic health-related quality of life?
D0013	What is the effect of abemaciclib on disease-specific quality of life?
Safety	
C0008	How safe is abemaciclib in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying abemaciclib?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of abemaciclib?
A0021	What is the reimbursement status of abemaciclib?

2 Drug description

Generic/Brand name/ATC code:

Abemaciclib/Verzinio™/LY2835219

B0001: What is abemaciclib?

CDK4/6 inhibitor

As key cell cycle regulators, cyclin-dependent kinases 4 and 6 (CDK4/6) interact with cyclin D1 to hyperphosphorylate retinoblastoma (Rb), causing the release of transcription factors that allow cell proliferation. Dysregulation of the cell cycle during cancer may occur through loss of Rb function, or amplification of cyclin D1 or CDK. Abemaciclib, the third small molecule CDK4/6 inhibitor to be developed, blocks phosphorylation and prevents cell cycle progression.

150 mg twice/day with a NSAI

Abemaciclib is administered as a 150 mg oral tablet taken twice daily with a nonsteroidal aromatase inhibitor (NSAI), either 1 mg of anastrozole or 2.5 mg of letrozole taken once daily. Treatment is continued in 28-day cycles until disease progression or unacceptable toxicity [2].

monitor CBC and LFT reduce/interrupt dose/discontinue for safety/tolerability

Patients require complete blood counts (CBCs) and liver function tests (LFTs) prior to starting abemaciclib and periodic monitoring during treatment due to the risks for neutropenia, hepatotoxicity and venous thromboembolism. Dose interruption, reduction (to 100 mg or 50 mg), or discontinuation may be required in patients that develop diarrhoea, hepatotoxicity, hematologic or other toxicities, or intolerance due to adverse events (AEs). Patients should avoid concomitant use of ketoconazole or strong CYP3A inducers, and have their dose reduced when using CYP3A inhibitors [3].

A0022: Who manufactures abemaciclib?

Eli Lilly and Company

3 Indication

A0007: What is the target population in this assessment?

postmenopausal women with HR-positive, HER2-negative ABC

Abemaciclib is indicated, in combination with a NSAI, as initial therapy for postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC) [2].

4 Current regulatory status

A0020: For which indications has abemaciclib received marketing authorisation?

In September 2017, the US Food and Drug Administration (FDA) granted approval of abemaciclib as monotherapy for patients with HR-positive, HER2-negative ABC with disease progression following endocrine therapy (ET) and chemotherapy for metastatic disease; and in combination with fulvestrant for patients with HR-positive, HER2-negative ABC with disease progression following ET [3, 4]. Approval was based on the results of the phase II MONARCH 1 and phase III MONARCH 2 trials [4-6].

FDA: licensed mono/+ fulvestrant for HR-positive, HER2-negative A/MBC in September 2017

In October 2017, the FDA granted a priority review for abemaciclib in combination with an aromatase inhibitor (AI) as initial endocrine-based therapy for the treatment of women with HR-positive, HER2-negative advanced or metastatic breast cancer (A/MBC) [4, 7]. The new drug application (NDA) was based on interim results of the phase III MONARCH 3 trial [2].

NDA: + AI as initial therapy for HR-positive, HER2-negative A/MBC in October 2017

Regulatory submissions for abemaciclib were completed for Europe and Japan in the fall of 2017 [4]. Abemaciclib does not currently have marketing authorisation in Europe for any indication. However, in February 2018, a Marketing Authorisation Application (MAA) for abemaciclib was submitted to the European Medicines Agency (EMA) for the treatment of patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer (MBC) [8].

EMA: MMA for HR-positive, HER2-negative A/MBC in February 2018

5 Burden of disease

A0002: What is breast cancer?

Breast cancer is the most common cancer in women worldwide and the leading cause of cancer death in women. As a heterogeneous malignancy, breast cancer is molecularly subtyped as luminal A, luminal B, HER2-enriched, basal-like, or claudin-low [9]. Luminal HR-positive, HER2-negative breast cancer, characterized by oestrogen receptor (ER) expression in the absence of HER2 amplification, accounts for approximately 70% of all breast cancers. ETs target this subtype effectively reducing the relative risk of recurrence by approximately 40% [10]. However, some patients inevitably develop resistance to ET.

HR-positive, HER2-negative breast cancer accounts for 70% of all breast cancers

CDK4/6 are key drivers of cell proliferation in ER-positive luminal breast cancer; and cyclin D1 is frequently overexpressed while Rb function may be reduced. Approximately 50% of all breast cancers overexpress cyclin D1 and the coding region for cyclin D1 (CCDND1) is amplified in 15–20% of cases [11]. Low Rb expression occurs in 20% of cases [12]

CDK4/6 drive cell proliferation: cyclin D1 overexpression in 50% of all breast cancers; Rb function reduced in 20% of cases

A0004: What is the natural course of breast cancer?

staged I–IV by invasiveness

Breast cancer typically arises when epithelial cells lining the milk ducts and/or lobules undergo aberrant cell growth due to 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 the breast tissue.

metastasize to bone, liver, brain, lymph nodes
5 year survival <25%

Stage III, locally advanced breast cancer includes tumours larger than five centimetres in diameter that involve the skin, underlying muscle, lymph nodes or inflammatory breast cancer (IBC). Breast cancer cells commonly travel through the lymphatic system and blood stream forming metastatic tumours in bone, liver, lungs and brain. Between 5% and 10% of patients are diagnosed with stage IV MBC that has spread to distant parts of the body and have a five-year survival rate of less than 25% [13, 14].

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 [15]. Approximately 30% of women diagnosed with early stage breast cancer develop advanced or MBC despite treatment [13]. 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 [16]. Breast cancer resulted in 1,548 deaths with an overall mortality of 8.9 per 1000,000 persons; 0.3 per 100,000 men and 16.0 per 100,000 women (based on the WHO-world population 2011) [17].

A0023: How many people belong to the target population?

incidence rate based on the European Standard Population: 63.3 per 100,000 persons/year

About 30% of all malignant neoplasm cases in Austria are due to breast cancer. It is the most common cause of death due to cancer in females. The age standardised incidence rate for the European Standard Population (2015) is 63.3 per 100,000 persons per year. In 2015, 5,480 persons were newly diagnosed with breast cancer in Austria, of whom approximately 98% were women. Moreover, around 86% of female breast cancer patients and 78% of male breast cancer patients (all stages are included) are alive at least five years after diagnosis [17]. The median age at diagnosis of breast cancer is 62 years (range 55 to 64 years) in women [18].

HR-positive, HER2-negative most common subtype
~3,836 cases in Austria in 2015

HR-positive disease accounts for approximately 65% and 80% of breast cancers in pre- and postmenopausal women, respectively. Approximately 70% of breast cancer patients have HR-positive, HER2-negative; the most common type of breast cancer. Therefore, about 3,836 of the 5,480 persons diagnosed with breast cancer in 2015 in Austria were affected by HR-positive, HER2-negative disease. Between 5% and 10% of patients present with MBC at diagnosis, and about 30% of people with localized disease will later develop metastases [13, 19].

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 locally ABC 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 [14, 15].

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, cigarette smoking and genetic factors. 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 (one in 44 women) for women aged 50 to 59 years, 3.5 (one in 29 women) for those aged 60 to 69 years (one in 15 women) for women above the age of 70 years [14, 15].

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, computed tomography (CT) and Positron-emission tomography (PET) scans may be conducted to determine whether breast cancer has spread to bone, liver, lungs or brain [15, 20].

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 [21].

First-line ET involves:

- a third generation AI (anastrozole, letrozole, or exemestane) for postmenopausal patients;

- tamoxifen and ovarian suppression with luteinizing hormone-receptor releasing hormone (LHRH) agonists or tamoxifen alone for premenopausal patients; and

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

2nd-line: fulvestrant or exemestane with everolimus

- a non-cross-resistant AI, tamoxifen, the selective oestrogen down regulator (SERD) fulvestrant, fulvestrant plus an AI, an AI plus a CDK4/6 inhibitor (palbociclib or ribociclib), any ET in combination with the rampamycin inhibitor everolimus [20, 21].

A/MBC: continue treatment or palliative care

If A/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 [14].

7 Evidence

systematic literature search in 5 databases: 105 hits

A literature search was conducted on 12 January 2018 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "abemaciclib", "verzenio", "breast cancer", "breast neoplasms", "mamma carcinoma", and "advanced". The manufacturer was also contacted and submitted no further evidence other than that identified by systematic literature search. A manual search identified two FDA regulatory documents [3, 7], an EMA marketing authorization application notification [8], seven clinical guidance documents [13-15, 20-23], three statistical documents [16-18], and two cost documents [24, 25]. Ongoing trials information was found on www.clinicaltrials.gov.

manual search: 15 additional references

Overall, 120 references were identified. Included in this reported are:

overall: 120 references included: 3 studies

- MONARCH 3, phase III [2]
- MONARCH 2, phase III [6]
- MONARCH 1, phase II [5]

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

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [26]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 of the Appendix.

external validity

The external validity of the included trials was assessed using the EUnetHTA guideline on applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator, outcomes and setting [26].

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 the clinically meaningful benefit scale are reported in Table 3.

7.1 Quality assurance

internal and external review

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence, amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

quality assurance method

The LBI-HTA considers the external assessment by scientific experts from different disciplines a method of quality assurance of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

7.2 Clinical efficacy and safety – phase III studies

MONARCH 3: NSAI ± abemaciclib as initial therapy for HR-positive, HER2-negative ABC

MONARCH 3 (NCT02246621) is a multicentre, randomised, placebo-controlled phase III study involving 493 postmenopausal women with HR-positive, HER2-negative ABC who had not received prior systemic therapy in the advanced setting [2]. The study was designed to evaluate the safety and efficacy of abemaciclib in combination with a NSAI compared to placebo plus a NSAI, as initial treatment for HR-positive, HER2-negative advanced breast cancer. Efficacy analyses were based on all randomly assigned patients comprising the intent-to-treat (ITT) population. Safety analyses involved 488 patients who received at least one dose of the study drug.

ITT (n = 493) stratified by metastatic site and prior neoadjuvant or adjuvant ET

Eligible women were 18 years or older, with locally tested HR-positive, HER2-negative locoregionally recurrent breast cancer not amenable to surgical resection or radiotherapy with curative or palliative intent. Patients must have had adequate organ function; an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1, measurable disease or non-measurable bone-only disease defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and must not have received systemic therapy for advanced disease. Neoadjuvant or adjuvant ET was permitted if the patient was disease-free more than twelve months after completing therapy. Patients were excluded if they had visceral crisis, lymphangitic spread,

leptomeningeal carcinomatosis, inflammatory breast cancer, evidence or history of central nervous system metastases, or prior treatment with everolimus or a CDK4/6 inhibitor.

NSAI ± abemaciclib (150 mg twice daily), 28-day cycle; median 16 cycles of abemaciclib vs 15 cycles of placebo; median follow-up 17.8 months

Patients were randomised 2:1 to receive abemaciclib (150 mg twice daily) or matching placebo plus a NSAI (either 1 mg anastrozole or 2.5 mg letrozole). All drugs were administered orally and taken daily during 28-day cycles until disease progression, unacceptable toxicity, death or patient withdrawal. Dose interruptions and reductions were allowed for abemaciclib but not applicable to NSAI. Randomised patients were stratified by metastatic site (visceral, bone only, or other) and prior neoadjuvant or adjuvant ET (AI, no ET, or other). At interim analysis, after 194 progression-free survival (PFS) events (n = 108 [32.9%] for abemaciclib versus n = 86 [52.1%] for placebo), the median follow-up was 17.8 months. At the data cut-off, 162 (49.4% of) abemaciclib and 64 (38.8% of) placebo patients continued treatment. Abemaciclib patients received a median of 16 cycles of therapy versus 15 cycles for placebo recipients. The median relative dose intensity was 86% for abemaciclib and 98% for placebo.

primary endpoint: investigator-assessed PFS
secondary endpoints: ORR, DOR, CBR, and safety

OS, QoL, pharmacokinetic and biomarker analyses were not reported in this analysis

The primary endpoint of investigator-assessed PFS was evaluated from randomisation until objective disease progression or death. Secondary endpoints reported in the article include objective response rate (ORR; percentage of patients with best response of complete response [CR] or partial response [PR]), duration of response (DOR; time from CR or PR until disease progression or death), clinical benefit rate (CBR; percentage of patients with best response of CR, PR, or stable disease [SD] ≥6 months), and safety and tolerability. Other endpoints not reported in the current analysis include overall survival (OS), quality of life (QoL), pharmacokinetics, and biomarker analyses. Tumours were assessed according to RECIST version 1.1 at baseline, every second cycle during cycles two to 18, every third cycle thereafter, and within 14 days of progression. AEs were graded for severity according to the National Cancer Institute Common Terminology Criteria version (CTCAE) version 4.0.

ITT: median age 63 years, 78% were PR-positive, 47% had previous ET

The ITT population (n = 493) had a median age of 63 years (range 32–88), 58.4% were Caucasian, 52.9% had visceral disease, 39.8% presented with de novo metastatic breast cancer, 77.5% were progesterone receptor (PR) positive, and 46.7% had previously received neo-adjuvant or adjuvant ET, including 27.4% who received prior AI therapy. Detailed patient characteristics including inclusion- and exclusion criteria can be found in Table 5 and study quality is described in Table 6 of the appendix, respectively. Clinical efficacy data are presented in Table 1 and AEs are listed in Table 2.

7.2.1 Clinical efficacy

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

OS: not planned for interim analysis will be conducted after 315 events

While OS data were not mature at interim analysis, there were 32 (9.8%) deaths in the abemaciclib group and 17 (10.3%) deaths in the placebo group (hazard ratio [HR]: 0.97). Regarding deaths occurring either while receiving treatment or within 30 days of discontinuation, 11 (34% of) deaths occurred in the abemaciclib group (eight due to adverse events [AEs]) versus three (1.9%) in the placebo group (two due to AEs). A final OS analysis will be conducted after 315 events.

D0006: How does abemaciclib affect progression (or recurrence) of breast cancer?

Interim analysis were performed after 194 PFS events (n = 108 [32.9%] for abemaciclib versus n = 86 [52.1%] for placebo), at a median follow-up of 17.8 months. The primary endpoint, investigator-assessed median PFS, was not reached (NR) in the abemaciclib group and was 14.7 months in the placebo group (HR 0.54, 95% CI 0.41–0.72; p = 0.000021). Compared with placebo, abemaciclib increased PFS as observed by independent central review (ICR) (HR 0.51, 95% CI 0.36–0.72; p = 0.000102).

median investigator-assessed PFS: NR for abemaciclib vs 14.7 months for placebo

While a PFS benefit was demonstrated across all pre-specified subgroups, Asians demonstrated a greater benefit than Caucasians (n = 148 Asians, HR 0.30, 95% CI 0.17–0.52 versus n = 288 Caucasians, HR 0.69, 95% CI 0.48–0.99). Abemaciclib demonstrated consistent PFS over placebo across subgroups related to prognosis and endocrine sensitivity (treatment-free interval, metastatic site); however, greater benefit was observed in patients with a short treatment-free interval (NR for abemaciclib vs 9.0 months for placebo) or liver metastases, though not a pre-specified subgroup, (15.0 months for abemaciclib vs 7.2 months for placebo). Placebo patients with adverse prognostic factors (treatment-free interval <36 months, median PFS, 9.0 months; or liver metastases, median PFS, 7.2 months) demonstrated greater progression than those with good prognostic factors treatment-free interval >36 months, or bone only disease (median not reached for either group).

greater median PFS: Asians, treatment-free interval <36 months, and liver metastases

D0005: How does abemaciclib affect symptoms and findings (severity, frequency) of breast cancer?

The ORR in the ITT population was 48.2% (95% CI 42.8–53.6%, n = 328) in the abemaciclib group and 34.5% (95% CI 27.3–41.8%, n = 165) in the placebo group (odds ratio [OR] 1.8, 95% CI 1.3–2.3; p = 0.002). Clinical benefit was achieved in 78% (95% CI 73.6–82.5%) of abemaciclib patients versus 71.5% (95% CI 64.6–78.4%) of placebo recipients. Of the responders, 101 (63.9% of) abemaciclib recipients and 34 (59.6% of) placebo recipients continued treatment at interim analysis. The ORR in patients with measurable disease was 59.2% (95% CI 53.3–65.1%) in abemaciclib recipients and 43.8% (95% CI 35.3%–52.4%) in placebo recipients (OR 1.9, 95% CI 1.4–2.5; p = 0.004). The median DOR was NR for the abemaciclib group and was 14.1 months in placebo group.

ORR ITT: abemaciclib: 48.2% placebo: 34.5%

DOR: abemaciclib: NR placebo: 14.1 months

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

According to central laboratory analysis, abemaciclib may cause increased serum creatinine, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST), decreased white blood cells, neutrophils, and lymphocytes, and anaemia.

increased creatinine, ALT & AST, leukopenia, neutropenia, lymphocytopenia, & anaemia

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

No evidence was reported regarding the effect of abemaciclib on generic health-related QoL

generic health-related QoL: no evidence

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

disease-specific QoL: no evidence

No evidence was reported regarding the effect of abemaciclib on disease-specific QoL.

Table 1: Efficacy results of MONARCH 3 [2]

Descriptive statistics and estimate variability	**Treatment group**	**Abemaciclib + NSAI**	**Placebo + NSAI**
	Number of subjects	328	165
	Interim analysis (17 months) 194 PFS events, n (%)	108 (32.9)	86 (52.1)
	ICR-assessed median PFS, months Investigator-assessed median PFS, months PFS, months, TFI<36 months PFS, months, TFI>36 months PFS, months, with BOD PFS, months, without BOD PFS, months, with liver metastasis PFS, months, without liver metastases	NR NR NR (n = 42) NR (n = 94) NR (n = 70) NR (n = 258) 15.0 (n = 48) NR (n = 280)	19.2 14.7 9.0 (n = 32) NR (n = 40) NR (n = 39) 11.7 (n = 126) 7.2 (n = 30) 15.4 (n = 135)
	Best overall response, % (CI) CR PR SD ≥6 months PD NE	 1.5 (0.2–2.9) 46.6 (41.2–52.0) 40.5 (35.2–45.9) 29.9 (24.9–34.8) 4.3 (2.1–6.5) 7.0 (4.2–9.8)	 0.0 (NA) 34.5 (27.3–41.8) 52.1 (44.5–59.7) 37.0 (29.6–44.3) 7.3 (3.3–11.2) 6.1 (2.4–9.7)
	ORR, % (95% CI), all patients ORR, % (CI), measurable disease	48.2 (42.8–53.6) 59.2 (53.3–65.1)	34.5 (27.3–41.8) 43.8 (35.3–52.4)
	CBR, % (95%) all patients with CR, PR or SD ≥6 months CBR, % (95%) measurable disease with CR, PR or SD ≥6 months	78.0 (73.6–82.5) 79.4 (74.5–84.3)	71.5 (64.6–78.4) 69.2 (61.3–77.2)
	DOR, months	NR	14.1
	Median OS, months	NA	NA
	QoL	NA	NA
Effect estimate per comparison	*Comparison groups*		Abemaciclib + NSAI versus Placebo + NSAI
	ICR-assessed PFS (primary endpoint)	HR	0.51
		95% CI	0.36–0.72
		Log-rank test p-value	0.000102
	Investigator-assessed PFS (primary endpoint)	HR	0.54
		95% CI	0.41–0.72
		Log-rank test p-value	0.000021
	Investigator-assessed PFS (subgroup analysis)	HR Caucasian versus HR Asian	0.69 versus 0.30
		95% CI Caucasian versus 95% CI Asian	0.48–0.99 versus 0.17–0.52
		Log-rank test p-value	NA
	ORR, all patients	OR	1.8
		95% CI	1.3–2.3
		Log-rank test p-value	0.002

	ORR, measureable disease	OR	1.9
		95% CI	1.4–2.5
		Log-rank test p-value	0.004
	CBR, all patients with CR, PR or SD ≥6 months	OR	1.4
		95% CI	1.0–2.0
		Log-rank test p-value	0.101
	CBR, measurable disease, patients with CR, PR or SD ≥6 months	OR	1.7
		95% CI	1.2–2.5
		Log-rank test p-value	0.024

Abbreviations: BOD = bone-only disease; CBR = clinical benefit rate; CR = complete response; DOR = duration of response; ICR = independent central review; NA = not applicable; NE = not evaluable; NSAI = non-steroidal aromatase inhibitor; NR = not reached; PD = progressive disease; PFS = progression-free survival; PR = partial response; OR = odds ratio; ORR = objective response rate; OS = overall survival; SD = stable disease; TFI = treatment-free interval

7.2.2 Safety

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

common grade ≥3 AEs: neutropenia, diarrhoea, leukopenia, increased ALT, anaemia, and infections

The most frequent investigator-assessed AEs reported in the abemaciclib group of the safety population (n = 327 abemaciclib) were diarrhoea, neutropenia, fatigue, infections, and nausea. Grade ≥3 AEs were observed in 180 (55.0% of) abemaciclib patients and 35 (21.8 % of) placebo patients. The most common AEs of grade ≥3 severity in the abemaciclib group were neutropenia (21.1%), diarrhoea (9.5%), leukopenia (7.6%), increased ALT (6.1%), anaemia (5.8%) and infections (4.9%).

diarrhoea: median onset 8 days, duration 8-10.5 days; 73% used antidiarrhoeals

Diarrhoea was predominantly of grade 1 (44.6%) or 2 (27.2%) for abemaciclib recipients versus 21.7% and 6.8%, respectively for placebo recipients. In the abemaciclib group, the median onset was 8.0 days with a median duration of 10.5 days (grade 2) and 8.0 days (grade 3). While most patients (76.3%) who experienced diarrhoea did not undergo treatment modification, 73.3% reported using antidiarrhoeal therapy.

neutropenia: 45%, reversible following discontinuation

Neutropenia was reported in 41.3% abemaciclib recipients. Once decreased, typically by cycle 2, neutrophil count remained stable and was reversible following discontinuation of abemaciclib. Infections occurred more frequently in the abemaciclib group (39.1%) compared to placebo (28.6%); predominantly of grades 1 and 2 (33.3% for abemaciclib versus 25.5% for placebo). Venous thromboembolic events occurred in 16 (4.9% of) abemaciclib recipients versus one (0.6% of) placebo recipient.

AE-related deaths: abemaciclib: 2.4% placebo: 1.2%

Serious adverse events (SAEs) were more common in the abemaciclib group (27.5%) than in the placebo group (14.9%); the most frequent were lung infections (2.8% versus 0%, respectively). During therapy or within 30 days of discontinuation, eleven (3.4%) deaths occurred in the abemaciclib group versus three (1.9%) in the placebo group. Death due to AEs occurred in eight (2.4%) abemaciclib patients and two (1.2%) placebo patients. Of the eight AE-related deaths in the abemaciclib group three were due to lung infection, two embolism, one cerebral ischemia, one pneumonitis and one respiratory failure.

C0002: Are the harms related to dosage or frequency of applying abemaciclib?

dose interruptions: abemaciclib: 56.3% placebo: 19.3%

discontinued due to progression: abemaciclib: 27.7% placebo: 52.1%

Abemaciclib dose reductions due to AEs occurred in 142 (43.4% of) patients versus ten (6.2% of) patients receiving placebo. AE-related dosage interruptions were reported in 184 (56.3% of) abemaciclib recipients versus 31 (19.3% of) placebo recipients. A total of 64 (19.6%) of the abemaciclib group and four (2.5%) of the placebo group discontinued treatment due to AEs. The most frequent cause of treatment discontinuation was disease progression for 91 (27.7%) of abemaciclib recipients versus 86 (52.1%) of placebo recipients. Approximately 2.3% of the abemaciclib group discontinued use as a result of diarrhoea.

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

susceptibles: reduce dose frequency in patients with hepatic impairment

Study participants had a median age of 63 years, adequate organ function and an ECOG performance status of ≤1. While PFS benefit was observed across age subgroups (<65 years versus ≥65 years), the safety and effectiveness of abemaciclib have not been established in pediatric patients. While no dosage adjustment is necessary for patients with mild or moderate renal impairment (CLcr ≥30–89 mL/min), the pharmacokinetics of abemaciclib in patients with severe renal impairment, end stage renal disease, or patients on dialysis is unknown. Patients with severe hepatic impairment may be required to reduce the dosing frequency as the liver metabolizes abemaciclib.

abemaciclib may cause foetal harm

Abemaciclib may cause foetal harm and adverse reaction in breastfed infants, females are advised to use effective contraception and not to breast feed for at least three weeks following the last dose of abemaciclib [3].

Table 2: Most frequent adverse events of MONARCH 3 [2]

Adverse Event (according to CTCAE version 4.0)	**Abemaciclib + NSAI** (n = 327)			**Placebo + NSAI** (n = 161)		
≥15% in either Arm	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any AE	322 (98.5)	159 (48.6)	21 (6.4)	145 (90.1)	32 (19.9)	3 (1.9)
Diarrhea	266 (81.3)	31 (9.5)	0 (0.0)	48 (29.8)	2 (1.2)	0 (0.0)
Neutropenia	135 (41.3)	64 (19.6)	5 (1.5)	3 (1.9)	1 (0.6)	1 (0.6)
Fatigue	131 (40.1)	6 (1.8)	—	51 (31.7)	0 (0.0)	—
Infections and infestations	128 (39.1)	13 (4.0)	3 (0.9)	46 (28.6)	4 (2.5)	1 (0.6)
Nausea	126 (38.5)	3 (0.9)	—	32 (19.9)	2 (1.2)	—
Abdominal pain	95 (29.1)	4 (1.2)	—	19 (11.8)	2 (1.2)	—
Anaemia	93 (28.4)	19 (5.8)	0 (0.0)	8 (5.0)	2 (1.2)	0 (0.0)
Vomiting	93 (28.4)	4 (1.2)	0 (0.0)	19 (11.8)	3 (1.9)	0 (0.0)
Alopecia	87 (26.6)	—	—	17 (10.6)	—	—
Decreased appetite	80 (24.5)	4 (1.2)	0 (0.0)	15 (9.3)	1 (0.6)	0 (0.0)
Leukopenia	68 (20.8)	24 (7.3)	1 (0.3)	4 (2.5)	0 (0.0)	1 (0.6)
Increased blood creatinine	62 (19.0)	7 (2.1)	0 (0.0)	6 (3.7)	0 (0.0)	0 (0.0)
Constipation	52 (15.9)	2 (0.6)	0 (0.0)	20 (12.4)	0(0.0)	0 (0.0)
Increased ALT	51 (15.6)	19 (5.8)	1 (0.3)	11 (6.8)	3 (1.9)	0 (0.0)
Headache	51 (15.6)	2 (0.6)	—	24 (14.9)	0 (0.0)	—
Decreased lymphocytes	165 (52.7)	23 (7.3)	2 (0.6)	40 (25.6)	3 (1.9)	0 (0.0)
Increased AST	115 (36.7)	12 (3.8)	0 (0.0)	26 (23.2)	1 (0.6)	0 (0.0)

Abbreviations: AE = adverse event; CTCAE = common terminology for cancer adverse events; NSAI = non-steroidal aromatase inhibitor

7.3 Clinical effectiveness and safety – further studies

MONARCH 2: fulvestrant ± abemaciclib for HR-positive, HER2-negative ABC with progression on prior ET

MONARCH 2 (NCT02107703) is an ongoing multicentre, randomised, double-blind, placebo-controlled, phase III study to evaluate abemaciclib in combination with fulvestrant for the treatment of HR-positive, HER2-negative ABC in 667 postmenopausal women whose disease progressed while receiving prior ET [6]. Patients were randomly assigned 2:1 to receive abemaciclib or placebo (150 mg twice daily) with fulvestrant (500 mg, per label) in 28-day cycles until disease progression, death or unacceptable toxicity. The primary endpoint was investigator-assessed PFS and secondary endpoints included OS, ORR, DOR, CBR, QoL and safety. Clinical response was based on investigator-assessment (RECIST v1.1) within 28 days of randomisation, every eight weeks the first year, every 12 weeks thereafter, and within two weeks of clinical progression. AEs were evaluated at each patient visit until follow-up and graded according to CTCAE v4.0.

median investigator-assessed PFS: 16.4 months for abemaciclib vs 9.3 months for placebo

ORR: abemaciclib: 35.2% placebo: 16.1%

common AEs: diarrhoea, neutropenia, nausea, and fatigue

At a median follow-up of 19.5 months, the primary endpoint median PFS was 16.4 months in abemaciclib recipients versus 9.3 months in placebo recipients (HR 0.55, 95% CI 0.45-0.68; $p < 0.001$). A benefit in PFS was observed across all patient subgroups and consistent with those obtained through ICR (HR 0.46, 95% CI 0.36–0.58; $p < 0.001$). OS data were not mature at primary analysis for PFS. The ORR in the ITT population was 35.2% (95% CI 30.8–39.6%) in the abemaciclib group versus 16.1% (95% CI 11.3–21.0%) in the placebo group ($p < 0.001$); including 14 CRs (3.1%) in the abemaciclib group and one CR (0.4%) in the placebo group. The median DOR was NR in the abemaciclib group with 90 responders (57.3%) continuing treatment at interim analysis. Patients with measurable disease achieved an ORR of 48.1% (95% CI 42.6–53.6%) in abemaciclib recipients and 21.3% (95% CI 15.1–27.6%) for placebo recipients ($p < 0.001$). The most common AEs in the abemaciclib versus placebo groups were diarrhoea (86.4% versus 24.7%), neutropenia (46.0% versus 4.0%), nausea (45.1% versus 22.9%), and fatigue (39.9% versus 26.9%).

MONARCH 1: abemaciclib monotherapy for refractory HR-positive, HER2-negative MBC with progression during prior ET, chemotherapy in a metastatic setting

MONARCH 1 (NCT02102490) is an ongoing multinational, single-arm, open-label, phase II study to evaluate abemaciclib monotherapy for the treatment of refractory HR-positive, HER2-negative MBC [5]. All 132 women in the trial had experienced disease progression during or following prior ET, had received one or two chemotherapy regimens for metastatic disease, and had received a taxane in any setting. Approximately 90% of patients had visceral disease, and 85% had at least two metastatic sites. Patients received abemaciclib (200 mg every twelve hours) continuously until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed ORR and secondary endpoints included CBR, PFS, OS and safety. Clinical response was based on investigator-assessment (RECIST v1.1) with primary analysis 12 months after the last patient entered. AEs were evaluated at baseline and during the study, and graded according to CTCAE v4.0.

ORR: 19.7%
CBR: 42.4%
median PFS: 6.0 months
median OS: 17.7 months
AEs: diarrhoea, fatigue, nausea

At the twelve month final analysis, investigator-assessed ORR was 19.7% (95% CI 13.3–27.5), the CBR (≥6 months) was 42.4%, median PFS was 6.0 months, and median OS was 17.7 months. The median time to response was 3.7 months, and the median DOR was 8.6 months. The most common treatment-related AEs of any grade were diarrhoea, fatigue, and nausea; 7.6% of patients discontinued treatment due to AEs.

8 Estimated costs

A0021: What is the reimbursement status of abemaciclib?

cost: no price estimate for Europe
US $ 10,948/month

Currently, there are no price estimates for Europe.

Abemaciclib cost approximately US $ 10,948 (~ € 8,843) per month, or US $ 131,376 (~ € 106,1238) per year [24].

9 Ongoing research

16 registered studies

Several studies are ongoing to investigate abemaciclib as monotherapy or in combination with NSAI, selective oestrogen receptor degraders (SERDs), chemotherapy or other anti-cancer agents to treat ABC. In February 2018, searches of www.clinicaltrials.gov and www.clinicaltrialsregister.eu using the search terms "abemaciclib" and "breast cancer" yielded 16 registered studies (four phase III, eight phase II, three phase I and an expanded access study). Most studies were industry-sponsored or conducted in collaboration with industry.

4 industry sponsored ongoing phase III
8 phase II

Selected ongoing phase II and III studies evaluating abemaciclib in combination with a NSAI or SERD (MONARCH plus), and with tamoxifen or loperamide (nextMONARCH 1) for ABC; in combination with transtuzumab with or without a SERD (monarcHER) for HER2-positive ABC; in combination with a NSAI (neoMONARCH), with or without standard adjuvant ET for early-stage breast cancer (MonarchE); and as monotherapy for triple negative breast cancer (TNBC):

- **NCT02763566:** MONARCH plus is a phase III, multicentre, randomised, double-blind, placebo-controlled trial to evaluate the efficacy of abemaciclib in combination with NSAI or fulvestrant for the treatment of HR-positive, HER2-negative ABC in postmenopausal women. Estimated study completion date is January 2020.
- **NCT02747004:** nextMONARCH 1 is a phase II, multicentre, randomised, open-label study to investigate the safety and efficacy of abemaciclib plus tamoxifen or abemaciclib monotherapy in women with previously treated HR-positive, HER2-negative MBC. Estimated study completion date is May 2019.
- **NCT02675231:** monarcHER is a phase II, multicentre, randomised, open-label study to determine the effectiveness of abemaciclib plus trastuzumab with or without fulvestrant versus standard care physician's choice chemotherapy plus trastuzumab for women with HR-positive, HER2-positive ABC. Estimated study completion date is February 2021.
- **NCT02441946:** neoMONARCH is a phase II, multicentre, randomised, open-label study to investigate the effectiveness of abemaciclib in combination with anastrozole compared with abemaciclib alone and anastrozole alone in postmenopausal women with HR-positive, HER2-negative, early stage BC. Estimated study completion date is January 2018.
- **NCT03155997:** monarchE is a phase III, multicentre, randomised, open-label trial to evaluate the safety and efficacy of abemaciclib with standard adjuvant ET versus standard adjuvant ET alone for high risk, node positive, early stage, HR-positive, HER2-negative BC. Estimated study completion date is June 2027.
- **NCT03130439:** is a phase II, open-label study to evaluate the safety and effectiveness of abemaciclib monotherapy for Rb-positive TNBC. Estimated study completion date is November 2024.

In addition, abemaciclib is currently under investigation for non-small cell lung cancer (NSCLC), brain metastases secondary to melanoma, or HR-positive breast cancer, recurrent glioblastoma, liposarcoma, mantle cell lymphoma, and pancreatic cancer.

10 Discussion

FDA: licensed mono/+ fulvestrant for HR-positive, HER2-negative A/MBC; NDA: + NSAI

EMA: MAA submitted for HR-positive, HER2-negative A/MBC

In September 2017, the FDA approved abemaciclib monotherapy for postmenopausal women with HR-positive, HER2-negative ABC that progressed following ET and chemotherapy for metastatic disease; and in combination with fulvestrant for HR-positive, HER2-negative ABC patients who progress following ET [3, 4]. In October 2017, a NDA for abemaciclib in combination with a NSAI as initial therapy for A/MBC was granted priority review [7]. Abemaciclib does not currently have market authorisation in Europe for any indication. However, in February 2018, a MAA for abemaciclib was submitted to the EMA for the treatment of patients with HR-positive, HER2-negative locally A/MBC [8].

MONARCH 3: abemaciclib increased PFS, ORR versus placebo at 17.8 months

abemaciclib reduced risk of progression by 46%; PFS benefit across subgroups; poor prognosis derive greatest benefit

median DOR: abemaciclib: NR placebo: 14.1 months

immature OS

The NDA to the FDA regarding the use of abemaciclib with an AI as first-line therapy for ABC is based on results of an interim analysis of a phase III study [2]. MONARCH 3, a double-blind, randomised trial, compared the safety and efficacy of abemaciclib (150 mg twice daily) or placebo plus a NSAI for HR-positive, HER2-negative ABC in 493 postmenopausal women without prior systemic therapy for advanced disease. At a median follow-up of 17.8 months, the investigator-assessed median PFS was 14.7 months in the placebo group but had not yet been reached in the abemaciclib group. Consistent with PFS observed by ICR, abemaciclib reduced the risk of disease progression (DP) by 46%, with consistent PFS benefit across subgroups. However, patients with indicators of poor prognosis such as a short treatment-free interval or liver metastases derived greater benefit from the addition of abemaciclib than patients with a longer treatment-free interval or bone-only disease. In the ITT population, the ORRs and CBRs were 48.2% and 78% in abemaciclib recipients versus 34.5% and 71.5% in placebo recipients, respectively. The median DOR was 14.1 months in the placebo group but had not yet been reached in the abemaciclib group. OS data were not mature at the time of interim analysis for PFS; however, 32 (9.8%) deaths occurred in the abemaciclib group and 17 (10.3%) in the placebo group.

grade ≥3 AEs: neutropenia, diarrhoea, leukopenia, increased ALT, anaemia, infections

8 deaths due to lung infections, embolisms, cerebral ischemia, pneumonitis and respiratory failure

The most frequently reported AEs in abemaciclib recipients were diarrhoea, neutropenia, fatigue, infections and nausea. Grade ≥3 AEs were more common in the abemaciclib group compared to placebo (55.0% versus 21.7%); notably neutropenia (21.1%), diarrhoea (9.5%), leukopenia (7.6%), increased ALT (6.1%), anaemia (5.8%), and infections (4.9%). While the 76.3% of patients that experienced diarrhoea did not undergo treatment modification, 73.3% used antidiarrhoeals. The neutropenia noted in 41.3% of abemaciclib recipients was reversible upon discontinuation of therapy. AE-related dose interruptions and discontinuations occurred more frequently in abemaciclib users compared to placebo (56.3% and 19.6% for abemaciclib versus 19.3% and 2.5%, respectively, for placebo). Disease progression

was the most frequent cause of discontinuation for 27.7% of abemaciclib recipients and 52.1% of placebo recipients. AE-related deaths were more common in the abemaciclib group compared to placebo (3.4% versus 1.9%); attributed to lung infections, embolisms, cerebral ischemia, pneumonitis and respiratory failure.

MONARCH 3 limitations: lack of data regarding OS, QoL, biomarkers predictive of response

Results of the MONARCH 3 study hold some limitations. While PFS, ORR, DOR and discontinuation data are useful outcomes for evaluation in clinical trials, follow-up is insufficient to evaluate OS and long-term safety. No evidence was reported regarding the effect of abemaciclib on generic or disease-specific QoL. Mature OS data and QoL measures are needed to ensure patients achieve a clinically relevant benefit over time in the context of increased toxicity. While patients with indicators of poor prognosis derived greater benefit from the addition of abemaciclib than patients with better prognosis, biomarker analyses were not reported in this analysis. It is important to identify which patients may benefit most from adding abemaciclib as initial treatment versus treatment following progression on ET. Biomarkers that track cellular proliferation and those that evaluate Rb protein and ER activity may prove useful in this regard [29, 30]. Biomarker trials may help to identify patients for whom CDK4/6 inhibition is cost-effective [11].

generalizability of the study population

The overall generalizability of the MONARCH 3 results may be limited in that study participants had good performance status (ECOG 0–1), with adequate organ function, without having received prior ET for MBC; however, the clinical effectiveness of abemaciclib may differ in patients with greater comorbidity, reduced functional reserve, gastrointestinal disorders, and those with moderate to severe renal or hepatic impairment.

differences from existing data: indicated as initial ET; Asians derive greater PFS benefit than Caucasians

The clinical efficacy and safety data from MONARCH 3 are consistent with data from MONARCH 1 and MONARCH 2 in that abemaciclib improves PFS and ORR in patients with HR-positive, HER2-negative ABC [2, 5, 6]. Abemaciclib was evaluated as initial ET in MONARCH 3, where postmenopausal participants had no prior systemic therapy in the advanced setting, while MONARCH 1 and MONARCH 2 participants had disease progression on or after prior ET, and had not received chemotherapy or more than one line of ET for metastatic disease. While subgroup analysis in MONARCH 3 suggests Asians may derive greater PFS than Caucasians, no differences in PFS were noted by race in MONARCH 2. Similar to safety data from MONARCH 1 and MONARCH 2, the most frequent grade ≥3 AEs in MONARCH 3 were diarrhoea, neutropenia, and leukopenia. Various ongoing studies are evaluating abemaciclib in combination with a NSAI or SERD (MONARCH plus), and with tamoxifen or loperamide (nextMONARCH 1) for ABC; in combination with trastuzumab with or without a SERD (monarcHER) for HER2-positive ABC; in combination with a NSAI (neoMONARCH), with or without standard adjuvant ET for early-stage breast cancer (MonarchE); and as monotherapy for TNBC.

low risk of bias: randomised, double-blind, placebo-controlled, industry funded

MONARCH 3 is a phase III trial with few methodological limitations. There is no risk of bias in the generation of randomisation sequence or allocation concealment. Patients were randomly assigned 2:1 to abemaciclib or matching placebo plus a NSAI using an interactive web-based response system. Patients, physicians and outcome assessors were blinded as the placebo was identical in appearance. Selective outcome reporting is unlikely as all outcomes were reported as specified in the clinical trial registry. The risk of bi-

as may be increased by industry involvement in funding, study design, data collection, analysis and interpretation.

ESMO-MCBS evaluations were not applicable due to immature PFS data

Given the non-curative setting of abemaciclib and the statistically significant primary endpoint PFS we applied form 2b of the ESMO-MCBS in order to assess whether abemaciclib satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5) [27]. However, since the median PFS was not reached in the abemaciclib group no score calculations could be applied.

evidence needed: comparative trials, CDK4/6 with chemotherapy, radiotherapy, or immune-checkpoint inhibitors vs monotherapy; higher incidence of VTE

Although several studies are ongoing, trials are needed to compare the safety and efficacy of abemaciclib with palbociclib and ribociclib, two CDK4/6 inhibitors currently approved for the treatment of early and advanced HR-positive, HER2-negative breast cancer. While all three oral CDK4/6 inhibitors are similar in mechanism of action, abemaciclib shows greater affinity for CDK4 than palbociclib and ribociclib. CDK4 plays a greater role than CDK6 in breast cancer. Compared to other CDK4/6 inhibitors, abemaciclib tases and causes fewer cases of neutropenia [9]. Other differences include higher rates of diarrhoea and venous thromboembolism (VTE) with abemaciclib and more neutropenia than with palbociclib and ribociclib. Aside from existing combinations, it is important to determine whether CDK4/6 inhibitors in combination with chemotherapy, radiotherapy or immune-checkpoint inhibitors are also more effective than monotherapy [9].

cost: no price estimate for Europe; US $ 10,948/month

The cost of abemaciclib is approximately US $ 10,948 (~ € 8,843) per month, or US $ 131,376 (~ € 106,1238) per year [24]. This is in keeping with a 21-day supply of ribociclib for € 4,380, or palbociclib for € 3,381 [25]. Currently, there are no price estimates for abemaciclib in Europe.

MONARCH 3: phase III RCT reporting benefit in PFS and ORR as initial therapy for ABC

patient selection: 30% have good prognosis and may not warrant combination therapy

Overall, MONARCH 3 is the first phase III, randomised, placebo-controlled trial to demonstrate that abemaciclib with ET substantially reduces the risk of disease progression and increases ORR versus ET alone as initial therapy for HR-positive, HER2-negative ABC in postmenopausal women. While a PFS benefit was observed across subgroups, perhaps not all patients warrant combination therapy. Approximately 30% of patients have good prognosis for which a CDK4/6 inhibitor could be delayed avoiding untimely toxicity and cost [23]. OS and QoL data are needed to confirm patients achieve a clinically relevant benefit over time in the context of increasing toxicity. As there are no comparative trials, differences in the safety profiles of CDK4/6 inhibitors may assist physicians in selecting the most appropriate CDK4/6 inhibitor to meet individual patient needs.

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

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	abemaciclib	breast cancer	NC	PFS	2b	(14.7 months)	NR	0.51 0.36–0.72	-	-	+33.2% grade 3–4 AEs	x	-	NA[1]
Original ESMO-MCBS	abemaciclib	breast cancer	NC	PFS	2b	(14.7 months)	NR	0.51 0.36–0.72	-	-	x	x	-	NA[1]

Abbreviations: AJ = Adjustments; CI = confidence interval; FM = final adjusted magnitude of clinical benefit grade; HR = hazard ratio; m = months; MG = median gain; NA = not applicable; NC = non-curative; NR = not reached; PE = primary endpoint; PFS = progression-free survival; 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 resulting from 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. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

[1] no score calculations could be applied, since the median progression-free survival was not reached in the abemaciclib group

11 References

[1] European Network for Health Technology Assessment (eunethta). HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals Version 3.0. 2013 [cited 2015-10-30];Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.

[2] Goetz MP, Toi M, Klise S, Frenzel M, Bourayou N, Leo A. MONARCH 3: a randomized phase III study of anastrozole or letrozole plus abemaciclib, a CDK4/6 inhibitor, or placebo in first-line treatment of women with HR+, HER2-locoregionally recurrent or metastatic breast cancer (MBC). Journal of clinical oncology [Internet]. 2015; (15 suppl. 1). Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/372/CN-01130372/frame.html.

[3] U.S. Food and Drug Administration Drugs@FDA Verzenio™ Label Information. 2017 [cited 2018-01-24];Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208716Orig1s000lbl.pdf.

[4] Kim ES. Abemaciclib: First Global Approval. Drugs. 2017;77(18):2063-70.

[5] Dickler MN, Tolaney SM, Rugo HS, Cortes J, Dieras V, Patt D, et al. MONARCH 1, A Phase II Study of Abemaciclib, a CDK4 and CDK6 Inhibitor, as a Single Agent, in Patients with Refractory HR+/HER2- Metastatic Breast Cancer. Clinical cancer research : an official journal of the American Association for Cancer Research. 2017;23(17):5218-24.

[6] Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2-advanced breast cancer who had progressed while receiving endocrine therapy. Journal of clinical oncology. 2017;35(25):2875-84.

[7] FDA grants priority review for potential new indication for Lilly's Verzenio™ (abemaciclib) as initial treatment for advanced breast cancer. 2017 [cited 2018-02-08];Available from: https://www.prnewswire.com/news-releases/fda-grants-priority-review-for-potential-new-indication-for-lillys-verzenio-abemaciclib-as-initial-treatment-of-advanced-breast-cancer-300535365.html.

[8] European Medicines Agency. Applications for new human medicines under evaluation by the Committee for Medicinal Products for Human Use. 2018 [cited 2018-02-09];Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2018/02/WC500243465.pdf

[9] Xu H, Yu S, Liu Q, Yuan X, Mani S, Pestell RG, et al. Recent advances of highly selective CDK4/6 inhibitors in breast cancer. Journal of hematology & oncology. 2017;10(1):97.

[10] Turner NC, Neven P, Loibl S, Andre F. Advances in the treatment of advanced oestrogen-receptor-positive breast cancer. The Lancet. 2017;389(10087):2403-14.

[11] Polk A, Kolmos IL, Kumler I, Nielsen DL. Specific CDK4/6 inhibition in breast cancer: a systematic review of current clinical evidence. ESMO open. 2016;1(6):e000093.

[12] Zardavas D, Pondé N, Tryfonidis K. CDK4/6 blockade in breast cancer: current experience and future perspectives. Expert opinion on investigational drugs. 2017;26(12):1357-72.

[13] Brufsky AM. Delaying chemotherapy in the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer. Clinical Medicine Insights: Oncology. 2015;9:137-47.

[14] United States National Institutte for Health, National Cancer Institute, Metastatic Cancer. 2016 [cited 2018-02-10];Available from: https://www.cancer.gov/types/metastatic-cancer.

[15] Clinical features, diagnosis, staging, risk factors, treatment of breast cancer in women. UpToDate [Internet]. 2017 [cited 2018-02-10];Avlaiable from: https://www.uptodate.com Subscription required.

[16] Global Burden of Disease, Injuries, and Risk Factors Study 2010. 2010 [cited 2017-01-10];Available from: https://www.healthdata.org/sites/default/files/files/country_profiles/GBD/ihme_gbd_country_report_austria.pdf.

[17] Statistik Austria. Krebserkrankungen - Brust. [cited 2018-02-10];Available from: https://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/brust/index.html.

[18] National Cancer Institute. Cancer Stat Facts: Female Breast Cancer. [cited 2018-02-10];Available from: https://seer.cancer.gov/csr/1975_2014/results_merged/topic_med_age.pdf.

[19] Vidula N, Rugo HS. Cyclin-Dependent Kinase 4/6 Inhibitors for the Treatment of Breast Cancer: A Review of Preclinical and Clinical Data. Clinical breast cancer. 2016;16(1):8-17.

[20] Cardoso F, Costa A, Senkus E. Clinical Practice Guidelines: 3rd ESMO International Consensus Guidelines for advanced breast cancer (ABC 3). Annals of Oncology. 2017 [cited 2018-02-10];Available from: http://www.esmo.org/Guidelines/Breast-Cancer/3rd-ESO-ESMO-International-Consensus-Guidelines-for-Advanced-Breast-Cancer-ABC-3/eUpdate-Treatment-Algorithms.

[21] Treatment approach to metastatic hormone receptor positive, HER2-negative breast cancer: Endocrine Therapy. UpToDate [Internet]. 2017 [cited 2018-02-10];Available from: http://www.uptodate.com Subscription required.

[22] Clinical features, diagnosis, and staging of breast cancer. UpToDate [Internet]. 2018 [cited 2018-02-10];Available from: http://www.uptodate.com Subscription required.

[23] Abemaciclib plus endocrine therapy extends progression-free survival in first-line therapy for advanced breast cancer. The ASCO Post. 2017 [cited 2018-02-14];Available from: http://www.ascopost.com/issues/october-10-2017/abemaciclib-plus-endocrine-therapy-extends-progression-free-survival-in-first-line-therapy-for-advanced-breast-cancer/.

[24] FDA approves abemaciclib for advanced HR-positive breast cancer. Pharmacy Practice News. 2017 [cited 2018-02-12];Available from: https://www.pharmacypracticenews.com/Article/PrintArticle?articleID=44726.

[25] Warenverzeichnis Apothekerverlag Online. [cited 2017-01-05];Available from: http://warenverzeichnis.apoverlag.at.

[26] EUnetHTA - European network for Health Technology Assessment. Internal validity of randomized controlled trials 2013. 2013 [cited 2018-02-02];Available from: http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

[27] Cherny NI, Sullivan R, Dafni U, Kerst JM, Sobrero A, Zielinski C, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Annals of Oncology. 2015;26(8):1547-73.

[28] Wild C, Grössmann N, Bonanno PV, Bucsics A, Furst J, Garuoliene K, et al. Utilisation of the ESMO-MCBS in practice of HTA. Annals of Oncology. 2016;27(11):2134-6.

[29] Malorni L, Piazza S, Ciani Y. A gene expression signature of retinoblastoma loss-of-function is a predictive biomarker of resistance to palbociclib in breast cancer cell lines and is prognostic in patients with ER positive early breast cancer. ONcotarget. 2018;7:68012-22.

[30] Finn RS, Dering J, Conklin D. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. Breast Cancer Research 2009;11: R77.

12 Appendix

Table 4: Administration and dosing and of abemaciclib or placebo plus NSAI [2, 3]

	Abemaciclib + NSAI	Placebo + NSAI
Administration mode	Orally, swallow whole with or without food, twice daily at approximately the same time each day [3].	Matching placebo [2]
Description of packaging	7-day dose package 14-tablet package of 150 mg, oval, yellow tablets debossed with "Lilly" on one side and "150" on the other side [3]	Matching placebo [2]
Total volume contained in packaging for sale	14-tablet package of 150 mg dose pack contains 14 tablets (150 mg per tablet, 150 mg twice daily) [3]	Matching placebo [2]
Dosing	The recommended starting dose is 150 mg abemaciclib every 12 hours plus either 1 mg anastrozole or 2.5 mg letrozole orally once daily for 28 days [2]. If a patient vomits or misses a dose, the next dose should be taken at its scheduled time. Abemaciclib dosage may be reduced to 100 mg or 50 mg twice daily to manage AEs. Patients unable to tolerate 50 mg twice daily should discontinue use [3].	Matching placebo taken orally every 12 hours plus either 1 mg anastrozole or 2.5 mg letrozole orally once daily for 28 days. [2]
Median treatment duration	28-day cycle until disease progression, unacceptable toxicity, death or withdrawal Median of 16 cycles [2]	28-day cycle until disease progression or unacceptable toxicity, death or withdrawal Median of 15 cycles [2]
Contraindications	None [3]	None
Drug interactions	Avoid concomitant use of ketoconazole. Reduce abemaciclib dose with concomitant use of other strong CYP3A inhibitors. Avoid concomitant use of strong CYP3A inducers [3].	Matching placebo [2]

Abbreviations: AE = adverse events; NSAI = nonsteroidal aromatase inhibitors

Table 5: Characteristics of the phase III MONARCH 3 trial

Title: MONARCH 3: Abemaciclib as initial therapy for ABC [2]			
Study identifier	NCT02246621, EudraCT 2014-001502-18, Eli Lilly and Company 13Y-MC-JPBM, 15417, MONARCH 3		
Design	International (22 countries), multicentre (158 centres), randomized, double-blind, placebo-controlled, phase III		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		November 2014-November 2015: 493 patients randomized 2:1 to receive abemaciclib (n = 328) or placebo (n = 165) plus NSAI Interim analysis: after 194 PFS events (108 abemaciclib, 86 placebo); median follow-up: 17.8 months Not applicable Not applicable
Hypothesis	Interventional The study was designed to evaluate how effective NSAI plus abemaciclib are in postmenopausal women with BC.		
Funding	Eli Lilly		
Treatments groups	Abemaciclib + NSAI (n = 328 ITT, n = 327 safety)		Abemaciclib 150 mg orally every 12 h plus either 1 mg anastrozole or 2.5 mg letrozole orally once daily for 28 days
	Placebo + NSAI (n = 165 ITT, n = 161 safety)		Placebo orally every 12 hours plus either 1 mg anastrozole or 2.5 mg letrozole orally once daily for 28 days
Endpoints and definitions	Progression-free survival Primary endpoint	PFS	Time from baseline to measured progressive disease or death from any cause (approximately 34 months)
	Overall survival Secondary endpoint	OS	Time from baseline to date of death from any cause (approximately 82 months)
	Duration of response Secondary endpoint	DOR	Time from date of CR or PR to date of objective disease progression or death due to any cause (estimated up to 34 months)
	Disease control rate Secondary endpoint	DCR	Time from baseline to disease progression (approximately 34 months)
	Clinical benefit rate Secondary endpoint	CBR	Time from baseline to disease progression (approximately 34 months)
	Cancer Quality of Life Questionnaire-Core 30 Secondary endpoint	EORTC QLQ-C30	Change from baseline to end of study in symptom burden on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (up to 34 months)
	Symptom burden on the EORTC QLQ-Breast23 Questionnaire Secondary endpoint	EORTC QLQ-Breast23	Change from baseline to end of study in symptom burden on the EORTC QLQ-Breast23 Questionnaire (up to 34 months)
	Health Status on the EuroQuol 5-Dimension 5 Level Secondary endpoint	EuroQuol-5D 5L	Change from baseline to end of study in health status on the EuroQuol 5-Dimension 5 Level (up to 34 months)
	Objective Response Rate Secondary endpoint	ORR	Time from baseline to disease progression (approximately 34 months)
	Pharmacokinetics Secondary endpoint	PK	Volume of distribution of abemaciclib, metabolites and NSAI therapy (cycle 1 post dose through cycle 4, approximately 4 months)
Database lock	Last verified June 2017		
Results and Analysis			

Title: MONARCH 3: Abemaciclib as initial therapy for ABC [2]				
Study identifier	NCT02246621, EudraCT 2014-001502-18, Eli Lilly and Company 13Y-MC-JPBM, 15417, MONARCH 3			
Analysis description	**Primary Analysis** ITT: PFS was analysed using a log-rank test stratified by metastatic site and prior neoadjuvant or adjuvant endocrine therapy. The study was powered to 80% at one-sided α = 0.025 assuming a HR of 0.67 in favour of the abemaciclib arm, with a final analysis at 240 PFS events. A pre-specified interim analysis was planned after 189 events. A positive study at the interim required a HR <0.56 and a two-sided p<0.0005. Stratified tests using the Cochran-Mantel-Haenszel test were performed to compare response rates between treatment arms. Hypothesis tests were performed at the two-sided 0.05 level and used 95% CIs. Exploratory subgroup analyses were performed on subgroups pre-specified in the protocol and on subgroups identified in the literature as associated with prognosis and/or sensitivity to endocrine therapy. Analysis of AEs was performed in the safety population, defined as all patients who received at least one dose of study drug. Statistical analyses were performed using SAS (version 9.2 or later).			
Analysis population	Inclusion	✪ Postmenopausal women >18 years with locally tested HR+, HER2- locoregionally recurrent breast cancer non-amenable to resection or radiation therapy with curative intent or metastatic disease ✪ Measurable disease defined by RECIST v1.1, or non-measurable bone-only disease with ECOG PS ≤ 1 with adequate organ function ✪ Have not received systemic therapy for advanced disease; ET in the neoadjuvant or adjuvant setting was permitted provided the patient was disease-free >12 months from completion of ET ✪ Able to swallow capsules		
	Exclusion	✪ Presence of visceral crisis, lymphangitic spread, or leptomeningeal carcinomatosis, inflammatory breast cancer, evidence or history of CNS metastases ✪ Prior treatment with everolimus or a CDK 4/6 inhibitor ✪ Currently receiving or previously received chemotherapy or ET for locoregionally recurrent or MBC ✪ Prior neoadjuvant ET with a disease-free interval >12 months from completion of treatment ✪ Initiated bisphosphonates or approved RANK-L targeted agents <7 days prior to randomization, or had major surgery within 14 days prior to randomization		
	Characteristics	Abemaciclib + NSAI (n = 328)	Placebo + NSAI (n = 165)	Total (n = 493)
	Median age (range), years	63 (38–87)	63 (32–88)	63 (32–88)
	Race Caucasian Asian Other	 186 (56.7) 103 (31.4) 11 (3.4)	 102 (61.8) 45 (27.3) 7 (4.2)	 288 (58.4) 148 (30.0) 18 (3.7)
	ECOG 0 1	 192 (58.5) 136 (41.5)	 104 (63.0) 61 (37.0)	 296 (60.0) 197 (40.0)
	Disease setting, N (%) De novo metastatic Metastatic recurrent Locoregionally recurrent	 135 (41.2) 182 (55.5) 11 (3.4)	 61 (37.0) 99 (60.0) 5 (3.0)	 195 (39.8) 281 (57.0) 16 (3.2)
	Progesterone receptor status, N (%) Positive Negative	 255 (77.7) 70 (21.3)	 127 (77.0) 36 (21.8)	 382 (77.5) 106 (21.5)
	Metastatic site, N (%) Visceral Bone only Other	 172 (52.4) 70 (21.3) 86 (26.2)	 89 (53.9) 39 (23.6) 37 (22.4)	 261 (52.9) 109 (22.1) 123 (24.9)
	Prior neoadjuvant or adjuvant chemotherapy, N (%) Yes No	 125 (38.1) 203 (61.9)	 66 (40.0) 99 (60.0)	 191 (38.7) 302 (61.3)

Title: MONARCH 3: Abemaciclib as initial therapy for ABC [2]				
Study identifier	NCT02246621, EudraCT 2014-001502-18, Eli Lilly and Company 13Y-MC-JPBM, 15417, MONARCH 3			
	Prior ET, N (%) None AI Other ET	 178 (54.3) 85 (25.9) 65 (19.8)	 85 (51.5) 50 (30.3) 30 (18.2)	 263 (53.3) 135 (27.4) 95 (19.3)
	Treatment-free interval, N (%) <36 months ≥36 months Unknown	 42/150 (28.0) 94/150 (62.7) 14/150 (9.3)	 32/80 (40.0) 40/80 (50.0) 8/80 (10.0)	 74/230 (32.2) 134/230 (58.3) 22/230 (9.6)
	Measurable disease, N (%) Yes No	 267 (81.4) 61 (18.6)	 130 (78.8) 35 (21.2)	 397 (80.5) 96 (19.5)
	N of organ sites, N (%) 1 2 ≥3	 96 (29.3) 76 (23.2) 154 (47.0)	 47 (28.5) 42 (25.5) 75 (45.5)	 143 (29.0) 118 (23.9) 229 (46.5)
Applicability of evidence				
Population	The MONARCH 3 trial was conducted in postmenopausal women with HR+, HER2- ABC who had no prior systemic therapy in the advanced setting. Study participants had good performance status, adequate organ function without having received prior ET for MBC; however, results may differ in patients with greater comorbidity, reduced functional reserve, and those with moderate to severe renal or hepatic impairment.			
Intervention	The dosage, administration and frequency of cycles used in MONARCH 3 is consistent with the dosage, administration and schedule recommended for abemaciclib used in combination with fulvestrant for the treatment of women with HR+, HER2- advanced or MBC [3]. Treatment continued until disease progression, unacceptable toxicity, death or patient withdrawal. Dose interruptions and reductions were permitted as per recommended dose adjustments for the management of AEs. Patients were permitted to discontinue either abemaciclib/placebo or NSAI and continue the other drug.			
Comparators	While a matching placebo was used as comparator for MONARCH 3, two other CDK4/6 inhibitors (palbociclib and ribociclib) are currently available and may have formed a suitable comparator.			
Outcomes	While abemaciclib improved PFS and ORR compared with NSAI alone in MONARCH 3, OS data were not mature and QoL was not reported in this analysis.			
Setting	MONARCH 3 was a multinational trial conducted in 22 countries, approximately 63% of patients were Caucasian, 33% were Asian and 4% were of other race.			

Abbreviations: ABC = advanced breast cancer; BC = breast cancer; CBR = clinical benefit rate; CDK = cyclin-dependent kinase; CNS = central nervous system; CR = complete response; DCR = disease control rate; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; ET = endocrine therapy; HER2- = human epidermal growth factor receptor 2-negative; HR = hazard ratio; HR+ = hormone receptor-positive; ITT = intent-to-treat; MBC = metastatic breast cancer; NSAI = nonsteroidal aromatase inhibitors; OS = overall survival; PFS = progression free survival; PR = partial response; PS = performance status; QoL = quality of life; RANK-L = receptor activator of nuclear factor kappa-B ligand; RECIST = Response Evaluation Criteria in Solid Tumours

Table 6: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [26]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: randomised 2:1 abemaciclib versus placebo via an interactive web-based response system; stratified by metastatic site (visceral, bone only, or other) and prior neoadjuvant or adjuvant endocrine therapy (AI, no ET, or other)		no
Adequate allocation concealment: participants and investigators could not foresee assignment as the study drug was determined by the centralised interactive web-based response system		no
Blinding:	**Patient:** blind to study drug allocation; centralised randomisation	no
	Treating physician: blinded to drug allocation; identical matching placebo	no
	Outcome assessment: centralised randomisation and allocation; sensitivity analysis was planned to assess PFS by full, blinded, ICR	no
Selective outcome reporting unlikely: primary endpoints include investigator-assessed PFS, ORR, CR, PR, DOR, CBR, safety and tolerability; other endpoints not included in this analysis include OS, QoL, pharmacokinetics and biomarker analyses; as per clinicaltrials.gov		no
No other aspects which increase the risk of bias: while all authors were accountable for all aspects of the work, industry was involved in funding, study design, study materials, data collection, analysis and interpretation		yes
Risk of bias – study level		low

Abbreviations: AI = aromatase inhibitor; CBR = clinical benefit rate; CR = complete response; DOR = duration of response; ET = endocrine therapy; ICR = independent central review; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR: partial response; QoL = quality of life