Horizon Scanning in Oncology

Ribociclib in combination with letrozole for the first-line therapy of HR-positive, HER2-negative recurrent or metastatic breast cancer

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 65
ISSN online 2076-5940

Horizon Scanning in Oncology

Ribociclib in combination with letrozole for the first-line therapy of HR-positive, HER2-negative recurrent or metastatic breast cancer

Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, February 2017

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

Authors: Sarah Wolf, MSc
Nicole Grössmann, MSc
Internal review: Priv.-Doz. Dr. phil. Claudia Wild
External review: Assoc. Prof. Priv.-Doz. Dr. med. univ. Rupert Bartsch
Univ. Klinik für Innere Medizin I, Allgemeines Krankenhaus der Stadt Wien

DISCLAIMER

This technology summary is based on information available at the time of research and on a limited literature search. It is not a definitive statement on safety, effectiveness or efficacy and cannot replace professional medical advice, nor should it be used for commercial purposes.

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 A working version (unpublished) of V3.0 of the Model was used.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.

CONTACT INFORMATION

Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

Responsible for Contents:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
http://hta.lbg.ac.at/

Decision support documents of the LBI-HTA do not appear on a regular basis and serve to publicize the research results of the Ludwig Boltzmann Institute of Health Technology Assessments.

Decision support documents of the LBI-HTA are only available to the public via the Internet at http://eprints.hta.lbg.ac.at

DSD: Horizon Scanning in Oncology No. 65
ISSN-online: 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

Table of Contents

List of Tables

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 ribociclib?
A0022	Who manufactures ribociclib?
A0007	What is the target population in this assessment?
A0020	For which indications has ribociclib 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 breast cancer currently managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of ribociclib on mortality?
C0005	How does ribociclib affect symptoms and findings (severity, frequency) of breast cancer?
D0006	How does ribociclib affect progression (or recurrence) of breast cancer?
D0011	What is the effect of ribociclib on patients' body functions?
D0012	What is the effect of ribociclib on generic health-related quality of life?
D0013	What is the effect of ribociclib on disease-specific quality of life?
Safety	
C0008	How safe is ribociclib in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying ribociclib?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of ribociclib?
A0021	What is the reimbursement status of ribociclib?

2 Drug description

Generic/Brand name/ATC code:

Ribociclib/LEE011

B0001: What is ribociclib?

orally bioavailable, selective, small-molecule inhibitor of CDK 4/6

Ribociclib (LEE011) is a selective cyclin-dependent kinase inhibitor. It helps slow the progression of cancer by inhibiting two proteins, the cyclin-dependent kinase 4 and 6 (CDK 4/6), which interact with cyclin D1. Thereby, the retinoblastoma (Rb) protein phosphorylation is inhibited and CDK-mediated G1 to S phase transitions are prevented [2, 3]. As a consequence, the cell cycle in the G1 phase is arrested, which stops the cancer cell growth [4-10].

600 mg/day for 3 weeks, 1 week off

According to clinical trials, the recommended dose of ribociclib is 600 mg administered orally every day for three weeks followed by one week off in combination with 2.5 mg of letrozole daily, given continuously [6, 11, 12].

A0022: Who manufactures ribociclib?

Novartis Pharmaceuticals

3 Indication

A0007: What is the target population in this assessment?

HR-positive, HER2-negative recurrent or MBC

Ribociclib is indicated for the first-line therapy in postmenopausal women with locally confirmed hormone-receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative recurrent or metastatic breast cancer (MBC), who have not undergone systemic treatment for advanced disease [11, 13, 14].

4 Current regulatory status

A0020: For which indications has ribociclib received marketing authorisation?

priority review for ribociclib in November 2016

Ribociclib has not yet been approved by the US Food and Drug Administration (FDA). However, it received priority review in conjunction with the older aromatase inhibitor (AI) letrozole as a first-line treatment in postmen-

opausal women with HR-positive, HER2-negative recurrent or MBC in November 2016 [15].

Currently, ribociclib does not have a marketing authorisation in Europe for any indication, but the European Medicines Agency (EMA) has accepted the drug for review in the same patient population as the FDA [15, 16].

ribociclib has not yet been approved by the EMA

5 Burden of disease

A0002: What is breast cancer?

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 of diagnosis and the rate of growth [17]. Prognostically and therapeutically a distinction can be made between precancerous conditions like in situ tumours (obligatory precancerous condition: ductal carcinoma in situ [DCIS]; optional precancerous condition: lobular carcinoma in situ [LCIS]) and invasive breast cancer.

heterogeneous disease that arise from the tissue of the breast

A0004: What is the natural course of breast cancer?

Mostly, cancer begins in the cells of the ducts. Abnormal cells are found in the lining of the ducts; however, they have not spread into the surrounding tissue and thus state a precancerous condition like DCIS (stage 0) [18, 19]. Normally, LCIS accompanies DCIS, whereas aggressive subtypes often do not show DCIS. 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 area where the first abnormal cells arose. In stage II, abnormal cells have spread beyond the ducts or glands into the breast tissue (invasive ductal carcinoma [IDC] or invasive lobular carcinoma [ILC]). Stage III breast cancer is stratified according to the tumour size and includes tumours >5 cm involving the skin, underlying muscle or the lymph nodes [20]. 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 MBC [21].

stages of breast cancer

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 primary tumour characteristics (T), the presence or absence of regional lymph node involvement (N), and the presence or absence of distant metastases (M). The TNM staging system is especially relevant for inflammatory and stage IV breast cancer.

AJCC-TNM staging system

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 a main risk factor for cancer, the incidence of cancer will increase over time [22, 23]. Globally, around 30.0% of the patients with early breast cancer develop advanced or MBC [20]. In Austria, breast cancer accounts for approximately 28,000 (2.6% of total) life-years lost due to premature deaths [24]. Moreover, the incidence of breast cancer is highest for higher socioeconomic groups, whereas survival is lowest in lower socioeconomic groups [16].

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 30.0% 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 98.0% were women. Moreover, around 86.0% of female breast cancer patients and 78.0% of male breast cancer patients (all stages are included) are alive at least five years after diagnosis [25]. The median age at diagnosis of breast cancer is 62 years, ranging from 55 to 64 years [21]. HR-positive disease accounts for approximately 65.0% and 80.0% of breast cancers in pre- and postmenopausal women, respectively. Accounting for approximately 70.0% of breast cancer patients, HR-positive and HER2-negative is the most common type of breast cancer. Between 5.0%–10.0% of the patients are primarily diagnosed with MBC that has spread to other parts of the body, e.g., bone, liver, lung and brain [20].

median age at diagnosis: 62

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

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

main symptoms: breast mass, skin irritation, pain

A hard, immovable, single dominant lesion (breast mass) with irregular borders is the most common symptom of breast cancer [21, 26, 27]. In addition, symptoms like swelling of the whole or only parts of the breast, skin irritation or dimpling (peau d'orange), breast or nipple pain, nipple retraction, redness, scaliness, thickening of the nipple or breast skin, nipple discharge or axillary adenopathy can occur [21, 27, 28]. In advanced stages of breast cancer weight loss and reduced performance can be present [28]. Symptoms due to metastases include swelling of the arm by lymphedema in 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 [16, 21, 28].

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 certain genes like BRCA1, BRCA2 and TP53 are associated with an increased risk of breast cancer in premenopausal and postmenopausal women [16, 28-31]. In addition, increased exposure to oestrogen like early menarche or late menopause can also be a risk factor for the diagnosis of breast cancer [28, 29]. Furthermore, reproductive factors that increase risk are a first pregnancy at

late age, absence of breastfeeding and nulliparity [29, 30]. Other risk factors that may lead to breast cancer are alcohol consumption, smoking, family and personal history of breast cancer [30].

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

diagnosis of breast cancer via CBE, x-ray mammography, ultrasound exam, MRI, biopsy

There are several ways to diagnose breast cancer, such as the clinical breast exam (CBE), the x-ray mammography or radiological examinations like the ultrasound exam or magnetic resonance imaging (MRI). However, an abnormal mammogram detected in countries with established screening programs is the most common reason for suspecting breast cancer. If breast cancer is suspected via a mammography, a biopsy (punch biopsy and vacuum-assisted biopsy) is performed. An additional breast MRI can increase the detection rate of additional lesions, but it does not improve the prognosis. In the later stage of the disease, liver function tests, brain MRIs, abdominal diagnostic scans, bone scans, sodium fluoride positron emission tomographies (PETs) or fluorodeoxyglucose (FDG) can be applied [28, 31].

HR and HER2 status

stratification into disease stages

As breast cancer is a heterogeneous disease, it is essential to establish HR and HER2 status [18, 31]. Additionally, the stratification into the different disease stages, described in the section "A0004: What is the natural course of breast cancer?", is crucial to ensure the best therapy.

6 Current treatment

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

factors for treatment decisions

Generally, breast cancer can be treated by surgery, adjuvant irradiation or systemic therapies [28]. To determine which treatment strategy is the most suitable for the patient, several factors are important [28]:

- stage of cancer (AJCC TNM staging system)
- grade of disease
- tumour site
- 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 and is dependent on the eligibility of a breast-conserving therapy (BCT) and whether it is a clinically node-negative breast cancer. For patients who are eligible for a BCT, the following treatment options in this sequence may be applied [28]:

- primary neoadjuvant systematic therapy (node-negative breast cancer)

- surgery (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 who are not eligible for a BCT and for locally advanced breast cancer (stage IIB, IIIA/B), the previously mentioned treatment options can be applied as well. However, instead of a BCT, a mastectomy may be applied. In the case of metastatic disease (stage IV), treatment with a palliative intent (systematic therapy, best supportive care, etc.) can be used [28].

In particular, palliative treatment options for HR-positive, HER2-negative recurrent or MBC in postmenopausal women are:

- local therapy, such as surgery or irradiation in case of an acute threat to organ functions, e.g., liver, lung, brain or sternum
- first-line endocrine therapy for HR-positive postmenopausal patients:
  - endocrine therapy alone, followed by endocrine therapy plus CDK 4/6 inhibitors [28, 31-33]
  - endocrine therapy plus CDK 4/6 inhibitors, followed by endocrine therapy alone or combined with everolimus [28]
  - in case of rapid disease progression within the first few months → switching to chemotherapy in the second-line [34]

endocrine stage IV treatment options

chemotherapy

- first-line chemotherapy for patients with rapidly progressive, symptomatic disease or visceral metastases with end-organ dysfunction; after four to six months switching to maintenance endocrine therapy [34]

7 Evidence

systematic literature search in 5 databases: 113 hits

A literature search was conducted on 27 December 2016 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were “ribociclib”, “LEE011”, “breast cancer”, “breast neoplasms” and “mamma carcinoma”. The manufacturer was also contacted and submitted 14 references (all of which had already been identified by systematic literature search). A manual search identified 26 additional references (web documents and journal articles). Overall, 139 references were identified. Included in this report are:

- One phase III study assessing ribociclib in HR-positive, HER2-negative recurrent or MBC patients who have not undergone systemic treatment for advanced disease [35]
- One phase Ib/II study assessing the safety, tolerability, pharmacokinetic profile and preliminary clinical antitumor activity of ribociclib and letrozole used in combination for HR-positive, HER2-negative advanced breast cancer [36]

The methodological quality of the evidence was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for RCTs [37]. 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 4 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 [38]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [39]. Further details about the ESMO-MCBS are reported in the discussion.

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

7.1 Clinical efficacy and safety – phase III study

MONALEESA-2 [35] a randomised, double-blind, placebo-controlled phase III study was conducted to assess the efficacy and safety of the selective CDK 4/6 inhibitor ribociclib combined with letrozole for the first-line treatment in postmenopausal women with HR-positive, HER2-negative recurrent or MBC, who had not received previous systemic therapy for advanced disease.

MONALEESA-2: randomised, double-blind, placebo-controlled phase III study (n = 668)

A total of 668 patients were enrolled to receive either a 600 mg daily dose of ribociclib for three weeks and one week off, plus a daily dose of 2.5 mg of letrozole (n = 334) or placebo with letrozole (n = 334). The randomisation was stratified according to the presence or absence of liver or lung metastases. In order to detect a hazard ration of 0.67 with a power of 93.5% at a one-sided alpha level of 0.025, 302 patients who had disease progression or died were required.

daily dose of 600 mg

hazard ratio of 0.67

After at least 211 (70.0% of 302) patients had disease progression or died, the interim analysis was released. Finally, due to a delay in reporting from local trial centres, the results of 243 patients who had disease progression or died were reported and 302 patients were on treatment at the time of data cut-off (January 2016). Moreover, the median duration of follow-up was 15.3 months at the time of data cut-off. 87 (26.0% of 334) patients of the intention-to-treat population discontinued treatment due to disease progression in the ribociclib group, compared to 146 (44.0% of 334) patients of the intention-to-treat population in the placebo group.

time of data cut-off: results of 243 patients reported

median follow-up duration: 15.3 months

Enrolled patients were postmenopausal women with a median age of 62 years. All patients had HR-positive disease and all but one patient in each group had HER2-negative disease. A total of 227 (34.0% of 668) patients had newly diagnosed advanced or metastatic disease. Detailed patient characteristics can be found in Table 3 of the Appendix, together with inclusion and exclusion criteria.

median age of 62 years

The primary endpoint of the MONALEESA-2 trial was locally assessed PFS, according to RECIST (response evaluation criteria in solid tumours) version 1.1. Secondary outcomes comprised the proportion of patients with overall response (ORR) and clinical benefit (CBR), overall survival (OS), safety and

primary endpoint: locally assessed PFS, main secondary endpoints: ORR, CBR, OS, safety

quality-of-life (QoL). Exploratory endpoints included pharmacokinetic and biomarkers of response or resistance. However, the results of the QoL assessments and the exploratory analyses were not reported in the study.

7.1.1 Clinical efficacy

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

median OS has not been reached with 23 versus 20 deaths in the ribociclib group

At the time of data cut-off the median OS has not been reached. In the ribociclib group 23 deaths had occurred, while 20 deaths occurred in the placebo group. Table 1 represents the efficacy of ribociclib.

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

ribociclib significantly improved the locally assessed PFS rate

At the time of data cut-off (January 2016), the median duration of PFS in the placebo group was 14.7 months (13.0–16.5), but was not reached in the ribociclib group. However, the rate of locally assessed PFS was significantly higher in the treatment group compared to the control group. The estimated 12-month PFS rate was 72.8% (67.3–77.6) in the ribociclib group and 60.9% (55.1–66.2) in the placebo group. After 18 months, the PFS rate was 63.0% (54.6–70.3) and 42.2% (34.8–49.5) respectively.

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

improved ORR and CBR in the ribociclib group compared to the placebo group

The ORR was 40.7% (35.4–46.0) in the ribociclib group and 27.5% (22.8–32.8) in the placebo group of the intention-to-treat population and 52.7% (46.6–58.9) and 37.1% (31.1–43.2) respectively among patients with measurable disease. The CBR was 79.6% (75.3–84.0) in the ribociclib group and 72.8% (68.0–77.5) in the placebo group of the intention-to-treat population and 80.1% (75.2–85.0) and 71.8% (66.2–77.5), respectively, among patients with measurable disease.

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

No evidence was found to answer this research question.

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

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

QoL assessments were not reported

The results of the QoL assessments were not reported in the MONALEESA-2 trial.

Table 1: Efficacy results of MONALEESA-2 trial

Descriptive statistics and estimate variability (data cut-off 24 January 2016)	Treatment group	Ribociclib	Placebo
	Number of subject	334	334
	Median PFS, months	NR (19.3–NR)	14.7 (13.0–16.5)
	12-month PFS rate, %	72.8 (67.3–77.6)	60.9 (55.1–66.2)
	18-month PFS rate, %	63.0 (54.6–70.3)	42.2 (34.8–49.5)
	OS	NR	NR
	QoL	NR	NR
	ORR intention-to-treat, %	40.7 (35.4–46.0)	27.5 (22.8–32.8)
	ORR measurable disease, %	52.7 (46.6–58.9)	37.1 (31.1–43.2)
	CBR intention-to-treat, %	79.6 (75.3–84.0)	72.8 (68.0–77.5)
	CBR measurable disease, %	80.1 (75.2–85.0)	71.8 (66.2–77.5)
Effect estimate per comparison	*Comparison groups*		*ribociclib+letrozole versus placebo+letrozole*
	median PFS	HR	0.56
		95% CI	0.43–0.72
		Two-sided log-rank test p value	$p = 3.29x10^{-6}$
	ORR	Two-sided log-rank test p value	p <0.001
	CBR	Two-sided log-rank test p value	p = 0.020

Abbreviations: CI = confidence interval, HR = hazard ratio, PFS = progression-free survival, OS = overall survival, QoL = quality of life, ORR = overall response rate, CBR = clinical benefit rate, NR = not reported

7.1.2 Safety

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

In the safety population including 334 patients in the ribociclib group and 330 patients in the placebo group, only patients who received at least one dose of study regimen and who had at least one safety assessment after baseline were included. Adverse events (AEs) occurred in at least 35% of the patients in either group. The AEs included neutropenia (74.3% in the ribociclib group and 5.2% in the placebo group), nausea (51.5% and 28.5%), infections (50.3% and 42.4%), fatigue (36.5% and 30.0%), and diarrhoea (35.0% and 22.1%). Most of these AEs were of grade 1 or 2. AEs of grade ≥3 occurred in 81.2% of the ribociclib patients and in 32.7% of the patients receiving placebo. In fact, this is an increase of 48.5% in grade 3 or 4 AEs in the ribociclib group. The most common grade 3 or 4 AEs in the ribociclib group (≥5% of the patients in either group) were neutropenia (59.3% and 0.9%), leukopenia (21.0% and 0.6%), hypertension (9.9% and 10.9%), increased alanine aminotransferase level (9.3% and 1.2%), lymphopenia (6.9% and 0.9%) and increased aspartate aminotransferase level (5.7% and 1.2%).

most common grade 3-4 AEs: neutropenia, leukopenia, hypertension, increased alanine aminotransferase level, lymphopenia, increased aspartate aminotransferase level
4 AE-related deaths

Moreover, serious AEs occurred in 71 patients (21.3%) in the ribociclib group and in 39 (11.8%) in the placebo group during the treatment. Additionally, four AE-related deaths in the ribociclib group and one in the placebo group were stated. All treatment-emergent AEs can be found in Table 2.

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

54.0% ribociclib dose reductions, 77.0% of the patients dose interruption of ribociclib

In a total of 54.0% of the ribociclib group and 7.0% of the placebo group, dose reductions were required most commonly due to AEs. Interruptions in the dose of ribociclib occurred in 257 patients (77.0%) and of letrozole in 132 patients (40.0%) in the ribociclib group. Among the 330 patients in the placebo group, placebo was interrupted in 134 (41.0%) and letrozole in 107 patients (32.0%).

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

cardiac disease or dysfunction

Patients with a historic cardiac disease or dysfunction including a QT interval corrected for heart rate according to Fridericia's formula (QTcF) of >450 msec at screening are more likely to be harmed through the use of ribociclib [35]. Therefore, patients with cardiac disease or a dysfunction were excluded from the study.

Table 2: Most frequent adverse events[1]

Adverse Event (according to CTCAE version 4.03)	**Ribociclib** (n = 334)		**Placebo** (n = 330)	
	Any Grade n (%)	Grade 3-4 n (%)	Any Grade n (%)	Grade 3-4 n (%)
Any disease-related AEs	329 (98.5)	271 (81.2)	320 (97.0)	108 (32.7)
Neutropenia	248 (74.3)	198 (59.3)	17 (5.2)	3 (0.9)
Nausea	172 (51.5)	8 (2.4)	94 (28.5)	2 (0.6)
Infections	168 (50.3)	14 (4.2)	140 (42.4)	8 (2.4)
Fatigue	122 (36.5)	8 (2.4)	99 (30.0)	3 (0.9)
Diarrhoea	117 (35.0)	4 (1.2)	73 (22.1)	3 (0.9)
Alopecia	111 (33.2)	NA	51 (15.5)	NA
Leukopenia	110 (32.9)	70 (21.0)	13 (3.9)	2 (0.6)
Vomiting	98 (29.3)	12 (3.6)	51 (15.5)	3 (0.9)
Arthralgia	91 (27.2)	3 (0.9)	95 (28.8)	3 (0.9)
Constipation	83 (24.9)	4 (1.2)	63 (19.1)	0 (0)
Headache	74 (22.2)	1 (0.3)	63 (19.1)	1 (0.3)
Hot flash	70 (21.0)	1 (0.3)	78 (23.6)	0 (0)
Back pain	66 (19.8)	7 (2.1)	58 (17.6)	1 (0.3)

[1] AEs occurring in at least 15% of patients in any group.

Cough	65 (19.5)	0 (0)[2]	59 (17.9)	0 (0)[2]
Anaemia	62 (18.6)	4 (1.2)	15 (4.5)	4 (1.2)
Decreased appetite	62 (18.6)	5 (1.5)	50 (15.2)	1 (0.3)
Rash	57 (17.1)	2 (0.6)	26 (7.9)	0 (0)
Increased alanine amino-transferase	52 (15.6)	31 (9.3)	13 (3.9)	4 (1.2)
Increased aspartate amino-transferase	50 (15.0)	19 (5.7)	12 (3.6)	4 (1.2)

Abbreviation: CTCAE = Common Terminology Criteria for Adverse Events, NA = not applicable

7.2 Clinical effectiveness and safety – further studies

A multicentre, open-label phase Ib/II study was conducted to assess the safety, tolerability, pharmacokinetic profile, as well as the preliminary clinical antitumor activity of ribociclib, alpelisib and letrozole used in combination for HR-positive, HER2-negative advanced breast cancer. In the phase II study three arms were compared, the first of which is of particular interest for this assessment: As of 22 August 2014, 29 patients had been treated with ribociclib (daily 600 mg for three weeks and one week off) in combination with letrozole (2.5 mg/day continuously).

P5-19-24: efficacy, safety and pharmacokinetic profile of ribociclib in HR-positive and HER2-negative advanced breast cancer

Treatment discontinuations were mostly due to disease progression and occurred in 35% of the patients. The most common all-grade drug-related AEs were neutropenia (72.0%) and nausea (35.0%). Moreover, the most common grade 3-4 drug-related AE, neutropenia, occurred in 52.0% of the patients. Furthermore, there has been one confirmed partial response, seven patients with stable disease and six patients with neither complete response nor progressive disease. The patient with the confirmed partial response had been pre-treated with the AI fulvestrant and a PI3K/AKT/mTOR inhibitor and had PIK3CA and TP53 mutations [36].

ribociclib combined with letrozole demonstrated grade 3-4 neutropenia in 52.0% of the patients

8 Estimated costs

A0021: What is the reimbursement status of ribociclib?

To date, ribociclib has not been approved in the US or in Europe. No price estimates are therefore available at this point.

no cost estimates available yet

[2] Data for the respective grade 4 AE were not applicable, since they are not included in the CTCAE.

9 Ongoing research

3 phase III studies are ongoing, investigating ribociclib in patients with HR-positive, HER2 negative advanced breast cancer

In January 2016, a search in the databases www.clinicaltrials.gov and www.clinicaltrialsregister.com was conducted. The following three ongoing phase III trials are investigating ribociclib in pre- or postmenopausal women with HR-positive, HER2-negative advanced breast cancer:

- NCT02941926 (COMPLEEMENT-1): An open-label, multicentre, phase IIIb study is assessing the safety and efficacy of ribociclib in combination with letrozole for the treatment of men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer, who had not received prior hormonal therapy for advanced disease. Estimated study completion date is November 2020.
- NCT02422615 (MONALEESA-3): A randomised, double-blind, placebo-controlled, international phase III study is evaluating the efficacy and safety of ribociclib or matching placebo in combination with fulvestrant in men and postmenopausal women with HR-positive, HER2-negative advanced breast cancer, who have received no or only one line of prior ET for advanced disease. As of 20 April 2016, the phase III study is open at approximately 220 sites in 29 countries and global recruitment is ongoing with a target accrual of approximately 660 patients worldwide [40]. Estimated study completion date is February 2020.
- NCT02278120 (MONALEESA-7): A randomised, double-blind, placebo-controlled phase III study, in which pre- or perimenopausal women with HR-positive, HER2-negative advanced breast cancer are treated with goserelin and either tamoxifen or NSAI plus ribociclib or matching placebo. As of 2 February 2016, the phase III study is open at 237 sites in 30 countries and global recruitment is ongoing with a planned target accrual of approximately 660 patients [41]. Estimated study completion date is February 2018.

2 ongoing studies (phase I and II) in different treatment lines and regimes

Currently, two studies are ongoing in different treatment lines and regimens in patients with HR-positive, HER2-negative advanced breast cancer (e.g., NCT01857193, NCT02732119). In addition, ribociclib is also being investigated for other indications like glioblastoma, solid tumours, endometrial carcinoma, prostate carcinoma, liposarcoma, squamous cell carcinoma of the head and neck, teratoma.

10 Discussion

no marketing authorisation in the US and in the EU

The CDK 4/6 inhibitor ribociclib has not yet been approved by the US FDA or by the EMA. However, in November 2016 the FDA approved priority review for ribociclib in conjunction with the older AI letrozole as a first-line therapy of postmenopausal women with HR-positive, HER2-negative recurrent or MBC. The EMA has accepted the drug for review in the same patient population as the FDA [15, 16].

report based on interim analysis of the MONALLEESA-2 phase III study

This report is based on the interim analysis of the randomised, double-blind, placebo-controlled MONALEESA-2 phase III study, which assessed the safety and efficacy of ribociclib in combination with letrozole for postmenopausal women with HR-positive, HER2-negative recurrent or MBC. The results of the interim analysis were reported after disease progression or death had occurred in 243 patients. OS outcomes were not mature, with 23 deaths in the ribociclib group and 20 deaths in the placebo group at the time of data cut-off. Additionally, no data on PFS in months and QoL were available. However, ribociclib plus letrozole recipients showed an improvement in the primary endpoint of PFS (72.8% vs. 60.9%, 12-month PFS rate; 63.0% vs. 42.2%, 18-month PFS rate), as well as in the ORR (40.7% vs. 27.5%, intention-to-treat population) and in the CBR (79.6% vs. 72.8%, intention-to-treat population) compared to placebo recipients.

no data on PFS in months and QoL available

ESMO-MCBS on clinical meaningful benefit not applicable due to lack of data

Due to the fact that the median duration of OS and PFS had not been reached in the ribociclib group, the ESMO-MCBS, as well as its adapted version, could not have been applied. Consequently, the magnitude of the clinically meaningful benefit of ribociclib could not have been assessed accurately. Hence, further studies are needed to investigate the gain in the median duration of OS and PFS of ribociclib compared to the placebo.

most common AEs: neutropenia, nausea, infections, fatigue, diarrhoea

Grade 3 or 4 neutropenia, leukopenia, hypertension, increased alanine aminotransferase level, lymphopenia, and increased aspartate aminotransferase level occurred in ≥5% of the patients in either group. However, the ribociclib group showed an increase of AEs of grade ≥3 of 48.5% compared to the placebo group. Additionally, AEs of any grade including neutropenia, nausea, infections, fatigue and diarrhoea were significantly more common in the ribociclib group. Furthermore, 54.0% of the ribociclib recipients needed a dose reduction due to an AE and 77.0% required a dose interruption.

no results of biomarker analyses and QoL assessments

In the MONALEESA-2 study, results of biomarker analyses and QoL assessments had not been reported. However, considering the fact that CDK 4/6 inhibitors are known to cause significant AEs, the identification of biomarkers is crucial [42]. Therefore, further investigations are necessary to assess potential biomarkers in order to identify the patients with the greatest clinical benefit and, as a result, enrich the responsive patient population [43, 44]. Moreover, as no QoL outcomes had been outlined in the study, uncertainty exists whether the efficacy of ribociclib overrules its AEs. Thus, it is important to include QoL assessments in future studies to take into account the burden a specific health state places upon a person, as well as which value a person assigns to his or her health state [45].

stratification according to molecular subtypes

Furthermore, patients were not stratified according to molecular subtypes, but rather based on the presence or absence of liver or lung metastases. However, especially among patients with luminal B tumours there might be variations in ER and PR expressions between the different disease stages. On these grounds, it might be necessary to stratify the patients according to molecular subtypes to enable a more accurate assessment of the benefit of ribociclib in the different subtypes of advanced breast cancer [46].

first CDK 4/6 inhibitor, palbociclib, received marketing authorisation in the US and EU

Currently, the CDK 4/6 inhibitor ribociclib is also being investigated in patients with early breast cancer and for other indications like glioblastoma, solid tumours, endometrial carcinoma, prostate carcinoma, liposarcoma, squamous cell carcinoma of the head and neck and teratoma. In the US, the first CDK 4/6 inhibitor, palbociclib, received marketing authorisation in combination with letrozole as first-line treatment for postmenopausal women with HR-positive, HER2-negative advanced breast cancer in February 2015. In February 2016 licensing was expanded to include palbociclib plus fulvestrant for women with HR-positive, HER2-negative advanced or MBC with disease progression during or following ET. In November 2016 palbociclib was approved by the EMA for the same indications. Additionally, a third CDK 4/6 inhibitor, abemaciclib, is under development for the treatment of breast cancer [47, 48]. A comparison of the two CDK 4/6 inhibitors, palbociclib and ribociclib, might be necessary in order to investigate which the patients would benefit the most from. Furthermore, it might be crucial to assess the impact of the treatment with CDK 4/6 inhibitors on the endocrine sensitivity of subsequent therapies.

impact of CDK 4/6 therapies on endocrine sensitivity of subsequent treatments not assessed

palbociclib costs as a proxy variable for lacking ribociclib costs

Reimbursement decisions are based on crucial factors including clinical effectiveness, costs, safety, etc. However, there is no efficacy evidence in terms of an OS improvement of ribociclib in combination with letrozole compared to placebo. Moreover, there are no price estimates available for ribociclib, as it has not yet received marketing authorisation in the US or in Europe. In this case, the costs of palbociclib of €4,582.55 per 28-day cycle could be taken as a proxy variable for ribociclib costs, since both drugs have the same cycle length and are indicated for the same target population [49].

gained PFS benefit from ribociclib

median duration in OS and in PFS in months not reached

further investigation of endocrine sensitivity of subsequent treatments, QoL outcomes and biomarkers

Overall, even if the addition of ribociclib to letrozole increases the rate of toxicity significantly, there may be a benefit gained from adding it, since ribociclib increased the PFS rate by 11.9% and 20.8% (12 months vs. 18 months). However, apart from this, no evidence regarding the comparative OS advantage of ribociclib in combination with letrozole and no median gain in PFS in months could have been reported. Nevertheless, it might be crucial to investigate the impact of the treatment with CDK 4/6 inhibitors on the endocrine sensitivity of subsequent therapies. Furthermore, the effectiveness of ribociclib has not been supported by QoL outcomes. These and potential biomarkers should be reported in order to identify the target patient population benefitting the most from the treatment of ribociclib. Finally, the stratification according to molecular subtypes may lead to a more accurate assessment of the benefit of ribociclib.

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 2016-27-12]; Available from: http://meka.thl.fi/htacore/model/HTA%20Core%20Model%20for%20Rapid%20REA%20of%20Pharmaceuticals%203.0.pdf.
2. Wolff AC. CDK4 and CDK6 inhibition in breast cancer - A new standard. New England Journal of Medicine. 2016;375(20):1993-5.
3. Abraham J. Lessons learned from using CDK 4/6 inhibitors to treat metastatic breast cancer. Journal of Community and Supportive Oncology. 2016;14(10).
4. National Cancer Institute (NCI) metathesaurus. Ribociclib (CUI C2987342). [2017/10/01]; Available from: https://ncim.nci.nih.gov/ncimbrowser/ConceptReport.jsp?dictionary=NCI Metathesaurus&code=C2987342.
5. Novartis. Novartis LEE011 (ribociclib) granted FDA Priority Review for first-line treatment of HR+/HER2- advanced breast cancer. 2016 [2017/10/01]; Available from: https://www.novartis.com/news/media-releases/novartis-lee011-ribociclib-granted-fda-priority-review-first-line-treatment.
6. Barroso-Sousa R, Shapiro GI, Tolaney SM. Clinical Development of the CDK4/6 Inhibitors Ribociclib and Abemaciclib in Breast Cancer. Breast care (Basel, Switzerland). 2016;11(3):167-73. Epub 2016/08/06.
7. Witzel I, Müller V. The role of CDK 4/6 inhibitors in breast cancer treatment. Breast Care. 2016;11(3):165-6.
8. 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. Epub 2015/08/26.
9. O'Sullivan CC. Overcoming Endocrine Resistance in Hormone-Receptor Positive Advanced Breast Cancer-The Emerging Role of CDK4/6 Inhibitors. International journal of cancer and clinical research. 2015;2(4). Epub 2016/01/05.
10. Clark AS, DeMichele A. The Cyclin D/Cyclin-dependent Kinase 4/6 Complex as a Target in the Treatment of Breast Cancer. Current Breast Cancer Reports. 2015;7(4):175-82.
11. Horizon Scanning Research & Intelligence Centre (NIHR). Ribociclib for advanced hormone receptor positive, HER2 negative breast cancer – first line. Birmingham: NIHR Horizon Scanning Research & Intelligence Centre; 2015.
12. Janni W, Nusch A, Grischke EM, Marschner N, Wilke J, Decker T, et al. Ribociclib + letrozole for postmenopausal women with hormone receptor-positive (HR+), HER2-negative, advanced breast cancer (ABC) who received no prior therapy for advanced disease. Oncology Research and Treatment. 2016;39((Janni W.) Universitätsklinikum Ulm, Department of Obstetrics and Gynecology, Ulm, Germany):214-5.
13. Burki TK. Ribociclib in HR-positive, HER2-negative breast cancer. The Lancet Oncology. 2016;17(11):e482. Epub 2016/10/18.
14. McKee S. Novartis' breast cancer drug ribociclib gets US, EU review. PharmaTimes2016 [2017/10/01]; Available from: http://www.pharmatimes.com/news/novartis_breast_cancer_drug_ribociclib_gets_us,_eu_review_1175217.
15. Adams B. Novartis gains FDA priority review for ribociclib, as EMA accepts med FierceBiotech2016 [2017/10/01]; Available from: http://www.fiercebiotech.com/biotech/novartis-adds-priority-review-to-its-ribociclib-fda-tags-as-ema-accepts-med.
16. Horizon Scanning Research & Intelligence Centre (NIHR). Ribociclib with tamoxifen and goserelin, or a non-steroidal aromatase inhibitor and goserelin - breast cancer: advanced; hormone-receptor positive, human epidermal growth factor receptor 2 (HER2) negative; premenopausal women – first line. Birmingham: NIHR Horizon Scanning Research & Intelligence Centre; 2016.

17. Liedtke C, Kiesel L. Breast cancer molecular subtypes - Modern therapeutic concepts for targeted therapy of a heterogeneous entity. Maturitas. 2012;73(4):288-94.

18. National Cancer Institute (NIH). Breast Cancer Treatment (PDQ®)–Patient Version. 2016 [cited 2017-01-11]; Available from: https://www.cancer.gov/types/breast/patient/breast-treatment-pdq.

19. Laronga C. Patient education: Breast cancer guide to diagnosis and treatment (Beyond the Basics). In: Hayes DF, Chagpar AB, editors. UpToDate. Waltham, MA. (cited 11.01.2017): UpToDate; 2016.

20. 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((Brufsky A.M., brufskyam@upmc.edu) University of Pittsburgh School of Medicine, Pittsburgh, United States):137-47.

21. National Cancer Institute (NIH). Breast Cancer. [2017/10/01]; Available from: https://www.cancer.gov/types/breast.

22. Berger NA, Savvides P, Koroukian SM, Kahana EF, Deimling GT, Rose JH, et al. Cancer in the Elderly. Transactions of the American clinical and climatological association. 2005;VOL. 117.

23. Hayes DF. Tumor node metastasis (TNM) staging classification for breast cancer. In: Chagpar AB, editor. UpToDate. Waltham, MA. (cited 11.01.2017): UpToDate; 2014.

24. Institute for Health Metrics and Evaluation. Global burden of Disease, Injuries, and Risk Factors Study 2010. 2010 [cited 2017-01-30]; Available from: http://www.healthdata.org/sites/default/files/files/country_profiles/GBD/ihme_gbd_country_report_austria.pdf.

25. Statisitk Austria. Krebserkrankungen - Brust. 2016 [2017/10/01]; Available from: http://www.statistik.at/web_de/statistiken/menschen_und_gesellschaft/gesundheit/krebserkrankungen/brust/index.html.

26. American Cancer Society. Signs and symptoms of breast cancer. 2016 [2017/12/01]; Available from: http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-signs-symptoms.

27. Esserman LJ, Joe BN. Clinical features, diagnosis, and staging of newly diagnosed breast cancer. Harold Burstein M, PhD, editor: UpToDate; 2016 [2017/12/01].

28. Wörmann B, Aebi S, Decker T, Fehm T, Greil R, Harbeck R, et al. Mammakarzinom der Frau. 2016 [2017/10/01]; Available from: https://www.onkopedia.com/de/onkopedia/guidelines/mammakarzinom-der-frau/@@view/html/index.html.

29. Chen WY. Factors that modify breast cancer risk in women. In: Chagpar AB, Hayes DF, editors. UpToDate. Waltham, MA. (cited 12.01.2017): UpToDate; 2016.

30. National Cancer Institute (NIH). Breast Cancer Treatment (PDQ®)–Health Professional Version. 2016; Available from: https://www.cancer.gov/types/breast/hp/breast-treatment-pdq.

31. Natinoal Comprehensive Cancer Network (NCCN). Stage IV Breast Cancer. 2014 [2017/10/01]; Available from: https://www.nccn.org/patients/guidelines/stage_iv_breast/index.html.

32. Garrido-Castro AC, Metzger-Filho O. Novel Strategies in Hormone Receptor-Positive Advanced Breast Cancer: Overcoming Endocrine Resistance. Current Breast Cancer Reports. 2016;8(4):193-205.

33. Yamamoto-Ibusuki M, Arnedos M, André F. Targeted therapies for ER+/HER2- metastatic breast cancer. BMC Medicine. 2015;13(1).

34. UpToDate. Systemic treatment for metastatic breast cancer general principles. [2017/24/01]; Available from: https://www.uptodate.com/contents/systemic-treatment-for-metastatic-breast-cancer-general-princi-ples?source=search_result&search=her2%20negative%20breast%20cancer&selectedTitle=7~150.

35. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer. The New England journal of medicine. 2016;375(18):1738-48. Epub 2016/11/03.

36. Juric D, cartographer Phase Ib/II Study of LEE011, Alpelisib (BYL719), and Letrozole in ER+, HER2- Breast Cancer: Safety, Preliminary Efficacy, and Molecular Analysis. San Antonic Breast Cncer Symposium, USA2014.

37. European Network for Health Technology Assessment (EUnetHTA). Internal validity of randomized controlled trials 2013 [cited 2016-12-27]; Available from: https://eunethta.fedimbo.belgium.be/sites/5026.fedimbo.belgium.be/files/Internal_Validity.pdf.

38. 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.

39. 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.

40. Fasching PA. Phase III study of ribociclib (LEE011) plus fulvestrant for the treatment of men and postmenopausal women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced breast cancer (aBC) who have received no or only one line of prior endocrine treatment (ET): MONALEESA-3. ASCO Annual Meeting, Chicago2016; Available from: http://meetinglibrary.asco.org/content/126845?media=vm&poster=1.

41. Tripathy D, Bardia A, Hurvitz SA, Harbeck N, Colleoni M, Franke FA, et al., cartographers. A Phase III, double-blind, placebo-controlled study of ribociclib (LEE011) in combination with either tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with HR+, HER2- advanced breast cancer (aBC): MONALEESA-7. Miami Breast Cancer Conference, Miami, Florida, USA2016.

42. Asghar U, Witkiewicz AK, Turner NC, Knudsen ES. The history and future of targeting cyclin-dependent kinases in cancer therapy. Nature Reviews Drug Discovery. 2015;14(2):130-46.

43. Finn RS, Slamon DJ. Targeting CDK 4-6 pathway. Breast (Edinburgh, Scotland). 2015;24((Finn R.S.; Slamon D.J.) Division of Hematology/Oncology, Geffen School of Medicine, UCLA Medical Center, Santa Monica, United States):S9.

44. Johnston SRD. Enhancing Endocrine Therapy for Hormone Receptor-Positive Advanced Breast Cancer: Cotargeting Signaling Pathways. Journal of the National Cancer Institute. 2015;107(10).

45. Calaminus G, Barr R. Economic evaluation and health-related quality of life. Pediatric Blood & Cancer. 2008;50:1112-5.

46. de Gramont A, Herrera A, de Gramont A. Ribociclib for HR-Positive, Advanced Breast Cancer. New England Journal of Medicine. 2017.

47. European Mecicines Agency (EMA). Medicines. [2017/01/11]; Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/includes/medicines/medicines_landing_page.jsp.

48. Food and Drug Administration (FDA). Drugs. US Department of Health and Human Services [2017/01/11]; Available from: http://www.fda.gov/Drugs/.

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

12 Appendix

Table 3: Characteristics of the MONALEESA-2 trial

Title: Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer			
Study identifier	NCT01958021, EudraCT 2013-003084-61, MONALEESA-2		
Design	Randomised, double-blind, placebo-controlled, phase III trial		
	Duration of main phase (interim analysis):		*24 January 2014 to 24 March 2015 + ongoing follow-up*
	Duration of run-in phase:		*NA*
	Duration of extension phase:		*NA*
Hypothesis	*Superiority* *The study was designed to assess the efficacy and safety of the selective CDK 4/6 inhibitor ribociclib combined with letrozole for the first-line treatment in postmenopausal women with HR-positive, HER2-negative recurrent or MBC, who had not received previous systemic therapy for advanced disease. A pre-planned interim analysis was planned on 29 January 2016, after 211 patients had disease progression or died. Pre-specified criteria for superiority required a hazard ratio of 0.56 or less with $p<1.29 \times 10^{-5}$.*		
Funding	Novartis Pharmaceuticals		
Treatments groups	Ribociclib group (n = 334)		600 mg ribociclib per day on a 3-weeks-on, 1-week-off schedule in combination with 2.5 mg of letrozole per day (continuously)
	Placebo group (n = 334)		Placebo combined with letrozole
Endpoints and definitions	Progression-free survival	PFS	Number of days from the date of first dose to the date of earliest disease progression or death
	Overall response rate	ORR	Overall CR or PR according to RECIST v1.1. Proportion of participants with CR or PR relative to all randomised participants and randomised participants with measurable disease at baseline, assessed up to 12 months
	Clinical benefit rate	CBR	Overall response plus stable disease lasting 24 weeks or more
	Overall survival	OS	Number of days from the date of first dose to the date of death for all dosed patients
Database lock	Last verified: August 2016		
Results and analysis			
Analysis description	**Primary analysis** The primary endpoint was assessed once 243 patients had disease progression or died. Efficacy analyses (primary and secondary endpoints) were performed in the intention-to-treat population, which was defined as all randomly assigned patients. Safety analyses were performed in the safety population, which was defined as all patients who received at least one dose of study treatment and who had at least one safety assessment after base-line. A determination that 302 patients had disease progression or died was required to detect a hazard ratio of 0.67 with a power of 93.5% at a one-sided alpha level of 0.025 with the use of a two-look Haybittle-Peto efficacy stopping boundary. A stratified Cox regression analysis was performed to estimate the hazard ratio and 95% confidence interval of progression-free survival.		

Title: Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer			
Study identifier	NCT01958021, EudraCT 2013-003084-61, MONALEESA-2		
Analysis population	Inclusion criteria	❁ postmenopausal women ❁ locally confirmed HR-positive, HER2-negative recurrent or MBC ❁ without previous systematic therapy for advanced disease ❁ measureable disease according to Response Evaluation Criteria in Solid Tumours [RECIST], version 1.1 ❁ OR at least one predominantly lytic bone lesion, along with an Eastern Cooperative Oncology Group performance status of 0 or 1 ❁ adequate bone marrow and organ function	
	Exclusion criteria	❁ previous CDK 4/6 inhibitor or any previous systemic chemotherapy ❁ OR previous ET for advanced disease ❁ previous neoadjuvant or adjuvant therapy with a non-steroidal AI, unless disease-free interval was more than 12 months ❁ patients with inflammatory breast cancer ❁ patients with CNS metastases ❁ patients with a history of cardiac disease or dysfunction (including a QT interval corrected for heart rate according to Fridericia's formula [QTcF] of >450 msec at screening) ❁ patients with impaired gastrointestinal function that altered drug absorption	
	Characteristics	Ribociclib	Placebo
	Median age (range), years	62 (23-91)	63 (29-88)
	Race White, n (%) Asian, n (%) Black, n (%) Other or unknown, n (%)	 269 (80.5) 28 (8.4) 10 (3.0) 27 (8.1)	 280 (83.8) 23 (6.9) 7 (2.1) 24 (7.2)
	ECOG performance status, n (%) 0 1	 205 (61.4) 129 (38.6)	 202 (60.5) 132 (39.5)
	Disease stage, n (%) III IV	 1 (0.3) 333 (99.7)	 3 (0.9) 331 (99.1)
	Hormone-receptor status, n (%) ER-positive PR-positive	 332 (99.4) 271 (81.1)	 333 (99.7) 278 (83.2)
	Disease-free interval, n (%) Newly diagnosed disease Existing disease ≤12 months >12 to ≤24 months >24 months Unknown	 114 (34.1) 220 (65.9) 4 (1.2) 14 (4.2) 202 (60.5) 0	 113 (33.8) 221 (66.2) 10 (3.0) 15 (4.5) 195 (58.4) 1 (0.3)

Title: Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer			
Study identifier	NCT01958021, EudraCT 2013-003084-61, MONALEESA-2		
Analysis population (continuation)	Previous treatment, n (%) Neoadjuvant or adjuvant chemotherapy Neoadjuvant or adjuvant ET Anastrozole Exemestane Goserelin Letrozole Tamoxifen Other	 146 (43.7) 175 (52.4) 47 (14.1) 19 (5.7) 6 (1.8) 34 (10.2) 140 (41.9) 2 (0.6)	 145 (43.4) 171 (51.2) 42 (12.6) 25 (7.5) 3 (0.9) 25 (7.5) 145 (43.4) 4 (1.2)
	Metastatic sites, n (%) 0 1 2 ≥3	 2 (0.6) 100 (29.9) 118 (35.3) 114 (34.1)	 1 (0.3) 117 (35.0) 103 (30.8) 113 (33.8)
	Site of metastases, n (%) Breast Bone Any Only Visceral Lymph nodes Other	 8 (2.4) 246 (73.7) 69 (20.7) 197 (59.0) 133 (39.8) 35 (10.5)	 11 (3.3) 244 (73.1) 78 (23.4) 196 (58.7) 123 (36.8) 22 (6.6)

Abbreviations: MBC = metastatic breast cancer, CR = complete response, PR = partial response, QoL = quality of life, ET = endocrine therapy, AI = aromatase inhibitor, CNS = central nervous system, ER = oestrogen receptor, PR = progesterone receptor, ECOG = Eastern Cooperative Oncology Group, NA = not available

Table 4: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [37]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: Randomisation was stratified according to the presence or absence of liver or lung metastases. Patients were not stratified according to their molecular subtype.		unclear
Adequate allocation concealment: No information is given about the allocation concealment of the randomisation system.		unclear
Blinding:	**Patient** double-blind study	yes
	Treating physician: double-blind study	yes
	Outcome assessment: blinded central analysis of PFS by an independent review committee	yes
Selective outcome reporting unlikely: outcomes reported as pre-specified		yes
No other aspects which increase the risk of bias: consistency in reporting pre-planned interim analyses led to premature study termination, described in detail study funded by the manufacturer		 yes (low) yes (low) no (high)
Risk of bias – study level		low