Kisqali®

KISQALI® 200 mg film-coated tablets

Description and composition

Pharmaceutical form

Film-coated tablet 200 mg

Light greyish violet, unscored, round, curved with beveled edges, debossed with "RIC" on one side and "NVR" on the other side.

Active substance

Each tablet containing 200 mg of ribociclib, as the succinate salt.

Excipients

Tablet core: Microcrystalline cellulose; low-substituted hydroxypropylcellulose; crospovidone (Type A); colloidal silicon dioxide; magnesium stearate.
Coating material: Polyvinyl alcohol (partially hydrolysed); titanium dioxide (E171); iron oxide black (E172); iron oxide red (E172); talc: lecithin (soy) (E322); xanthan gum.

Indications

Advanced or metastatic breast cancer

Kisqali is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy in pre/perimenopausal or postmenopausal women or in men; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

Dosage regimen and administration

Treatment with Kisqali® should be initiated by a physician experienced in the use of anticancer therapies.

Kisqali can be taken with or without food (see section Interactions).

Pre/peri-menopausal women or men treated with the combination of Kisqali plus an aromatase inhibitor should also receive a luteinizing hormone-releasing hormone (LHRH) agonist according to local clinical practice standards.

Men treated with the combination of Kisqali plus fulvestrant should be treated with a luteinizing hormone-releasing hormone (LHRH) agonist according to local clinical practice standards.

Patients should take their dose of Kisqali and aromatase inhibitor at approximately the same time each day, preferably in the morning.

If the patient vomits after taking the dose, or misses a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time. Kisqali tablets should be swallowed whole (tablet should not be chewed, crushed or split prior to swallowing). No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Dosage regimen
General target population

Advanced or metastatic breast cancer

The recommended dose of Kisqali is 600 mg (3 x 200 mg film-coated tablets) taken orally, once daily for 21 consecutive days followed by 7 days off treatment resulting in a complete cycle of 28 days..

In patients with advanced or metastatic breast cancer, when co-administered with Kisqali, refer to the full prescribing information for the recommended dose of the aromatase inhibitor to be used.

In patients with advanced or metastatic breast cancer, when co-administered with Kisqali, the recommended dose of fulvestrant is 500mg administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Please refer to the full prescribing information of fulvestrant.

Dose modifications

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction, or discontinuation of Kisqali. If dose reduction is required, the recommended dose reduction guidelines for adverse drug reactions (ADRs) are listed in Table 1.

Table 1 Dose modification guidelines for adverse drug reactions

	Kisqali	
Advanced or metastatic breast cancer	**Dose**	**Number of Tablets**
Starting dose	600 mg/day	3 × 200 mg tablets
First dose reduction	400 mg/day	2 × 200 mg tablets
Second dose reduction	200 mg/day*	1 × 200 mg tablet

**If further dose reduction below 200mg/day is required, discontinue the treatment.*

Tables 2, 3, 4, 5 and 6 summarize recommendations for dose interruption, reduction, or discontinuation of Kisqali in the management of specific ADRs. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (see sections Warnings and precautions, Adverse drug reactions).

Table 2 Dose modification and management for neutropenia

Neutropenia	**Grade 1 or 2** (ANC 1,000/mm^3 – <LLN)	**Grade 3** (ANC 500 - <1,000/mm^3)	**Grade 3 febrile* neutropenia**	**Grade 4** (ANC <500/mm^3)
	No dose adjustment is required.	Interrupt Kisqali until recovery to Grade ≤2. Resume Kisqali at the same dose level. If toxicity recurs at Grade 3, interrupt Kisqali dose until recovery to Grade ≤2, then resume Kisqali at the next lower dose level.	Interrupt Kisqali until recovery of neutropenia to Grade ≤2. Resume Kisqali at the next lower dose level.	Interrupt Kisqali until recovery to Grade ≤2. Resume Kisqali at the next lower dose level.
	Perform Complete Blood Counts (CBC) before initiating treatment with Kisqali. After initiating treatment with Kisqali, monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.			

**Grade 3 neutropenia with a single episode of fever >38.3˚C (or a sustained temperature 38˚C or above for more than one hour and/or concurrent infection)*

Grading according to CTCAE Version 4.03 CTCAE=Common Terminology Criteria for Adverse Events.

Table 3 Dose modification and management for hepatobiliary toxicity

AST and/or ALT elevations from baseline*, without increase in total bilirubin above 2 x ULN	**Grade 1 (>ULN – 3 x ULN)**	**Grade 2 (>3 to 5 x ULN)**	**Grade 3 (>5 to 20 x ULN)**	**Grade 4 (>20 x ULN)**
	No dose adjustment is required.	Baseline at <Grade 2: Interrupt Kisqali until recovery to ≤baseline Grade, then resume Kisqali at same dose level. If Grade 2 recurs, resume Kisqali at next lower dose level. --- Baseline at Grade 2: No dose interruption.	Interrupt Kisqali until recovery to ≤baseline Grade, then resume at next lower dose level. If Grade 3 recurs, discontinue Kisqali.	Discontinue Kisqali
Combined elevations in AST and/or ALT together with total bilirubin increase, in the absence of cholestasis	If patients develop ALT and/or AST >3 x ULN along with total bilirubin >2 x ULN irrespective of baseline Grade, discontinue Kisqali.			
Perform Liver Function Tests (LFTs) before initiating treatment with Kisqali. After initiating treatment with Kisqali, monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.				

If Grade ≥2 abnormalities are observed, more frequent monitoring is recommended.
**Baseline = prior to treatment initiation.* *Grading according to CTCAE Version 4.03 CTCAE=Common Terminology Criteria for Adverse Events.*

Table 4 Dose Modification and Management for QT prolongation

QTcF* prolongation	Advanced or metastatic breast cancer
>480 ms and ≤500 ms	Interrupt Kisqali treatment and wait until QTcF resolves to <481ms
	Reduce to the next lower level dose
	If QTcF ≥481 recurs, interrupt Kisqali treatment and wait until QTcF resolves to <481ms, then resume at next lower level dose.
>500 ms	Interrupt Kisqali treatment and wait until QTcF resolves to <481ms, then resume at next lower level dose. If QTcF > 500ms recurs, discontinue Kisqali.
If QTcF interval is greater than 500 ms or shows a greater than 60 ms change from baseline in combination with Torsade de Pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, permanently discontinue Kisqali.	
Note: If further dose reductions are required at the 200 mg dose, Kisqali should be discontinued. Electrocardiograms (ECGs) should be assessed prior to initiation of treatment in all patients. Repeat ECGs at approximately Day 14 of the first cycle, and as clinically indicated. In case of QTcF prolongation at any given time during treatment, more frequent ECG monitoring is recommended in patients with advanced or metastatic breast cancer.	
**QTcF = QT interval corrected by Fridericia's formula.*	

Table 5 Dose modification and management for ILD/Pneumonitis

ILD/pneumonitis	Grade 1 (asymptomatic)	Grade 2 (symptomatic)	Grade 3 or 4 (severe)
	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Interrupt Kisqali until recovery to Grade ≤1, then resume Kisqali at the next lower dose level*.	Discontinue Kisqali
Grading according to CTCAE Version 4.03. ** An individualized benefit-risk assessment should be performed when considering resuming Kisqali* *ILD = Interstitial Lung Disease*			

Table 6 Dose Modification and Management for Other Toxicities*

Other toxicities	Grade 1 or 2	Grade 3	Grade 4
	No dose adjustment is required. Initiate appropriate medical therapy and monitor as clinically indicated.	Interrupt Kisqali dose until recovery to Grade ≤1, then resume Kisqali at the same dose level. If Grade 3 recurs, resume Kisqali at the next lower dose level.	Discontinue Kisqali.
**excluding hematological toxicities, hepatobiliary toxicity QT interval prolongation, and ILD/ Pneumonitis* *Grading according to CTCAE Version 4.03. CTCAE=Common Terminology Criteria for Adverse Events.*			

Dose modification for use of Kisqali with strong CYP3A inhibitors

Concomitant use of Kisqali should be avoided with strong CYP3A inhibitors and an alternative concomitant medication should be considered with less potential for CYP3A inhibition.

In patients with advanced or metastatic breast cancer, if a strong CYP3A inhibitor must be co-administered, the Kisqali dose should be reduced to 400 mg once daily. If the strong inhibitor is discontinued, the Kisqali dose should be changed (after at least 5 elimination half-lives of the strong CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor (see sections Warnings and precautions, Interactions and Clinical pharmacology).

Special populations

Renal impairment

Based on population pharmacokinetic analysis, and data from cancer patients in clinical trials, no dose adjustment is necessary in patients with mild or moderate renal impairment (see section Clinical pharmacology).

Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment, a starting dose of 200 mg is recommended. Kisqali has not been studied in breast cancer patients with severe renal impairment. (see section Clinical pharmacology).

Hepatic impairment

Based on a hepatic impairment study in healthy subjects and non-cancer subjects with impaired hepatic function, no dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). A dose adjustment is required in patients with advanced or metastatic breast cancer with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) and the starting dose of 400mg is recommended. Kisqali has not been studied in breast cancer patients with moderate and severe hepatic impairment (see section Clinical pharmacology).

Review the full prescribing information for the aromatase inhibitor, fulvestrant or the LHRH agonist for dose modifications related to hepatic impairment.

Pediatric patients

There are limited data in pediatric patients and the safety and efficacy of Kisqali in this population have not been established.

Geriatric patients (65 years of age or older)

No dose adjustment is required in patients over 65 years of age (see section Clinical pharmacology).

Method of administration

Kisqali should be taken orally once daily at the same time every day, preferably in the morning, with or without food. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. Kisqali tablets should be swallowed whole (tablets should not be chewed, crushed, or split prior to swallowing). Tablets that are broken, cracked, or otherwise not intact should not be ingested.

Contraindications

Kisqali is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Neutropenia

In patients with advanced or metastatic breast cancer (3 phase III clinical studies MONALEESA-2 (A2301), MONALEESA-7 (E2301-NSAI) and MONALEESA-3 (F2301)), neutropenia was the most frequently reported adverse drug reaction (75.4%) and a Grade 3 or 4 decrease in neutrophil counts (based on laboratory findings) was reported in 62.0% of patients receiving Kisqali plus any combination in the phase III clinical studies.

Among the patients with advanced or metastatic breast cancer who had Grade 2, 3 or 4 neutropenia in the phase III clinical studies, the median time to Grade 2, 3 or 4 neutropenia was 17 days. The median time to resolution of Grade ≥3 (to normalization or Grade <3) was 12 days in the Kisqali plus any combination treatment arm. Febrile neutropenia was reported in 1.7% of patients exposed to Kisqali in the phase III clinical studies.

A complete blood count (CBC) should be performed before initiating therapy with Kisqali. CBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles then as clinically indicated.

Based on the severity of the neutropenia, Kisqali may require dose interruption, reduction, or discontinuation as described in Table 2 (see section Dosage regimen and administration).

In patients who develop Grade 1 or 2 neutropenia, no Kisqali dose adjustment is required. In patients who develop Grade 3 neutropenia without fever, the Kisqali dose should be interrupted until recovery to Grade ≤2 and then Kisqali should be resumed at the same dose level. If Grade 3 neutropenia without fever recurs, Kisqali dose should be interrupted until recovery, then Kisqali should be resumed at the next lower dose level.

In patients who develop Grade 3 febrile neutropenia (ANC <1,000/mm^3 with a single episode of fever >38.3°C or a sustained temperature 38°C or above for more than one hour), or patients who develop Grade 4 neutropenia, Kisqali dose should be interrupted until recovery to Grade ≤2, then Kisqali should be resumed at the next lower dose level.

Hepatobiliary toxicity

In the phase III clinical trials in patients with advanced or metastatic breast cancer, increases in transaminases were observed.

In patients with advanced or metastatic breast cancer, Grade 3 or 4 increases in ALT (11.2% vs. 1.7%) and AST (7.8% vs. 2.1%) were reported in the Kisqali plus any combination and placebo plus any combination arms respectively. Grade 4 increases in ALT (2.0% vs. 0.2%) and AST (1.1% vs. 0.1%) were reported in the Kisqali plus any combination treatment and placebo plus any combination treatment arms respectively.

In the phase III clinical studies, 70.9% (90/127) of Grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment (see section Adverse drug reactions). The majority of increases in ALT and AST were reported without concurrent elevations of bilirubin. Among the

patients who had Grade 3 or 4 ALT/AST elevation, the median time-to-onset was 92 days for the Kisqali plus any combination treatment arm . The median time to resolution (to normalization or Grade ≤2) was 21 days in the Kisqali plus any combination treatment arm.

Concurrent elevations of ALT or AST >3 x ULN and of total bilirubin >2 x ULN, with normal alkaline phosphatase levels, and in the absence of cholestasis occurred in 6 patients (4 patients in Study A2301, whose levels recovered to normal within 154 days; and 2 patients in Study F2301, whose levels recovered to normal within 121 and 532 days, respectively, after discontinuation of Kisqali. There were no such cases reported in Study E2301).

LFTs should be performed before initiating therapy with Kisqali in patients with advanced or metastatic breast cancer. The LFTs should be monitored every 2 weeks for first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.

Based on the severity of the transaminase elevations, Kisqali may require dose interruption, reduction, or discontinuation as described in Table 3 (see section Dosage regimen and administration). Recommendations for patients who have elevated AST/ALT Grade ≥3 at baseline have not been established.

The following dose modification and management guidelines are provided for hepatobiliary toxicity.:

- For patients with AST and/or ALT elevations from baseline (prior to treatment initiation), without an increase in total bilirubin (TB) above 2 x ULN no Kisqali dose adjustment is required for Grade 1 (AST and/or ALT elevations of >ULN to 3 x ULN).
- In patients with a baseline of Grade <2 (AST and/or ALT elevations of <ULN to 3 x ULN), if Grade 2 (AST and/or ALT elevations of >3 to 5 x ULN) develops, Kisqali dose should be interrupted until values return to ≤baseline Grade, then Kisqali should be resumed at the same dose level. If Grade 2 recurs, then Kisqali should be resumed at next lower dose level.
- In patients with a baseline of Grade 2 (AST and/or ALT elevations of >3 to 5 x ULN), if Grade 2 continues, no Kisqali dose interruption is required.
- In patients who develop Grade 3 (ALT and/or AST elevations of >5 to 20 x ULN), Kisqali dose should be interrupted until values return to ≤baseline Grade, then Kisqali should be resumed at next lower dose level. If Grade 3 recurs, Kisqali should be discontinued.
- In patients who develop Grade 4 (ALT and/or AST elevations of >20 x ULN), Kisqali should be discontinued.

The following dose modification and management guidelines are provided for patients with concurrent elevations in AST and/or ALT together with an increase in total bilirubin (TB), in the absence of cholestasis:

- In patients who develop total bilirubin >2 x ULN along with ALT and/or AST >3 x ULN, irrespective of baseline Grade, Kisqali should be discontinued.

QT interval prolongation

Kisqali should be avoided in patients who already have or who are at significant risk of developing QTc interval prolongation. This includes patients with:

- Long QT syndrome.
- Uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina and bradyarrhythmia.

- Electrolyte abnormalities.

Kisqali should be avoided in combination with medicinal products known to prolong the QTc interval and/or strong CYP3A inhibitors as this may lead to clinically meaningful prolongation of the QTcF interval (see sections Dosage regimen and administration, Interactions and Clinical pharmacology). Based on the findings in MONALEESA-7 (E2301), Kisqali is not recommended for use in combination with tamoxifen (see section Clinical studies).

In the phase III clinical studies, in patients with advanced or metastatic breast cancer who received the 600 mg Kisqali plus any combination partners, review of ECG data showed that 15 patients (1.4%) had >500 ms post-baseline QTcF interval value , and 61 patients (5.8%) had a >60 ms QTcF interval increase from baseline. There were no reported cases of Torsade de Pointes.

In study E2301 (MONALEESA-7), the observed mean QTcF interval increase from baseline was approximately more than 10 ms higher in the tamoxifen plus placebo sub-group compared with NSAI plus placebo sub-group, suggesting that tamoxifen had a QTcF interval prolongation effect which can contribute to the QTcF interval observed in the Kisqali plus tamoxifen arm (see section Clinical pharmacology – Cardiac electrophysiology). In the placebo arm, an increase of >60 ms from baseline occurred in 6/90 (6.7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of >60 ms from baseline in the QTcF interval was observed in 14/87 (16.1%) of patients receiving Kisqali plus tamoxifen and in 18/245 (7.3%) of patients receiving ribociclib plus an NSAI. Ribociclib is not indicated for concomitant use with tamoxifen.

An ECG should be assessed prior to initiation of treatment. Treatment with Kisqali should be initiated only in patients with QTcF interval values less than 450 ms . The ECG should be repeated at approximately Day 14 of the first cycle, and then as clinically indicated.

Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorous, and magnesium) should be performed in patients with advanced or metastatic breast cancer prior to initiation of treatment, at the beginning of the first 6 cycles, and then as clinically indicated. Any abnormality should be corrected before and during Kisqali therapy.

Based on the observed QT prolongation during treatment, Kisqali may require dose interruption, reduction, or discontinuation in patients with advanced or metastatic breast cancer as described in Table 4 (see sections Dosage regimen and administration, Adverse drug reactions and Clinical pharmacology).

In the event of ECGs with QTcF interval >480 ms and ≤500 ms:

- The treatment with Kisqali should be interrupted.
  If QTcF interval prolongation is resolved to <481 ms, Kisqali should be resumed at the next lower dose level if the starting dose was 600 mg (in patients with advanced or metastatic breast cancer).
- If QTcF interval ≥481 ms recurs, Kisqali dose should be interrupted until QTcF resolves to <481 ms, then Kisqali should be resumed at the next lower dose level.

In the event of ECGs with QTcF interval>500 ms, repeat ECG should be performed:

- The treatment with Kisqali should be interrupted.
- If QTcF interval prolongation resolves to <481 ms, Kisqali should be resumed at next lower dose level (see sections Dosage regimen and administration, Adverse drug reactions and Clinical pharmacology).

If QTcF interval prolongation greater than 500 ms recurs or the QTcF interval has a greater than 60 ms change from baseline in combination with Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia, Kisqali should be permanently discontinued.

Reproductive toxicity

Based on animal findings and its mechanism of action, Kisqali can cause fetal harm when administered to a pregnant woman. Women of reproductive potential should be advised to use effective contraception during therapy with Kisqali and for at least 21 days after the last dose (see section Pregnancy, lactation, females and males of reproductive potential).

Severe cutaneous reactions

Toxic epidermal necrolysis (TEN) has been reported with Kisqali treatment. If signs and symptoms suggestive of severe cutaneous reactions (e.g., progressive widespread skin rash often with blisters or mucosal lesions) appear, Kisqali should be immediately and permanently discontinued.

Interstitial Lung Disease (ILD)/Pneumonitis

ILD/pneumonitis has been reported with CDK4/6 inhibitors including reports of fatal cases.

In the phase III clinical studies in patients with advanced or metastatic breast cancer, ILD (any Grade 0.3%, including 0.1% Grade 3) was reported in the Kisqali treated group, with no cases in the placebo treated group. Pneumonitis (any Grade 0.6%, vs 0.4%) was reported in the Kisqali and placebo treated groups, respectively, with no Grade 3/4 events in either treatment group. Additional cases of ILD/pneumonitis have been observed with Kisqali in the post-marketing setting (see section Adverse drug reactions).

Based on the severity of the ILD/pneumonitis, which may be fatal, patients may require treatment interruption, dose reduction or permanent discontinuation as described in Table 5 (see section Dosage regimen and administration).

Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough, and dyspnea. In patients who develop Grade 1 ILD/pneumonitis, no dose adjustment is required. Appropriate medical therapy and monitoring should be initiated as clinically indicated. In patients who developed Grade 2 ILD/pneumonitis, the treatment with Kisqali should be interrupted until recovery to Grade ≤1, and then Kisqali can be resumed at the next lower dose level. For Grade 3 or 4 ILD/pneumonitis Kisqali should be permanently discontinued (see section Dosage regimen and administration).

Adverse drug reactions

Summary of the safety profile

Advanced or metastatic breast cancer

The overall safety profile reported below is based on the pooled data set of 1065 patients who received Kisqali in combination with endocrine therapy (N=582 in combination with an aromatase inhibitor, and N=483 in combination with fulvestrant), in double blind, placebo controlled phase III clinical studies (MONALEESA-2, MONALEESA-7-NSAI arm, MONALEESA-3) in HR-positive, HER2-negative advanced or metastatic breast cancer. The median duration of exposure

to study treatment across the pooled phase III studies data set was 19.2 months with 61.7% patients exposed for ≥12 months.

Dose reductions due to adverse events (AEs), regardless of causality occurred in 39.5% of patients receiving Kisqali in phase III clinical studies regardless of the combination and in 4.3% of patients receiving placebo. Permanent discontinuations due to adverse events were reported in 8.7% of patients receiving Kisqali plus any combination and in 3.1% of patients receiving placebo plus any combination. The most common AEs leading to permanent discontinuation of Kisqali with any combination treatment partner were ALT increased (4.5%), AST increased (2.5%) and vomiting (1.1%).

In the pooled analysis of three phase III studies, on treatment deaths, were reported in 22 patients (2.1%) treated with Kisqali plus any combination vs 16 patients (2.0%) treated with placebo plus any combination treatment. Excluding the most frequent cause of death disease progression, three treatment related causes of deaths were reported in patients treated with Kisqali plus any combination treatment. Causes of death were acute respiratory distress syndrome 1 (0.1%), acute respiratory failure 2 (0.2%), and sudden death (in a patient who had Grade 3 hypokalaemia and Grade 2 QT prolongation that improved to Grade 1 on the same day, both reported 10 days before the event) 1 (0.1%).

The most common ADRs across the pooled phase III studies (reported at a frequency of ≥20% and exceeding the frequency for placebo) were neutropenia, infections, nausea, fatigue, diarrhoea, leukopenia, vomiting, headache, constipation, alopecia, cough, rash, back pain, anaemia and abnormal liver function tests.

The most common Grade 3/4 ADRs in the pooled data (reported at a frequency of ≥2% and for which the frequency for Kisqali exceeds the frequency for placebo) were neutropenia, leukopenia, abnormal liver function tests, lymphopenia, infections, back pain, anaemia, fatigue, hypophosphataemia and vomiting.

In addition, the safety of Kisqali in combination with letrozole was evaluated in men (n=39) in an open-label, multicenter clinical study (COMPLEEMENT-1) for the treatment of patients with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease. The median duration of exposure to Kisqali was 20.8 months (range: 0.5 to 30.6 months).

Adverse reactions occurring in men treated with Kisqali plus letrozole and goserelin or leuprolide were similar to those occurring in women treated with Kisqali plus endocrine therapy.

Tabulated summary of adverse drug reactions

ADRs from the phase-III clinical studies in patients with advanced or metastatic breast cancer (Table 7, Table 8) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Advanced or metastatic breast cancer

Table 7 Adverse drug reactions based on pooled dataset from 3 phase III clinical studies in patients with advanced or metastatic breast cancer

Adverse drug reactions	Kisqali N=1,065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N=1,065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
Infections and infestations					
Infections[1]	502 (47.1)	282 (34.5)	49 (4.6)	12 (1.5)	Very common
Blood and lymphatic system disorders					
Neutropenia	803 (75.4)	54 (6.6)	662 (62.2)	18 (2.2)	Very common
Leukopenia	350 (32.9)	27 (3.3)	184 (17.3)	5 (0.6)	Very common
Anaemia	228 (21.4)	69 (8.4)	41 (3.8)	18 (2.2)	Very common
Lymphopenia	124 (11.6)	21 (2.6)	67 (6.3)	8 (1.0)	Very common
Thrombocytopenia	105 (9.9)	15 (1.8)	9 (0.8)	2 (0.2)	Common
Febrile neutropenia	18 (1.7)	2 (0.2)	17 (1.6)	2 (0.2)	Common
Eye disorders					
Lacrimation increased	77 (7.2)	11 (1.3)	0	0	Common
Dry eye	64 (6.0)	24 (2.9)	0	0	Common
Metabolism and nutrition disorders					
Decreased appetite	182 (17.1)	110 (13.4)	6 (0.6)	1 (0.1)	Very common
Hypocalcaemia	50 (4.7)	14 (1.7)	12 (1.1)	0	Common
Hypokalaemia	44 (4.1)	23 (2.8)	16 (1.5)	6 (0.7)	Common
Hypophosphataemia	35 (3.3)	12 (1.5)	22 (2.1)	7 (0.9)	Common
Nervous system disorders					
Headache	290 (27.2)	191 (23.3)	7 (0.7)	5 (0.6)	Very common
Dizziness	149 (14.0)	93 (11.4)	2 (0.2)	1 (0.1)	Very common
Vertigo	64 (6.0)	14 (1.7)	2 (0.2)	0	Common
Cardiac disorders					
Syncope	25 (2.3)	13 (1.6)	18 (1.7)	8 (1.0)	Common
Respiratory, thoracic and mediastinal disorders					
Cough	258 (24.2)	152 (18.6)	0	0	Very common
Dyspnoea	155 (14.6)	95 (11.6)	20 (1.9)	8 (1.0)	Very common
Musculoskeletal and connective tissue disorders					
Back pain	256 (24.0)	180 (22.0)	23 (2.2)	11 (1.3)	Very common
Gastrointestinal disorders					
Nausea	496 (46.6)	242 (29.6)	18 (1.7)	5 (0.6)	Very common
Diarrhoea	354 (33.2)	191 (23.3)	20 (1.9)	6 (0.7)	Very common

Adverse drug reactions	Kisqali N=1,065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N=1,065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
Vomiting	307 (28.8)	143 (17.5)	23 (2.2)	3 (0.4)	Very common
Constipation	271 (25.4)	140 (17.1)	9 (0.8)	0	Very common
Abdominal pain[2]	208 (19.5)	121 (14.8)	16 (1.5)	5 (0.6)	Very common
Stomatitis	147 (13.8)	59 (7.2)	4 (0.4)	1 (0.1)	Very common
Dyspepsia	108 (10.1)	48 (5.9)	1 (0.1)	0	Very common
Dysgeusia	75 (7.0)	39 (4.8)	1 (0.1)	0	Common
Hepatobiliary disorders					
Hepatotoxicity[3]	20 (1.9)	7 (0.9)	16 (1.5)	4 (0.5)	Common
Skin and subcutaneous tissue disorders					
Alopecia	268 (25.2)	102 (12.5)	0	0	Very common
Rash[4]	253 (23.8)	81 (9.9)	10 (0.9)	1 (0.1)	Very common
Pruritus	197 (18.5)	57 (7.0)	5 (0.5)	0	Very common
Dry skin	96 (9.0)	23 (2.8)	0	0	Common
Erythema	55 (5.2)	13 (1.6)	2 (0.2)	1 (0.1)	Common
Vitiligo	30 (2.8)	0	1 (0.1)	0	Common
General disorders and administration site conditions					
Fatigue	373 (35.0)	263 (32.2)	23 (2.2)	5 (0.6)	Very common
Peripheral oedema	171 (16.1)	83 (10.1)	2 (0.2)	0	Very common
Pyrexia	168 (15.8)	60 (7.3)	5 (0.5)	1 (0.1)	Very common
Asthenia	161 (15.1)	108 (13.2)	10 (0.9)	3 (0.4)	Very common
Oropharyngeal pain	87 (8.2)	46 (5.6)	0	0	Common
Dry mouth	83 (7.8)	51 (6.2)	1 (0.1)	0	Common
Investigations					
Abnormal liver function tests[5]	216 (20.3)	89 (10.9)	105 (9.9)	17 (2.1)	Very common
Blood creatinine increased	84 (7.9)	20 (2.4)	7 (0.7)	0	Common
Electrocardiogram QT prolonged	73 (6.9)	14 (1.7)	14 (1.3)	2 (0.2)	Common

[1]Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (<1%).

[2]Abdominal pain: abdominal pain, abdominal pain upper.

[3]Hepatotoxicity: hepatic cytolysis,hepatocellular injury, drug induced liver injury, hepatotoxicity, hepatic failure, autoimmune hepatitis (single case).

[4]Rash: rash, rash maculopapular, rash pruritic

[5]Abnormal liver function tests: ALT increased, AST increased, blood bilirubin increased.

Laboratory abnormalities

Clinically relevant abnormalities of routine haematological or biochemical laboratory values from the data set of 3 pooled phase III studies in patients with advanced or metastatic breast cancer are presented in Table 8.

Table 8 Laboratory abnormalities based on pooled dataset from phase III clinical studies in patients with advanced or metastatic breast cancer

Laboratory abnormalities	Kisqali N=1,065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N=1,065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category (all Grades)
Hematological parameters					
Leukocyte count decreased	1,009 (94.7)	268 (32.8)	380 (35.7)	10 (1.2)	Very common
Neutrophil count decreased	994 (93.3)	227 (27.8)	660 (62.0)	20 (2.4)	Very common
Haemoglobin decreased	728 (68.4)	339 (41.4)	54 (5.1)	19 (2.3)	Very common
Lymphocyte count decreased	703 (66.0)	228 (27.9)	209 (19.6)	37 (4.5)	Very common
Platelet count decreased	366 (34.4)	86 (10.5)	16 (1.5)	5 (0.6)	Very common
Biochemical parameters					
Aspartate aminotransferase increased	580 (54.5)	343 (41.9)	83 (7.8)	17 (2.1)	Very common
Gamma glutamyl transferase increased[1]	390 (53.4)	229 (46.9)	67 (9.2)	51 (10.5)	Very common
Alanine aminotransferase increased	548 (51.5)	315 (38.5)	119 (11.2)	14 (1.7)	Very common
Creatinine increased	447 (42.0)	121 (14.8)	14 (1.3)	2 (0.2)	Very common
Glucose serum decreased	216 (20.3)	113 (13.8)	3 (0.3)	2 (0.2)	Very common
Phosphorous decreased	190 (17.8)	79 (9.7)	46 (4.3)	8 (1.0)	Very common
Albumin decreased	122 (11.5)	53 (6.5)	1 (0.1)	1 (0.1)	Very common
Potassium decreased	118 (11.1)	76 (9.3)	22 (2.1)	10 (1.2)	Very common
Bilirubin increased	64 (6.0)	46 (5.6)	12 (1.1)	9 (1.1)	Common

[1] Data collected from study MONALEESA-3 and study MONALEESA-7. Data based on sample size N=731 for ribociclib arm and N=488 for placebo arm.

Post-marketing data

The following ADRs are derived from post-marketing experience with Kisqali via spontaneous case reports and literature cases. As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known.

Table 9 Adverse drug reactions derived from spontaneous reports and literature (frequency not known)

Respiratory, thoracic and mediastinal disorders
Interstitial lung disease (ILD)/pneumonitis
Skin and subcutaneous tissue disorders
Toxic epidermal necrolysis (TEN)

Description of selected adverse drug reactions

Neutropenia

Severity of neutropenia is concentration dependent.

Neutropenia was most frequently reported by laboratory findings in the phase III studies in patients with advanced or metastatic breast cancer. Treatment discontinuation due to neutropenia was low (0.8%) in patients receiving Kisqali plus any combination partner (see sections Dosage regimen and administration and Warnings and precautions).

Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. All patients should be instructed to report any fever promptly.

Hepatobiliary toxicity

In the phase III clinical studies in patients with advanced or metastatic breast cancer, hepatobiliary toxicity events occurred in a higher proportion of patients in the Kisqali plus any combination arms vs the placebo plus any combination arms (27.3% vs 19.6%, respectively), with more Grade 3/4 AEs reported in patients treated with Kisqali plus any combination treatment (13.2% vs. 6.1%, respectively). Dose interruptions and/or adjustments due to hepatobiliary toxicity events were reported in 12.3% of Kisqali treated patients, primarily due to ALT increased (7.9%) and/or AST increased (7.3%). Discontinuation of treatment with Kisqali due to abnormal liver function tests and, hepatotoxicity occurred in 2.4% and 0.3% of patients respectively (see section Warnings and precautions).

QT prolongation

In the phase III clinical studies in patients with advanced or metastatic breast cancer, 9.3% of patients in the Kisqali arm and 3.5% in the placebo arm had at least one event of QT interval prolongation (including ECG QT interval prolonged, syncope). Dose interruptions-adjustments were reported in 2.3% of Kisqali treated patients due to electrocardiogram QT interval prolonged and syncope.

A central analysis of ECG data (average of triplicate) showed 55 patients (5.2%) and 12 patient (1.5%) with at least one post-baseline QTcF interval >480 ms for the Kisqali treatment arm and the placebo arm respectively. Among the patients who had QTcF interval prolongation of >480 ms, the median time to onset was 15 days, regardless of the combination and these changes were reversible with dose interruption and/or dose adjustment (see sections Dosage regimen and administration, Warnings and precautions and Clinical pharmacology).

Interactions

Ribociclib is primarily metabolized by CYP3A and is a time-dependent inhibitor of CYP3A *in vivo*. Therefore, medicinal products which can influence CYP3A enzyme activity may alter the pharmacokinetics of ribociclib.

Medicinal products that may increase ribociclib plasma concentrations

Co-administration of a strong CYP3A4 inhibitor (ritonavir) increased single dose 400 mg ribociclib exposure in healthy subjects by 3.21-fold. Physiologically-based pharmacokinetic (PBPK) simulations with co-administered ritonavir (100 mg twice daily) estimated that the steady state Cmax and AUC0-24h of ribociclib (400 mg once daily) increase by 1.29- and 1.47-fold, respectively, in patients with advanced or metastatic breast cancer. Concomitant use of strong CYP3A inhibitors including but not limited to clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole (see section Warnings and precautions) should be avoided. Alternative concomitant medications with a low potential to inhibit CYP3A should be considered, and patients should be monitored for ADRs (see sections Dosage regimen and administration, Warnings and precautions and Clinical Pharmacology).

In patients with advanced or metastatic breast cancer who are receiving 600 mg Kisqali, if co-administration of Kisqali with a strong CYP3A inhibitor cannot be avoided, the Kisqali dose should be reduced to 400 mg. However, there are no clinical data with this dose adjustment (see section Dosage regimen and administration).

In patients with advanced or metastatic breast cancer, if the strong inhibitor is discontinued, the Kisqali dose should be resumed (after at least 5 elimination half-lives of the CYP3A inhibitor) to the dose used prior to the initiation of the strong CYP3A inhibitor. Due to inter-patient variability, the recommended dose adjustments may not be optimal in all patients, therefore close monitoring for ADRs is recommended. In the event of Kisqali related toxicity, the dose should be modified (see section Dosage regimen and administration), or treatment should be interrupted until toxicity has resolved (see sections Dosage regimen and administration and Clinical Pharmacology).

Patients should be instructed to avoid grapefruits or grapefruit juice, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib.

Medicinal products that may decrease ribociclib plasma concentrations

Co-administration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89%. Avoid concomitant use of strong CYP3A inducers, including but not limited to phenytoin, rifampin, carbamazepine, and St John's Wort *(Hypericum perforatum)*. An alternate concomitant medication with no or minimal potential to induce CYP3A should be considered (see sections Warnings and precautions and Clinical pharmacology).

Medicinal products that may have their plasma concentrations altered by ribociclib

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of Kisqali (400mg) increased the midazolam exposure by 280% (3.80-fold) in healthy subjects, compared with administration of midazolam alone. Simulations using physiologically-based PK (PBPK) models suggested that Kisqali given at the clinically relevant dose of 600mg is expected to increase the midazolam AUC by 5.2-fold. Therefore caution is recommended when Kisqali is administered

with CYP3A substrates with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, may need to be reduced as ribociclib has the potential to increase their exposure (see section Clinical pharmacology). Concomitant use of ribociclib with statins that are substrates of CYP3A4 and/or BCRP may increase the risk of rhabdomyolysis due to increased plasma statin concentrations (e.g. simvastatin and atorvastatin). Caution is required in the event of concomitant treatment with such statins.

Co-administration of caffeine (CYP1A2 substrate) with multiple doses of Kisqali (400 mg) increased caffeine exposure by 20% (1.20-fold) in healthy subjects, compared with administration of caffeine alone. At the clinically relevant dose of 600 mg, simulations using PBPK models predicted only weak inhibitory effects of ribociclib on CYP1A2 substrates (<2-fold increase in AUC) (see section Clinical pharmacology).

Medicinal products that are substrates of transporters

In vitro evaluations indicated that ribociclib has a low potential to inhibit the activities of drug transporters P-gp, OAT1/3, OATP1B1/B3, MATE2K and OCT1 at clinically relevant concentrations. Ribociclib may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations (see section Clinical pharmacology).

Drug-food interactions

Kisqali can be administered with or without food (see section Dosage regimen and administration).

Compared to the fasted state, oral administration of a single 600mg dose of Kisqali film-coated tablets with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib (C_{max} GMR: 1.00; 90% CI: 0.898, 1.11; AUC_{inf} GMR: 1.06; 90% CI: 1.01, 1.12 (see section Clinical pharmacology).

Gastric pH elevating medications

Ribociclib exhibits high solubility at or below pH 4.5 and in bio-relevant media (at pH 5.0 and 6.5). Co-administration of Kisqali with medicinal products that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption was not observed in the population pharmacokinetic analysis nor in simulations using PBPK models (see section Clinical pharmacology).

Anticipated interactions

Antiarrhythmic medicines and other medicinal products that may prolong the QT interval: Co-administration of Kisqali should be avoided with medicinal products with known potential to prolong the QT interval such as antiarrhythmic medicines. Concomitant use of anti-arrhythmic medicines (including but not limited to amiodarone, disopyramide, procainamide, quinidine, and sotalol), other medicinal products that are known to prolong the QT interval, including but not limited to, chloroquine, halofantrine, clarithromycin, ciprofloxacin, levofloxacin, azithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide, and ondansetron (i.v), should be avoided. Kisqali is not recommended for use in combination with tamoxifen (See section Warnings and precautions).

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk summary

Based on animal data and its mechanism of action, it is possible that Kisqali can cause fetal harm when administered to a pregnant woman.

The patient should be advised of the risk to a fetus if Kisqali is used during pregnancy or if the patient becomes pregnant while taking this medicinal product.

There are no adequate and well-controlled studies in pregnant women. Reproductive studies in rats and rabbits have demonstrated ribociclib-induced embryotoxicity, fetotoxicity and teratogenicity. Following prenatal exposure, increased incidences of post-implantation loss and reduced fetal weights were observed in rats and ribociclib was teratogenic in rabbits as evidenced by increased incidences of fetal abnormalities (malformations and external, visceral, and skeletal variants) at exposures lower than or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600mg/day based on AUC. There are no available human data informing the drug-associated risk.

Data

Animal data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1,000mg/kg/day and 60mg/kg/day, respectively, during the period of organogenesis.

In rats, 1,000mg/kg/day was lethal in the maternal animals. At 300mg/kg/day, a slight, non-adverse trend towards reduced maternal body weight gain and fetal toxicity evidenced by reduced fetal weights accompanied by skeletal changes were considered to be transitory and/or related to the lower fetal weights. There were no effects upon embryo-fetal mortality or adverse effects on fetal morphology at 50 or 300mg/kg/day. The no-observed-adverse-effect level (NOAEL) for maternal toxicity was considered to be 300mg/kg/day. The no-observed-effect-level (NOEL) for embryo-fetal development was considered to be 50mg/kg/day.

In rabbits at doses ≥30mg/kg/day, there were adverse effects on embryo-fetal development as evidenced by increased incidences of fetal abnormalities (malformations and external, visceral and skeletal variants) and fetal growth (lower fetal weights). These findings included reduced/small lung lobes and additional vessel on the aortic arch and diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes and reduced/small accessory lung lobe (30 and 60mg/kg), extra/rudimentary 13^{th} ribs and misshapen hyoid bone and reduced number of phalanges in the pollex. There was no evidence of embryo-fetal mortality. The no-observed-effect level (NOEL) for maternal toxicity was considered to be at least 30mg/kg/day and the NOEL for the embryo-fetal development was 10mg/kg/day.

At 300mg/kg/day in rats and 30mg/kg/day in rabbits, the maternal systemic exposure (AUC) were 13,800ng*hr/mL and 36,700ng*hr/mL, lower than or at 1.5 times, the one achieved in patients at the highest recommended dose of 600mg/day in patients with advanced or metastatic breast cancer.

Lactation

Risk summary

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed child or the effects of ribociclib on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants from Kisqali, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. It is recommended that women taking Kisqali should not breastfeed for at least 21 days after the last dose.

Data

Animal data

In lactating rats administered a single dose of 50mg/kg, exposure to ribociclib was 3.56 fold higher in milk than in maternal plasma.

Females and males of reproductive potential

Based on animal studies, Kisqali can cause fetal harm when administered to a pregnant woman (see section Non clinical safety data).

Pregnancy testing

For females of reproductive potential the pregnancy status should be verified prior to initiating treatment with Kisqali.

Contraception

Females of reproductive potential should be advised that animal studies have been performed showing ribociclib to be harmful to the developing fetus. Sexually active females of reproductive potential should use effective contraception (methods that result in < 1 % pregnancy rates) when using Kisqali during treatment and for 21 days after stopping treatment with Kisqali.

Infertility

In a fertility study in female rats, ribociclib did not affect the reproductive function, fertility or early embryonic development at any dose up to 300mg/kg/day (likely at an exposure lower than or equal to patients clinical exposure, at the highest recommended dose of 600mg/day based on AUC).

A fertility study in male rats has not been performed, however atrophic changes in testes were reported in repeated dose toxicity studies in rats and dogs at exposures that were less or equal to the human exposure at the highest recommended daily dose of 600mg/day based on AUC (see section Non-clinical safety data). There are no clinical data available regarding the effects of Kisqali on fertility. Based on animal studies, Kisqali may impair fertility in males of reproductive potential.

Overdosage

There is limited experience with reported cases of Kisqali overdose in humans. General symptomatic and supportive measures should be initiated in all cases of overdosage where necessary.

Clinical pharmacology

Pharmacotherapeutic group, ATC

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EF02

Mechanism of action (MOA)

Ribociclib is a selective inhibitor of cyclin-dependent kinase (CDK) 4 and 6. These kinases are activated upon binding to D-cyclins and play a crucial role in signaling pathways which lead to cell cycle progression, and cellular proliferation. The cyclin D-CDK4/6 complex regulates cell cycle progression through phosphorylation of the retinoblastoma protein (pRb).

In vitro, ribociclib decreased pRb phosphorylation, resulting in arrest in the G1 phase of the cell cycle, reduced proliferation, and a senescent phenotype in breast cancer-derived models. *In vivo,* treatment with single agent ribociclib led to tumor regressions which correlated with inhibition of pRb phosphorylation at well tolerated doses.

In vivo studies using patient-derived estrogen positive breast cancer xenograft models combinations of ribociclib and antiestrogen therapies (i.e., letrozole) resulted in superior inhibition of tumor growth compared to each drug alone. When administered to patients, ribociclib can also be immunomodulatory, decreasing regulatory T-cells and relative levels of CD3+ T-cells. Tumor regrowth was delayed for 33 days after stopping dosing. Additionally, the in vivo antitumor activity of ribociclib in combination with fulvestrant was assessed in immune-deficient mice bearing the ZR751 ER+ human breast cancer xenografts. The combination of ribociclib and fulvestrant resulted in complete tumor growth inhibition.

Pharmacodynamics (PD)

Ribociclib inhibits the CDK4/cyclin-D1 and CDK6/cyclin-D3 enzyme complexes with concentration resulting in 50% inhibition (IC_{50}) values of 0.01 (4.3ng/mL) and 0.039 micro molar (16.9ng/mL) in biochemical assays, respectively.

In cell-based assays, ribociclib inhibits CDK4/6-dependent pRb phosphorylation with an average IC_{50} of 0.06 micro molar (26ng/mL). Ribociclib halts G1 to S phase cell cycle progression measured by flow cytometry with an average IC_{50} of 0.11 micromolar (47.8ng/mL). Ribociclib also inhibits cellular proliferation measured by bromodeoxyuridine (BrdU) uptake with an IC_{50} of 0.8 micromolar (34.8ng/mL). The similar IC_{50} values obtained from the target modulation, cell cycle and proliferation assays confirms that the blockade of pRb phosphorylation by ribociclib directly leads to G1 to S phase arrest and subsequent inhibition of cellular proliferation. When tested in a panel of breast cancer cell lines with known ER status, ribociclib was demonstrated to be more efficacious in ER+ breast cancer cell lines than in the ER- ones. In the preclinical models tested so far, intact pRb was required for ribociclib activity.

Cardiac electrophysiology

Serial, triplicate ECGs were collected following a single dose and at steady state to evaluate the effect of ribociclib on the QTc interval in patients with advanced cancer. A pharmacokinetic-pharmacodynamic analysis included a total of 997 patients treated with ribociclib at doses ranging from 50 to 1,200mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval.

In patients with advanced or metastatic breast cancer, the estimated QTcF interval mean change from baseline for Kisqali 600mg dose in combination with NSAI or fulvestrant was 22.00 ms (90% CI: 20.56, 23.44) and 23.7ms (90% CI: 22.31, 25.08) respectively, at the geometric mean C_{max} at steady state compared to 34.7 ms (90% CI: 31.64, 37.78) in combination with tamoxifen (see section Warnings and precautions).

Pharmacokinetics (PK)

The pharmacokinetics of ribociclib were investigated in patients with advanced cancer following oral daily doses of 50mg to 1,200mg. Healthy subjects received single oral doses of 400 or 600mg or repeated daily oral doses (8 days) of 400mg.

Absorption

Following oral administration of Kisqali to patients with advanced solid tumors or lymphomas peak plasma levels (C_{max}) of ribociclib were achieved between 1 and 4 hours (time to reach maximum concentration, T_{max}). The geometric mean absolute bioavailability of ribociclib after a single oral dose of 600 mg was 65.8% in healthy subjects. Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range tested (50 to 1,200mg). Following repeated once daily dosing, steady state was generally achieved after 8 days and ribociclib accumulated with a geometric mean accumulation ratio of 2.51 (range: 0.972 to 6.40).

Food effect:

Compared to the fasted state, oral administration of a single 600mg dose of ribociclib film-coated tablet formulation with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib (C_{max} GMR: 1.00; 90% CI: 0.898, 1.11; AUC_{inf} GMR: 1.06; 90% CI: 1.01, 1.12) (see section Interactions).

Distribution

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and independent of concentration (10 to 10,000ng/mL). Ribociclib was equally distributed between red blood cells and plasma with a mean in vivo blood-to-plasma ratio of 1.04. The apparent volume of distribution at steady state (Vss/F) was 1,090 L based on the population pharmacokinetic analysis.

Biotransformation/metabolism

In vitro and *in vivo* studies indicated that ribociclib undergoes extensive hepatic metabolism mainly via CYP3A4 in humans. Following oral administration of a single 600mg dose of [^{14}C]ribociclib to humans, the primary metabolic pathways for ribociclib involved oxidation (dealkylation, C and/or N-oxygenation, oxidation (-2H)) and combinations thereof. Phase II conjugates of ribociclib phase I metabolites involved N-acetylation, sulfation, cysteine conjugation, glycosylation and glucuronidation. Ribociclib was the major circulating drug-derived

entity in plasma (43.5%). The major circulating metabolites included metabolite M13 (CCI284, N-hydroxylation), M4 (LEQ803, N-demethylation), and M1 (secondary glucuronide), each representing an estimated 9.39%, 8.60%, and 7.78% of total radioactivity, and 21.6%, 19.8%, and 17.9% of ribociclib exposure, respectively. Clinical activity (pharmacological and safety) of ribociclib was primarily due to parent drug, with negligible contribution from circulating metabolites.

Ribociclib was extensively metabolized with the unchanged drug accounting for 17.3% and 12.1% of the dose in feces and urine, respectively. Metabolite LEQ803 was a significant metabolite in excreta and represented approximately 13.9% and 3.74% of the administered dose in feces and urine, respectively. Numerous other metabolites were detected in both feces and urine in minor amounts (≤2.78% of the administered dose).

Elimination

The geometric mean plasma effective half-life (based on accumulation ratio) was 32.0 hours (63% CV) and the geometric mean apparent oral clearance (CL/F) was 25.5 L/hr (66% CV) at steady state at 600mg in patients with advanced cancer. The geometric mean plasma terminal half-life ($T_{1/2}$) of ribociclib ranged from 29.7 to 54.7 hours and the geometric mean CL/F of ribociclib ranged from 39.9 to 77.5 L/hr at 600mg across studies in healthy subjects.

Ribociclib is eliminated mainly via the feces, with a small contribution from the renal route. In 6 healthy male subjects, following a single oral dose of [^{14}C] ribociclib, 91.7% of the total administered radioactive dose was recovered within 22 days; feces were the major route of excretion (69.1%), with 22.6% of the dose recovered in the urine.

Linearity/non-linearity

Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range of 50mg to 1,200mg following both single dose and repeated doses. This analysis is limited by the small sample sizes for most of the dose cohorts with a majority of the data coming from the 600mg dose cohort.

Special populations

Renal impairment

The effect of renal function on the pharmacokinetics of ribociclib was also assessed in a renal impairment study in non-cancer subjects that included 14 subjects with normal renal function (absolute Glomerular Filtration Rate (aGFR) ≥90 mL/min), 8 subjects with mild renal impairment (aGFR 60 to <90 mL/min), 6 subjects with moderate renal impairment (aGFR 30 to <60 mL/min), 7 subjects with severe renal impairment (aGFR 15 to <30 mL/min), and 3 subjects with end stage renal disease (ESRD) (aGFR <15 mL/min) at a single oral ribociclib dose of 400 mg/day.

In the subjects with normal, mild, moderate, severe renal impairment and ESRD, the geometric mean AUCinf (geometric %CV, n) was 4,100 ng*hr/mL (53.2%, 14), 6,650 ng*hr/mL (36.4%, 8), 7,960 ng*hr/mL (45.8%, 6), 10,900 ng*hr/mL (38.1%, 7), 13,600 ng*hr/mL (20.9%, 3), respectively, and Cmax (geometric %CV, n) was 234 ng/mL (58.5%, 14), 421 ng/mL (31.6%, 8), 419 ng/mL (30.3%, 6), 538 ng/mL (43.3%, 7), 593 ng/mL (11.3%, 3), respectively.

AUCinf increased to 1.62-fold, 1.94-fold, and 2.67-fold, and Cmax increased to 1.80-fold, 1.79-fold and 2.30-fold in subjects with mild, moderate and severe renal impairment, relative to the

exposure in subjects with normal renal function. A fold difference for subjects with ESRD was not calculated due to the small number of subjects (see section 4 Dosage regimen and administration).

No dose adjustment is necessary in breast cancer patients with mild or moderate renal impairment. The effect of renal function on the pharmacokinetics of ribociclib was also assessed in cancer patients. Based on a population pharmacokinetic analysis that included 438 advanced cancer patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2), 488 patients with mild renal impairment (eGFR 60 to <90 mL/min/1.73m^2) and 113 patients with moderate renal impairment (eGFR 30 to <60 mL/min/1.73 m^2), mild and moderate renal impairment had no effect on the exposure of ribociclib. In addition, in a sub-group analysis of PK data from studies in advanced cancer patients following oral administration of ribociclib 600 mg as a single dose or repeat doses (MONALEESA-7, CLEE011X2101 and CLEE011X2107), AUC and Cmax of ribociclib following a single dose or at steady state in patients with mild or moderate renal impairment were comparable to patients with normal renal function, suggesting no clinically meaningful effect of mild or moderate renal impairment on ribociclib exposure. (see section Dosage regimen and administration).

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A); in patients with advanced or metastatic breast cancer, a dose adjustment is required in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) and a starting dose of 400mg is recommended. Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for C_{max}; 1.28 for AUC_{inf}) and severe (GMR: 1.32 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment. Based on a population pharmacokinetic analysis that included 160 advanced cancer patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study (see section Dosage regimen and administration).

Effect of age, weight, gender and race

The population pharmacokinetic analysis showed that there are no clinically relevant effects of age, body weight, gender, or race on the systemic exposure of ribociclib that would require a dose adjustment.

Geriatric patients

Of the 334 patients with advanced or metastatic breast cancer who received Kisqali in the phase III study (MONALEESA 2, ribociclib plus letrozole arm), 150 patients (44.9%) were ≥65 years of age and 35 patients (10.5%) were ≥75 years of age. Of 483 patients who received Kisqali in the phase III study (MONALEESA 3, ribociclib plus fulvestrant arm), 226 patients (46.8%) were ≥65 years of age and 65 patients (13.5%) were ≥75 years of age. No overall differences in the safety or effectiveness of Kisqali were observed between these patients and younger patients (see section Dosage regimen and administration).

Interactions

Strong CYP3A inhibitors: A drug interaction study in healthy subjects was conducted with ritonavir (strong CYP3A inhibitor). Compared to ribociclib alone, ritonavir (100mg b.i.d for 14 days) increased ribociclib C_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, following a

single 400mg ribociclib dose. C_{max} and AUC_{last} for LEQ803 (a prominent metabolite of ribociclib, accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively. PBPK simulations with co-administered ritonavir (100 mg twice daily) estimated that the steadystate Cmax and AUC0-24h of ribociclib (400 mg once daily) increase by 1.29- and 1.47-fold, respectively, in patients with advanced or metastatic breast cancer.

Simulations using PBPK suggested that a moderate CYP3A4 inhibitor (erythromycin) may increase C_{max} and AUC of ribociclib 400mg steady state by 1.08-fold and 1.13-fold, respectively, in patients with advanced breast cancer (see sections Dosage regimen and administration, Warnings and precautions and Interactions).

Strong CYP3A inducers: A drug interaction study in healthy subjects was conducted with rifampicin (strong CYP3A4 inducer). Compared to ribociclib alone, rifampicin (600mg daily for 14 days) decreased ribociclib C_{max} and AUC_{inf} by 81% and 89%, respectively, following a single 600mg ribociclib dose. LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by 27%, respectively.

Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease ribociclib single dose C_{max} and AUC by 37% and 60%**,** respectively, in patients with advanced breast cancer (see section Interactions).

Cytochrome P450 enzymes (CYP3A4 and CYP1A2 substrates): A drug interaction study in healthy subjects was conducted as a cocktail study with midazolam (sensitive CYP3A4 substrate) and caffeine (sensitive CYP1A2 substrate). Compared to midazolam and caffeine alone, multiple doses of ribociclib (400mg once daily for 8 days) increased midazolam C_{max} and AUC_{inf} by 2.1-fold and 3.8-fold, respectively. Simulations using PBPK suggested that at a 600mg ribociclib dose, midazolam C_{max} and AUC may increase 2.4-fold and 5.2-fold, respectively. The effect of multiple doses of ribociclib on caffeine was minimal, with C_{max} decreasing by 10% and AUC_{inf} increasing slightly by 20%. Simulations using PBPK suggested only weak inhibitory effects on CYP1A2 substrates at a 600mg ribociclib dose (see section Interactions).

Ribociclib exhibited no capacity to inhibit CYP2E1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, and showed no apparent time-dependent inhibition of CYP1A2, CYP2C9, and CYP2D6 at clinically relevant concentrations. No induction of CYP1A2, CYP2B6, CYP2C9 or CYP3A4 was observed *in vitro* at clinically relevant concentrations. (see section Interactions).

Gastric pH-elevating agents: Ribociclib exhibits high solubility at or below pH 4.5 and in bio-relevant media (at pH 5.0 and 6.5). Co-administration of ribociclib with medicinal products that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption was not observed in population pharmacokinetic analysis nor in simulations using PBPK models (see sections Dosage regimen and administration and Interactions).

Letrozole: Data from clinical trials in patients with breast cancer and population PK analysis indicated no drug interaction between ribociclib and letrozole following co-administration of the drugs.

Exemestane: Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and exemestane following co-administration of the drugs.

Anastrozole: Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrazole following coadministration of the drugs.

Fulvestrant: Data from a clinical trial in patients with breast cancer indicated no clinically relevant effect of fulvestrant on ribociclib exposure following co-administration of the drugs.

Tamoxifen: Data from a clinical trial in patients with breast cancer indicated that tamoxifen exposure was increased approximately 2 fold following co-administration of ribociclib and tamoxifen.

Effect of ribociclib on transporters: *In vitro* evaluations indicated that Kisqali has a low potential to inhibit the activities of drug transporters P-gp, OATP1B1/B3, OCT1, MATE2K at clinically relevant concentrations. Kisqali may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations (see section Interactions).

Effect of transporters on ribociclib: Based on *in vitro* data, P-gp and BCRP mediated transport are unlikely to affect the extent of oral absorption of ribociclib at therapeutic doses. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 or OCT-1 *in vitro* (see section Interactions).

Clinical studies

Study CLEE011A2301 (MONALEESA-2)

Kisqali was evaluated in a randomized, double-blind, placebo-controlled, multicenter phase III clinical study in the treatment of postmenopausal women with HR positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease in combination with letrozole versus letrozole alone.

A total of 668 patients were randomized in a 1:1 ratio to receive either Kisqali 600mg and letrozole (n= 334) or placebo and letrozole (n= 334), stratified according to the presence of liver and/or lung metastases [Yes (n=292 (44%))] vs No [n=376 (56%))]). Demographics and baseline disease characteristics were balanced and comparable between study arms. Kisqali was given orally at a dose of 600mg daily for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5mg once daily for 28 days. Patients were not allowed to cross over from placebo to Kisqali during the study or after disease progression.

Patients enrolled in this study had a median age of 62 years (range 23 to 91). 44.2% patients were of age 65 years and older, including 69 patients (10.3%) of age 75 years and older. The patients included were Caucasian (82.2%), Asian (7.6%), and Black (2.5%). All patients had an ECOG performance status of 0 or 1. A total of 46.6% of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 51.3% had received antihormonal therapy in the neo/adjuvant setting prior to study entry. 34.1% of patients had de novo metastatic disease. 22.0% of patients had bone only disease and 58.8% of patients had visceral disease.

Primary analysis

The primary endpoint for the study was met at the planned interim analysis conducted after observing 80% of targeted progression-free survival (PFS) events using Response Evaluation Criteria in Solid Tumors (RECIST v1.1), based on the investigator assessment in the full

population (all randomized patients) and confirmed by a blinded independent central radiological assessment.

The efficacy results (29 January 2016 cut-off) demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus letrozole compared to patients receiving placebo plus letrozole in the full analysis set (FAS) (HR = 0.556; 95% CI: 0.429, 0.720, one-sided stratified log-rank test p-value=0.00000329), with an estimated 44% reduction in risk of progression for patients treated with the combination of Kisqali plus letrozole. The median PFS was not reached in the Kisqali plus letrozole arm (95% CI: 19.3, NE) at the time of the primary analysis. The median PFS was 14.7 months (95% CI: 13.0, 16.5) for the placebo plus letrozole arm. Results were consistent across the sub-groups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastasic disease.

The results for PFS based on the blinded independent central radiological assessment were consistent with the primary efficacy results based on the investigator's assessment (HR: 0.592 with 95% CI: 0.412, 0.852). The one-sided stratified log-rank test p-value was 0.002.

The global health status/QoL showed no relevant difference between the Kisqali plus letrozole arm and the placebo plus letrozole control arm.

A more mature update of efficacy data (02 January 2017 cutoff) is provided in Table 10 and Figure 1. Median PFS was 25.3 months (95% CI: 23.0, 30.3) for Kisqali plus letrozole treated patients and 16.0 months (95% CI: 13.4, 18.2) for patients receiving placebo plus letrozole. 54.7% of patients receiving Kisqali plus letrozole were estimated to be disease progression free at 24 months compared with 35.9% in the placebo plus letrozole arm.

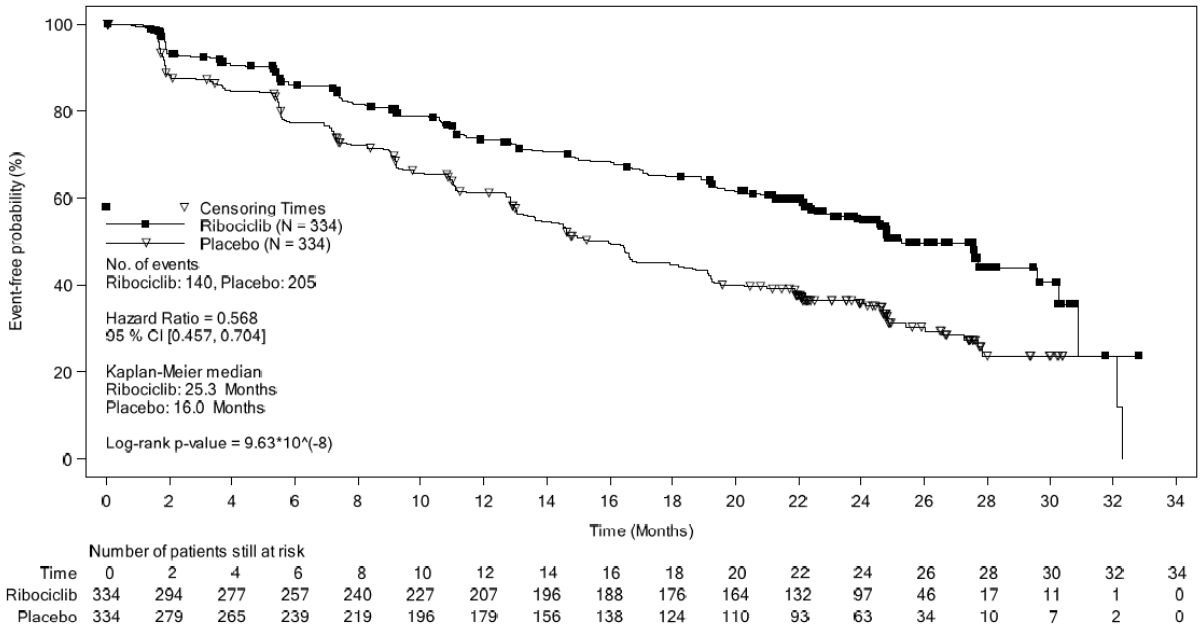
Hazard ratios based on a pre-specified sub-group analysis are in favor of the Kisqali plus letrozole arm, demonstrating that patients benefit independent of age, race, prior adjuvant/ neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastasis disease

Table 10 MONALEESA-2 (A2301) primary efficacy results (PFS) based on investigator radiological assessment (02 January 2017 cutoff)

	Kisqali plus letrozole N=334	Placebo plus letrozole N=334
Progression free survival		
Median PFS [months] (95% CI)	25.3 (23.0-30.3)	16.0 (13.4-18.2)
Hazard ratio (95% CI)	0.568 (0.457-0.704)	
p-value[a]	9.63×10^{-8}	

CI=confidence interval; N=number of patients;
[a]p-value is obtained from the one-sided stratified log-rank test.

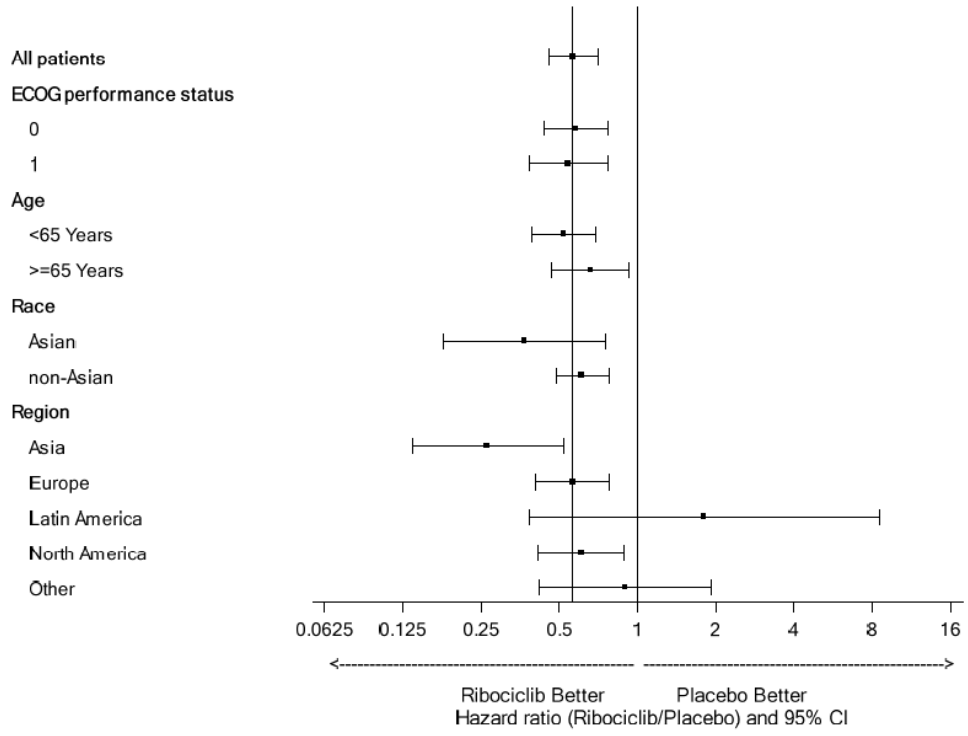
Figure 1 **MONALEESA-2 (A2301) Kaplan-Meier plot of PFS based on Investigator assessment (FAS) (02 January 2017 cut-off)**

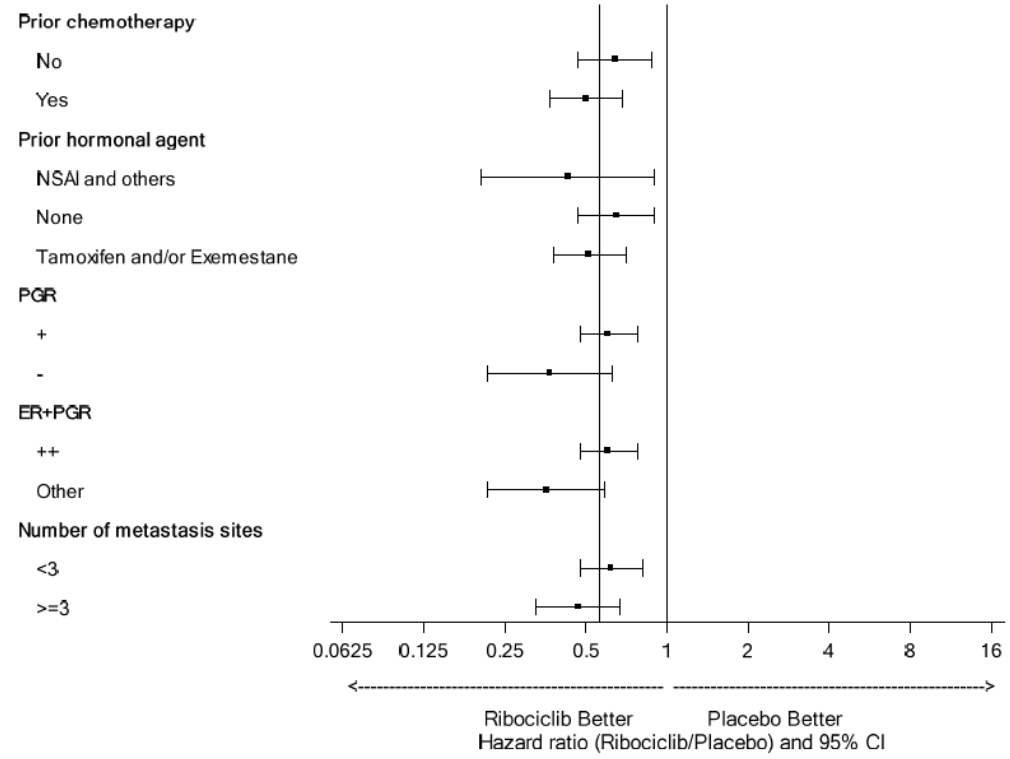


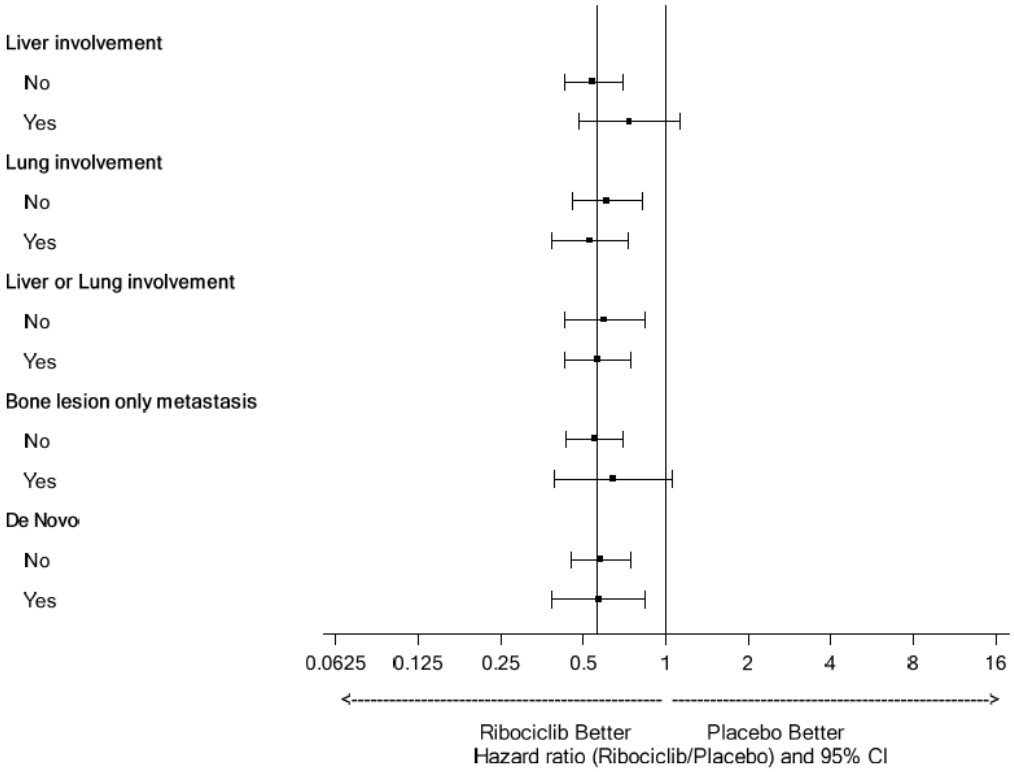
Number of patients still at risk

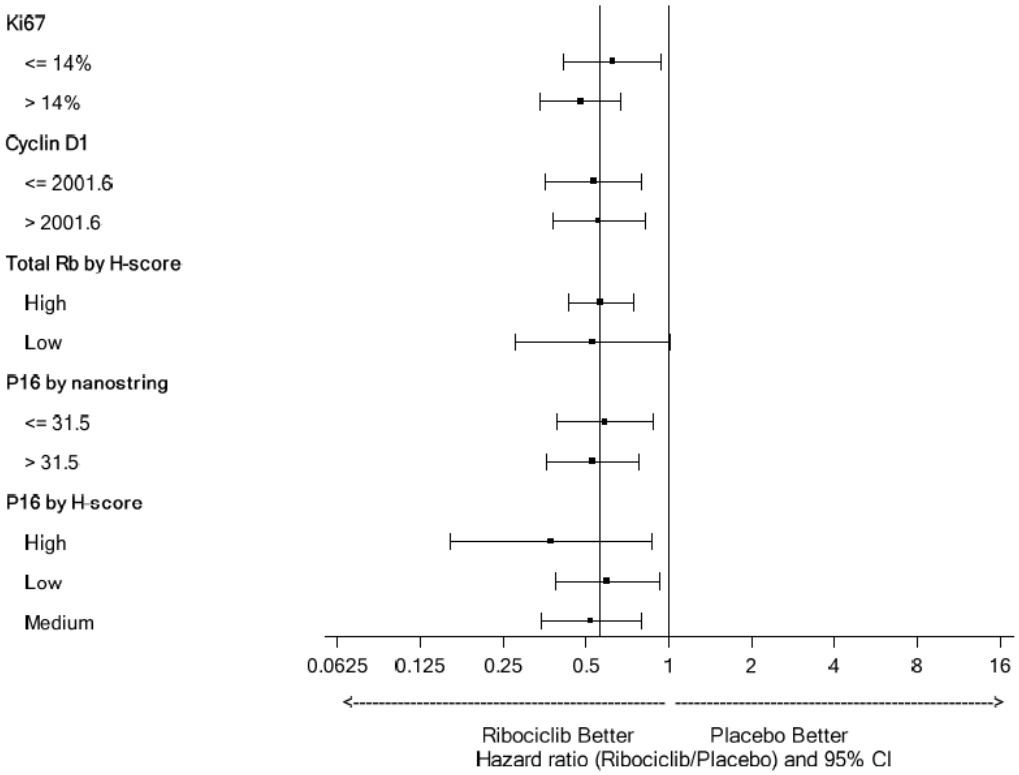
Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Ribociclib	334	294	277	257	240	227	207	196	188	176	164	132	97	46	17	11	1	0
Placebo	334	279	265	239	219	196	179	156	138	124	110	93	63	34	10	7	2	0

Figure 2 **MONALEESA-2 (A2301) Forest plot of PFS based on Investigator assesment (FAS) (02 January 2017 cut-off)**




Prior chemotherapy
No
Yes
Prior hormonal agent
NSAI and others
None
Tamoxifen and/or Exemestane
PGR
+
-
ER+PGR
++
Other
Number of metastasis sites
<3
>=3
0.0625
0.125
0.25
0.5
1
2
4
8
16
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI


Liver involvement
No
Yes
Lung involvement
No
Yes
Liver or Lung involvement
No
Yes
Bone lesion only metastasis
No
Yes
De Novo
No
Yes
0.0625
0.125
0.25
0.5
1
2
4
8
16
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI



Other secondary endpoints included overall response rate (ORR), time to deterioration of ECOG performance status, safety, and tolerability, and change in patient-reported outcomes (PROs) for health-related quality of life. In the FAS, the overall response rate according to the local radiologist assessment was 40.7% of patients (95% CI: 35.4%, 46.0%) in the Kisqali plus letrozole arm and 27.5% (95% CI: 22.8%, 32.3%) in the placebo plus letrozole arm (p=0.000155). The clinical benefit rate (CBR) was 79.6% of patients (95% CI: 75.3%, 84.0%) in the Kisqali plus letrozole arm and 72.8% (95% CI: 68.0%, 77.5%) in the placebo plus letrozole arm (p=0.018). In patients with measurable disease, the overall response rate according to the local radiologist assessment was 52.7% of patients (95% CI: 46.6%, 58.9%) in the Kisqali plus letrozole and 37.1% (95% CI: 31.1%, 43.2%) in the placebo plus letrozole arm (p=0.00028).

The clinical benefit rate was 80.1% (95% CI: 75.2%, 85.0%) in the Kisqali plus letrozole arm and 71.8% (95% CI: 66.2%, 77.5%) in the placebo plus letrozole arm (p=0.020).

A series of pre-specified sub-group PFS analyses was performed based on prognostic factors and baseline characteristics to investigate the internal consistency of treatment effect (Figure 2). A reduction in the risk of disease progression or death in favour of the Kisqali plus letrozole arm was observed in all individual patient sub-groups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone-only metastatic disease. This was evident for patients with liver and/or lung disease (HR: 0.561 [95% CI: 0.424, 0.743]; median progression-free survival [mPFS] 24.8 months vs 13.4 months respectively for the Kisqali and placebo arms, respectively, the same benefit was observed for those patients without liver and/or lung disease (HR: 0.597 [95% CI: 0.426, 0.837]; mPFS 27.6 months vs 18.2 months).

Updated results for overall response and clinical benefit rates are displayed in Table 11.

Table 11 MONALEESA-2 (A2301) efficacy results (ORR, CBR) based on investigator assessment (02 January 2017 cut-off)

Analysis	Kisqali + letrozole (%, 95% CI)	Placebo + letrozole (%, 95% CI)	p-value[c]
Full analysis set	**N=334**	**N=334**	
Overall response rate[a]	42.5 (37.2, 47.8)	28.7 (23.9, 33.6)	9.18×10^{-5}
Clinical benefit rate[b]	79.9 (75.6, 84.2)	73.1 (68.3, 77.8)	0.018
Patients with measurable disease	**N=257**	**N=245**	
Overall response rate[a]	54.5 (48.4, 60.6)	38.8 (32.7, 44.9)	2.54×10^{-4}
Clinical benefit rate[b]	80.2 (75.3, 85.0)	71.8 (66.2, 77.5)	0.018

[a] ORR: Overall response rate = proportion of patients with complete response + partial response
[b] CBR: Clinical benefit rate = proportion of patients with complete response + partial response (+ stable disease or non-complete response/Non-progressive disease ≥24 weeks)
[c] p-values are obtained from one-sided Cochran-Mantel-Haenszel chi-square test

Final OS analysis

At the time of the final overall survival (OS) analysis (10-Jun-2021 cut-off), the study met its key secondary endpoint demonstrating a statistically significant and clinically meaningful improvement in OS with a 23.5% relative reduction in risk of death (HR: 0.765, 95% CI: 0.628, 0.932; p-value=0.004).

OS benefit increased over time, with a 6-year survival rate of 44.2% (38.5, 49.8) for Kisqali vs. 32.0% (26.8, 37.3) for placebo. The median OS was 63.9 months (95% CI: 52.4, 71.0) for the Kisqali arm and 51.4 months (95% CI: 47.2, 59.7) for the placebo arm, with a 12.5-months improvement in median OS for the Kisqali arm. The exploratory OS results from subgroup analyses demonstrated that the OS benefit was generally consistent across the patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease (see Figure 4). This was evident for patients with liver and/or lung disease (HR: 0.806 [95% CI: 0.621, 1.045]; a similar benefit was observed for those patients without liver and/or lung disease (HR: 0.711 [95% CI: 0.526, 0.962].

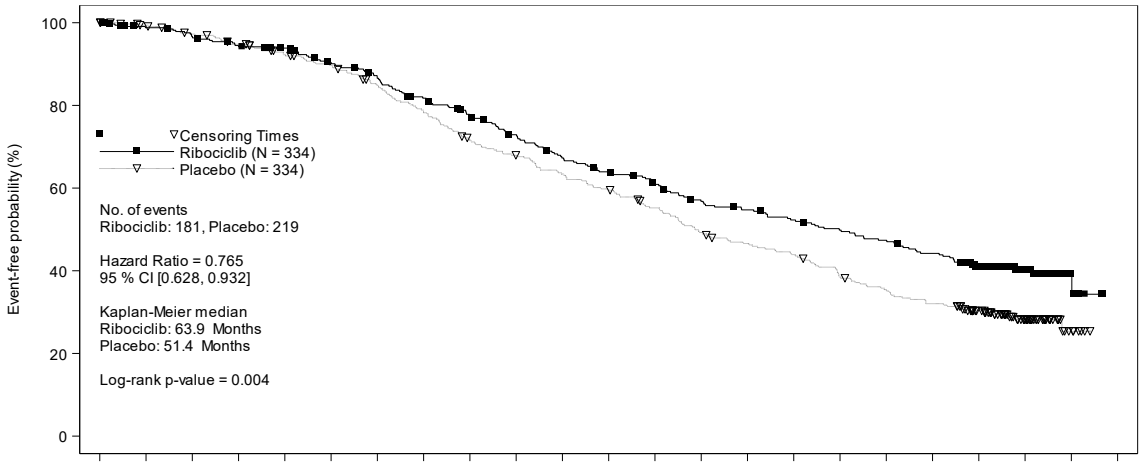
The OS results from this final analysis are summarized in Table 12 and the Kaplan-Meier curve is provided in Figure 3.

Table 12 MONALEESA-2 (A2301) efficacy results (OS) (10-Jun-21 cut-off)

Overall survival, overall study population	Kisqali 600 mg + letrozole N=334	Placebo + letrozole N=334
Number of events – n [%]	181 (54.2)	219 (65.6)
Median OS [months] (95% CI)	63.9 (52.4, 71.0)	51.4 (47.2, 59.7)
Hazard ratio[a] (95% CI)	0.765 (0.628, 0.932)	
p--value[b]	0.004	
OS event-free rate, (%) (95% CI)		
24 months	86.6 (82.3, 89.9)	85.0 (80.5, 88.4)
60 months	52.3 (46.5, 57.7)	43.9 (38.3, 49.4)
72 months	44.2 (38.5, 49.8)	32.0 (26.8, 37.3)

CI=confidence interval;
[a]Hazard ratio is obtained from stratified Cox PH model;
[b]p-value is obtained from the one-sided log-rank test. Stratification performed by lung and/or liver metastases status as per IRT.

Figure 3 **MONALEESA-2 (A2301) Kaplan-Meier plot for OS (FAS) (data cut-off 10-Jun-2021)**

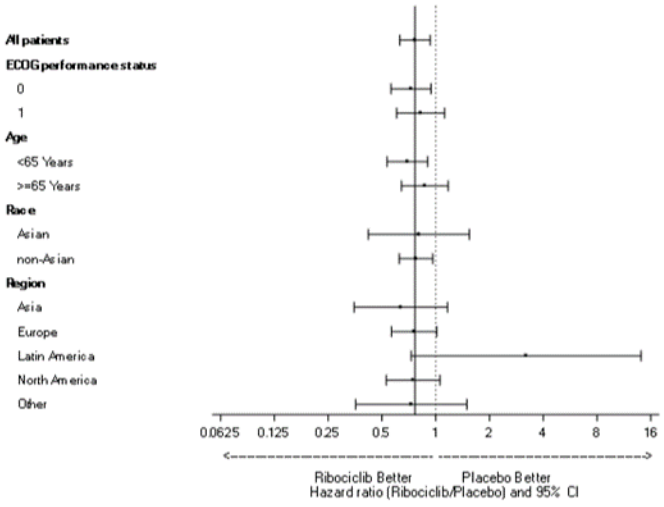


Number of patients still at risk

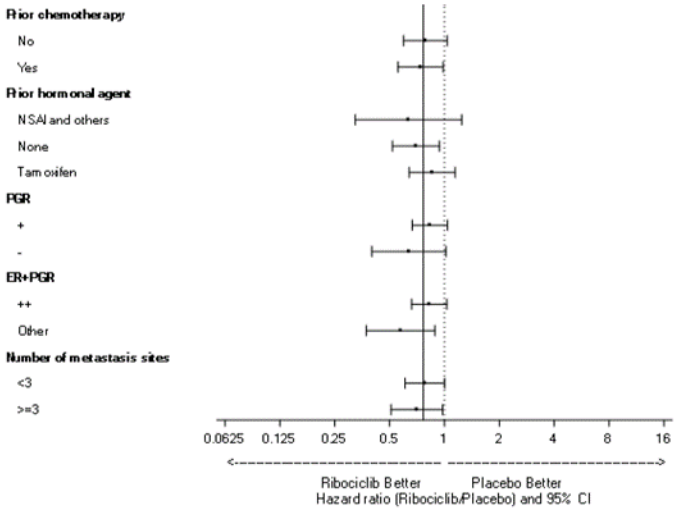
Time	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88
Ribociclib	334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
Placebo	334	326	316	306	293	283	265	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

Log-rank test and Cox PH model are stratified by liver and/or lung metastasis as per IRT.
One sided P-value is obtained from stratified log rank test.

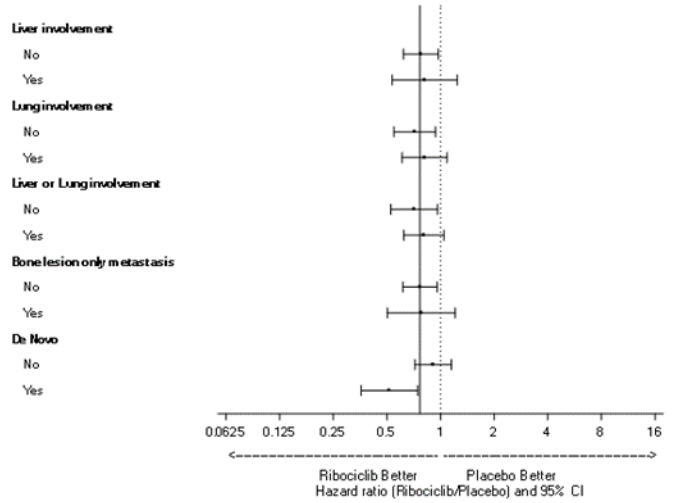
Figure 4 **MONALEESA-2 (A2301) Forest plot OS from subgroup analysis (FAS) (10-Jun-21 cut off)**



Hazard ratio (95% CI)	Ribociclib events n/N (%)	Placebo events n/N (%)
0.765(0.628, 0.932)	181/334(54.2)	219/334(65.6)
0.728(0.563, 0.942)	103/204(50.5)	135/202(66.8)
0.823(0.605, 1.121)	78/130(60)	84/132(63.6)
0.695(0.535, 0.902)	100/184(54.3)	129/189(68.3)
0.869(0.643, 1.175)	81/150(54)	90/145(62.1)
0.804(0.419, 1.544)	19/28(67.9)	19/23(82.6)
0.775(0.625, 0.962)	151/281(53.7)	184/287(64.1)
0.637(0.349, 1.164)	20/35(57.1)	24/33(72.7)
0.756(0.565, 1.012)	83/150(55.3)	101/146(69.2)
3.209(0.729, 14.12)	5/7(71.4)	4/7(57.1)
0.747(0.529, 1.057)	57/108(52.8)	74/121(61.2)



Hazard ratio (95% CI)	Ribociclib events n/N (%)	Placebo events n/N (%)
0.785(0.596, 1.033)	91/188(48.4)	117/189(61.9)
0.740(0.557, 0.984)	90/146(61.6)	102/145(70.3)
0.634(0.323, 1.242)	18/30(60)	18/23(78.3)
0.697(0.518, 0.938)	76/158(48.1)	103/162(63.6)
0.856(0.640, 1.145)	87/146(59.6)	98/149(65.8)
0.831(0.666, 1.037)	146/271(53.9)	171/278(61.5)
0.638(0.399, 1.019)	32/55(58.2)	41/49(83.7)
0.825(0.660, 1.031)	144/269(53.5)	170/277(61.4)
0.575(0.373, 0.886)	37/65(56.9)	49/57(86)
0.780(0.607, 1.001)	115/220(52.3)	136/222(61.3)
0.705(0.509, 0.977)	66/114(57.9)	83/112(74.1)



Hazard ratio (95% CI)	Ribociclib events n/N (%)	Placebo events n/N (%)
0.775(0.619, 0.969)	145/275(52.7)	163/262(62.2)
0.814(0.535, 1.239)	36/59(61)	56/72(77.8)
0.716(0.548, 0.937)	97/181(53.6)	119/185(64.3)
0.814(0.609, 1.088)	84/153(54.9)	100/149(67.1)
0.711(0.526, 0.962)	80/152(52.6)	90/144(62.5)
0.806(0.621, 1.045)	101/182(55.5)	129/190(67.9)
0.768(0.615, 0.959)	144/265(54.3)	172/255(67.5)
0.780(0.504, 1.209)	37/69(53.6)	47/79(59.5)
0.909(0.718, 1.150)	134/220(60.9)	144/221(65.2)
0.516(0.358, 0.744)	47/114(41.2)	75/113(66.4)

Dotted line shows no effect point, and bold line shows overall treatment effect point.

Hazard ratio (95% CI) is based on stratified Cox PH model. Exception: for subgroup variables Liver involvement (Yes vs. No), Lung involvement (Yes vs. No), Liver or lung involvement (Yes vs. No),

De novo (Yes vs. No), unstratified Cox PH model is used.

Additionally, the median time to first subsequent chemotherapy was prolonged by 11.7 months in the Kisqali arm compared to the placebo arm (50.6 months, 95% CI: 38.9, 60.0 months vs 38.9 months, 95% CI: 31.4, 45.4). The probability of chemotherapy usage was reduced by 25.8% in the Kisqali arm compared to the placebo arm (HR: 0.742; 95% CI: 0.606, 0.909).

Study CLEE011E2301 (MONALEESA-7)

Pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy

MONALEESA-7 was a randomized, double-blind, placebo-controlled, multicenter phase III clinical study of KISQALI plus either a non-steroidal aromatase inhibitor (NSAI) or tamoxifen and goserelin versus placebo plus either a NSAI or tamoxifen and goserelin conducted in pre/peri-menopausal women with HR-positive, HER2-negative, advanced breast cancer who received no prior endocrine therapy for advanced disease.

A total of 672 patients were randomized to receive KISQALI plus NSAI or tamoxifen plus goserelin (n= 335) or placebo plus NSAI or tamoxifen plus goserelin (n= 337), stratified according to the presence of liver and/or lung metastases, prior chemotherapy for advanced disease and endocrine combination partner (tamoxifen and goserelin vs NSAI and goserelin).

NSAI (letrozole 2.5 mg or anastrozole 1 mg) or tamoxifen 20 mg or were given orally once daily on a continuous daily schedule, goserelin was administered as a sub-cutaneous injection on Day 1 of each 28-day cycle, with either KISQALI 600 mg or placebo orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Patients enrolled in MONALEESA-7 had a median age of 44 years (range 25 to 58) and were primarily Caucasian (58%), Asian (29%), or Black (3%). Nearly all patients (99%) had an ECOG performance status of 0 or 1. Of the 672 patients, 33% had received chemotherapy in the adjuvant vs. 18% in the neoadjuvant setting and 40% had received endocrine therapy in the adjuvant vs 0.7% in the neoadjuvant setting prior to study entry. Forty percent (40%) of patients had de novo metastatic disease, 24% had bone only disease, and 57% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms, and endocrine combination partner.

In the pre-specified sub-group analysis of 495 patients who had received Kisqali or placebo in combination with NSAI plus goserelin, the median PFS (95% CI) was 27.5 months (19.1, NE) in the Kisqali plus NSAI sub-group and 13.8 months (12.6, 17.4) in the placebo plus NSAI sub-group [HR: 0.569 (95% CI: 0.436, 0.743)]. Efficacy results are summarized in Table 13 and the Kaplan-Meier curves for PFS are provided in Figure 5.

Results in the Kisqali plus NSAI subgroup were consistent across subgroups of age, race, prior adjuvant/ neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement and bone only metastatic disease.

In the NSAI sub-group, the median time to response (TTR) was not reached in either the Kisqali arm or the placebo arm and the probability of response by 6 months was 34.7% (95% CI: 29.0, 41.1) in the Kisqali arm and 23.7% (95% CI: 18.8, 29.6) in the placebo arm, indicating that a larger proportion of patients derived an earlier benefit in the Kisqali arm.

In the NSAI sub-group, the median duration of response (DOR) was not reached (95% CI: 18.3 months, NE) in the Kisqali arm and was 17.5 months (95% CI: 12.0, NE) in the placebo arm. Among patients with confirmed complete response or partial response, the probability of

subsequent progression was 23.5% (95% CI: 15.6, 34.5) in the Kisqali arm and 36.4% (95% CI: 25.6, 49.8) in the placebo arm at 12 months.

Table 13 MONALEESA-7 (E2301) Primary efficacy Results (PFS) based on investigator assessment in patients who received NSAI (20-Aug-2017 cut-off)

	Kisqali plus NSAI plus goserelin N=248	Placebo plus NSAI plus goserelin N=247
Progression free survival[a]		
Median PFS [months] (95% CI)	27.5 (19.1, NE)	13.8 (12.6, 17.4)
Hazard ratio (95% CI)	0.569 (0.436, 0.743)	

CI=confidence interval; N=number of patients; NE = Not estimable.

[a] – PFS based on investigator radiological assessment

Figure 5 MONALEESA-7 (E2301) Kaplan-Meier plot of PFS based on investigator assessment in patients who received NSAI (20-Aug-2017 cut-off)

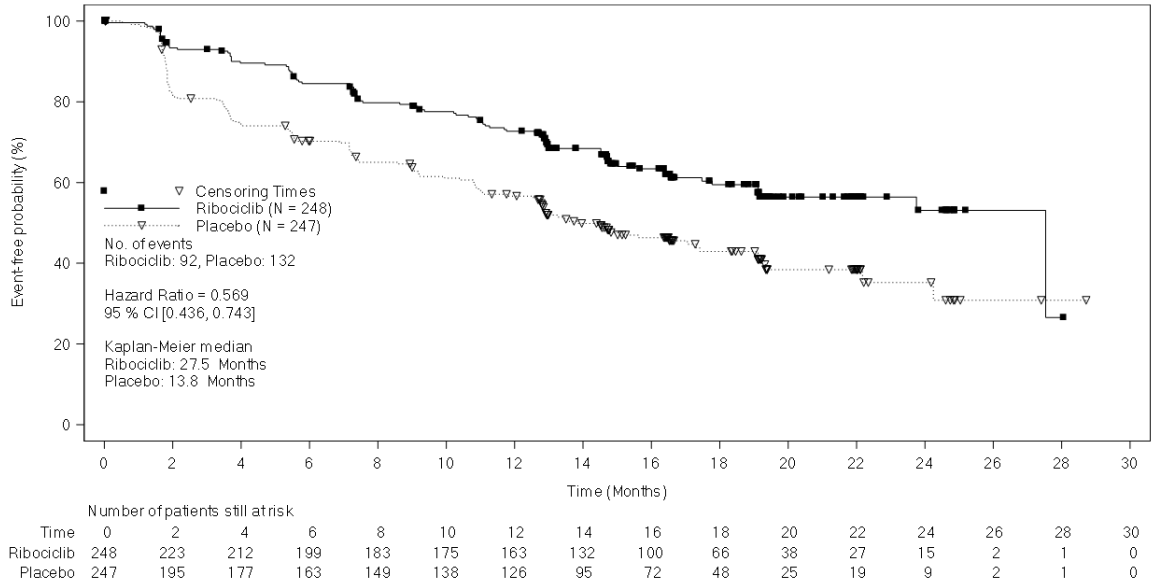
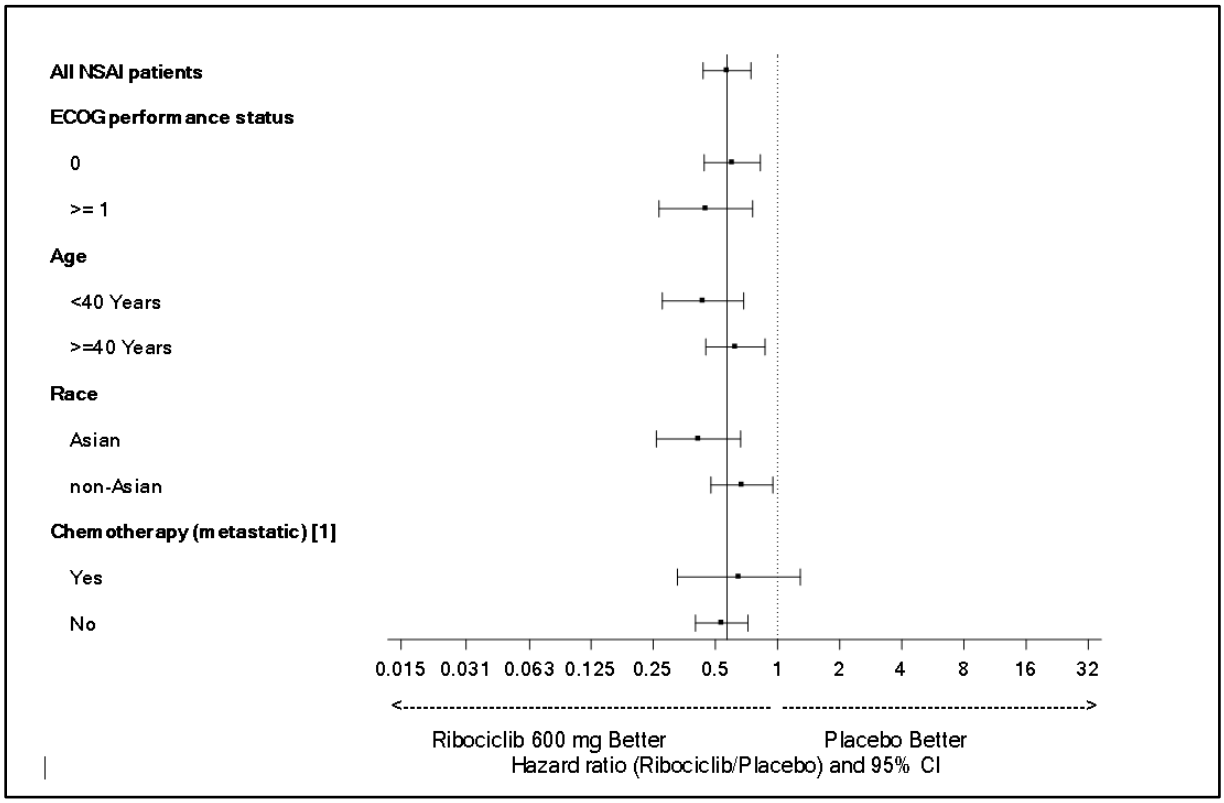


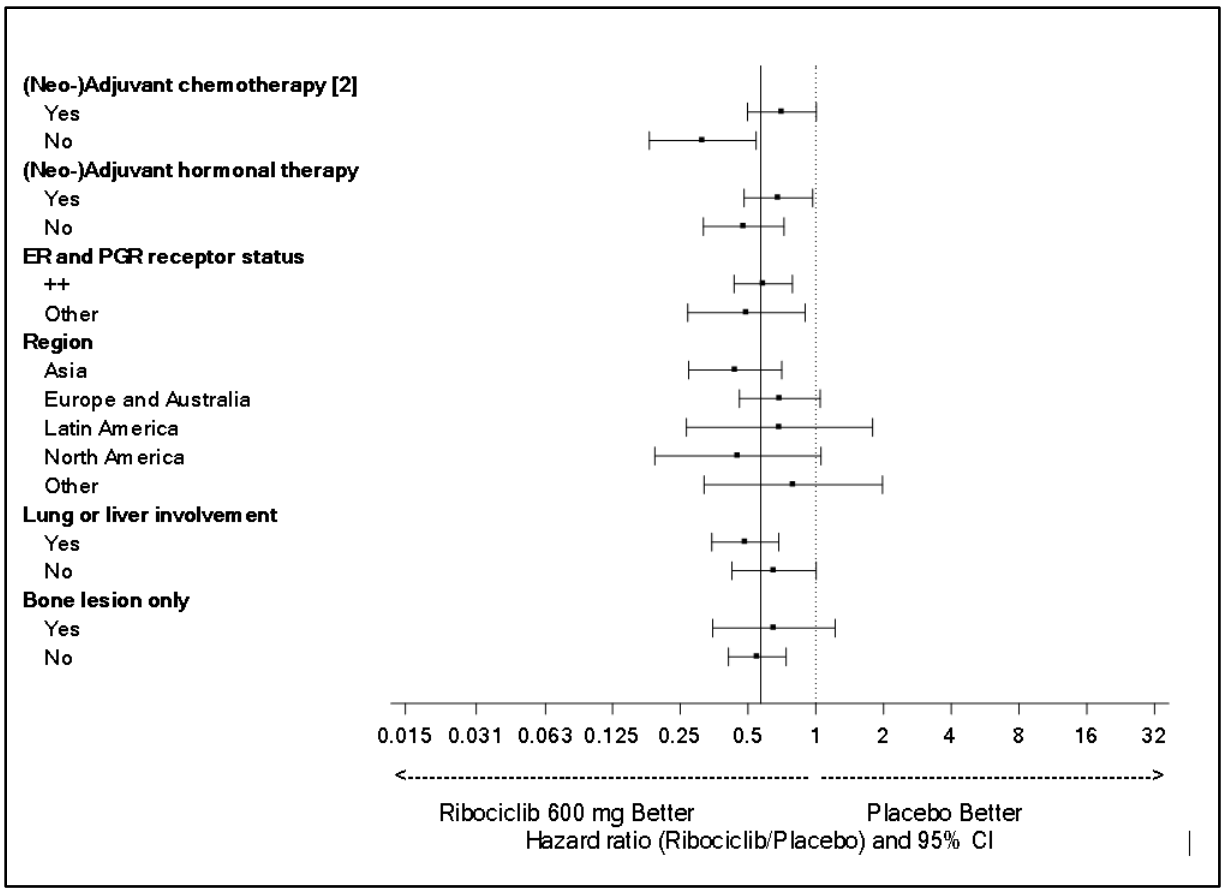
Table 14 MONALEESA-7 (E2301) efficacy results (ORR, CBR) based on investigator assessment in patients who received NSAI (20-Aug-17 cut off)

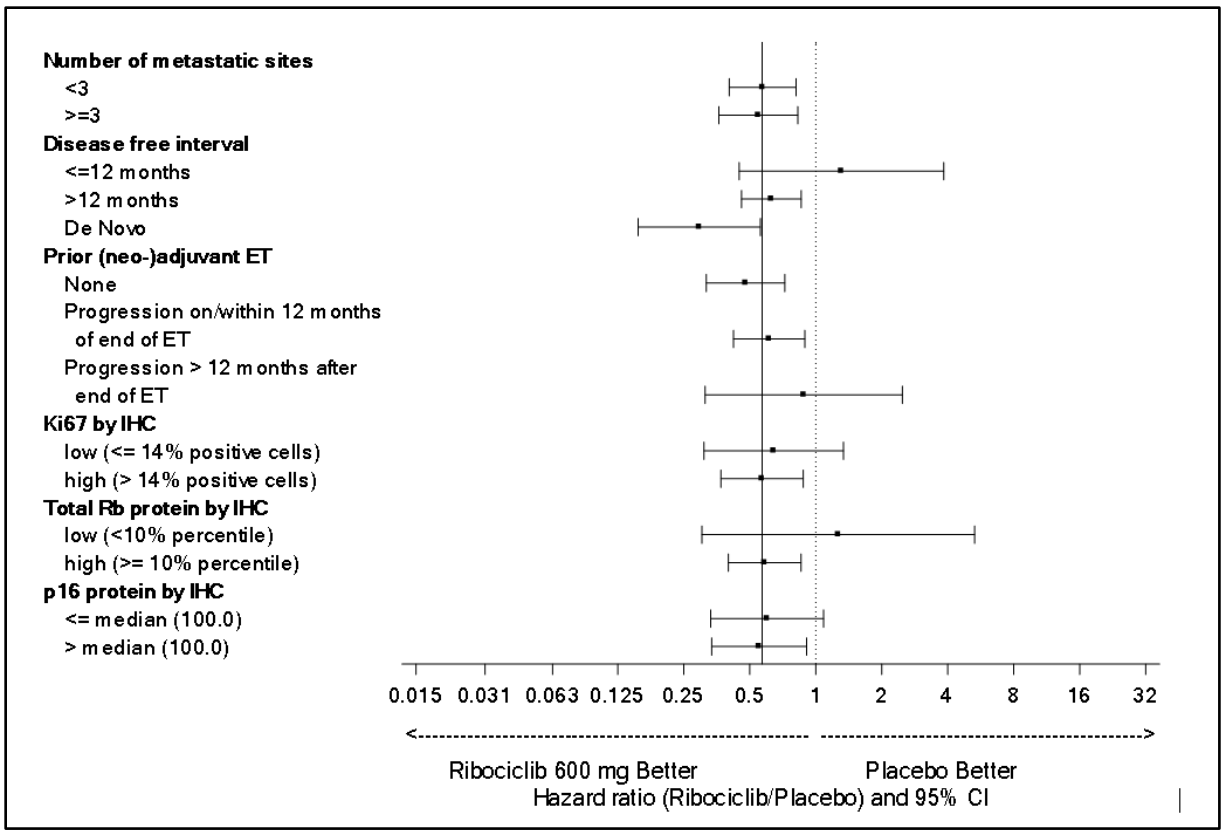
Analysis	Kisqali plus NSAI plus goserelin (%, 95% CI)	Placebo plus NSAI plus goserelin (%, 95% CI)
Full analysis set	N=248	N=247
Overall Response Rate[a]	39.1 (33.0, 45.2)	29.1 (23.5, 34.8)
Clinical Benefit Rate[b]	80.2 (75.3, 85.2)	67.2 (61.4, 73.1)
Patients with measurable disease	**N=192**	**N=199**
Overall Response Rate[a]	50.5 (43.4, 57.6)	36.2 (29.5, 42.9)
Clinical Benefit Rate[b]	81.8 (76.3, 87.2)	63.8 (57.1, 70.5)

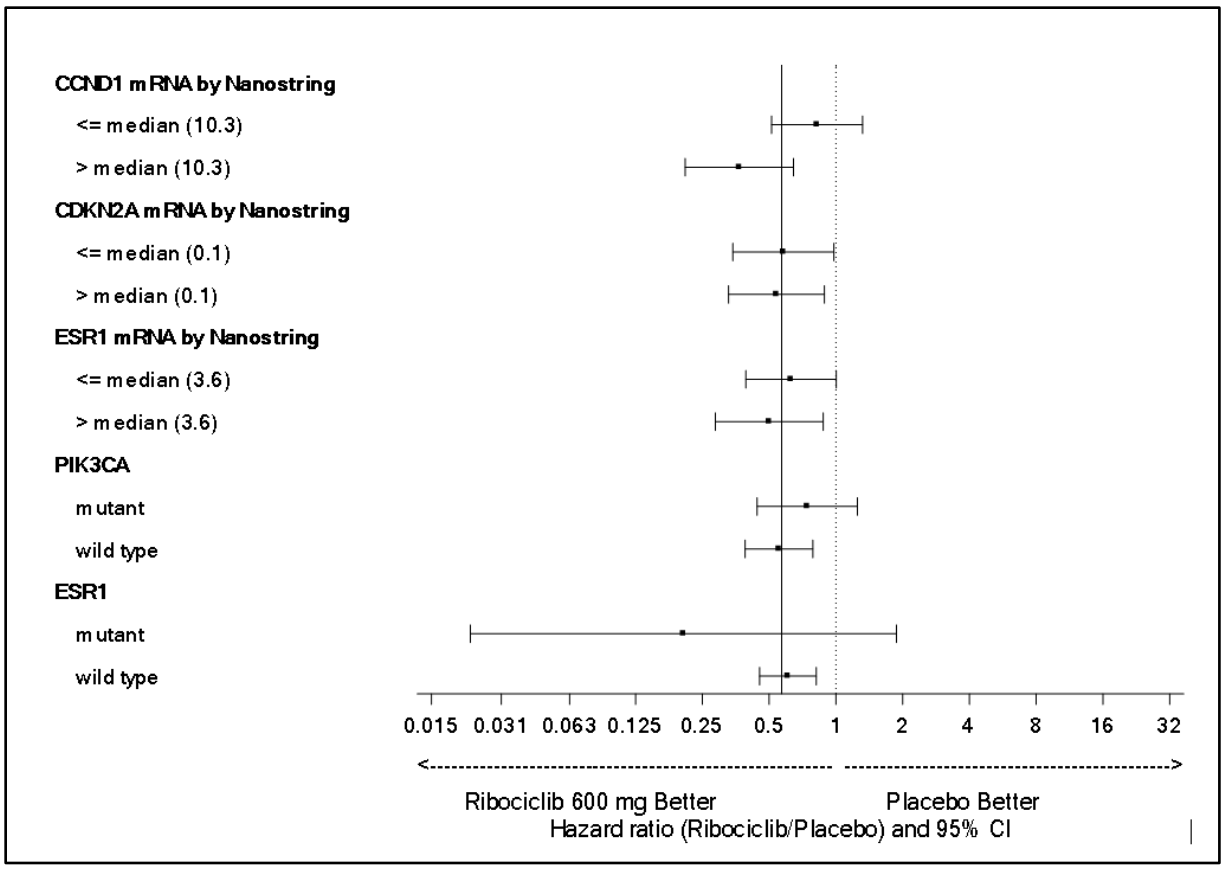
[a] *ORR: proportion of patients with complete response + partial response*
[b] *CBR: proportion of patients with complete response + partial response + (stable disease or non-complete response/non-progressive disease ≥24 weeks)*

Figure 6 MONALEESA-7 (E2301) Forest plot of PFS based on investigator assessment in patients who received NSAI (20-Aug-17 cut off)




(Neo-)Adjuvant chemotherapy [2]
Yes
No
(Neo-)Adjuvant hormonal therapy
Yes
No
ER and PGR receptor status
++
Other
Region
Asia
Europe and Australia
Latin America
North America
Other
Lung or liver involvement
Yes
No
Bone lesion only
Yes
No
0.015 0.031 0.063 0.125 0.25 0.5 1 2 4 8 16 32
Ribociclib 600 mg Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI


Number of metastatic sites
<3
>=3
Disease free interval
<=12 months
>12 months
De Novo
Prior (neo-)adjuvant ET
None
Progression on/within 12 months of end of ET
Progression > 12 months after end of ET
Ki67 by IHC
low (<= 14% positive cells)
high (> 14% positive cells)
Total Rb protein by IHC
low (<10% percentile)
high (>= 10% percentile)
p16 protein by IHC
<= median (100.0)
> median (100.0)
0.015 0.031 0.063 0.125 0.25 0.5 1 2 4 8 16 32
Ribociclib 600 mg Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI



In patients receiving a NSAI as endocrine combination partner, there were 61/248 deaths (24.6%) in the ribociclib arm and 80/247 (32.4%) in the placebo arm, with an OS hazard ratio of 0.699 (95% CI: 0.501, 0.976). Median OS was not reached in the ribociclib arm and was 40.7 months (95% CI: 37.4, NE) in the placebo arm. Per the study protocol, OS was only formally tested in the overall study population.

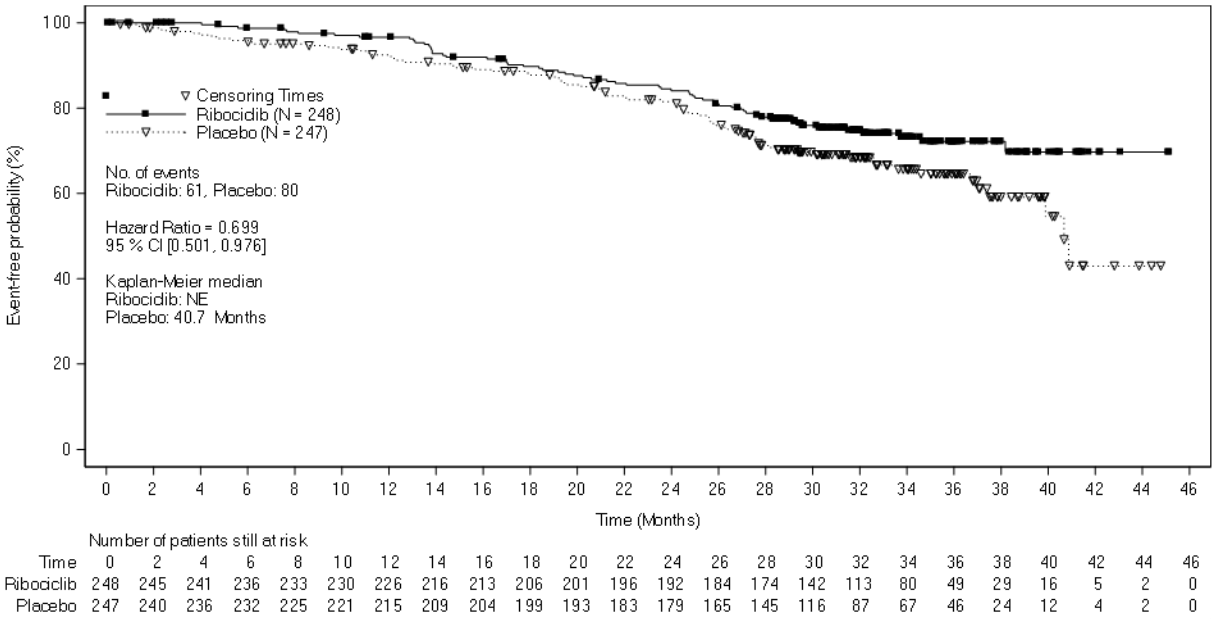
Data for patients receiving NSAI as combination partner are presented in Table 15 and Figure 7.

Table 15 MONALEESA-7 (E2301) efficacy results (OS) in patients who received NSAI (30-Nov-18 cut-off)

	Kisqali 600 mg	Placebo
NSAI sub-group	N=248	N=247
Number of events – n [%]	61 (24.6)	80 (32.4)
Median OS [months] (95% CI)	NE (NE, NE)	40.7 (37.4, NE)
HR (95% CI)	0.699 (0.501, 0.976)	

NE = Not estimable
NSAI = non-steroidal aromatase inhibitor

Figure 7 MONALEESA-7 (E2301) Kaplan Meier plot of OS in patients who received NSAI (30-Nov-18 cut-off)



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Ribociclib	248	245	241	236	233	230	226	216	213	206	201	196	192	184	174	142	113	80	49	29	16	5	2	0
Placebo	247	240	236	232	225	221	215	209	204	199	193	183	179	165	145	116	87	67	46	24	12	4	2	0

Hazard ratio is based on unstratified Cox model.

Similar results were observed in the NSAI sub-group (HR: 0.660 (95% CI: 0.503, 0.868); median PFS2: 32.3 months (95% CI: 26.9, 38.3) in the placebo arm vs not reached (95% CI: 39.4, NE) in the ribociclib arm).

Study CLEE011F2301 (MONALEESA-3)

Postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer for initial endocrine based therapy or after disease progression on endocrine therapy

MONALEESA-3 was a randomized double-blind, placebo-controlled, multi-centre phase III clinical study in the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment.

A total of 726 female patients were randomized in a 2:1 ratio to receive KISQALI 600 mg and fulvestrant (n= 484) or placebo and fulvestrant (n= 242), stratified according to the presence of liver and/or lung metastases and prior endocrine therapy for advanced or metastatic disease.

First-line patients with advanced breast cancer (A) include de novo advanced breast cancer with no prior endocrine therapy, and patients who relapsed after 12 months of (neo)adjuvant endocrine therapy completion.

Second-line patients' subgroup (B) includes those patients whose disease relapsed during adjuvant therapy or less than 12 months after endocrine adjuvant therapy completion, and those who progressed to first line endocrine therapy.

Fulvestrant 500 mg was administered intramuscularly on days 1, 15, 29, and once monthly thereafter, with either KISQALI 600 mg or placebo given orally once daily for 21 consecutive days followed by 7 days off until disease progression or unacceptable toxicity. The major efficacy outcome measure for the study was investigator-assessed progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Patients enrolled in this study had a median age of 63 years (range 31 to 89). Of the patients enrolled, 47% were 65 years and older, including 14% age 75 years and older. The patients enrolled were primarily Caucasian (85%), Asian (9%), and Black (0.7%). Nearly all patients (99.7%) had an ECOG performance status of 0 or 1. First and second line patients were enrolled in this study (of which 19% had de novo metastatic disease). Forty three percent (43%) of patients had received chemotherapy in the adjuvant vs. 13% in the neoadjuvant setting and 59% had received endocrine therapy in the adjuvant vs. 1% in the neoadjuvant setting prior to study entry. Twenty one percent (21%) of patients had bone only disease and 61% had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms.

Primary analysis

The primary endpoint for the study was performed after observing 361 PFS events using RECIST v1.1, based on the investigator assessment in the full analysis set (all randomized patients) and confirmed by a random central audit of 40% imaging subset by a blinded independent review committee (BIRC). The median follow-up time at the time of primary PFS analysis was 20.4 months.

PFS analyses based on the BIRC were supportive of the primary efficacy results, the PFS hazard ratio was 0.492 (95% CI, 0.345 to 0.703).

The primary efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kisqali plus fulvestrant compared to patients receiving placebo plus fulvestrant in the full analysis set (HR: 0.593; 95% CI: 0.480, 0.732; one-sided stratified log-rank test p-value $4.1x10^{-7}$), with an estimated 41% reduction in relative risk of progression or death in favor of the Kisqali plus fulvestrant arm. The median (95% CI) PFS was 20.5 months (18.5, 23.5) in the Kisqali plus fulvestrant and 12.8 months (10.9, 16.3) in the placebo plus fulvestrant arm.

Figure 8 **MONALEESA-3 (F2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (03-Nov-17 cut-off)**

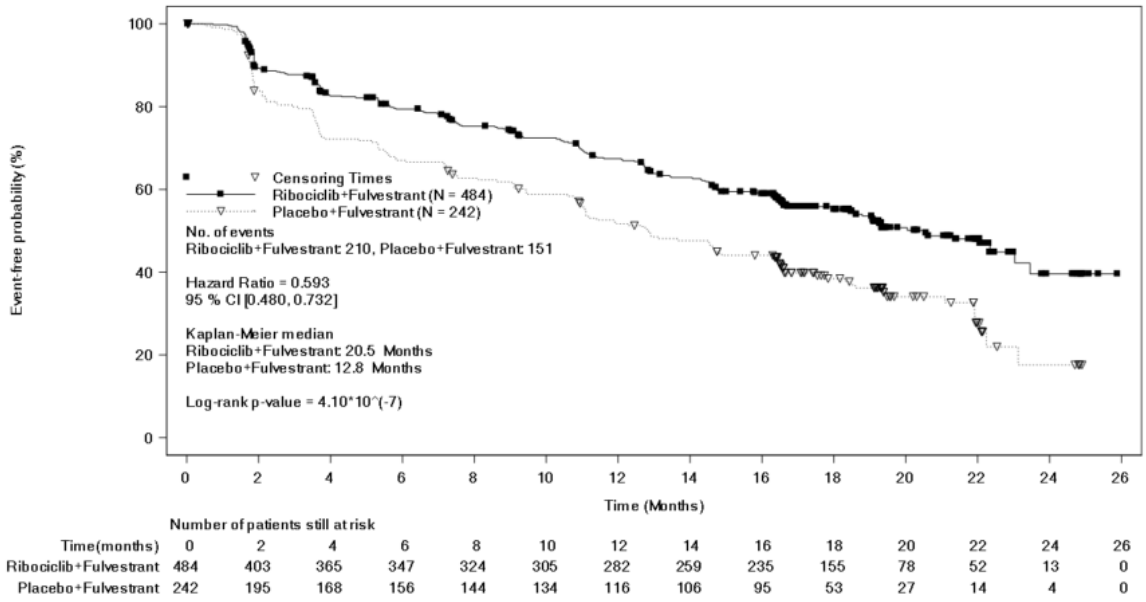
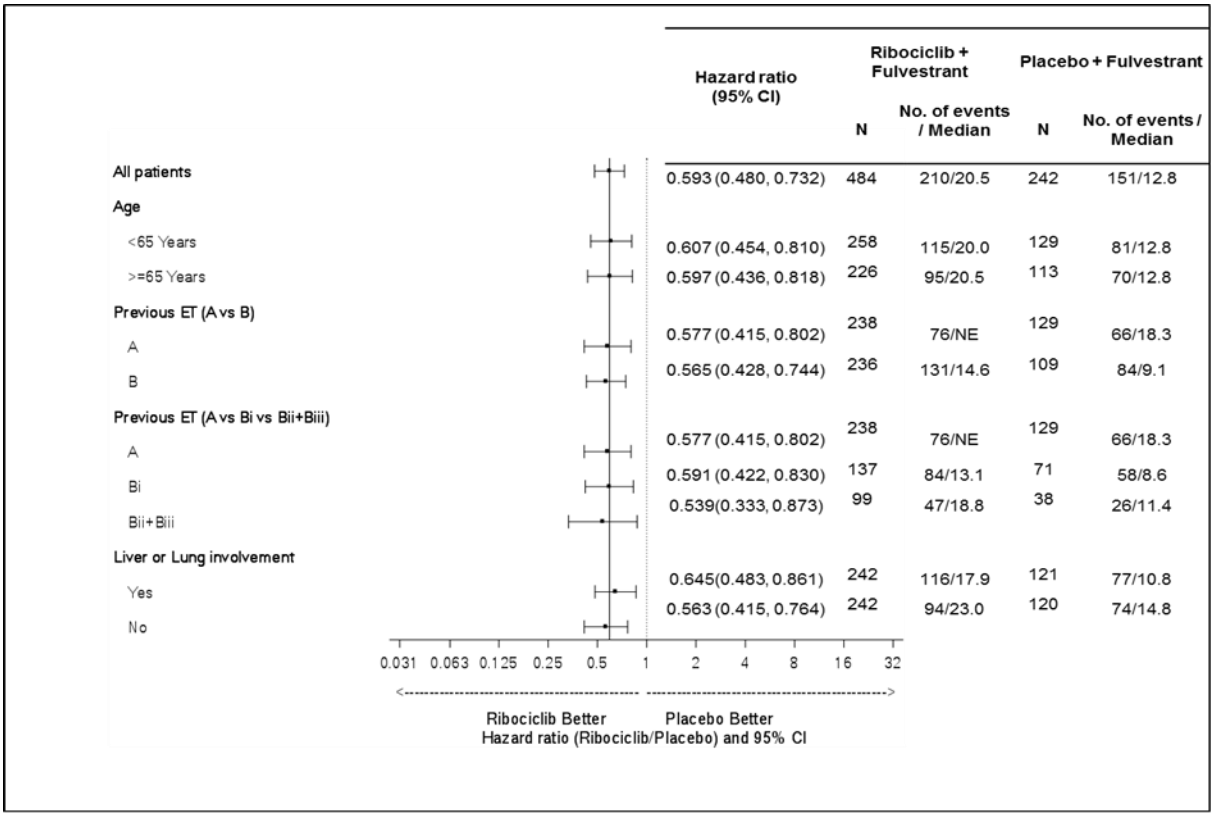
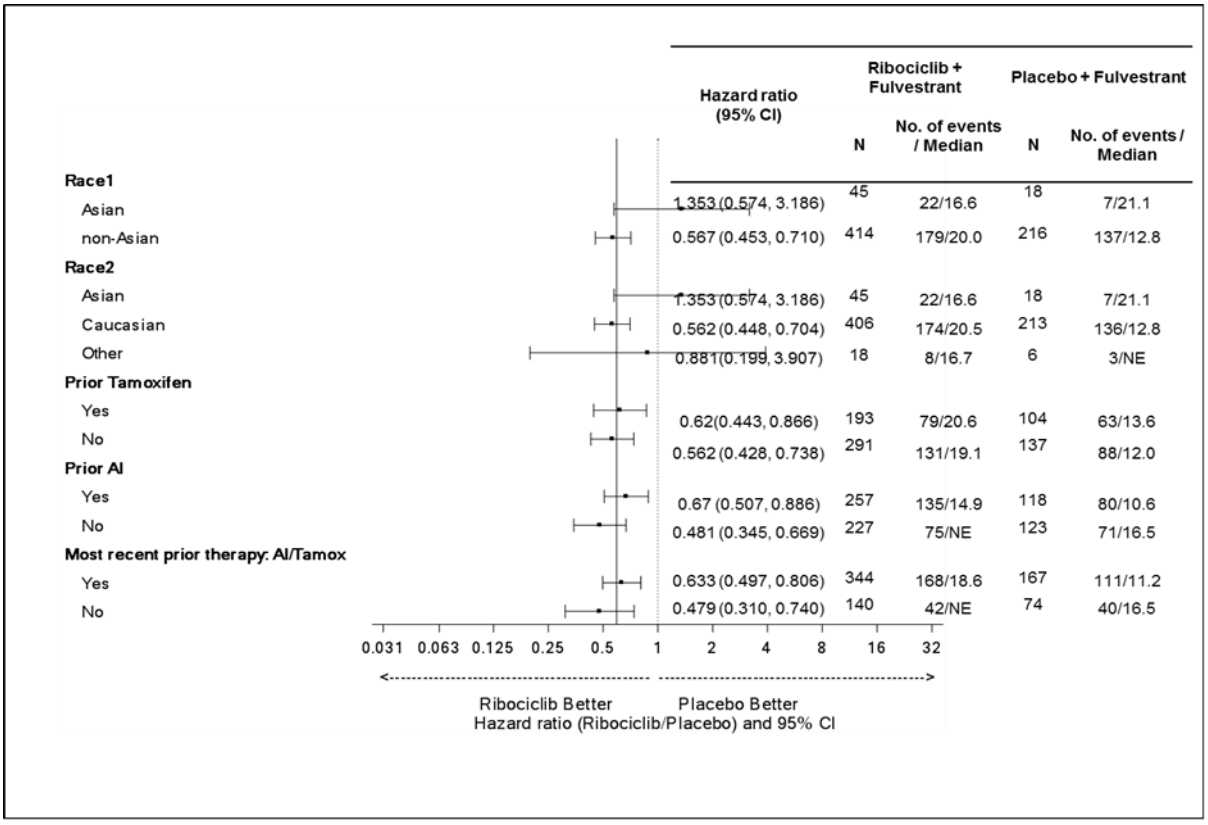
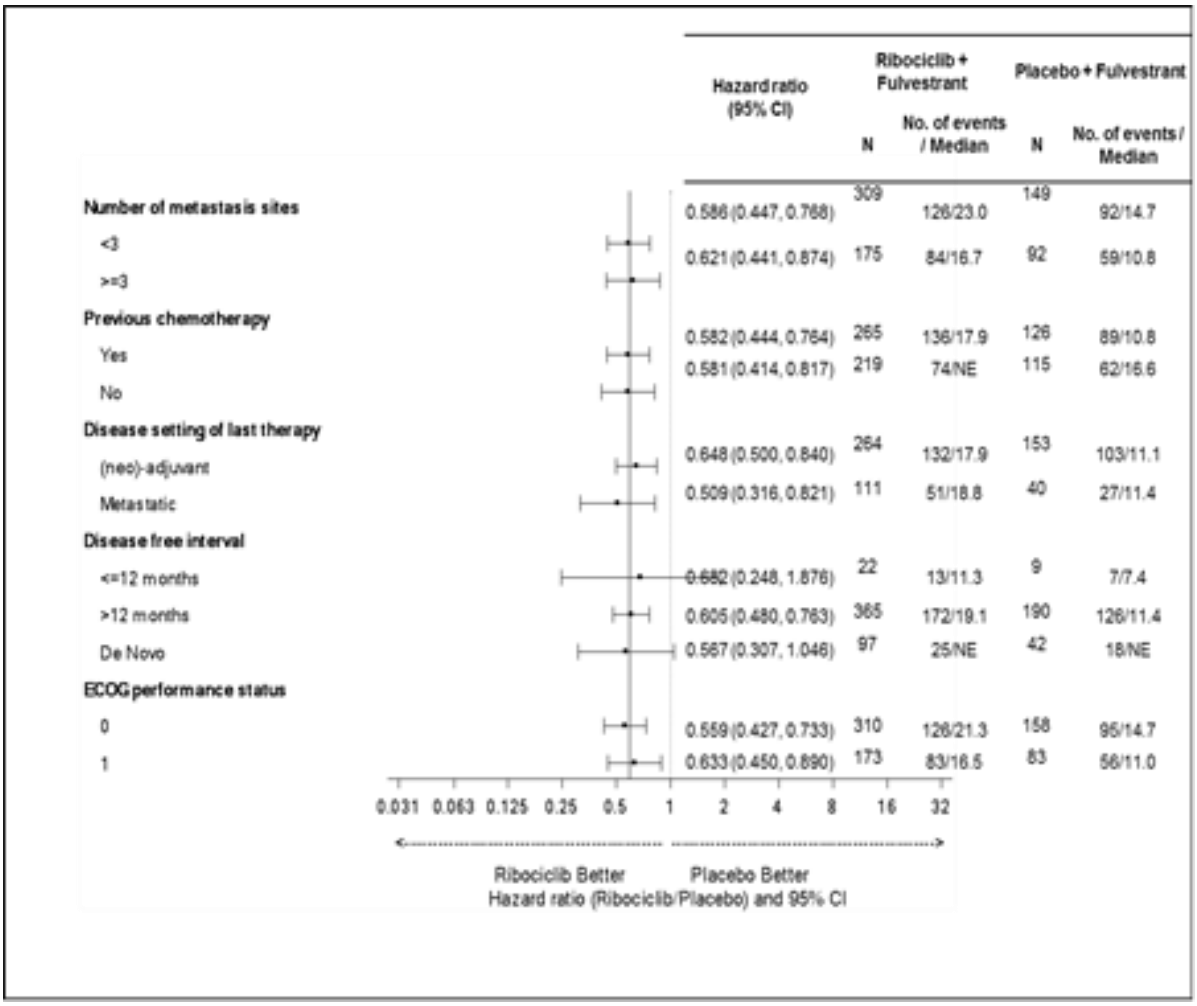
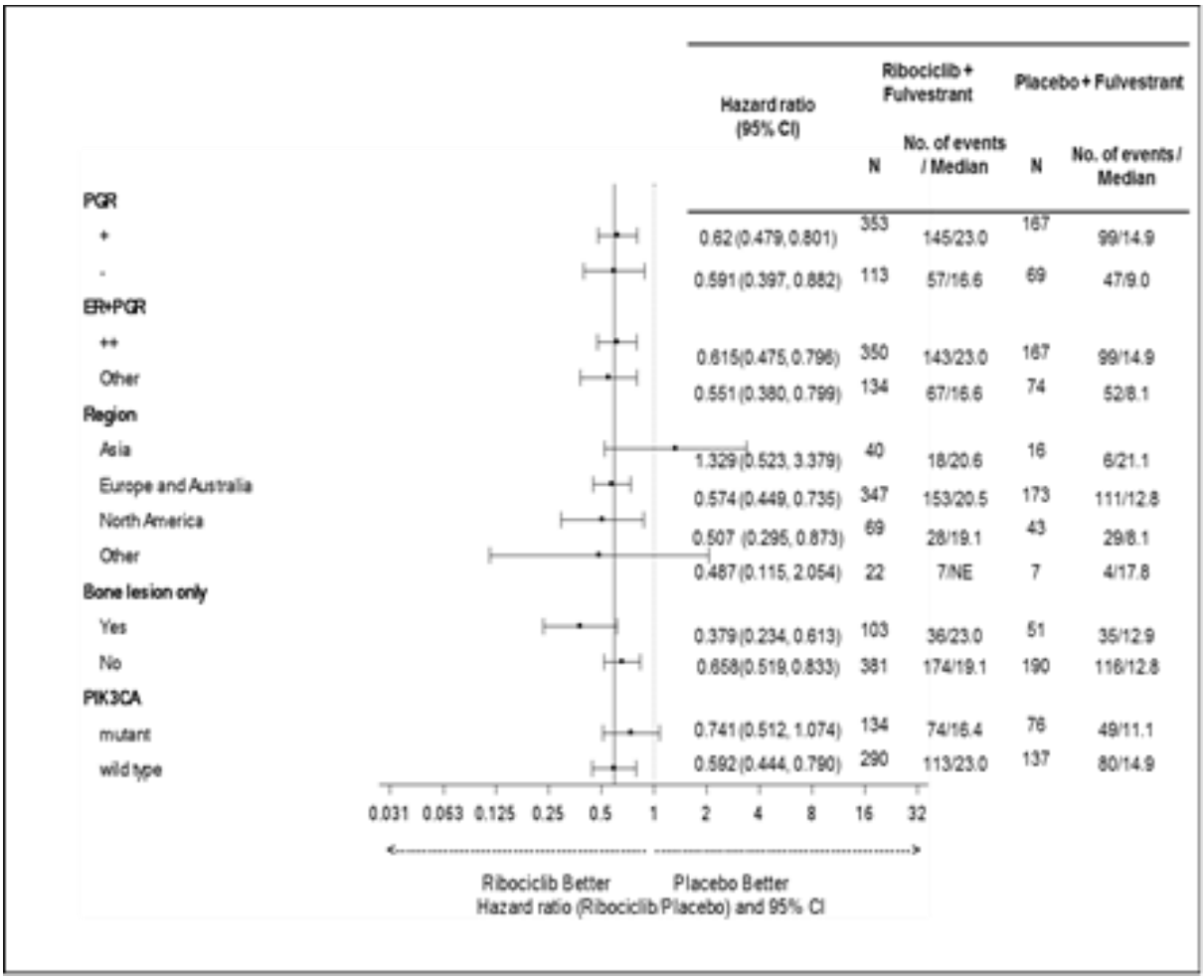


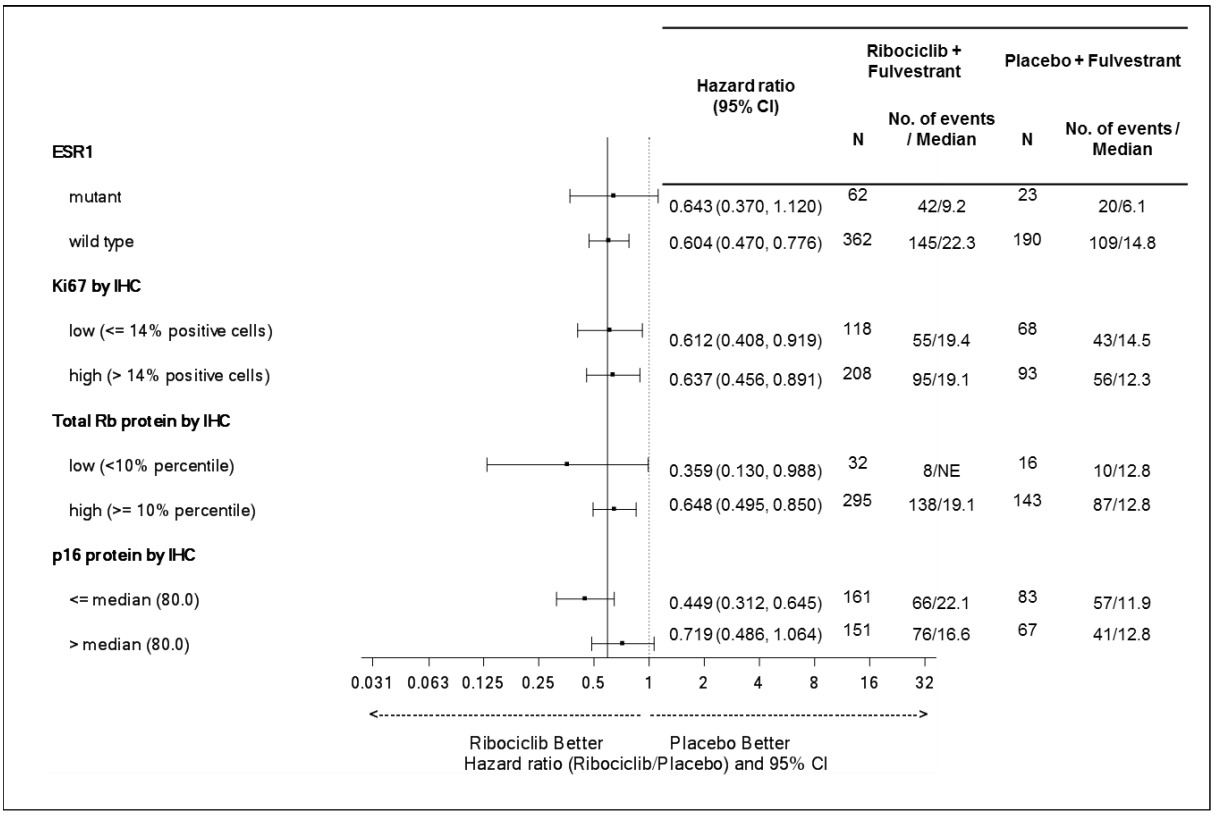
Figure 9 **MONALEESA-3 (F2301) Forest plot of PFS based on investigator assessment (FAS) (03-Nov-17 cut-off)**

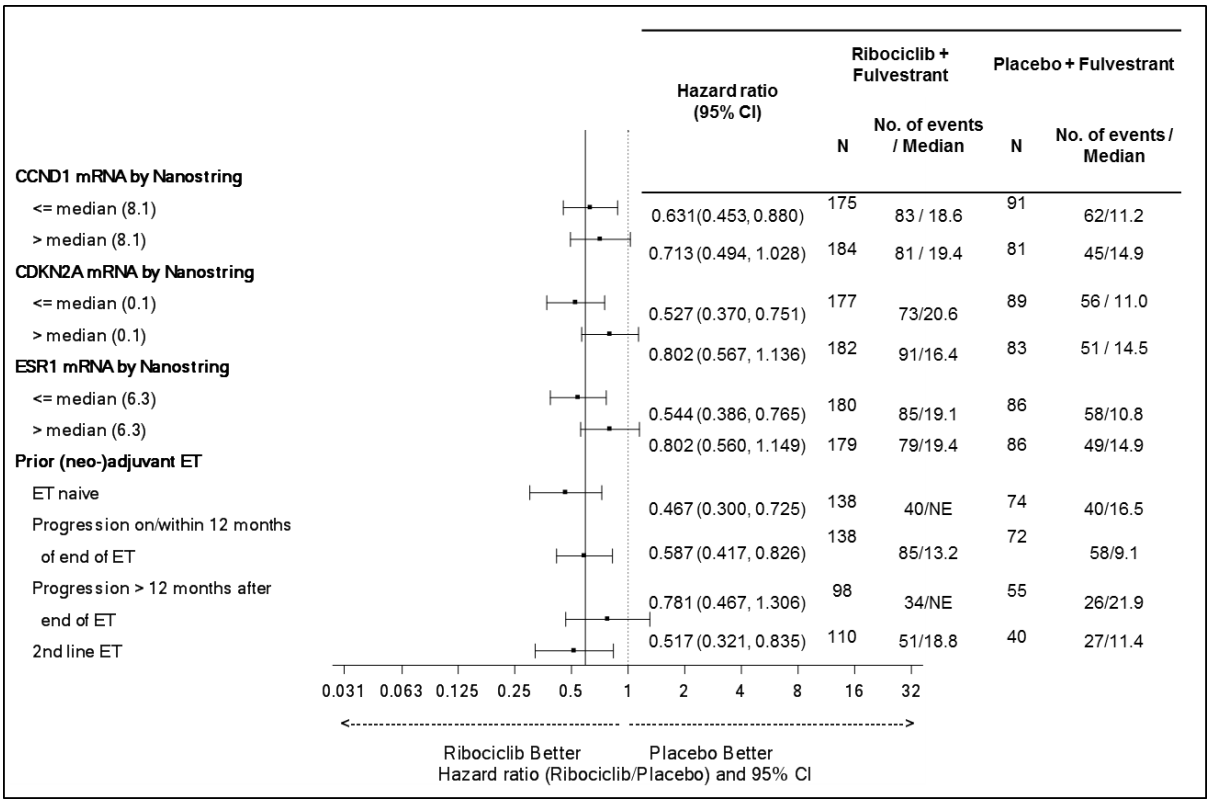



Hazard ratio (95% CI)
Ribociclib + Fulvestrant
Placebo + Fulvestrant
N
No. of events / Median
N
No. of events / Median
Race1
Asian 1.353 (0.574, 3.186) 45 22/16.6 18 7/21.1
non-Asian 0.567 (0.453, 0.710) 414 179/20.0 216 137/12.8
Race2
Asian 1.353 (0.574, 3.186) 45 22/16.6 18 7/21.1
Caucasian 0.562 (0.448, 0.704) 406 174/20.5 213 136/12.8
Other 0.881 (0.199, 3.907) 18 8/16.7 6 3/NE
Prior Tamoxifen
Yes 0.62 (0.443, 0.866) 193 79/20.6 104 63/13.6
No 0.562 (0.428, 0.738) 291 131/19.1 137 88/12.0
Prior AI
Yes 0.67 (0.507, 0.886) 257 135/14.9 118 80/10.6
No 0.481 (0.345, 0.669) 227 75/NE 123 71/16.5
Most recent prior therapy: AI/Tamox
Yes 0.633 (0.497, 0.806) 344 168/18.6 167 111/11.2
No 0.479 (0.310, 0.740) 140 42/NE 74 40/16.5
0.031 0.063 0.125 0.25 0.5 1 2 4 8 16 32
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI


Hazard ratio (95% CI)
Ribociclib + Fulvestrant
Placebo + Fulvestrant
N
No. of events / Median
N
No. of events / Median
Number of metastasis sites
0.586 (0.447, 0.768) 309 126/23.0 149 92/14.7
<3
0.621 (0.441, 0.874) 175 84/16.7 92 59/10.8
>=3
Previous chemotherapy
0.582 (0.444, 0.764) 265 136/17.9 126 89/10.8
Yes
0.581 (0.414, 0.817) 219 74/NE 115 62/16.6
No
Disease setting of last therapy
0.648 (0.500, 0.840) 264 132/17.9 153 103/11.1
(neo)-adjuvant
0.509 (0.316, 0.821) 111 51/18.8 40 27/11.4
Metastatic
Disease free interval
0.682 (0.248, 1.876) 22 13/11.3 9 7/7.4
<=12 months
0.605 (0.480, 0.763) 365 172/19.1 190 126/11.4
>12 months
0.567 (0.307, 1.046) 97 25/NE 42 18/NE
De Novo
ECOG performance status
0.559 (0.427, 0.733) 310 126/21.3 158 95/14.7
0
0.633 (0.450, 0.890) 173 83/16.5 83 56/11.0
1
0.031 0.063 0.125 0.25 0.5 1 2 4 8 16 32
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI


Hazard ratio (95% CI)
Ribociclib + Fulvestrant
Placebo + Fulvestrant
N
No. of events / Median
N
No. of events / Median
PGR
+ 0.62 (0.479, 0.801) 353 145/23.0 167 99/14.9
- 0.591 (0.397, 0.882) 113 57/16.6 69 47/9.0
ER+PGR
++ 0.615 (0.475, 0.796) 350 143/23.0 167 99/14.9
Other 0.551 (0.380, 0.799) 134 67/16.6 74 52/8.1
Region
Asia 1.329 (0.523, 3.379) 40 18/20.6 16 6/21.1
Europe and Australia 0.574 (0.449, 0.735) 347 153/20.5 173 111/12.8
North America 0.507 (0.295, 0.873) 69 28/19.1 43 29/8.1
Other 0.487 (0.115, 2.054) 22 7/NE 7 4/17.8
Bone lesion only
Yes 0.379 (0.234, 0.613) 103 36/23.0 51 35/12.9
No 0.658 (0.519, 0.833) 381 174/19.1 190 116/12.8
PIK3CA
mutant 0.741 (0.512, 1.074) 134 74/16.4 76 49/11.1
wild type 0.592 (0.444, 0.790) 290 113/23.0 137 80/14.9
0.031 0.063 0.125 0.25 0.5 1 2 4 8 16 32
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib Placebo) and 95% CI


Hazard ratio (95% CI)
Ribociclib + Fulvestrant
Placebo + Fulvestrant
N
No. of events / Median
N
No. of events / Median
ESR1
mutant
0.643 (0.370, 1.120)
62
42/9.2
23
20/6.1
wild type
0.604 (0.470, 0.776)
362
145/22.3
190
109/14.8
Ki67 by IHC
low (<= 14% positive cells)
0.612 (0.408, 0.919)
118
55/19.4
68
43/14.5
high (> 14% positive cells)
0.637 (0.456, 0.891)
208
95/19.1
93
56/12.3
Total Rb protein by IHC
low (<10% percentile)
0.359 (0.130, 0.988)
32
8/NE
16
10/12.8
high (>= 10% percentile)
0.648 (0.495, 0.850)
295
138/19.1
143
87/12.8
p16 protein by IHC
<= median (80.0)
0.449 (0.312, 0.645)
161
66/22.1
83
57/11.9
> median (80.0)
0.719 (0.486, 1.064)
151
76/16.6
67
41/12.8
0.031
0.063
0.125
0.25
0.5
1
2
4
8
16
32
Ribociclib Better
Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI



[Foot note source: FIR, F2301, Table 3 foot note] Previous endocrine therapy (A vs B) is classified as the following using CRF data:
A) Treatment naïve for metastatic/advanced disease (aBC), including:
i. Relapse >12 months after completion of (neo)adjuvant ET (endocrine therapy) with no subsequent treatment for aBC, OR
ii. De novo aBC (no prior exposure to ET).
B) Receiving up to 1 line ET for aBC, including:
i. Relapse on or within 12 months from completion of (neo)adjuvant ET with no subsequent treatment for aBC, OR
ii. Relapse >12 months from completion of (neo)adjuvant ET and progression on or after subsequent ET for aBC, OR
iii. aBC at the time of diagnosis that progressed on or after ET for aBC with no prior (neo)adjuvant treatment for early disease.

The clinical benefit rate in the Kisqali plus fulvestrant arm and in the placebo plus fulvestrant arm is summarized in Table 16.

Table 16 MONALEESA-3 (F2301) efficacy results (ORR, CBR) based on investigator assessment (03-Nov-17 cut-off)

Analysis	Kisqali plus fulvestrant (%, 95% CI)	Placebo plus fulvestrant (%, 95% CI)	p-value
Full analysis set	N=484	N=242	
Overall Response Rate[a]	32.4 (28.3, 36.6)	21.5 (16.3, 26.7)	0.000912
Clinical Benefit Rate[b]	70.2 (66.2, 74.3)	62.8 (56.7, 68.9)	0.020
Patients with measurable disease	**N=379**	**N=181**	
Overall Response Rate[a]	40.9 (35.9, 45.8)	28.7 (22.1, 35.3)	0.003
Clinical Benefit Rate[b]	69.4 (64.8, 74.0)	59.7 (52.5, 66.8)	0.015

[a] *ORR: proportion of patients with complete response + partial response*
[b] *CBR: proportion of patients with complete response + partial response + (stable disease or non-complete response/non-progressive disease ≥24 weeks)*

The global health status/ QoL were similar between the Kisqali plus fulvestrant arm and the placebo plus fulvestrant arm. The main pre-specified QoL measure was TTD in global health status. A definitive 10% deterioration was defined as a worsening in score (EORTC QLQ-C30 global health scale score) by at least 10% compared to baseline, with no later improvement above this threshold observed during the treatment period, or death due to any cause. Addition of Kisqali to fulvestrant resulted in delaying TTD in the EORTC QLQ-C30 global health scale score compared with placebo plus fulvestrant, (median not estimable versus 19.4 months; HR: 0.795 [95% CI: 0.602,1.050]; p-value 0.051.

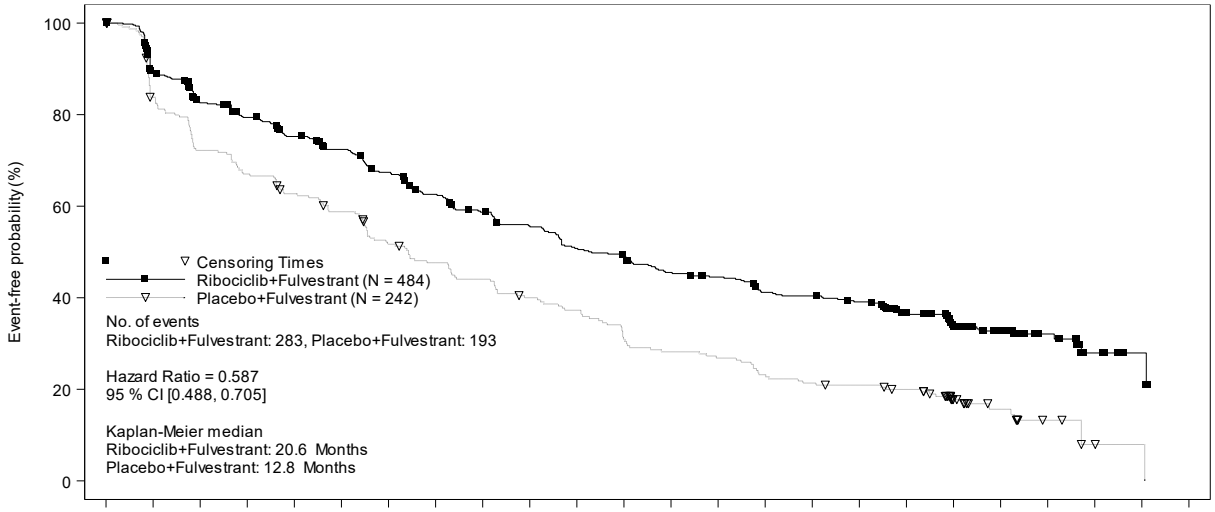
Final OS Analysis

Since the median PFS for first line patients had not been reached at the time of the primary analysis, a descriptive update of primary efficacy results (PFS) was performed at the time of the second OS interim analysis, and the updated PFS results are summarized in Table 21 and the Kaplan-Meier curve is provided in Figure 10

Table 17 MONALEESA-3 (F2301) primary efficacy results (PFS) based on investigator assessment (03-Jun-19 cut-off)

	Kisqali plus fulvestrant N=484	Placebo plus fulvestrant N=242
Progression-free survival		
Median PFS [months] (95% CI)	20.6 (18.6, 24.0)	12.8 (10.9, 16.3)
Hazard ratio (95% CI)	0.587 (0.488, 0.705)	

Figure 10 MONALEESA-3 (F2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (03-Jun-19 cut-off)



Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Ribociclib	484	403	364	346	323	305	282	258	239	225	205	198	181	174	159	156	149	127	92	65	29	11	4	0
Placebo	242	195	168	156	144	134	116	106	98	88	82	68	62	59	51	47	45	41	21	13	6	2	1	0

Results were consistent across pre-specified sub-groups of age, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone only metastatic disease. The subgroup analysis based on prior endocrine therapy is presented in Table 18.

Table 18 MONALEESA-3 (F2301) efficacy results (PFS) for prior endocrine therapy subgroup (03-Jun-19 cut-off)

	Updated analysis PFS subgroup for prior endocrine therapy (3 Jun 19 cut-off)	
First-line setting	**Ribociclib 600 mg N=237**	**Placebo N=128**
Number of events – n [%]	112 (47.3)	95 (74.2)
Median PFS [months] (95% CI)	33.6 (27.1, 41.3)	19.2 (14.9, 23.6)
Hazard ratio (95% CI)	0.546 (0.415, 0.718)	
Second-line setting or with an early relapse	**Ribociclib 600 mg N=237**	**Placebo N=109**
Number of events – n [%]	167 (70.5)	95 (87.2)
Median PFS [months] (95% CI)	14.6 (12.5, 18.6)	9.1 (5.8, 11.0)
Hazard ratio (95% CI)	0.571 (0.443, 0.737)	

CI=confidence interval

First-line setting = newly diagnosed (de novo) advanced breast cancer or relapse after 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced or metastatic disease

Second-line setting or with an early relapse = relapse on or within 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for advanced or metastatic disease (early relapse), relapse after 12 months from completion of (neo)adjuvant therapy with subsequent progression after one line of endocrine therapy for advanced or metastatic disease, or advanced or metastatic breast cancer at diagnosis that progressed after one line of endocrine therapy for advanced disease with no prior (neo)adjuvant treatment for early disease

In the pre-specified second OS interim analysis, the study crossed pre-specified Lan-DeMets (O'Brien-Fleming) stopping boundary, demonstrating a statistically significant improvement in OS.

The OS results from this interim analysis with a 03-Jun-19 cut-off are provided in Table 19 and Figure 11.

Table 19 MONALEESA-3 (F2301) efficacy results (OS) (03-Jun-19 cut-off)

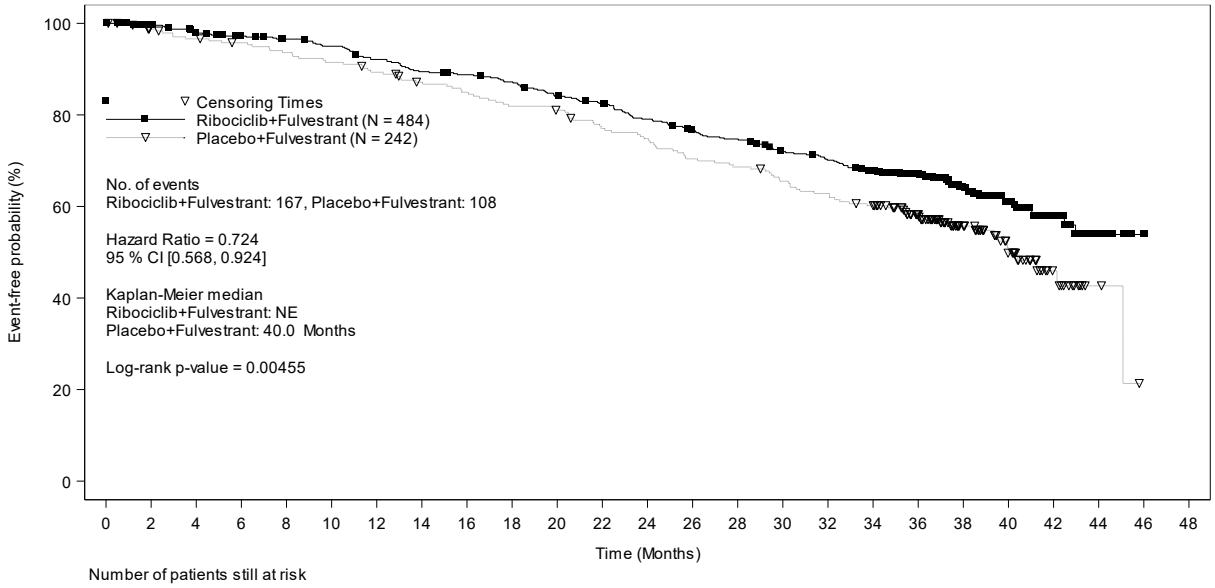
	Kisqali 600 mg	**Placebo**
Overall study population	N=484	N=242
Number of events - n [%]	167 (34.5)	108 (44.6)
Median OS [months] (95% CI)	NE, (42.5, NE)	40 (37, NE)
HR (95% CI)	0.724 (0568, 0924)	
p value	0.00455	

- [1] One-sided P-value is obtained from log-rank test stratified by lung and/or liver metastasis, previous endocrine therapy per IRT. P-value is one-sided and is compared against a threshold of 0.01129 as determined by the Lan-DeMets (O'Brien-Fleming) alpha-spending function for an overall significance level of 0.025.

- [2] Hazard ratio is obtained from the Cox PH model stratified by lung and/or liver metastasis, previous endocrine therapy per IRT.

NE = Not estimable

Figure 11 MONALEESA-3 (F2301) Kaplan Meier plot of OS (FAS) (03-Jun-19 cut-off)



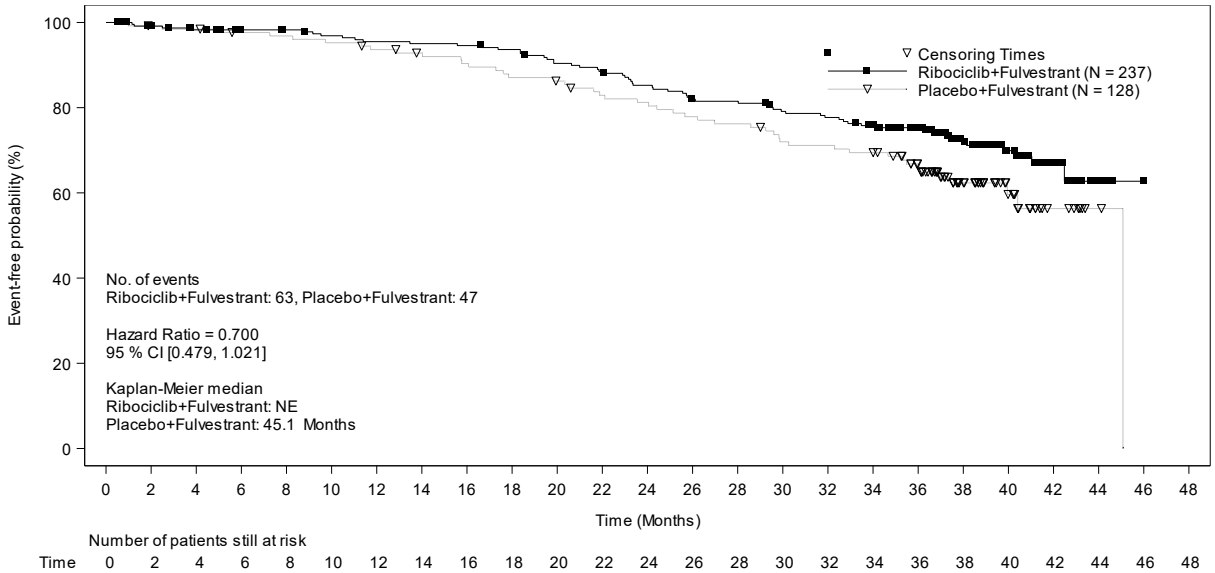
Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Ribociclib	484	470	454	444	436	428	414	402	397	389	374	365	348	334	326	309	300	287	237	159	92	41	14	2	0
Placebo	242	233	227	223	218	213	207	199	194	187	184	174	169	159	155	147	141	134	107	64	37	14	3	0	0

Log-rank test and Cox model are stratified by lung and/or liver metastasis, prior chemotherapy for advanced disease, and endocrine combination partner per IRT

OS results for subgroups analyses are presented in Figures 12, 13 and 14.

Figure 12 MONALEESA-3 (F2301) Kaplan Meier plot of OS treatment naïve patients in the metastatic/advanced disease setting (FAS) (03-Jun-19 cut-off)

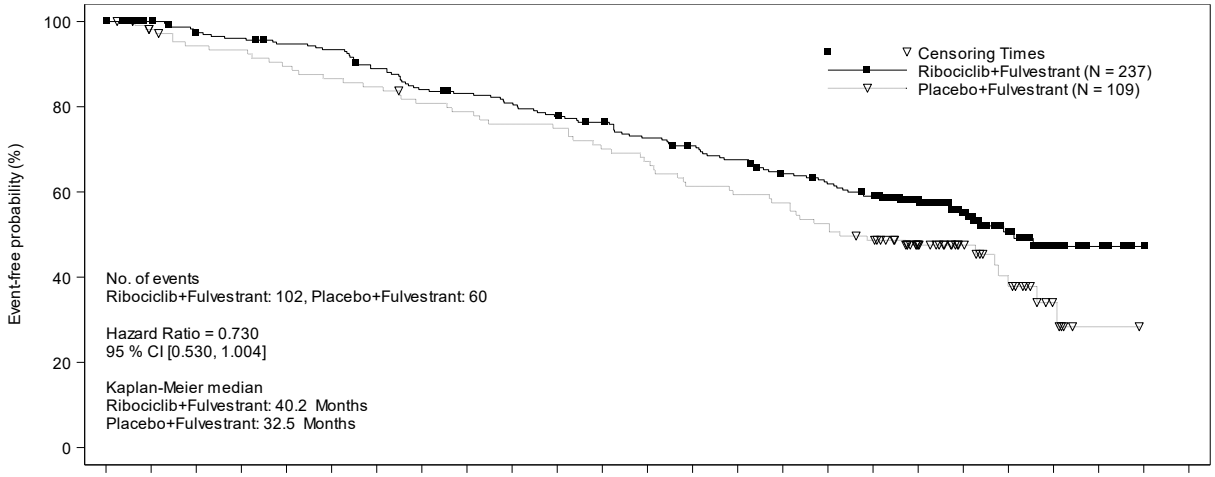


Number of patients still at risk

Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Ribociclib	237	229	222	217	214	210	207	206	205	202	194	190	182	174	173	166	163	157	138	92	54	22	6	1	0
Placebo	128	126	125	122	121	119	116	113	110	106	104	99	97	93	91	85	84	82	70	40	21	8	2	0	0

Hazard ratio is based on unstratified Cox model

Figure 13 **MONALEESA-3 (F2301) Kaplan Meier plot of OS in patients who received up to 1 line of treatment for metastatic/advanced disease setting (FAS) (03-Jun-19 cut-off)**

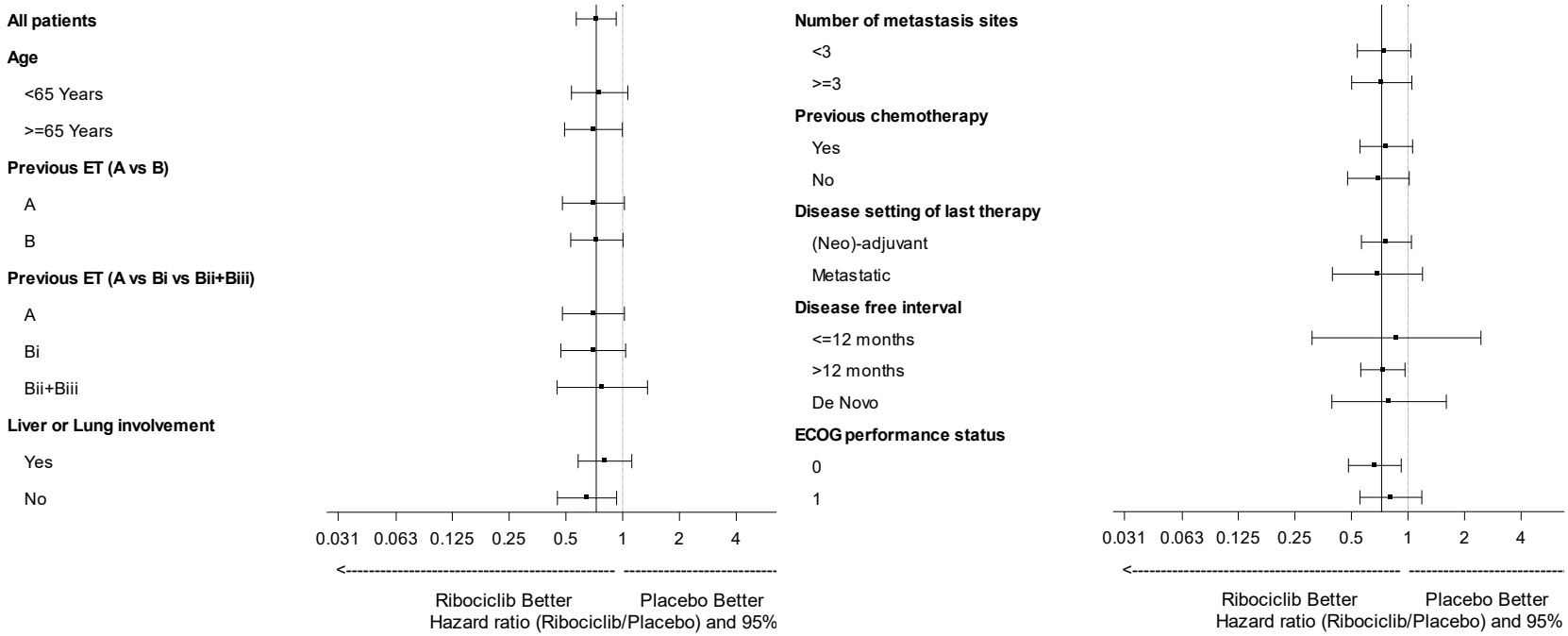


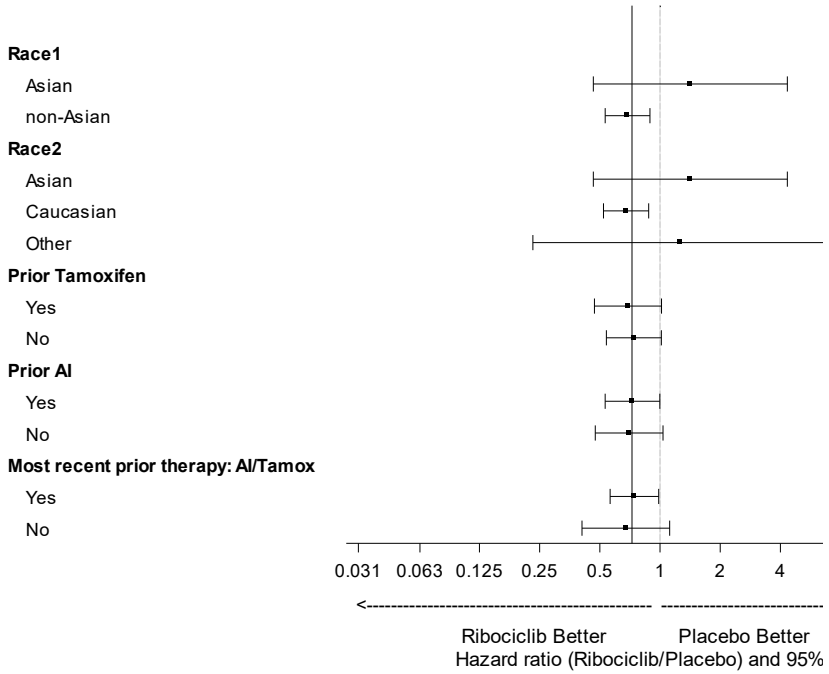
Number of patients still at risk

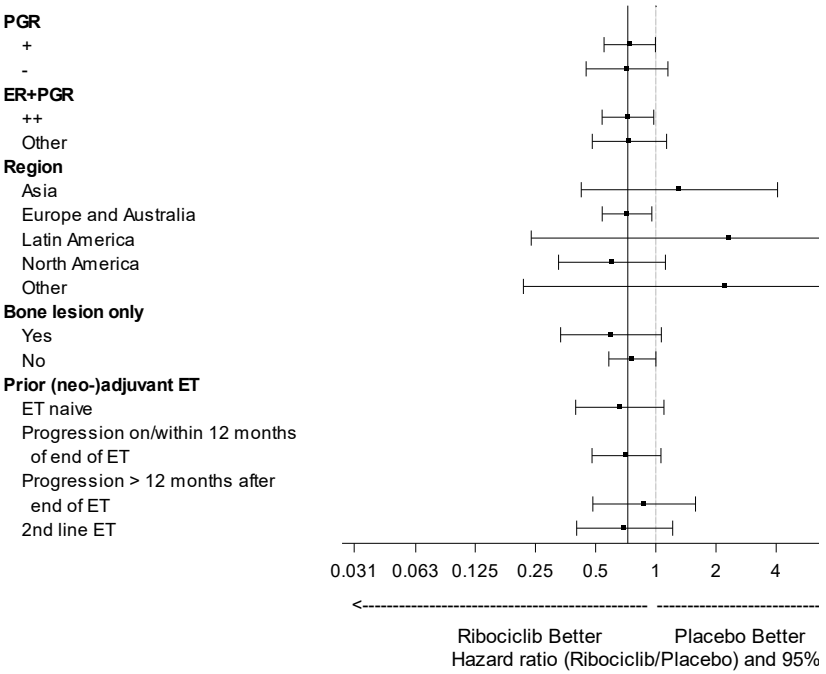
Time	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48
Ribociclib	237	231	222	218	213	210	199	188	184	179	172	167	158	152	145	135	129	122	94	63	36	17	7	1	0
Placebo	109	103	98	97	93	90	88	83	81	78	77	72	69	63	61	59	54	49	35	23	15	6	1	0	0

Hazard ratio is based on unstratified Cox model

Figure 14 MONALEESA-3 (F2301) Forest plot of OS from sub-group analysis (FAS) (03-Jun-19 cut off)







Dotted line shows no effect point, and bold line shows overall treatment effect point.
Hazard ratio (95% CI) is based on Cox PH model stratified by lung and/or liver metastasis, and previous endocrine therapy per IRT.
Exception: for subgroup analyses related to stratification factors (liver/lung metastasis and previous endocrine therapy), unstratified models are used.
Subgroups are derived based on CRF.

Additionally, time to progression on next-line therapy or death (PFS2) in patients in the Kisqali arm was longer compared to patients in the placebo arm (HR: 0.670 (95% CI: 0.542, 0.830)) in the overall study population. The median PFS2 was 39.8 months (95% CI: 32.5, NE) for the Kisqali arm and 29.4 months (95% CI: 24.1, 33.1) in the placebo arm.

Study CLEE011A2404 (COMPLEEMENT-1)

Kisqali was evaluated in an open-label, single arm, multicenter phase IIIb clinical study comparing ribociclib in combination with letrozole in pre/post-menopausal women and men with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease. Premenopausal women, and men, also received goserelin or leuprolide.

The study enrolled 3246 patients, including 39 male patients who received Kisqali 600 mg orally once daily for 21 consecutive days followed by 7 days off; and letrozole 2.5 mg orally once daily for 28 days; and goserelin 3.6 mg as injectable subcutaneous implant or leuprolide 7.5 mg as intramuscular injection administered on Day 1 of each 28-day cycle. Patients were treated until disease progression or unacceptable toxicity occurred.

Male patients enrolled in this study had a median age of 62 years (range 33 to 80). Of these patients, 38.5% were 65 years and older, including 10.3% aged 75 years and older. The male patients enrolled were Caucasian (71.8%), Asian (7.7%), and Black (2.6%), with 17.9% unknown. Nearly all male patients (97.4%) had an ECOG performance status of 0 or 1. The majority of male patients (97%) had 4 or less metastatic sites, which were primarily bone and visceral (69.2% each).

Table 20 summarizes the efficacy results in male patients.

Table 20 COMPLEEMENT-1 (A2404) efficacy results in male patients[1] based on investigator assessment (intent-to-treat population)

	Kisqali + Letrozole + Goserelin or Leuprolide
Overall Response Rate*,[2]	N = 32
(95% CI)	46.9 (29.1, 65.3)
Duration of Response[3]	N = 15
Median (months, 95% CI)	NR (21.3, NR)
Patients with DoR ≥ 12 months, n (%)	12 (80.0%)
Clinical Benefit Rate[4]	
(95% CI)	71.9 (53.3, 86.3)

Abbreviations: CI, confidence interval, NR, not reached.

**Based on confirmed responses.*

[1]Patients with measurable disease; 7 patients did not have measurable disease.

[2]Investigator Assessment.

[3]Proportion of patients with complete response or partial response.

[4]Proportion of patients with complete response + partial response + (stable disease or non-complete response/non-progressive disease ≥24 weeks)

Non-clinical safety data

Ribociclib was evaluated in safety pharmacology, repeated dose toxicity, genotoxicity, reproductive toxicity, and phototoxicity studies.

Safety pharmacology

Ribociclib did not have effects on CNS or respiratory functions . *In vivo* cardiac safety studies in dogs demonstrated dose and concentration related QTc interval prolongation at an exposure that would be expected to be achieved in patients following the highest recommended dose of 600mg. As well, there is potential to induce incidences of PVCs at elevated exposures (approximately 5-fold the anticipated clinical C_{max}).

Repeated dose toxicity

Repeated dose toxicity studies (treatment schedule of 3 weeks on/1 week off) in rats up to 27 weeks duration and dogs up to 39 weeks duration, revealed the hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) as the primary target organ of toxicity of ribociclib. Target organs associated with the pharmacological action of ribociclib in repeat dose studies include bone marrow (hypocellularity), lymphoid system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation), kidney (concurrent degeneration and regeneration of tubular epithelial cells) and testes (atrophy). Besides the atrophic changes seen in the testes, which showed a trend towards reversibility, all other changes were fully reversible after a 4-week treatment free period. These effects can be linked to a direct anti-proliferative effect on the testicular germ cells resulting in atrophy of the seminiferous tubules. Exposure to ribociclib in animals in the toxicity studies was generally less than or equal to that observed in patients receiving multiple doses of 600 mg/day (based on AUC).

Reproductive toxicity/Fertility

See section Pregnancy, lactation, females and males of reproductive potential.

Genotoxicity

Genotoxicity studies in bacterial *in vitro* systems and in mammalian *in vitro* and *in vivo* systems with and without metabolic activation did not reveal any evidence for a mutagenic potential of ribociclib.

Phototoxicity

Ribociclib was shown to absorb light in the UV-B and UV-A range. An *in vitro* phototoxicity test did not identify a relevant phototoxicity potential for ribociclib. The risk that ribociclib causes photosensitization in patients is considered very low.

Carcinogenesis

Ribociclib was assessed for carcinogenicity in a 2-year rat study.

Oral administration of ribociclib for 2 years resulted in an increased incidence of endometrial epithelial tumors and glandular and squamous hyperplasia in the uterus/cervix of female rats at doses ≥300 mg/kg/day as well as an increased incidence in follicular tumors in the thyroid glands of male rats at a dose of 50 mg/kg/day. Mean exposure at steady state (AUC0-24h) in female and male rats in whom neoplastic changes were seen was 1.2 and 1.4-fold that achieved in patients at the recommended dose of 600 mg/day, respectively. Mean exposure at steady state (AUC0-24h) in female and male rats in whom neoplastic changes were seen was 2.2- and 2.5-fold that achieved in patients at a dose of 400 mg/day, respectively.

Additional non-neoplastic proliferative changes consisted of increased liver altered foci (basophilic and clear cell) and testicular interstitial (Leydig) cell hyperplasia in male rats at doses of ≥5 mg/kg/day and 50 mg/kg/day, respectively.

The mechanism for the thyroid findings in males is considered to be a rodent-specific microsomal enzyme induction in the liver with no relevance to humans. The effects on the uterus/cervix and on the testicular interstitial (Leydig) cell are related to prolonged hypoprolactinemia secondary to CDK4 inhibition of lactotrophic cell function in the pituitary gland, altering the hypothalamus-pituitary-gonadal axis. Any potential increase of estrogen/progesterone ratio in humans by this mechanism would be compensated by an inhibitory action of concomitant anti-estrogen therapy on estrogen synthesis as in humans Kisqali is indicated in combination with estrogen-lowering agents.

The consequence of this mode of action in humans is unclear as there are differences between rodents and humans with regard to synthesis and role of prolactin.

Pharmaceutical information

Incompatibilities

Not applicable.

Storage

See folding box.

Kisqali should not be used after the date marked “EXP” on the pack.

Kisqali must be kept out of the sight and reach of children.

Instructions for use and handling

Not applicable.

Presentation:

PA/AL/PVC (Polyamide/Aluminium/Polyvinylchloride) blisters with aluminium foil containing 14 or 21 film-coated tablets.

Kisqali 200mg: 1 x 21s, 3 x 14s and 3 x 21s

Not all presentations may be available locally.

Novartis Pharma AG, Basel, Switzerland