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Abemaciclib (Verzenio®) in combination with fulvestrant for treatment of HR-positive, HER2-negative advanced breast cancer (ABC)

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Abstract

Introduction

Breast cancer arises from the tissues of the breast and most commonly originates in the cells that line the ducts due to dysregulation of the cell cycle. Abemaciclib has been approved by the US Food and Drug Administration (FDA) in September 2017 for the following two indications: abemaciclib as monotherapy for patients with hormone receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced breast cancer (ABC) who have received prior endocrine therapy (ET) and chemotherapy for metastatic disease, and abemaciclib in combination with fulvestrant in women with HR-positive, HER2-negative ABC who had disease progression following ET. Currently, abemaciclib is not approved in Europe.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer (overall: 141 references). 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, both the original and an adapted version of, the Magnitude of Clinical Benefit Scale (MCBS) developed by the European Society for Medical Oncology (ESMO).

Results of the MONARCH 2 trial

Between 7 August 2014 and 29 December 2015, 669 patients were randomly assigned to receive either abemaciclib plus fulvestrant (n = 446) or placebo plus fulvestrant (n = 223). At the median follow-up of 19.5 months, the primary endpoint progression-free survival (PFS) showed a statistically significant increase of 7.1 months (median) in the intention-to-treat (ITT) population of the abemaciclib arm. In addition, the improvement of the overall response rate (ORR) in the ITT population of the abemaciclib arm (+19.1%) was statistically significant. However, at the time of data cut-off (February 2017), overall survival (OS) results were not mature as well as quality of life (QoL) outcomes are not reported. The most frequent adverse events (AEs) of any grade were diarrhoea, neutropenia, nausea, fatigue, and abdominal pain. Grade ≥3 AEs could be observed more commonly in the abemaciclib group (60.5%) than in the placebo group (22.8%). In addition, discontinuation rates (15.9% vs. 1.3%) as well as dose reductions (42.9 vs. 1.3) due to AEs occurred more commonly in the abemaciclib group.

Conclusion

In conclusion, the treatment with abemaciclib offers a statistically significant improvement in PFS of 7.1 months and ORR (+19.1%) with an inferior safety profile at high costs. Due to the immature OS data and the missing QoL results there is a need of long-term data to avoid a systematic overestimation of the treatment effect of abemaciclib. In the future, the identification of a robust predictive biomarker to identify the most suitable patients will be crucial for the class of CDK4/6 inhibitors. Finally, direct comparisons of abemaciclib to palbociclib and ribociclib are essential to investigate which treatment option is most beneficial for HR-positive, HER2-negative ABC patients.

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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 cancer for 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?
A0025	How is the disease or health condition currently managed according to published guidelines and in practice?
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/Verzenio®/LY2835219

B0001: What is abemaciclib?

orally available, selective CDK inhibitor

Abemaciclib (LY2835219) is an orally available cyclin-dependent kinase (CDK) inhibitor, which specifically inhibits the activities of the cyclin D-dependent kinases CDK4 and CDK6. During the cell-division cycle abemaciclib arrests progression through the G1 phase and thereby promotes transient cell-cycle withdrawal into a quiescent state (G0) or into a permanent proliferation inhibition (senescence). As a result DNA synthesis is supressed and cancer cell growth stopped [2-5].

150 mg twice daily on a continuous schedule

According to clinical trials, the recommended dose of abemaciclib is 150 mg administered orally twice daily given continuously in combination with 500 mg of fulvestrant by intramuscular injection on days one and 15 of the first cycle (28 days) and on day one of subsequent cycles.

A0022: Who manufactures abemaciclib?

Eli Lilly and Company

3 Indication

A0007: What is the target population in this assessment?

HR-positive, HER2-negative ABC patients

Abemaciclib in combination with fulvestrant is indicated for treatment of hormone-receptor (HR)-positive, human epidermal growth factor 2 (HER2)-negative advanced breast cancer (ABC) patients, who have progressed while receiving endocrine therapy (ET).

4 Current regulatory status

A0020: For which indications has abemaciclib received marketing authorisation?

since September 2017 approved by the FDA

Abemaciclib has been approved by the US Food and Drug Administration (FDA) in September 2017 for the following two indications [6]:

- abemaciclib as monotherapy for patients with HR-positive, HER2-negative ABC who have received prior ET and chemotherapy for metastatic disease
- abemaciclib in combination with fulvestrant in women with HR-positive, HER2-negative ABC who had disease progression following ET

The submission is based on two clinical trials, the MONARCH 1 and MONARCH 2 [6].

abemaciclib is not approved in Europe

Currently, abemaciclib has not received marketing authorisation by the European Medicines Agency (EMA).

5 Burden of disease

A0002: What is breast cancer?

heterogeneous disease that arise from the tissue of the breast most commonly from cells lining the ducts

Owing to the molecular pathogenesis of breast cancer, it is designated as a heterogeneous malignancy. It arises from the tissues of the breast and most commonly originates in the cells that line the ducts due to dysregulation of the cell cycle. Breast cancer can be characterised by the pattern of expression of the HRs (oestrogen receptor [ER] and progesterone receptor [PR]), the HER2 receptor, a clinically relevant third molecular marker, the stage at the time of diagnosis and the rate of growth. Prognostically and therapeutically a distinction can be made between pre-cancerous conditions like in situ tumours (obligatory pre-cancerous condition: ductal carcinoma in situ [DCIS]; optional pre-cancerous condition: lobular carcinoma in situ [LCIS]) and invasive breast cancer [7, 8].

A0004: What is the natural course of breast cancer?

stages of breast cancer: stage 0, stage I, stage II, stage III and stage IV

Mostly, cancer begins in the cells of the ducts, called ductal carcinoma. Abnormal cells are found in the lining of the ducts; however, they have not spread into the surrounding tissue and thus state a pre-cancerous condition like DCIS (stage 0) [9, 10]. In fact, the development of type A, ductal hyperplasia over DCIS, into invasive breast cancer is not veritable. Invasive breast cancer, stage I, is restricted to the breast not larger than 2.0 cm (pT1) and with only micrometastasis (<2 mm) in the axillary lymph nodes (pNmi). In stage II, the tumour is pT0 or pT1 with 1-3 involved axillary lymph nodes (pN1) or pT2 with no or 1-3 involved axillary lymph nodes (pN1) or pT3

with no lymph node involvement. Under stage III, tumours are summarised that have different size and lymph node involvement apart from the above mentioned without distant metastasis [11]. If the cancer has spread to distant parts of the body (stage IV) via the lymph system or the blood, it can also be referred to as metastatic breast cancer (MBC) [10].

AJCC-TNM staging system

Breast cancer can be staged by using the American Joint Committee on Cancer (AJCC) tumour node metastasis (TNM) staging system. It involves important tumour characteristics as well as survival data to support the estimation of outcomes. The TNM staging system classifies tumours on the basis of the primary tumour characteristics (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastases (M).

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

increasing incidence of cancer

Due to the aging population and in combination with the fact that higher age is strongly related to breast cancer risk, the incidence of cancer will increase over time [12]. Globally, around 30% of the patients with early breast cancer develop advanced or MBC [13]. In Austria, breast cancer accounts for approximately 28,000 (2.6% of total) life-years lost due to premature deaths [14]. Moreover, the incidence of breast cancer is highest for higher socioeconomic groups, whereas survival is lowest in lower socioeconomic groups [15].

highest incidence rate in higher socioeconomic groups

A0023: How many people belong to the target population?

incidence rate based on the European Standard Population: 64.3 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 (2013) is 64.3 per 100,000 persons per year. In 2014, 5,454 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 [16]. The median age at diagnosis of breast cancer is 62 years in the US, ranging from 55 to 64 years [17].

median age at diagnosis: 62

HR-positive, HER2-negative most common breast cancer type; ~3,818 HR-positive, HER2-negative breast cancer cases in 2014 in Austria

HR-positive disease accounts for approximately 65% and 80% of breast cancers in pre- and postmenopausal women, respectively. Accounting for approximately 70% of breast cancer patients, HR-positive and HER2-negative is the most common type of breast cancer. Therefore, about 3,818 of the 5,454 persons diagnosed with breast cancer in 2014 in Austria were affected by HR-positive and HER2-negative disease. Between 5–10% of the patients at the time of first presentation have MBC that has spread to other parts of the body, e.g., bone, liver, lung and brain and about 30% of people who present with localised disease will later develop metastases [15, 18].

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

main symptoms: breast mass, skin irritation, pain

A breast mass with irregular borders is the most common symptom of breast cancer [19-21]. In addition, symptoms like swelling of the whole or only parts of the breast, skin irritation or dimpling (peau d'orange), less often breast or nipple pain, nipple retraction, redness, or thickening of the nipple or breast skin, nipple discharge or axillary adenopathy can occur [20-22]. In

advanced stages of breast cancer weight loss and reduced performance can be present [22]. Symptoms due to metastases include swelling of the arm because of lymph node metastases of the axilla, bone pain in skeletal metastases, cough and dyspnoea in pulmonary and/or pleural metastases, jaundice and hepatic failure in advanced liver metastases, or neurological symptoms in cerebral metastases [15, 21, 22].

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

main risk factors: age, gender, race, obesity, genes, menopausal status

Established high-risk factors for developing breast cancer are an increasing age, female gender and white race. Indeed, obesity as well as mutations in genes like BRCA1 and, BRCA2 are associated with an increased risk of breast cancer in pre- and postmenopausal women [15, 22-25]. In addition, increased exposure to oestrogen like early menarche or late menopause can also be a risk factor for the diagnosis of breast cancer [22, 23]. Furthermore, reproductive factors may influence the risk including a first pregnancy at late age, absence of breastfeeding and nulliparity [23, 24]. Other risk factors that may lead to breast cancer are alcohol consumption, smoking, family and personal history of breast cancer [24].

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

diagnosis of breast cancer via mammography, CBE, biopsy, blood chemistry and x-ray tests

There are several ways to diagnose breast cancer, such as the clinical breast exam (CBE) and imaging like mammography and sonography or magnetic resonance imaging (MRI). However, an abnormal mammogram is the most common reason for suspecting breast cancer. If breast cancer is suspected in the mammogram a sonography, followed by a biopsy (core needle biopsy and vacuum-assisted biopsy) have to be performed. An additional breast MRI can increase the detection rate of additional lesions, but it does not improve the prognosis [22]. In the later stages of the disease, abdominal and thoracic diagnostic scans, bone scans can be applied [25]. The positron emission tomography (PET) plays a less important role for the diagnosis and staging of breast cancer [25].

additional use of MRI possible to detect further lesions

HR and HER2 status

As breast cancer is a heterogeneous disease, it is essential to establish the HR and HER2 status [10, 25]. Additionally, the stratification into the different disease stages, described in section "A0004: What is the natural course of breast cancer?" is crucial to ensure the best therapy.

stratification into disease stage

6 Current treatment

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

factors for therapeutic decisions

Generally, breast cancer can be treated by surgery, adjuvant irradiation and/or systemic therapies [22]. To determine which treatment strategy is the most suitable for the patient, several factors are important [20, 22]:

- stage of cancer (AJCC TNM staging system)
- grade of disease
- menopausal status
- patient health
- HR and HER2 status
- proliferation rate estimated by means of a Ki67 test

curative treatment options for stage ≤3 breast cancer

The treatment of stage ≤3 breast cancer, where no distant metastases have been detected, has a curative intention. The following steps of therapy may apply depending on the biology and the stage of the tumour and the performance status of the patient [22]:

- neoadjuvant systemic therapy
- surgery (mastectomy versus breast conserving therapy [BCT], sentinel lymph node biopsy [SLNB]), axillary node dissection)
- adjuvant systematic therapy
- adjuvant radiation therapy

stage IV breast cancer treatment options with a palliative intent

For patients with locally ABC (stage IIB, IIIA/B) the previously mentioned treatment options can be applied as well. In case of metastatic disease (stage IV), treatment with a palliative intent (systemic therapy, best supportive care, etc.) can be used [22].

treatment options for HR-positive, HER2-negative ABC

In particular, treatment options for patients with HR-positive, HER2-negative advanced or MBC who have not responded to, relapsed or progressed while receiving ET are [26]:

- pre- or perimenopause
  - ovarian function suppressing (OFS) + tamoxifen
  - OFS + fulvestrant+ palbociclib,
  - tamoxifen,
  - OFS,
  - OFS + aromatase inhibitors (AI),
  - OFS + fulvestrant,
  - OFS + AI + palbociclib
- postmenopause
  - letrozol + palbociclib
  - fulvestrant + palbociclib
  - fulvestrant
  - AI 3rd generation
  - exemestan + everolimus
  - tamoxifen
  - eamoxifen + everolimus

7 Evidence

A literature search was conducted on 07 August 2017 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "abemaciclib", "LY2835219", "breast cancer", "breast neoplasms", "mamma carcinoma", and "advanced". The manufacturer was also contacted and submitted three references (of which one had already been identified by systematic literature search). A manual search identified 34 additional references (web documents and journal articles).

systematic literature search in 5 databases: 105 hits

manual search: 34 additional references

Overall, 141 references were identified. Included in this report are the following two studies to assess outcomes on clinical efficacy and safety:

overall: 141 references included: 2 studies to assess clinical efficacy and safety outcomes

- One phase III study, assessing abemaciclib in HR-positive, HER2-negative ABC patients, who had progressed while receiving neoadjuvant or adjuvant ET [27, 28]
- One phase II study, assessing the single-agent activity and safety of abemaciclib in women with refractory HR-positive, HER2-negative MBC, who have progressed on or after prior ET and have received one or two chemotherapy regimens [29]

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) [30]. 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.

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

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 [31]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [32]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

7.1 Clinical efficacy and safety – phase III studies

The MONARCH 2 trial, a randomised, double-blind, global, placebo-controlled phase III study, was conducted to assess the addition of abemaciclib to fulvestrant for the treatment of HR-positive, HER2-negative ABC (inoperable locally advanced or MBC) patients, who have progressed while receiving neoadjuvant or adjuvant ET, ≤12 months after adjuvant ET, or while receiving ET for ABC [27, 28].

MONARCH 2: randomised, placebo-controlled, double-blind, global, phase III trial

final analysis of the primary endpoint PFS

data cut-off: February 2017

Reported are results of the final analysis of the primary endpoint (progression-free survival [PFS]), which was planned after 378 PFS events (documented progression or death without documented progression) had occurred. At the time of data cut-off (February 14, 2017) 379 PFS events have occurred (n = 222 [49.8%] in the abemaciclib plus fulvestrant arm and n = 157 [70.4%] in the control arm) in the intention-to-treat (ITT) population. 170 patients (38.1%) in the abemaciclib arm versus 45 (20.2%) in the placebo arm were continuing to receive the study drug at the time of data cut-off, whereas 70 (15.9%) in the intervention arm versus seven patients (3.1%) in the placebo arm discontinued due to adverse events (AEs). The median length of follow-up at the time of data cut-off was 19.5 months; patients in the abemaciclib arm received a median of 15 cycles compared with nine cycles in the control arm.

median of 15 cycles (abemaciclib) and nine cycles (placebo)

efficacy and safety of abemaciclib and fulvestrant vs. placebo and fulvestrant

A total of 669 patients were randomly assigned in a 2:1 ratio to receive abemaciclib or placebo (150 mg twice daily) given continuously in combination with 500 mg of fulvestrant by intramuscular injection on days one and 15 of the first cycle (28 days) and on day one of subsequent cycles. The stratification of randomisation was based on the metastatic site (visceral, bone only, or other) and ET resistance (primary or secondary). Initially the study was planned to enrol 450 patients for the ITT population. However, the starting dose of the blinded-study drug was changed from 200 mg to 150 mg; therefore, the sample size was increased to 630 patients to ensure that at least 450 patients receive a dose of 150 mg. Before the mandatory dose-reduction, 121 (27.4%) patients have received 200 mg of abemaciclib for a median of 34 days.

amendment of the starting dose from 200 to 150 mg

median age of 59 years in the abemaciclib group and ECOG performance status of 0–1

Enrolled patients were at least 18 years old and had a median age of 59 (range, 32–91) and 62 (range, 32–87) years in the abemaciclib and placebo group, respectively. The study population had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Detailed patient characteristics including inclusion- and exclusion criteria can be found in Table 4.

primary outcome: PFS key secondary outcomes: ORR, DOR, CBR, safety and tolerability

The primary outcome of MONARCH 2 was investigator-assessed PFS; key secondary outcomes included objective response rate (ORR; e.g., proportion of patients with complete response [CR] or partial response [PR]), duration of response (DOR; time from CR or PR until progressive disease [PD] or death), clinical benefit rate (CBR, CR plus PR plus stable disease ≥6 months), tolerability and safety. Other secondary endpoints that are not reported in this analysis are overall survival (OS), quality of life (QoL) measures and pharmacokinetics.

OS and QoL not reported in this analysis

7.1.1 Clinical efficacy

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

immature OS data at the time of data cut-off

OS results were not mature at the time of data cut-off (February 2017); 85 deaths (19.1%) in the abemaciclib arm and 48 (21.5%) in the placebo arm have occurred.

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

PFS, the primary endpoint, showed a statistically significant improvement in the ITT population of the abemaciclib arm ($p < 0.001$). The investigator-assessed median PFS was 16.4 and 9.3 months in the abemaciclib group and the placebo group, respectively. The hazard ratio (HR) for disease progression of abemaciclib compared to placebo was 0.533 (95% CI 0.449–0.681). The blinded central analysis yielded a HR for disease progression of 0.460 (95% CI 0.363–0.584; $p < 0.001$). In addition, a sensitivity analysis was conducted that included only those patients, who were enrolled after the change of the starting dose, which resulted in a HR for disease progression of 0.588 (95% CI 0.458–0.754).

positive difference in investigator-assessed median PFS in the ITT population: 7.1 months

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

The ORR in the ITT population was 35.2% (95% CI 30.8–39.6%, n = 157) in the abemaciclib arm and 16.1% (95% CI 11.3–21.0%, n = 36) in the placebo arm; a CR occurred in 14 patients (3.1%) in the abemaciclib group and in one patient (0.4%) in the control group. ORR improvement in the abemaciclib arm was statistically significant ($p < 0.001$).

ORR in the ITT population
abemaciclib: 35.2%
placebo: 16.1%

In both study groups responses were durable, with 12-month DOR rates of 67.8% and 66.9% in the abemaciclib arm and the placebo arm, respectively. The median DOR had not been reached in the abemaciclib arm. At the time of data cut-off, 90 responders (57.3%) continuing to receive treatment. Patients with measurable disease showed an ORR of 48.1% (95% CI 42.6–53.6%) in the abemaciclib arm and 21.3% (95% CI 15.1–27.6%) in the control arm was observed ($p > 0.001$).

12-month DOR rates
abemaciclib: 67.8%
placebo: 66.9%

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

No evidence was found to answer this research question.

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?

No evidence was found to answer this research questions. Although QoL measures are secondary endpoints of the MONARCH 2 study they were not reported in the published final analysis of the primary endpoint, PFS.

QoL measures are not reported

Table 1: Efficacy results of the MONARCH 2 trial

Descriptive statistics and estimate variability	**Treatment group**	**Abemaciclib**	**Placebo**
	Number of subject	446	223
	Median PFS (ITT), months	16.4	9.3
	ORR (ITT), % (95% CI) CR PR	35.2 (30.8–39.6) 3.1 (1.5–4.8) 32.1 (27.7–36.4)	16.1 (11.3–21.0) 0.4 (-0.4–1.3) 15.7 (10.9–20.5)
	OS	NA	NA
	QoL	NA	NA
Effect estimate per comparison	*Comparison groups*		Abemaciclib+fulvestrant versus placebo+fulvestrant
	PFS (ITT)	HR	0.553
		95% CI	0.449–0.681
		Log-rank test p-value	< 0.001
	PFS (blinded central analysis)	HR	0.460
		95% CI	0.363–0.584
		Log-rank test p-value	< 0.001
	PFS (starting dose: 150 mg)	HR	0.588
		95% CI	0.458–0.754
		Log-rank test p-value	NA

Abbreviations: CI = confidence interval, CR = complete response, HR = hazard ratio, ITT = intention-to-treat population, NA = not available, OS = overall survival, PFS = progression-free survival, PR = partial response, QoL = quality of life

7.1.1.1. Safety

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

grade ≥3 AEs abemaciclib: 60.5% placebo: 22.8%

The most frequent AEs in the safety population (abemaciclib, n = 441; placebo = 223) of any grade were diarrhoea, neutropenia, nausea, fatigue, and abdominal pain. Grade ≥3 AEs could be observed in 267 (60.5%) patients in the abemaciclib group and in 51 (22.8%) patients in the placebo group. The most common grade ≥3 AEs in the abemaciclib group were neutropenia (26.5%), diarrhoea (13.4%), leukopenia (8.8%) and anaemia (7.2%). Infections, regardless of relatedness, occurred more frequently in the abemaciclib arm compared to the placebo arm (42.6% vs 24.7%). Serious adverse events (SAEs) were more common in the abemaciclib group (22.4%) than in the placebo group (10.8%).

9 deaths due to AEs in the abemaciclib group

In total 14 deaths (3.2%) occurred in the abemaciclib arm (nine because of AEs) and ten (4.5%) in the control arm (two due to AEs). Three deaths (0.7%) in the abemaciclib group were related to the study drug, two due to sepsis, and one because of viral pneumonia.

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

dose interruptions abemaciclib: 51.9% placebo: 11.7%

Discontinuation due to AEs occurred in 70 (15.9%) patients of the abemaciclib group and in seven (1.3%) patients of the placebo group. Dose reductions due to AEs were necessary in 189 (42.9%) patients of the abemaciclib

arm and in three (1.3%) patients of the placebo arm. Abemaciclib treatment due to AEs was interrupted in 229 (51.9%) patients and treatment interruptions in the placebo arm occurred in 26 (11.7%) patients.

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

No evidence was found to answer this research question.

Table 2: Most frequent treatment-emergent adverse events

Adverse Event (according to CTCAE version 4.0)[1]	**Intervention** (n = 441)			**Control** (n = 223)		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Any	435 (98.6)	241 (54.6)	26 (5.9)	199 (89.2)	46 (20.6)	5 (2.2)
Diarrhoea	381 (86.4)	59 (13.4)	0 (0)	55 (24.7)	1 (0.4)	0 (0)
Neutropenia	203 (46.0)	104 (23.6)	13 (2.9)	9 (4.0)	3 (1.3)	1 (0.4)
Nausea	199 (45.1)	12 (2.7)	-	51 (22.9)	2 (0.9)	–
Fatigue	176 (39.9)	12 (2.7)	-	60 (26.9)	1 (0.4)	–
Abdominal pain	156 (35.4)	11 (2.5)	-	35 (15.7)	2 (0.9)	–
Anaemia	128 (29.0)	31 (7.0)	1 (0.2)	8 (3.6)	2 (0.9)	0 (0)
Leukopenia	125 (28.3)	38 (8.6)	1 (0.2)	4 (1.8)	0 (0)	0 (0)
Decreased appetite	117 (26.5)	5 (1.1)	0 (0)	27 (12.1)	1 (0.4)	0 (0)
Vomiting	114 (25.9)	4 (0.9)	0 (0)	23 (10.3)	4 (1.8)	0 (0)
Headache	89 (20.2)	3 (0.7)	–	34 (15.2)	1 (0.4)	–
Dysgeusia	79 (17.9)	–	–	6 (2.7)	–	–
Alopecia	69 (15.6)	–	–	4 (1.8)	–	–
Thrombocytopenia	69 (15.6)	9 (2.0)	6 (1.4)	6 (2.7)	0 (0)	1 (0.4)
Stomatitis	67 (15.2)	2 (0.5)	0 (0)	23 (10.3)	0 (0)	0 (0)
Constipation	60 (13.6)	3 (0.7)	0 (0)	30 (13.5)	1 (0.4)	0 (0)
ALT increased	59 (13.4)	17 (3.9)	1 (0.2)	12 (5.4)	4 (1.8)	0 (0)
Cough	59 (13.4)	0 (0)	–	25 (11.2)	0 (0)	–
Pruritus	57 (12.9)	0 (0)	–	13 (5.8)	0 (0)	–
Dizziness	55 (12.5)	3 (0.7)	–	13 (5.8)	0 (0)	–
AST increased	54 (12.2)	10 (2.3)	0 (0)	15 (6.7)	6 (2.7)	0 (0)
Blood creatinine level increased	52 (11.8)	4 (0.9)	0 (0)	1 (0.4)	0 (0)	0 (0)
Arthralgia	51 (11.6)	1 (0.2)	-	32 (14.3)	1 (0.4)	–

Edema peripheral	51 (11.6)	0 (0)	-	15 (6.7)	0 (0)	–
Rash	49 (11.1)	5 (1.1)	0 (0)	10 (4.5)	0 (0)	0 (0)
URTI	49 (11.1)	0 (0)	0 (0)	17 (7.6)	2 (0.9)	0 (0)
Dyspnoea	48 (10.9)	11 (2.5)	1 (0.2)	25 (11.2)	3 (1.3)	0 (0)
Pyrexia	48 (10.9)	2 (0.5)	1 (0.2)	13 (5.8)	1 (0.4)	0 (0)
Muscular weakness	47 (10.7)	4 (0.9)	–	13 (5.8)	0 (0)	–
Hot flush	46 (10.4)	0 (0)	–	22 (9.9)	0 (0)	–
Weight decreased	46 (10.4)	1 (0.2)	–	5 (2.2)	1 (0.4)	–
Back pain	42 (9.5)	3 (0.7)	–	28 (12.6)	2 (0.9)	–

Abbreviations: ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, CTCAE = Common Terminology Criteria for Adverse Events, URTI = upper respiratory tract infection, [1] = ≥10% of adverse events in either arm, – = grade does not exist for this adverse event

7.2 Clinical effectiveness and safety – further studies

MONARCH 1: single-agent activity and safety of abemaciclib in HR-positive, HER2-negative refractory MBC

There is no further study available that has investigated the combination treatment of abemaciclib with fulvestrant in HR-positive, HER2-negative ABC patients. However, the single-agent activity and safety of abemaciclib was evaluated in women with refractory HR-positive, HER2-negative MBC, who have progressed on or after prior ET and have received one or two chemotherapy regimens [29]. In this single-arm, open-label, phase II study (MONARCH 1) 132 women were enrolled to receive 200 mg of abemaciclib on a continuous schedule every 12 hours until disease progression or unacceptable toxicities. The primary outcome was investigator-assessed ORR. Secondary endpoints included CBR, PFS and OS.

confirmed ORR: 19.7%
median PFS: 6.0 months
median OS: 17.7 months
CBR: 42.4%

Enrolled women had received a median of three (range, 1–8) lines of systemic therapy in the metastatic setting, 50.8% had ≥3 metastatic sites, and 90.2% had visceral disease. At the time of final analysis (12-month), the primary endpoint of confirmed ORR was 19.7% (95% CI 13.3–27.5); the CBR was 42.4%, median PFS was 6.0 months and median OS was 17.7 months. The most common treatment-emergent AEs of any grade were diarrhoea, fatigue, and nausea; the discontinuation rate due to AEs was 7.6%.

8 Estimated costs

A0021: What is the reimbursement status of abemaciclib?

no cost estimates available yet

To date, abemaciclib has not been approved in Europe. Therefore, no price estimates are available at this point.

9 Ongoing research

3 ongoing phase III studies investigating abemaciclib in breast cancer

In August 2017, a search in databases www.clinicaltrials.gov and www.clinicaltrialsregister.eu was conducted. Three ongoing phase III trials investigating abemaciclib in breast cancer were identified:

- **NCT03155997:** A randomized, open-label, phase III study of abemaciclib combined with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone in patients with high risk, node positive, early stage, hormone receptor positive, human epidermal receptor 2 negative, breast cancer. Estimated primary completion date is June 2027.
- **NCT02763566:** A randomized, double-blind, placebo-controlled, phase III study to compare NSAI (anastrozole or letrozole) plus abemaciclib, a CDK4 and CDK6 inhibitor, or plus placebo, and to compare fulvestrant plus abemaciclib or plus placebo in postmenopausal women with hormone receptor-positive, HER2-negative locoregionally recurrent or MBC. Estimated primary completion date is January 2020.
- **NCT02246621:** A randomized, double-blind, placebo-controlled, phase III study of nonsteroidal aromatase inhibitors (anastrozole or letrozole) plus LY2835219, a CDK4/6 inhibitor, or placebo in postmenopausal women with hormone receptor-positive, HER2-negative locoregionally recurrent or MBC with no prior systemic therapy in this disease setting. Estimated primary completion date is July 2021.

5 ongoing phase I and 7 ongoing phase II trials in different indications and treatment lines

Seven phase II and five phase I studies are currently ongoing in different treatment lines in patients with breast cancer, either using abemaciclib monotherapy or combination treatment (e.g., NCT03130439, NCT02747004, NCT02102490, NCT02675231 and NCT02831530). In addition, abemaciclib is currently under investigation in other indications, like dedifferentiated liposarcoma, non-small-cell lung cancer, recurrent glioblastoma, melanoma, and pancreatic ductal adenocarcinoma.

10 Discussion

since September 2017 approved in the US, but not in Europe

Currently, abemaciclib is approved for breast cancer since September 2017 in the US after receiving priority review in July 2017 for the following two indications: abemaciclib as monotherapy for patients with HR-positive, HER2-negative ABC who have received prior ET and chemotherapy for metastatic disease, and abemaciclib in combination with fulvestrant in women with HR-positive, HER2-negative ABC who had disease progression following ET [6]. However, it has not yet received marketing authorisation in Europe.

MONARCH 2 (data cut-off February 2017): statistically significant improvement in PFS and ORR, but OS was immature

The approval by the FDA for the combination treatment of abemaciclib plus fulvestrant is based on the MONARCH 2 trial [27, 28]. The study was conducted to compare abemaciclib plus fulvestrant to placebo plus fulvestrant in 669 patients with ABC, who have progressed while receiving ET. At the median follow-up of 19.5 months, the primary endpoint PFS showed a statistically significant increase of 7.1 months (median) in the ITT population of the abemaciclib arm compared to the placebo arm ($p < 0.001$). In addition, the ORR improvement in the ITT population of the abemaciclib arm (+19.1%) was statistically significant ($p < 0.001$). At the time of data cut-off (February 2017), OS results were not mature; 85 deaths (19.1%) in the abemaciclib arm and 48 (21.5%) in the placebo arm have occurred (+2.4%). QoL outcomes are not reported in the planned final analysis of the primary endpoint, PFS.

immature OS and missing QoL data

Mature OS data and QoL measures are needed as well as further follow-up data to ensure a clinical relevant patient benefit over time. In addition, to better reflect the most affected patient population, abemaciclib should also be investigated in an older patient population (median age of study population in the abemaciclib group: 59), as the median age of breast cancer diagnosis is 62 years [17]. A gain of 7.1 months in median PFS was not only observed in a slightly younger patient population, but also in a less diseased population (ECOG 0–1), and might not be reached in the general patient population. Therefore, these patients should be further analysed in future trials to identify any advantages or disadvantages, for less fit as well as older patients, when treated with abemaciclib.

health status and age of the study population was not representative for the actual patient population

grade ≥3 AEs more common in the abemaciclib group

In terms of safety, the most frequent AEs of any grade were diarrhoea, neutropenia, nausea, fatigue, and abdominal pain. Grade ≥3 AEs could be observed more commonly in the abemaciclib group (60.5%) than in the placebo group (22.8%). The most frequent grade ≥3 AEs in the abemaciclib group were neutropenia (26.5%), diarrhoea (13.4%), leukopenia (8.8%) and anaemia (7.2%). In addition, discontinuation rates (15.9% vs. 1.3%) as well as dose reductions (42.9 vs. 1.3) due to AEs occurred more commonly in the abemaciclib group. Moreover, three deaths (0.7%) in the abemaciclib group were linked to the study drug, two due to sepsis, and one was because of viral pneumonia.

three deaths related to abemaciclib

high incidence of gastrointestinal toxicities

Gastrointestinal toxicities were the dose-limiting factor in the MONARCH 2 trial, especially the incidence of diarrhoea was increased with abemaciclib (all grades: 86.4% versus 24.7%; grade 3-4: 13.4% versus 0.4%). Thus, the administered dose of abemaciclib was reduced from 200 mg to 150 mg after 121 (27.4%) patients have received the study drug. Therefore, additional investigations are necessary to better understand the safety profile of abemaciclib and to develop management strategies [5].

ESMO-MCBS original: 3 adapted: 2

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). Both the original as well as the adapted version of the MCBS were applied [31, 32]. The application of the ESMO-MCBS to the MONARCH 2 study resulted in a grade 3 and 2 in the original and the adapted version of the ESMO-MCBS, respectively (Table 3). Therefore, abemaciclib does not demonstrate a meaningful clinical benefit in either the adapted scale nor in the original framework. Differences in scores occur due to the higher implication of toxicities in the adapted ESMO-MCBS.

low risk of bias: double-blind, adequate generation of randomisation sequence, unlikely selective outcome reporting

There are methodological limitations of the MONARCH 2 trial that compromise internal and external validity. Although patients were randomized 2:1 to the abemaciclib or placebo arm via interactive, web-based randomization scheme, allocation concealment was not maintained, which may lead to a selection bias. Besides that, the missing follow-up data of the MONARCH 2 trial can lead to a systematic overestimation of the treatment effect of abemaciclib [33]. However, due to the double-blind study design, the adequate generation of randomisation sequence and an unlikely selective outcome reporting a low risk of bias could be detected.

two other approved CDK4/6 inhibitors are available

Two other CDK4/6 inhibitors (palbociclib and ribociclib) are already approved in Europe as well as in the US for the treatment of HR-positive, HER2-negative breast cancer [34-37]. Whilst palbociclib and ribociclib have comparable toxicity profiles, gastrointestinal toxicities and fatigue are more prevalent with abemaciclib [5]. Moreover, in the MONARCH 2 trial prior chemotherapy was an exclusion criteria, which was in contrast to the trial investigating palbociclib (PALOMA 3) [38]. All these factors have to be considered in future treatment schemes for HR-positive, HER2-negative breast cancer patients to determine the best place of treatment with abemaciclib. In addition, though 108 active trials involving these three CDK4/6 inhibitors are registered on clinicaltrials.gov none of them perform direct comparisons with one another. Consequently, direct comparisons of these agents are necessary in order to identify the best treatment option for HR-positive, HER2-negative ABC patients.

different safety profiles

direct comparisons of palbociclib, ribociclib and abemaciclib are needed

predictive biomarkers required

At the moment, the only predictive biomarker for CDK4/6 inhibitors clinically used is the HR-positive and HER2-negative breast cancer subtype [39]. Therefore, there is a lack of predictive biomarkers, to screen the appropriate patient population who would benefit most from these agents [39-43]. The selection of sensitive patients may increase patient benefit on the one hand, and also improve the cost-effectiveness ratio of these inhibitors on the other hand [40]. One candidate could be the retinoblastoma protein (Rb) expression which is currently evaluated in two ongoing phase I studies (NCT01976160, NCT01320592) investigating palbociclib, whereby Rb expression is one of their inclusion criteria [44]. Moreover, another biomarker study is ongoing (NCT03195192), that aims to identify multiomic advanced diagnostics to select CDK4/6 inhibitor response predictors [45]. In addition, the identification of the mechanisms of de novo and acquired resistance is important to prevent the limitation of efficacy of these therapies and to elucidate the most effective CDK4/6 inhibitor approaches [41, 43]. Thus, further clinical trials that tackle these important issues are needed.

ongoing biomarker studies

identification of resistance mechanisms

no price estimates available for abemaciclib

There are no price estimates available for abemaciclib, as it has not yet received marketing authorisation in Europe. However, the costs of the CDK4/6 inhibitor palbociclib of €4,582.55 per 28-day cycle could be taken as a proxy variable, since both drugs are indicated for the same target population [46].

significant PFS and OS improvement, immature OS data, missing QoL measures

lack of reliable biomarkers

comparative studies are needed

In conclusion, the treatment with abemaciclib offers a statistically significant improvement in PFS of 7.1 months and ORR (+19.1%) with an inferior safety profile at high costs. Due to the immature OS data and the missing QoL results there is a need of long-term data to avoid a systematic overestimation of the treatment effect of abemaciclib. In future, the identification of a robust predictive biomarker to identify the most suitable patients will be crucial for the class of CDK4/6 inhibitors. Finally, direct comparisons of abemaciclib to palbociclib and ribociclib are essential to investigate which treatment option is most beneficial for HR-positive, HER2-negative ABC patients.

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [31, 32]

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	>6 months	+7.1	0.55 0.45–0.68	HR ≤0.65 AND Gain ≥3 months	3	+37,7% grade 3–4 AEs[A]	x	-1	**2**
Original ESMO-MCBS	Abemaciclib	breast cancer	NC	PFS	2b	>6 months	+7.1	0.55 0.45–0.68	HR ≤0.65 AND Gain ≥3 months	3	x	x	x	**3**

Abbreviations: AJ = Adjustments, CI = confidence interval, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, NC = non-curative, 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.

[A] Downgrade due to a negative difference of at least 10% in grade ≥3 AEs

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12 Appendix

Table 4: Characteristics of trial MONARCH 2

Title: MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy [27, 28]			
Study identifier	NCT02107703, EudraCT number 2013-004728-13, MONARCH 2		
Design	Global, double-blind, phase III, randomised, placebo-controlled		
	Duration		Enrolment: August 2014 to December 2015 Median length of follow-up: 19.5 months Data cut-off: 2017-02-14
Hypothesis	Superiority The study was designed to compare the PFS for abemaciclib plus fulvestrant to that for placebo plus fulvestrant in patients with ABC. The primary end point, investigator-assessed PFS, was evaluated using a log-rank test stratified by metastatic site and ET resistance. The final analysis was planned at 378 PFS events, which would provide approximately 90% power assuming a HR of 0.703 at a one-sided α of 0.025, which corresponds to a 2.75-month improvement over the median PFS for the control arm of 6.5 months.		
Funding	Eli Lilly and Company		
Treatments groups	Intervention (n = 446)		Abemaciclib (150 mg twice daily) was administered continuously in combination with 500 mg of fulvestrant by intramuscular injection on days 1 and 15 of the first cycle (28 days) and on day 1 of subsequent cycles.
	Control (n = 223)		Placebo (150 mg twice daily) was administered continuously in combination with 500 mg of fulvestrant by intramuscular injection on days 1 and 15 of the first cycle (28 days) and on day 1 of subsequent cycles.
Endpoints and definitions	Progression-free survival (primary outcome)	PFS	Time of random assignment until objective progressive disease or death for any reason
	Overall survival	OS	Time from the date pf randomisation to the date of death
	Objective response rate	ORR	Proportion of patients with complete response or partial response
	Duration of response	DOR	Time from complete response or partial response until progressive disease or death
Database lock	June 2017		
Results and Analysis			
Analysis description	**Primary Analysis** Initially the study was planned to enrol 450 patients into the ITT population. However, the starting dose of the blinded-study drug was changed from 200 mg to 150 mg; therefore, the sample size was increased to 630 patients to ensure that at least 450 patients were enrolled at the 150 mg dose. The primary statistical analyses for investigator-assessed PFS were assessed in the ITT population, which included all patients independent of their starting dose. Sensitivity analyses were planned that (1) included only patients enrolled after the change in starting dose and that (2) determined progression on the basis of a blinded, independent central review.		

<table>
<tr><td colspan="4">Title: MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy [27, 28]</td></tr>
<tr><td>Study identifier</td><td colspan="3">NCT02107703, EudraCT number 2013-004728-13, MONARCH 2</td></tr>
<tr><td rowspan="4">Analysis population</td><td>Inclusion</td><td colspan="2">❁ ≥18 year old women
❁ Diagnosis of HR+, HER2- breast cancer
❁ Locally advanced disease not amenable to curative treatment by surgery or metastatic disease
❁ Disease that progressed while receiving neoadjuvant or adjuvant ET, ≤12 months after adjuvant ET, or while receiving ET for ABC. Patients must not have received more than one ET or any prior chemotherapy for ABC
❁ Postmenopausal status due to either surgical/natural menopause or ovarian suppression (initiated at least 28 days prior to Day 1 of Cycle 1) with a gonadotropin-releasing hormone (GnRH) agonist such as goserelin
❁ Negative serum pregnancy test at baseline (within 14 days prior to randomization) and agree to use medically approved precautions to prevent pregnancy during the study and for 12 weeks following the last dose of abemaciclib if postmenopausal status is due to ovarian suppression with a GnRH agonist
❁ Measurable disease or non-measurable bone only disease
❁ Performance status ≤1 on the ECOG scale
❁ Discontinued previous therapies for cancer for at least 21 days for myelosuppressive agents or 14 days for non-myelosuppressive agents prior to receiving study drug, and recovered from the acute effects of therapy (until the toxicity resolves to either baseline or at least Grade 1) except for residual alopecia or peripheral neuropathy</td></tr>
<tr><td>Exclusion</td><td colspan="2">❁ Are currently receiving an investigational drug in a clinical trial or participating in any other type of medical research judged not to be scientifically or medically compatible with this study
❁ Have visceral crisis, lymphangitis spread, or leptomeningeal carcinomatosis visceral crisis is not the mere presence of visceral metastases but implies severe organ dysfunction as assessed by symptoms and signs, laboratory studies, and rapid progression of the disease
❁ Have clinical evidence or history of CNS metastasis
❁ Have received prior treatment with chemotherapy (except for neoadjuvant/adjuvant chemotherapy), fulvestrant, everolimus, or any CDK4/6 inhibitor
❁ Have received treatment with a drug that has not received regulatory approval for any indication within 14 or 21 days prior to randomization of study drug for a non-myelosuppressive or myelosuppressive agent, respectively
❁ Have received recent (within 28 days prior to randomization) yellow fever vaccination
❁ Have had major surgery within 14 days prior to randomization of study drug to allow for post-operative healing of the surgical wound and site(s)
❁ Personal history within the last 12 months of any of the following conditions: syncope of cardiovascular etiology, ventricular tachycardia, ventricular fibrillation, or sudden cardiac arrest
❁ Inflammatory breast cancer or a history of any other cancer (except non-melanoma skin cancer or carcinoma in-situ of the cervix), unless in complete remission with no therapy for a minimum of 3 years
❁ Received an autologous or allogeneic stem-cell transplant
❁ Active bacterial or fungal infection, or detectable viral infection
❁ Initiated bisphosphonates or approved Receptor activator of nuclear factor kappa-B (RANK) ligand targeted agents <7 days prior to randomization</td></tr>
<tr><td colspan="2"><table>
<tr><td>Characteristics</td><td>Intervention
(n = 446)</td><td>Control
(n = 223)</td></tr>
<tr><td>Median age (range), years</td><td>59 (32-91)</td><td>62 (32-87)</td></tr>
<tr><td>ET resistance, n (%)
Primary
Secondary</td><td>
111 (24.9)
326 (73.1)</td><td>
58 (26.0)
163 (73.1)</td></tr>
<tr><td>Most recent ET, n (%)
Neoadjuvant or adjuvant
Metastatic</td><td>
263 (59.0)
171 (38.3)</td><td>
133 (59.6)
85 (38.1)</td></tr>
<tr><td>Prior AI, n (%)
Yes
No</td><td>
316 (70.9)
130 (29.1)</td><td>
149 (66.8)
74 (33.2)</td></tr>
</table></td></tr>
</table>

Title: MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2– advanced breast cancer who had progressed while receiving endocrine therapy [27, 28]			
Study identifier	NCT02107703, EudraCT number 2013-004728-13, MONARCH 2		
	PgR status, n (%) Positive Negative	 339 (76.0) 96 (21.5)	 171 (76.7) 44 (19.7)
	Metastatic site, n (%) Visceral Bone only Other	 245 (54.9) 123 (27.6) 75 (16.8)	 128 (57.4) 57 (25.6) 38 (17.0)
	Measurable disease, n (%) Yes No	 318 (71.3) 128 (28.7)	 164 (73.5) 59 (26.5)
	Race, n (%) Asian Caucasian Other	 149 (33.4) 237 (53.1) 29 (6.5)	 65 (29.1) 136 (61.0) 13 (5.8)
	ECOG performance status, n (%) 0 1	 264 (59.2) 176 (39.5)	 136 (61.0) 87 (39.0)
	Prior chemotherapy for neoadjuvant or adjuvant treatment, n (%) Yes No	 267 (59.9) 179 (40.1)	 134 (60.1) 89 (39.9)
	Menopausal status, n (%) Pre- or perimenopause Postmenopause	 72 (16.1) 371 (83.2)	 42 (18.8) 180 (80.7)

Abbreviations: ABC = advanced breast cancer, AI = aromatase inhibitor, CNS = central nervous system, DOR = duration of response, ECOG = Eastern Cooperative Oncology Group, ET = endocrine therapy, GnRH = Gonadotropin releasing hormone, HR = hazard ratio, ITT = intention-to-treat, ORR = overall response rate, OS = overall survival, PFS = progression-free survival, PgR = progesterone receptor

Table 5: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [30]

Criteria for judging risk of bias		**Risk of bias**
Adequate generation of randomisation sequence: interactive, web-based randomization scheme		yes
Adequate allocation concealment: no information available		unclear
Blinding: double-blind	**Patient**	yes
	Treating physician	yes
Selective outcome reporting unlikely: confidence intervals of the median PFS values for both treatment arms are not available as well as median PFS values of the blinded central analysis and the sensitivity analysis		no
No other aspects which increase the risk of bias: industry funded the study, provided study drugs, and was involved in conception and study design, provision of study material or patients, collection and assembly of data, data analysis and interpretation, and writing of the manuscript, missing follow-up data		no
Risk of bias – study level		low

Abbreviations: PFS = progression-free survival