1 Trade names

KISQALI[®/™] 200 mg film-coated tablets

KRYXANA[®/™] 200 mg film-coated tablets

2 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 [1].

Active substance

Each tablet contains 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 hydrolyzed); titanium dioxide (E171); iron oxide black (E172); iron oxide red (E172); talc; lecithin (soy) (E322); xanthan gum [1].

Information might differ in some countries.

3 Indications

Kisqali[®/™] is (a cyclin-dependent kinase inhibitor, CDKi) indicated for the treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (locally) advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant [14].

In pre- or perimenopausal women, or men, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist [14,39].

4 Dosage regimen and administration

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

Dosage regimen

General target population

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 [2]. Kisqali can be taken with or without food (see section 8 Interactions) [2].

When co-administered with Kisqali, the recommended dose of letrozole is 2.5 mg, taken once daily throughout the 28-day cycle [2]. Refer to the full prescribing information of letrozole.

For dosing and administration with the aromatase inhibitor, refer to the applicable full prescribing information.

Patients should take their dose of Kisqali and letrozole or the aromatase inhibitor at approximately the same time each day, preferably in the morning [7].

When co-administered with Kisqali, the recommended dose of fulvestrant is 500 mg administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Please refer to full prescribing information of fulvestrant [14].

Treatment of pre- or peri-menopausal women, or men, with Kisqali should include co-administration of an LHRH agonist according to local clinical practice standards [14,39].

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 4-1 [7].

Table 4-1   Dose modification guidelines for adverse drug reactions

	Kisqali	
	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 200 mg/day is required, discontinue the treatment.		

Tables 4-2, 4-3, 4-4, 4-5, and 4-6 summarize recommendations for dose interruption, reduction, or discontinuation of Kisqali in the management of specific adverse events [2,32]. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment (see sections 6 Warnings and precautions, 7 Adverse drug reactions).

Table 4-2   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 [2].			

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

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

Table 4-3   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 [2].

Baseline = prior to treatment initiation.

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

Table 4-4   Dose modification and management for QT-prolongation

ECGs with QTcF >480 ms	1. Interrupt the Kisqali dose; 2. If QTcF interval prolongation resolves to <481 ms, resume Kisqali at the next lower dose level [19]; 3. If QTcF interval ≥481 ms recurs, interrupt the Kisqali dose until QTcF interval resolves to <481ms; and then resume Kisqali at next lower dose level.
ECGs with QTcF >500 ms	If QTcF interval greater than 500 ms: Interrupt Kisqali until QTcF interval reaches <481 ms then resume Kisqali at next lower dose level. 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.

Assess ECG prior to initiation of treatment.

After initiating treatment with Kisqali, repeat ECG at approximately day 14 of the first cycle and at the beginning of the second cycle, then as clinically indicated.

In case of QTcF interval prolongation during treatment, more frequent ECG monitoring is recommended [2].

Table 4-5   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	Interrupt Kisqali until recovery to Grade ≤1, then resume Kisqali at	Discontinue Kisqali

		the next lower dose level*.	
	medical therapy and monitor as clinically indicated.		

Grading according to CTCAE Version 4.03.

* An individualized benefit-risk assessment should be performed when considering resuming Kisqali

ILD = Interstitial Lung Disease

Table 4-6   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 neutropenia, hepatobiliary toxicity, QT interval prolongation, and ILD/Pneumonitis.

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

Refer to the full prescribing information for the co-administered aromatase inhibitor, fulvestrant or LHRH agonist for dose modification guidelines in the event of toxicity and other relevant safety information.

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 low potential for CYP3A inhibition [3]. If a strong CYP3A inhibitor must be co-administered, the Kisqali dose should be reduced to 200 mg once daily [3]. 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 6 Warnings and precautions, 8 Interactions and 11 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 11 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 [3,14] (see section 11 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) [2]. A dose adjustment is required in patients with moderate (Child-Pugh

class B) and severe hepatic impairment (Child-Pugh class C) [2] and the starting dose of 400 mg is recommended [3]. Kisqali has not been studied in breast cancer patients with moderate and severe hepatic impairment [2] (see section 11 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 [2].

Geriatric patients (65 years of age or older)

No dose adjustment is required in patients over 65 years of age (see section 11 Clinical pharmacology) [3].

Method of administration

Kisqali should be taken orally once daily at the same time every day, preferably in the morning [7], with or without food [2]. 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 [7]. 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 [7].

5 Contraindications

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

6 Warnings and precautions

Neutropenia

In the 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 [2,~~15~~*,38,43].

Among the patients 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 $\geq$3 (to normalization or Grade <3) was 12 days [~~15~~*,38,43] in the Kisqali plus any combination treatment group [2]. Severity of neutropenia is concentration dependent [2]. Febrile neutropenia was reported in 1.7% [~~15~~*,38,43] of patients exposed to Kisqali in the phase III clinical studies [5]. Physicians should inform patients to promptly report any fever (see section 7 Adverse drug reactions).

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 [2].

Based on the severity of the neutropenia, Kisqali may require dose interruption/reduction or discontinuation as described in Table 4-2 (see section 4 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 above 38° C 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 studies, increases in transaminases were observed [5].

Grade 3 or 4 increases in ALT (11.2% vs. 1.7%) and AST (7.8% vs. 2.1%) [2] 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 [15*,38,43].

In the phase III clinical studies, 70.9% (90/127) [15*, 38,43] of Grade 3 or 4 ALT or AST elevation events occurred within the first 6 months of treatment [2,43] (see section 7 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 group [2,43]. The median time to resolution (to normalization or Grade ≤2) was 21 days in the Kisqali plus any combination treatment group [2,15*, 38,43].

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 [5,15*,38]. There were no such cases reported in Study E2301) [14].

LFTs should be performed before initiating therapy with Kisqali. 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 [2].

Based on the severity of the transaminase elevations, Kisqali may require dose interruption, reduction, or discontinuation as described in Table 4-3 (see section 4 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

In the phase III clinical studies, in patients with advanced or metastatic breast cancer who received 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 [2,15*,38,43].

In 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 group [19] (see section 11 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 [18]. 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 [14].

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 [7]. The ECG should be repeated at approximately Day 14 of the first cycle, at the beginning of the second cycle and then as clinically indicated [2].

Appropriate monitoring of serum electrolytes (including potassium, calcium, phosphorous, and magnesium) should be performed 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 [2,14].

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 [2].

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 4 Dosage regimen and administration, 8 Interactions and 11 Clinical pharmacology) [2]. Based on the findings in MONALEESA-7 (E2301), Kisqali is not recommended for use in combination with tamoxifen (see section 12 Clinical studies) [14].

Based on the observed QT prolongation during treatment, Kisqali may require dose interruption, reduction, or discontinuation as described in Table 4-4 (see sections 4 Dosage regimen and administration, 7 Adverse drug reactions and 11 Clinical pharmacology).

In the event of ECGs with QTcF interval >480 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 QTcF interval ≥481 ms recurs, Kisqali dose should be interrupted until QTcF interval 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 4 Dosage regimen and administration, 7 Adverse drug reactions and 11 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 [2]. 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 9 Pregnancy, lactation, females and males of reproductive potential) [2].

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 [35].

Interstitial Lung Disease (ILD)/Pneumonitis

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

In the three phase III clinical studies (MONALEESA-2 (A2301), MONALEESA-7 (E2301-NSAI) and MONALEESA-3 (F2301)), 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 [43]. Additional cases of ILD/pneumonitis have been observed with Kisqali in the post-marketing setting (see section 7 Adverse drug reactions) [32,46].

Based on the severity of the ILD/pneumonitis patients may require treatment interruption, dose reduction or permanent discontinuation as described in Table 4-5 (see section 4 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 4 Dosage regimen and administration).

7   Adverse drug reactions

Summary of the safety profile

The overall safety profile of Kisqali 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 [~~15~~,38,5,43].

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% [~~15~~*,38,43] of patients receiving placebo [2].

Permanent discontinuations due to adverse events were reported in 8.7% of patients receiving Kisqali plus any combination and in 3.1% [~~15~~*,38,43] of patients receiving placebo plus any combination [5].

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%) [5,~~15~~*,38,43].

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%) [5,~~15~~*,38,43].

The most common ADRs across the pooled phase III studies (reported at a frequency of $\geq$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 [2,43].

The most common Grade 3/4 ADRs in the pooled data (reported at a frequency of $\geq$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 [2,43].

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 [39,40].

Tabulated summary of adverse drug reactions based on pooled data set from 3 phase III clinical studies

ADRs from the phase III clinical studies (Table 7-1) 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 ($\geq$1/10); common ($\geq$1/100 to <1/10); uncommon ($\geq$1/1,000 to <1/100); rare ($\geq$1/10,000 to <1/1,000); very rare (<1/10,000) [2,14,~~15~~*,38,43].

Table 7-1   Adverse drug reactions based on pooled data set from 3 phase III clinical studies

Adverse drug reactions	Kisqali N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N=1065 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

Adverse drug reactions	Kisqali N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N=1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
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)	23.0 (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
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

Adverse drug reactions	Kisqali N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N=1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
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 hematological or biochemical laboratory values from the data set of 3 pooled phase III studies are presented in Table 7-2 [14].

Table 7-2   Laboratory abnormalities based on pooled dataset from phase III clinical studies

Laboratory abnormalities	Kisqali N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N= 1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category (all Grades)
Haematological parameters					
Leukocyte count decreased	1009 (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

Laboratory abnormalities	Kisqali N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kisqali N= 1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category (all Grades)
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					
AST increased	580 (54.5)	343 (41.9)	83 (7.8)	17 (2.1)	Very common
Gamma GT increased[1]	390 (53.4)	229 (46.9)	67 (9.2)	51 (10.5)	Very common
ALT 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 7-3   **Adverse drug reactions derived from spontaneous reports and literature (frequency not known)**

Respiratory, thoracic and mediastinal disorders
Interstitial lung disease (ILD)/pneumonitis [46]
Skin and subcutaneous tissue disorders
Toxic epidermal necrolysis (TEN) [35]

Description of selected adverse drug reactions

Neutropenia

Neutropenia was most frequently reported by laboratory findings in the phase III studies [5]. Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification [5]. Treatment discontinuation due to neutropenia was low (0.8%) [2,15*,38] in patients receiving Kisqali plus any combination partner (see sections 4 Dosage regimen and administration and 6 Warnings and precautions).

Hepatobiliary toxicity

In the phase III clinical studies, 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 [2,15*,38,43], primarily due to ALT increased (7.9%) and/or AST increased (7.3%) [15*,38,43]. Discontinuation of treatment with Kisqali due to abnormal liver function tests and hepatotoxicity occurred in 2.4% and 0.3% of patients, respectively [15*,38,43] (see section 6 Warnings and precautions).

QT prolongation

In the phase III clinical studies, 9.3% of patients in the Kisqali arm and 3.5% [15*,38,43] in the placebo arm had at least one event of QT interval prolongation (including ECG QT interval prolonged, syncope) [2]. Dose interruptions-adjustments were reported in 2.9% [15*,38,43] of Kisqali treated patients due to electrocardiogram QT interval prolonged and syncope [2].

A central analysis of ECG data (average of triplicate) showed 55 patients (5.2%) and 12 patients (1.5%) [15*,38,43] with at least one post-baseline QTcF interval >480 m sec for the Kisqali treatment arm and the placebo arm, respectively [2]. Among the patients who had QTcF interval prolongation of >480 ms, the median time to onset was 15 days regardless of the combination [2,15*,38] and these changes were reversible with dose interruption and/or dose adjustment [2] (see sections 4 Dosage regimen and administration, 6 Warnings and precautions and 11 Clinical pharmacology).

8   Interactions

Ribociclib is primarily metabolized by CYP3A and is a time-dependent inhibitor of CYP3A *in vivo* [3]. 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 ribociclib exposure in healthy subjects by 3.21-fold [3]. 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 [2] (see section 6 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 [3] (see sections 4 Dosage regimen and administration, 6 Warnings and precautions and 11 Clinical pharmacology).

If co-administration of Kisqali with a strong CYP3A inhibitor cannot be avoided, the Kisqali dose should be reduced to 200 mg [3]. However, there are no clinical data with this dose adjustment (see section 4 Dosage regimen and administration). 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 4 Dosage regimen and administration) or treatment should be interrupted until toxicity has resolved [3] (see sections 4 Dosage regimen and administration and 11 Clinical pharmacology).

Patients should be instructed to avoid [14] grapefruits or grapefruit juice, all of which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib [2].

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% [3]. 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 6 Warnings and precautions and 11 Clinical pharmacology) [3].

Medicinal products that may have their plasma concentrations altered by ribociclib

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of Kisqali (400 mg) increased the midazolam exposure by 280% (3.80-fold) in healthy subjects compared with administration of midazolam alone [3]. Simulations using physiologically-based PK (PBPK) models suggested that Kisqali given at the clinically relevant dose of 600 mg is expected to increase the midazolam AUC by 5.2-fold [3]. 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 [3] (see section 11 Clinical pharmacology).

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 [3]. 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) [3] (see section 11 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 [3] (see section 11 Clinical pharmacology).

Drug-food interactions

Kisqali can be administered with or without food (see section 4 Dosage regimen and administration).

Compared to the fasted state, oral administration of a single 600 mg 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 (Cmax GMR: 1.00; 90% CI: 0.898, 1.11; AUCinf GMR: 1.06; 90% CI: 1.01, 1.12 [3] (see section 11 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) [3]. 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 [3] (see section 11 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 [3]. Kisqali is not recommended for use in combination with tamoxifen (see section 6 Warnings and precautions) [14].

9 Pregnancy, lactation, females and males of reproductive potential

9.1 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 [6].

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 [5].

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 600 mg/day based on AUC [6]. There are no available human data informing the drug-associated risk [5].

Data

Animal data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1,000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis [6].

In rats, 1,000 mg/kg/day was lethal in the maternal animals. At 300 mg/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 300 mg/kg/day. The no-observed-adverse-effect level (NOAEL) for maternal toxicity was considered to be 300 mg/kg/day. The no-observed-effect-level (NOEL) for embryo-fetal development was considered to be 50 mg/kg/day [6].

In rabbits at doses ≥30 mg/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 60 mg/kg), extra/rudimentary 13th 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 30 mg/kg/day and the NOEL for the embryo-fetal development was 10 mg/kg/day [6].

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposure (AUC) were 13,800 ng*hr/mL and 36,700 ng*hr/mL, lower than or at 1.5 times, the one achieved in patients at the highest recommended dose of 600 mg/day [6].

9.2   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 [5]. Ribociclib and its metabolites readily passed into the milk of lactating rats [6]. 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 [5].

Data

Animal data

In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 3.56-fold higher in milk than in maternal plasma [6].

9.3   Females and males of reproductive potential

Based on animal studies, Kisqali can cause fetal harm when administered to a pregnant woman (see section 13 Non-clinical safety data) [6].

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 [6]. 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 [6].

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 300 mg/kg/day (likely at an exposure lower than or equal to patients clinical exposure at the highest recommended dose of 600 mg/day based on AUC) [25].

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 600 mg/day based on AUC

(see section 13 Non clinical safety data) [6]. 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 [6].

10   Overdosage

There is limited experience with reported cases of Kisqali overdose in humans [16]. General symptomatic and supportive measures should be initiated in all cases of overdosage where necessary [2].

11   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 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) [6].

In vitro, ribociclib decreased pRb phosphorylation, leading to arrest in the G1 phase of the cell cycle, and reduced cell proliferation in breast cancer cell lines. *In vivo,* treatment with single-agent ribociclib led to tumor regressions which correlated with inhibition of pRb phosphorylation at well-tolerated doses [6].

In vivo studies using patient-derived estrogen-positive breast cancer xenograft models, combination of ribociclib and antiestrogens (i.e. letrozole) resulted in superior inhibition of tumor growth compared to each drug alone. Tumor regrowth was delayed for 33 days after stopping dosing [6]. 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 (IC50) values of 0.01 (4.3 ng/mL) and 0.039 micromolar (16.9 ng/mL) in biochemical assays, respectively [6].

In cell-based assays, ribociclib inhibits CDK4/6-dependent pRb phosphorylation with an average IC50 of 0.06 micromolar (26 ng/mL). Ribociclib halts G1 to S phase cell cycle progression measured by flow cytometry with an average IC50 of 0.11 micromolar (47.8 ng/mL). Ribociclib also inhibits cellular proliferation measured by bromodeoxyuridine (BrdU) uptake with an IC50 of 0.8 micromolar (34.8 ng/mL). The similar IC50 values obtained from the target modulation, cell cycle and proliferation assays confirm 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 [6].

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 [19] patients treated with ribociclib at doses ranging from 50 to 1,200 mg. The analysis suggested that ribociclib causes concentration-dependent increases in the QTc interval. The estimated QTcF interval mean change from baseline for Kisqali 600 mg dose in combination with NSAI or fulvestrant was 22.00 ms (90% CI: 20.56, 23.44) and 23.7 ms (90% CI: 22.31, 25.08), respectively, at the geometric mean Cmax at steady-state compared to 34.7∘ms (90% CI: 31.64, 37.78) in combination with tamoxifen (see section 6 Warnings and precautions) [19].

Pharmacokinetics (PK)

The pharmacokinetics of ribociclib were investigated in patients with advanced cancer following oral daily doses of 50 mg to 1,200 mg. Healthy subjects received single oral doses of 400 or 600 mg or repeated daily oral doses (8 days) of 400 mg [3].

Absorption

Following oral administration of Kisqali to patients with advanced solid tumors or lymphomas peak plasma levels (Cmax) of ribociclib were achieved between 1 and 4 hours (time to reach maximum concentration, Tmax). The geometric mean absolute bioavailability of ribociclib after a single oral dose of 600 mg was 65.8% in healthy subjects [33]. Ribociclib exhibited slightly over-proportional increases in exposure (Cmax and AUC) across the dose range tested (50 to 1,200 mg). 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) [3].

Food effect

Compared to the fasted state, oral administration of a single 600 mg 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 (Cmax GMR: 1.00; 90% CI: 0.898, 1.11; AUCinf GMR: 1.06; 90% CI: 1.01, 1.12) [3] (see section 8 Interactions).

Distribution

Binding of ribociclib to human plasma proteins *in vitro* was approximately 70% and independent of concentration (10 to 10,000 ng/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 [3].

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 600 mg 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 [3].

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) [3].

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 600 mg in patients with advanced cancer [3]. The geometric mean plasma terminal half-life (T1/2) 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 600 mg across studies in healthy subjects [3].

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 21 days [3]; feces were the major route of excretion (69.1%), with 22.6% of the dose recovered in the urine [3].

Linearity/non-linearity

Ribociclib exhibited slightly over-proportional increases in exposure (Cmax and AUC) across the dose range of 50 mg to 1,200 mg 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 600 mg dose cohort [3].

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 [20,29].

In the subjects with normal, mild, moderate, severe renal impairment and ESRD, the geometric mean AUCinf (geometric %CV, n) was 4100 ng*hr/mL (53.2%, 14), 6650 ng*hr/mL (36.4%, 8), 7960 ng*hr/mL (45.8%, 6), 10900 ng*hr/mL (38.1%, 7), 13600 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 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 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 [27,28]. In addition, in a sub-group analysis of PK data from studies in 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 4 Dosage regimen and administration) [27].

Hepatic impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh A); a dose adjustment is required in patients with moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C) and a starting dose of 400 mg 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 Cmax; 1.28 for AUCinf) [22] and severe (GMR: 1.32 for Cmax; 1.29 for AUCinf) hepatic impairment [22]. Based on a population pharmacokinetic analysis that included 160 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 [3] (see section 4 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 [3].

Geriatric patients

Of the 334 patients who received Kisqali in the phase III study (MONALEESA 2, ribociclib plus letrozole arm), 150 patients (44.9%) were ≥65 years of age [7] 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 [17,43]. No overall differences in the safety or effectiveness of Kisqali were observed between these patients and younger patients (see section 4 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 (100 mg b.i.d for 14 days) increased ribociclib Cmax and AUCinf by 1.7-fold and 3.2-fold, respectively, following a single 400 mg ribociclib dose. Cmax and AUClast for LEQ803 (a prominent metabolite of ribociclib, accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively [3]. Simulations using PBPK suggested that a moderate CYP3A4 inhibitor (erythromycin) may increase Cmax and AUC of ribociclib 400 mg single dose [3] by 1.3-fold and 1.9-fold, respectively [3] (see sections 4 Dosage regimen and administration, 6 Warnings and precautions and 8 Interactions).

Strong CYP3A inducers: A drug interaction study in healthy subjects was conducted with rifampicin (strong CYP3A4 inducer). Compared to ribociclib alone, rifampicin (600 mg daily for 14 days) decreased ribociclib Cmax and AUCinf by 81% and 89%, respectively, following a single 600 mg ribociclib dose. LEQ803 Cmax increased 1.7-fold and AUCinf decreased by 27%, respectively [3]. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease ribociclib single dose [3] Cmax and AUC by 37% and 60%, respectively [3] (see section 8 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 (400 mg once daily for 8 days) increased midazolam Cmax and AUCinf by 2.1-fold and 3.8-fold, respectively [3]. Simulations using PBPK suggested that at a 600 mg ribociclib dose, midazolam Cmax and AUC may increase 2.4-fold and 5.2-fold, respectively [3]. The effect of multiple doses of ribociclib on caffeine was minimal, with Cmax decreasing by 10% and AUCinf increasing slightly by 20% [3]. Simulations using PBPK suggested only weak inhibitory effects on CYP1A2 substrates at a 600 mg ribociclib dose [3] (see section 8 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 [3] (see section 8 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) [3]. 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 [3] (see sections 4 Dosage regimen and administration and 8 Interactions).

Letrozole: Data from clinical trials in patients with breast cancer and a population PK analysis indicated no drug interaction between ribociclib and letrozole following co-administration of the drugs [3].

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 [11].

Anastrozole: Data from a clinical trial in patients with breast cancer indicated no clinically relevant drug interaction between ribociclib and anastrozole following coadministration of the drugs [18].

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 [17].

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 [21].

Effect of ribociclib on transporters: *In vitro* evaluations indicated that Kisqali has a low potential to inhibit the activities of the 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 [3] (see section 8 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 [3]. Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 [23] or OCT-1 *in vitro* [24] (see section 8 Interactions).

12   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 [2].

A total of 668 patients were randomized in a 1:1 ratio to receive either Kisqali 600 mg 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%)] [7]. Demographics and baseline disease characteristics were balanced and comparable between study arms [7]. Kisqali was given orally at a dose of 600 mg daily for 21 consecutive days followed by 7 days off treatment in combination with letrozole 2.5 mg once daily for 28 days [2]. Patients were not allowed to cross over from placebo to Kisqali during the study or after disease progression [7].

Patients enrolled in this study had a median age of 62 years (range 23 to 91). 44.2% [12] 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 [4]. A total of 46.6% [12,44] of patients had received chemotherapy in the neoadjuvant or adjuvant setting and 51.3% [12,44] had received antihormonal therapy in the neo/adjuvant setting prior to study entry [4]. 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 [4,44].

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 the Response Evaluation Criteria in Solid Tumors (RECIST v1.1), based on the investigator assessment in the full population (all randomized patients) [7] and confirmed by a blinded independent central radiological assessment.

The efficacy results 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 [4]. 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 [4]. 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 (Figure 12-3) [2].

Progression free survival is summarized in Table 12-1 and the Kaplan-Meier curve for PFS is provided in Figure 12-1 [4]. 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; 95% CI: 0.412, 0.852) [7]. The one-sided stratified log-rank test p-value was 0.002 [4].

The global health status/Quality of life (QoL) showed no relevant difference between the Kisqali plus letrozole arm and the placebo plus letrozole control arm [4].

A more mature update of efficacy data is provided in Table 12-2 and Figure 12-2. 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. [13].

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 [4,7].

Table 12-1   MONALEESA-2 (A2301) primary efficacy results (PFS) based on investigator assessment (29-Jan-16 cut-off)

	Kisqali plus letrozole N=334	Placebo plus letrozole N=334
Progression free survival		
Median PFS [months] (95% CI)	NE (19.3 - NE)	14.7 (13.0 - 16.5)
Hazard ratio (95% CI)	0.556 (0.429 to 0.720)	
p-value[a]	0.00000329	

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

[a] p-value is obtained from the one-sided stratified log-rank test.

Table 12-2   MONALEESA-2 (A2301) primary efficacy results (PFS) based on investigator assessment (02-Jan-17 cut-off)

	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 12-1   MONALEESA-2 (A2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (29-Jan-16 cut-off)
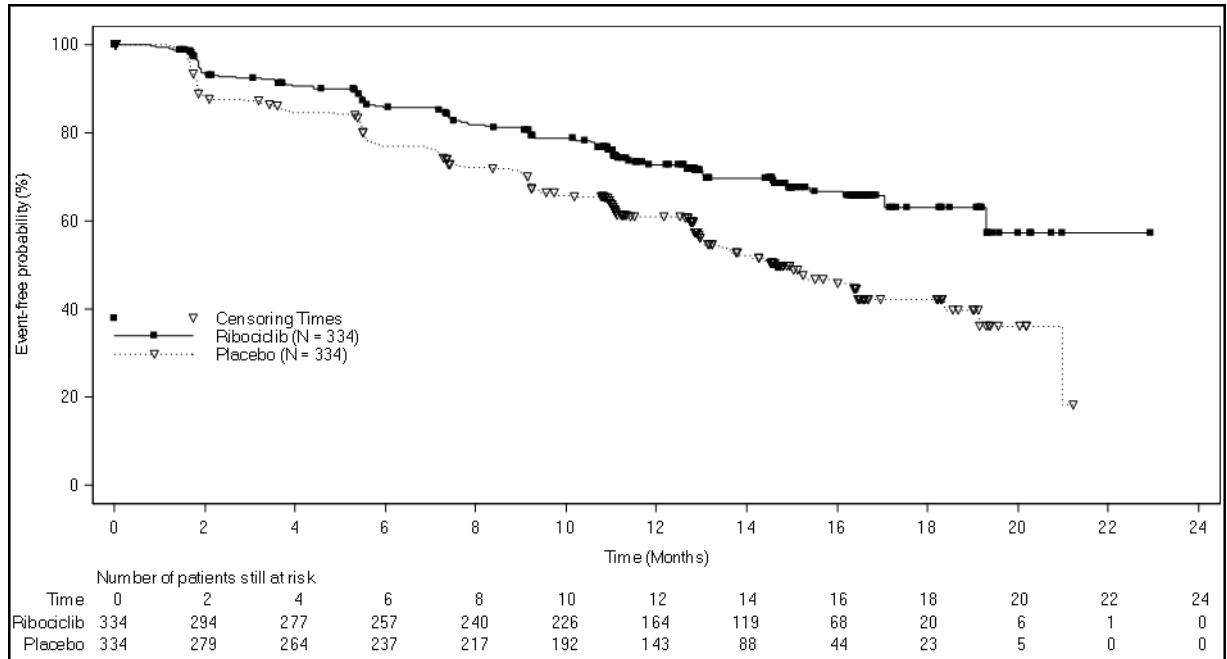
Figure 12-2   MONALEESA-2 (A2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (02-Jan-17 cut-off)
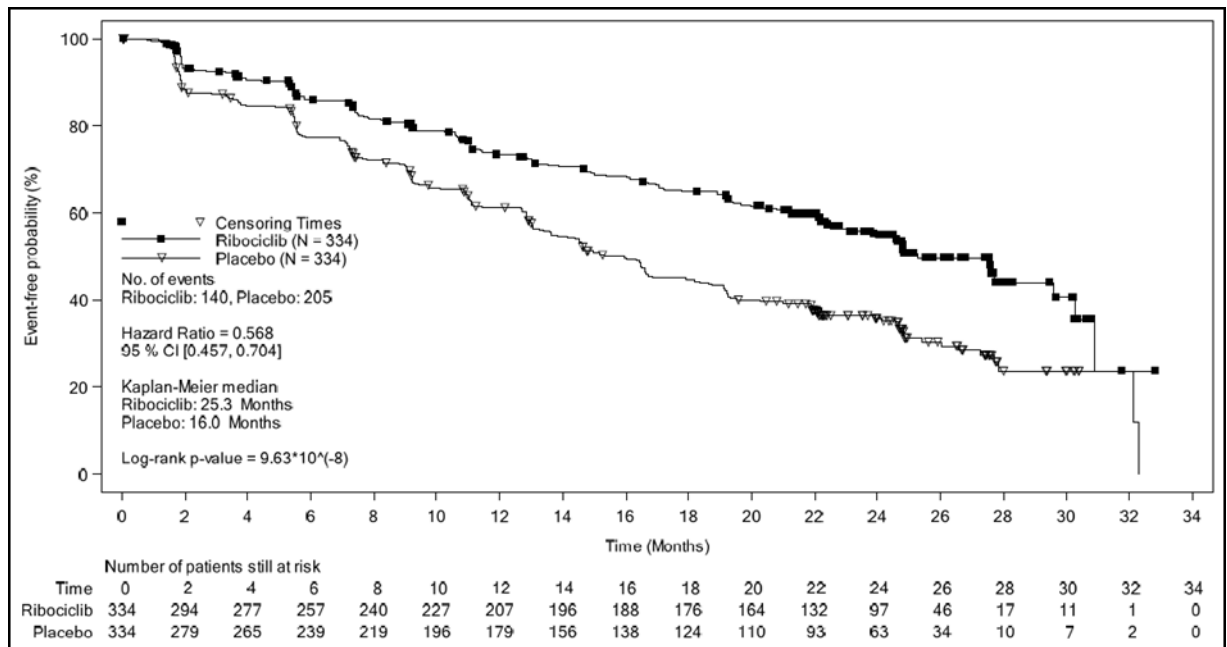
Figure 12-3   MONALEESA-2 (A2301) Forest plot of PFS based on investigator assessment (FAS) (29-Jan-16 cut-off)

Prior chemotherapy

  No

  Yes

Prior hormonal agent

  NSAI and others

  None

  Tamoxifen

PGR

  +

  -

ER+PGR

  ++

  Other

Number of metastasis sites

  <3

  >=3

0.0625　0.125　0.25　　0.5　　1　　2　　4　　8　　16

Hazard Ratio and 95% CI

<--- --->

Ribociclib　　　　　　　　　　Placebo

In favor of

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

Hazard Ratio and 95% CI

<-- -->

Ribociclib Placebo

In favor of

Ki67

   <= 14%

   > 14%

Cyclin D1

   <= 2001.6

   > 2001.6

Total Rb by H-score

   High

   Low

P16 by nanostring

   <= 31.5

   > 31.5

P16 by H-score

   High

   Low

   Medium

0.0625 0.125 0.25 0.5 1 2 4 8 16

Hazard Ratio and 95% CI

<--- -->
            Ribociclib   Placebo

In favor of

Prior chemotherapy=prior adjuvant or neoadjuvant chemotherapy; ER=estrogen receptor; PGR=progesterone receptor; Ribociclib=ribociclib 600 mg plus letrozole 2.5 mg;

Placebo=placebo plus letrozole 2.5 mg.

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 sub-group 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.

Figure 12-4   MONALEESA-2 (A2301) Forest plot of PFS based on investigator assessment (FAS) (02-Jan-17 cut-off)

Forest plot showing subgroup analyses:

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

X-axis: 0.0625 0.125 0.25 0.5 1 2 4 8 16

Ribociclib Better   Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI

Ki67
  <= 14%
  > 14%
Cyclin D1
  <= 2001.6
  > 2001.6
Total Rb by H-score
  High
  Low
P16 by nanostring
  <= 31.5
  > 31.5
P16 by H-score
  High
  Low
  Medium

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) [4]. 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=0.018) (see Table 12-3) [4,7].

A series of pre-specified sub-group PFS analyses was performed [14] based on prognostic factors and baseline characteristics to investigate the internal consistency of treatment effect. A reduction in the risk of disease progression or death in favor 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 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) [13].

Updated results for overall response and clinical benefit rates are displayed in Table 12-4 [13].

Table 12-3   MONALEESA-2 (A2301) efficacy results (ORR, CBR) based on investigator assessment (29-Jan-16 cut-off)

Analysis	Kisqali plus letrozole (%, 95% CI)	Placebo plus letrozole (%, 95% CI)	p-value[c]
Full analysis set	N=334	N=334	
Overall Response Rate[a]	40.7 (35.4, 46.0)	27.5 (22.8, 32.3)	0.000155
Clinical Benefit Rate[b]	79.6 (75.3, 84.0)	72.8 (68.0, 77.5)	0.018
Patients with measurable disease	**N=256**	**N=245**	
Overall Response Rate[a]	52.7 (46.6, 58.9)	37.1 (31.1, 43.2)	0.00028
Clinical Benefit Rate[b]	80.1 (75.2, 85.0)	71.8 (66.2, 77.5)	0.020

[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)

[c] p-values are obtained from one-sided Cochran-Mantel-Haenszel chi-square test.

Table 12-4 **MONALEESA-2 (A2301) efficacy results (ORR, CBR) based on investigator assessment (02-Jan-17 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: 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)
[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) [44,45].

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 [44,45]. 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 12-6) [44]. 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 12-5 and the Kaplan-Meier curve is provided in Figure 12-5.

Table 12-5 **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 12-5   MONALEESA-2 (A2301) Kaplan-Meier plot for OS (FAS) (data cutt-off 10-Jun-2021)
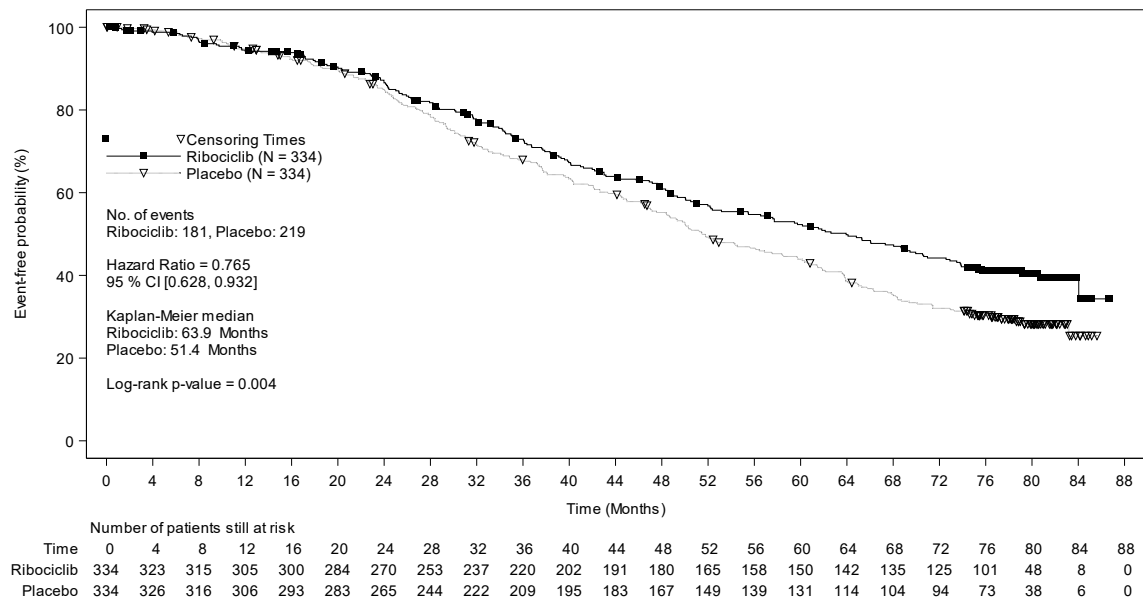
Log-rank test and Cox PH model are stratified by liver and/or lung metastasis as per IRT.
One sided P-value is obtained from stratified log rank test.

Figure 12-6 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 (%)
All patients	0.765(0.628, 0.932)	181/334(54.2)	219/334(65.6)
ECOG performance status			
0	0.728(0.563, 0.942)	103/204(50.5)	135/202(66.8)
1	0.823(0.605, 1.121)	78/130(60)	84/132(63.6)
Age			
<65 Years	0.695(0.535, 0.902)	100/184(54.3)	129/189(68.3)
>=65 Years	0.869(0.643, 1.175)	81/150(54)	90/145(62.1)
Race			
Asian	0.804(0.419, 1.544)	19/28(67.9)	19/23(82.6)
non-Asian	0.775(0.625, 0.962)	151/281(53.7)	184/287(64.1)
Region			
Asia	0.637(0.349, 1.164)	20/35(57.1)	24/33(72.7)
Europe	0.756(0.565, 1.012)	83/150(55.3)	101/146(69.2)
Latin America	3.209(0.729, 14.12)	5/7(71.4)	4/7(57.1)
North America	0.747(0.529, 1.057)	57/108(52.8)	74/121(61.2)
Other			

Ribociclib Better   Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI

	Hazard ratio (95% CI)	Ribociclib events n/N (%)	Placebo events n/N (%)
Prior chemotherapy			
No	0.785(0.596, 1.033)	91/188(48.4)	117/189(61.9)
Yes	0.740(0.557, 0.984)	90/146(61.6)	102/145(70.3)
Prior hormonal agent			
NSAI and others	0.634(0.323, 1.242)	18/30(60)	18/23(78.3)
None	0.697(0.518, 0.938)	76/158(48.1)	103/162(63.6)
Tamoxifen	0.856(0.640, 1.145)	87/146(59.6)	98/149(65.8)
PGR			
+	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)
ER+PGR			
++	0.825(0.660, 1.031)	144/269(53.5)	170/277(61.4)
Other	0.575(0.373, 0.886)	37/65(56.9)	49/57(86)
Number of metastasis sites			
<3	0.780(0.607, 1.001)	115/220(52.3)	136/222(61.3)
>=3	0.705(0.509, 0.977)	66/114(57.9)	83/112(74.1)

Ribociclib Better   Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI

	Hazard ratio (95% CI)	Ribociclib events n/N (%)	Placebo events n/N (%)
Liver involvement			
No	0.775(0.619, 0.969)	145/275(52.7)	163/262(62.2)
Yes	0.814(0.535, 1.239)	36/59(61)	56/72(77.8)
Lung involvement			
No	0.716(0.548, 0.937)	97/181(53.6)	119/185(64.3)
Yes	0.814(0.609, 1.088)	84/153(54.9)	100/149(67.1)
Liver or Lung involvement			
No	0.711(0.526, 0.962)	80/152(52.6)	90/144(62.5)
Yes	0.806(0.621, 1.045)	101/182(55.5)	129/190(67.9)
Bone lesion only metastasis			
No	0.768(0.615, 0.959)	144/265(54.3)	172/255(67.5)
Yes	0.780(0.504, 1.209)	37/69(53.6)	47/79(59.5)
De Novo			
No	0.909(0.718, 1.150)	134/220(60.9)	144/221(65.2)
Yes	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) [44,45].

Study CLEE011E2301 (MONALEESA-7)

Kisqali was evaluated in a randomized, double-blind, placebo-controlled, multicenter phase III clinical study comparing ribociclib or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of pre- and peri-menopausal women with hormone receptor (HR)-positive, HER2-negative, advanced breast cancer [18,30].

A total of 672 [18,30] patients were randomized to receive either Kisqali 600 mg plus tamoxifen or NSAI plus goserelin (n=335) or placebo plus tamoxifen or NSAI plus goserelin (n=337), stratified according to the presence of liver and/or lung metastases (Yes [n=344 (51.2%)] vs No [n=328 (48.8%)]), prior chemotherapy for advanced disease (Yes [n=120 (17.9%)] vs No [n=552 (82.1%)]), and endocrine combination partner (NSAI and goserelin) [n=493 (73.4%)] versus tamoxifen and goserelin [n=179 (26.6%)]. Demographics and baseline disease characteristics were balanced and comparable between study arms [18,30].

Tamoxifen 20 mg or NSAI (letrozole 2.5 mg or anastrazole 1 mg) were given orally once daily on a continuous schedule, goserelin 3.6 mg was administered as sub-cutaneous injection on day 1 of each 28 day cycle, 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. Patients were not allowed to cross over from placebo to Kisqali during the study or after disease

progression. Patients were not allowed to switch between endocrine combination partners [18,30].

Patients enrolled in the study had a median age of 44 years (range 25 to 58) and 27.7% of patients were younger than 40 years of age. The majority of patients were Caucasian (57.7%), Asian (29.5%), or Black (2.8%) and nearly all patients (99.0%) had an ECOG performance status of 0 or 1. Of the 672 patients, 32.6% of patients had received chemotherapy in the adjuvant vs 18.0% in neo-adjuvant setting and 39.6% had received endocrine therapy in the adjuvant vs 0.7% in the neoadjuvant setting. Prior to study entry 40.2% of patients had *de novo* metastatic disease, 23.7% had bone-only disease, and 56.7% had visceral disease [18,30].

Primary analysis

The primary endpoint for the study was met after observing 318 [18] progression-free survival (PFS) events using RECIST v1.1, based on the investigator assessment in the full analysis set (all randomized patients) and confirmed by a blinded independent central radiological assessment of a randomly selected subset of approximately 40% of randomized patients (BIRC). The median follow-up time at the time of the primary PFS analysis was 19.2 months [18].

In the overall study population, the median PFS (95% CI) was 23.8 months (19.2, NE) in the Kisqali plus tamoxifen or NSAI arm and 13.0 months (11.0, 16.4) in the placebo plus tamoxifen or NSAI arm [HR: 0.553 (95% CI: 0.441, 0.694); one-sided stratified long-rank test p-value: 9.83×10^{-8}]. Efficacy results are presented in the Kaplan-Meier curve for PFS in Figure 12-7. The results based on the BIRC were supportive of the primary efficacy results based on the investigator's assessment (HR: 0.427; 95% CI: 0.288, 0.633) [18].

Overall response rate (ORR) per investigator assessment based on RECISTv1.1 was higher in the Kisqali arm (40.9%; 95% CI: 35.6, 46.2) compared to the placebo arm (29.7%; 95% CI: 24.8, 34.6; p=0.00098) (see Table 12-7) [18].

The main pre-specified QoL measure was Time-To-Deterioration (TTD) in global health status. Definitive 10% deterioration was defined as a worsening in the 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 tamoxifen or NSAI resulted in delaying time-to-deterioration in the EORTC QLQ-C30 global health scale score compared with placebo plus tamoxifen or NSAI (median not estimable versus 21.2 months; HR: 0.699 [95% CI: 0.533, 0.916]; p=0.004 [18].

Figure 12-7   MONALEESA-7 (E2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (20-Aug-17 cut-off)
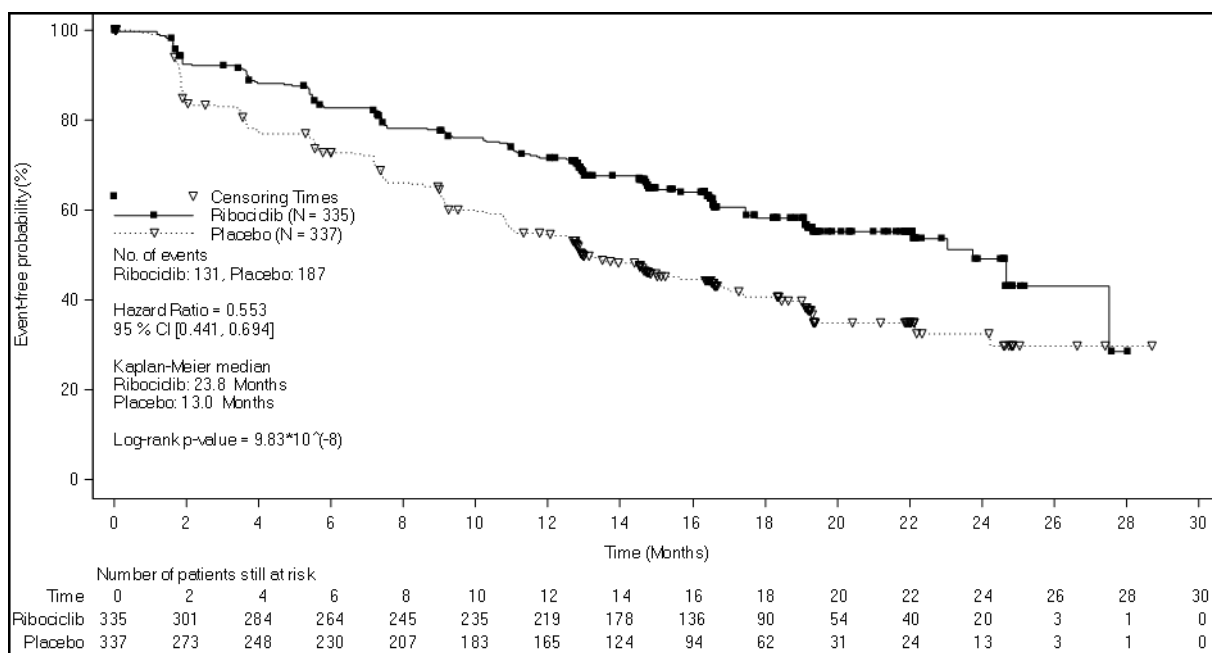
In the pre-specified sub-group analysis of 495 patients who had received Kisqali or placebo in combination with NSAI plus goserelin, the median PFS (95% CI) was 27.5 months (19.1, NE) in the Kisqali plus NSAI sub-group and 13.8 months (12.6, 17.4) in the placebo plus NSAI sub-group [HR: 0.569 (95% CI: 0.436, 0.743)]. Efficacy results are summarized in Table 12-6 and the Kaplan-Meier curves for PFS are provided in Figure 12-8. Kisqali is not recommended for use in combination with tamoxifen due to the risk of QTc interval prolongation (see section 6 Warnings and precautions) [18].

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 (see Figure 12-9) [18].

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 [18].

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 [18].

Table 12-6   **MONALEESA-7 (E2301) primary efficacy results (PFS) based on investigator assessment in patients who received NSAI (20-Aug-17 cut-off)**

	Kisqali plus NSAI plus goserelin	Placebo plus NSAI plus goserelin
	N=248	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 12-8   **MONALEESA-7 (E2301) Kaplan-Meier plot of PFS based on investigator assessment in patients who received NSAI (20-Aug-17 cut off)**
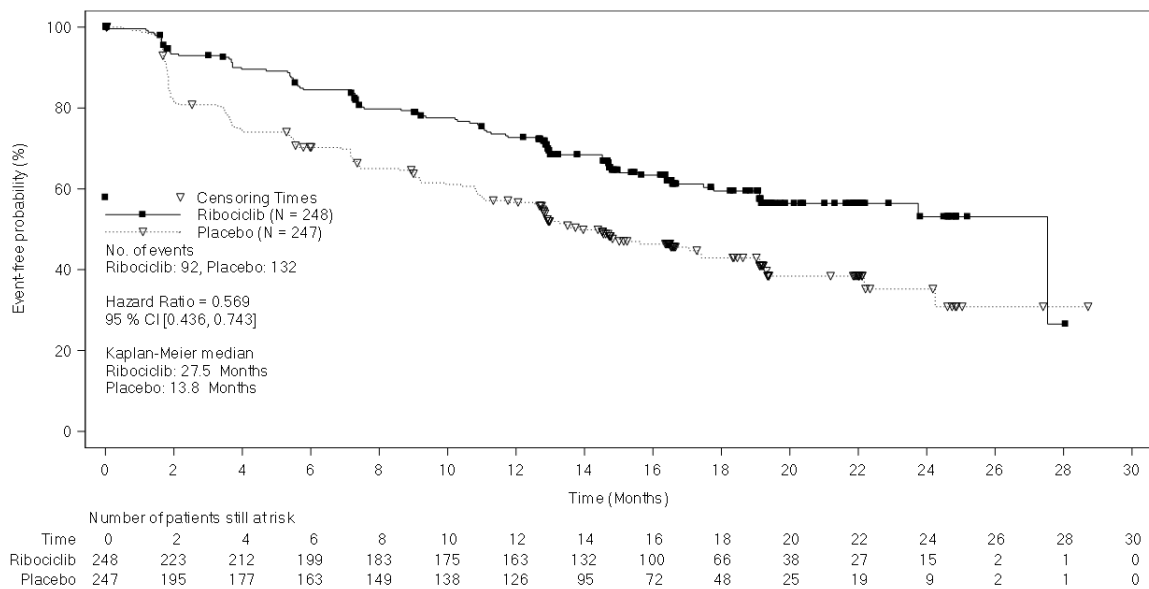
Table 12-7   MONALEESA-7 (E2301) efficacy results (ORR, CBR) based on investigator assessment in patients who received NSAI (20-Aug-17 cut off)

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 12-9   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

Final OS Analysis

At the time of the second OS analysis (30-Nov-2018 cut-off), the study met its key secondary endpoint, demonstrating a statistically significant improvement in OS.

The demonstrated OS benefit was consistent across exploratory subgroups and the safety profile of both treatment arms remained consistent with the results from the primary analysis.

A more mature update of overall survival data (30-Nov-2018 cut-off) is provided in Table 12-8 as well as in Figures 12-10 and 12-11 [30].

Table 12-8   MONALEESA-7 (E2301) efficacy results (OS) (30-Nov-18 cut-off)

Overall survival, overall study population	Ribociclib 600 mg N=335	Placebo N=337
Number of events – n [%]	83 (24.8)	109 (32.3)
Median OS [months] (95% CI)	NE (NE, NE)	40.9 (37.8, NE)
Hazard ratio (95% CI)	0.712 (0.535, 0.948)	
p-value[a]	0.00973	
Overall survival, NSAI subgroup	**Ribociclib 600 mg N=248**	**Placebo 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)
Hazard ratio (95% CI)	0.699 (0.501, 0.976)	

CI=confidence interval, NE=not estimable, N=number of patients, NSAI = non-steroidal aromatase inhibitor;

[a]p-value is obtained from the one-sided log-rank test stratified by lung and/or liver metastases, prior chemotherapy for advanced disease, and endocrine partner per IRT

Figure 12-10   MONALEESA-7 (E2301) Kaplan Meier plot of OS (FAS) (30-Nov-18 cut-off)
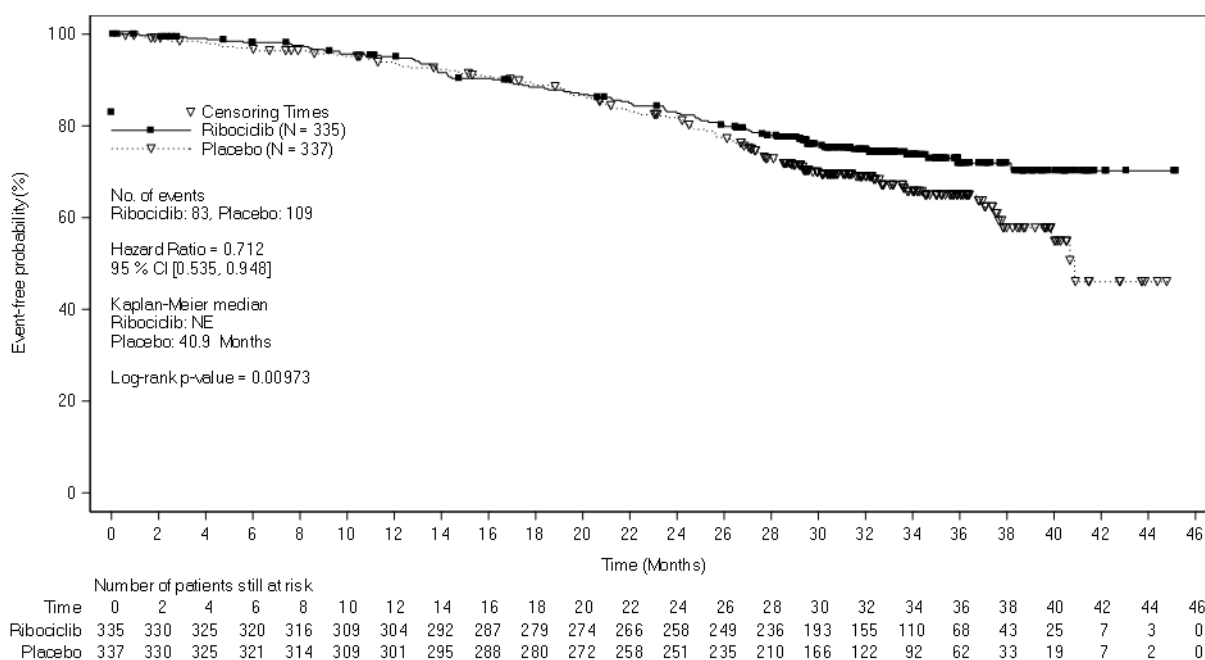
Log-rank test and Cox model are stratified by lung and/or liver metastasis, prior chemotherapy for advanced disease, and endocrine combination partner per IRT

Figure 12-11   MONALEESA-7 (E2301) Kaplan Meier plot of OS in patients who received NSAI (30-Nov-18 cut-off)

Hazard ratio is based on unstratified Cox model.

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: 0.692 (95% CI: 0.548, 0.875)) in the overall study population. The median PFS2 was 32.3 months (95% CI: 27.6, 38.3) in the placebo arm and was not reached (95% CI: 39.4, NE) in the Kisqali arm. 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) [30,31].

Study CLEE011F2301 (MONALEESA-3)

Kisqali was evaluated in a randomized double-blind, placebo controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced breast cancer who have received no or only one line of prior endocrine treatment [17].

A total of 726 patients were randomized in a 2:1 ratio to receive either Kisqali 600 mg and fulvestrant (n=484) or placebo and fulvestrant (n=242) stratified according to the presence of liver and/or lung metastases [Yes (n=351 (48.3%)) versus No (n=375 (51.7%))], prior endocrine therapy [A (n=354 (48.8%)) vs B (n=372 (51.2%)] 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. Demographics and baseline disease

characteristics were balanced and comparable between study arms. Kisqali 600 mg or placebo was given orally daily for 21 consecutive days followed by 7 days off treatment in combination with fulvestrant 500 mg administered intramuscularly on Cycle 1, Day 1, Cycle 1, Day 15, Cycle 2, Day 1 and every 28 days thereafter [17].

Patients enrolled in this study had a median age of 63 years (range 31 to 89). 46.7% of patients were aged 65 years and older, including 13.8% patients aged 75 years and older. The patients included were Caucasian (85.3%), Asian (8.7%) or 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 whom 19.1 % of patients had *de novo* metastatic disease). 42.7% of patients had received chemotherapy in the adjuvant vs 13.1% in the neo-adjuvant setting and 58.5% had received endocrine therapy in the adjuvant vs 1.4% in the neoadjuvant setting. Prior to study entry 21.2% of patients had bone-only disease and 60.5% of patients had visceral disease. Demographics and baseline disease characteristics were balanced and comparable between study arms [17].

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 [17].

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 4.1×10^{-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. Kaplan-Meier curve and Forest Plot for PFS are provided in Figures 12-12 and 12-13, respectively [17].

Figure 12-12   **MONALEESA-3 (F2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (03-Nov-17 cut-off)**

Figure 12-13   **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	137/12.6
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	136/12.6
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	168/16.6	167	111/11.2
No	0.479 (0.310, 0.740)	140	42/NE	74	40/16.5

Ribociclib Better   Placebo Better
Hazard ratio (Ribociclib/Placebo) and 95% CI

Forest plot of hazard ratios by subgroup.

	Hazard ratio (95% CI)	Ribociclib + fulvestrant N	No. of events / Median	Placebo + fulvestrant N	No. of events / Median
Number of metastasis sites		309	126/25.0	148	83/14.7
<3	0.586 (0.447, 0.768)				
>=3	0.621 (0.441, 0.874)	175	84/18.7	82	50/10.5
Previous chemotherapy					
Yes	0.582 (0.444, 0.764)	265	136/17.9	128	80/10.5
No	0.581 (0.414, 0.817)	219	74/NE	115	43/10.0
Disease setting of last therapy					
(neo)-adjuvant	0.648 (0.500, 0.840)	264	132/17.9	153	103/11.1
Metastatic	0.509 (0.316, 0.821)	111	51/18.0	49	27/11.4
Disease free interval					
<=12 months	0.682 (0.248, 1.876)	22	13/11.3	8	7/7.4
>12 months	0.605 (0.480, 0.763)	365	172/18.1	190	120/11.4
De Novo	0.567 (0.307, 1.046)	97	25/NE	42	10/NE
ECOG performance status					
0	0.559 (0.427, 0.733)	310	126/21.3	155	89/14.7
1	0.633 (0.450, 0.890)	173	83/18.5	69	39/11.0

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

Forest plot — Hazard ratio (Ribociclib/Placebo) and 95% CI. Ribociclib Better / Placebo Better.

Subgroup	Hazard ratio (95% CI)	N	Ribociclib + Fulvestrant No. of events / Median	N	Placebo + Fulvestrant No. of events / Median
PGR					
+	0.62 (0.479, 0.801)	353			
-	0.591 (0.397, 0.882)	113			
ER+PGR					
++	0.615 (0.475, 0.796)	350			
Other	0.551 (0.380, 0.799)	134			
Region					
Asia	1.329 (0.523, 3.379)	40			
Europe and Australia	0.574 (0.449, 0.735)	347			
North America	0.507 (0.295, 0.873)	69			
Other	0.487 (0.115, 2.054)	22			
Bone lesion only					
Yes	0.379 (0.234, 0.613)	103			
No	0.658 (0.519, 0.833)	381			
PIK3CA					
mutant	0.741 (0.512, 1.074)	134			
wild type	0.592 (0.444, 0.790)	290			

	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

	Hazard ratio (95% CI)	Ribociclib + Fulvestrant		Placebo + Fulvestrant	
		N	No. of events / Median	N	No. of events / Median
CCND1 mRNA by Nanostring					
<= median (8.1)	0.631 (0.453, 0.880)	175	83 / 18.6	91	62/11.2
> median (8.1)	0.713 (0.494, 1.028)	184	81 / 19.4	81	45/14.9
CDKN2A mRNA by Nanostring					
<= median (0.1)	0.527 (0.370, 0.751)	177	73/20.6	89	56 / 11.0
> median (0.1)	0.802 (0.567, 1.136)	182	91/16.4	83	51 / 14.5
ESR1 mRNA by Nanostring					
<= median (6.3)	0.544 (0.386, 0.765)	180	85/19.1	86	58/10.8
> median (6.3)	0.802 (0.560, 1.149)	179	79/19.4	86	49/14.9
Prior (neo-)adjuvant ET					
ET naive	0.467 (0.300, 0.725)	138	40/NE	74	40/16.5
Progression on/within 12 months of end of ET	0.587 (0.417, 0.826)	138	85/13.2	72	58/9.1
Progression > 12 months after end of ET	0.781 (0.467, 1.306)	98	34/NE	55	26/21.9
2nd line ET	0.517 (0.321, 0.835)	110	51/18.8	40	27/11.4

0.031 0.063 0.125 0.25 0.5 1 2 4 8 16 32

<-- -->
Ribociclib Better   Placebo Better
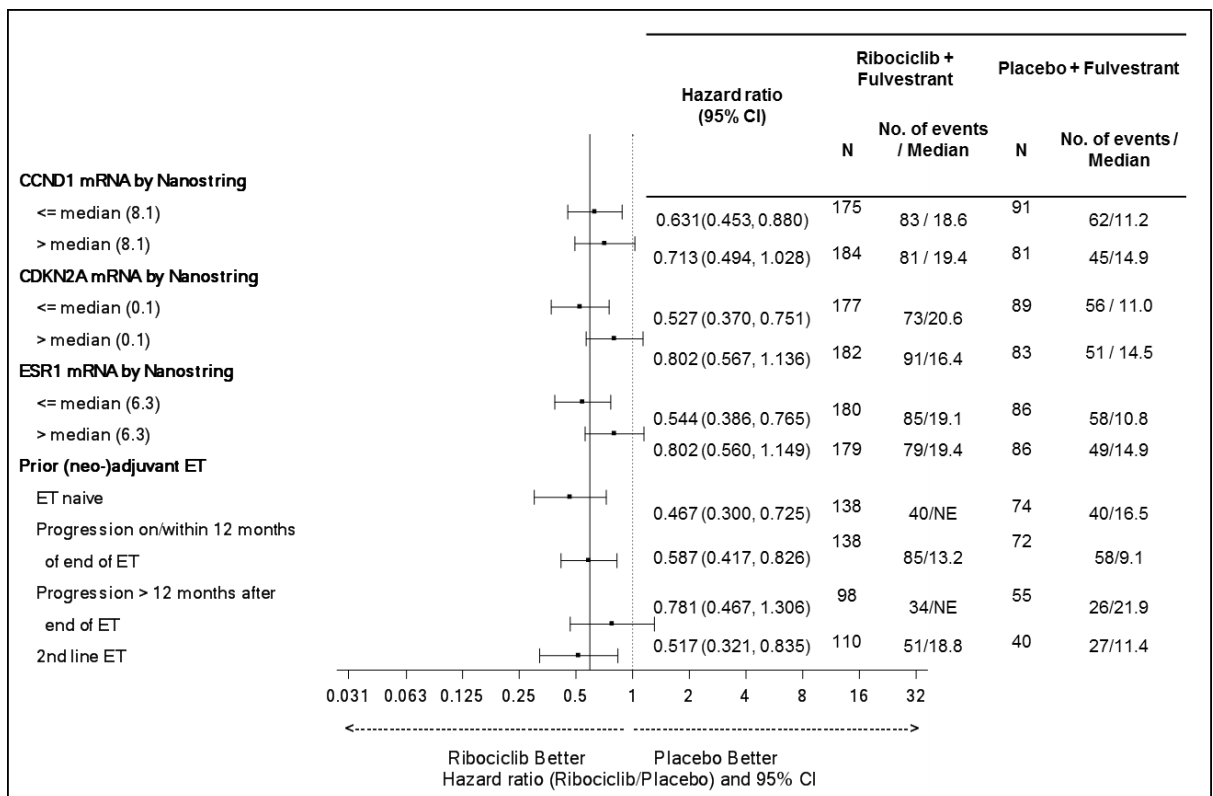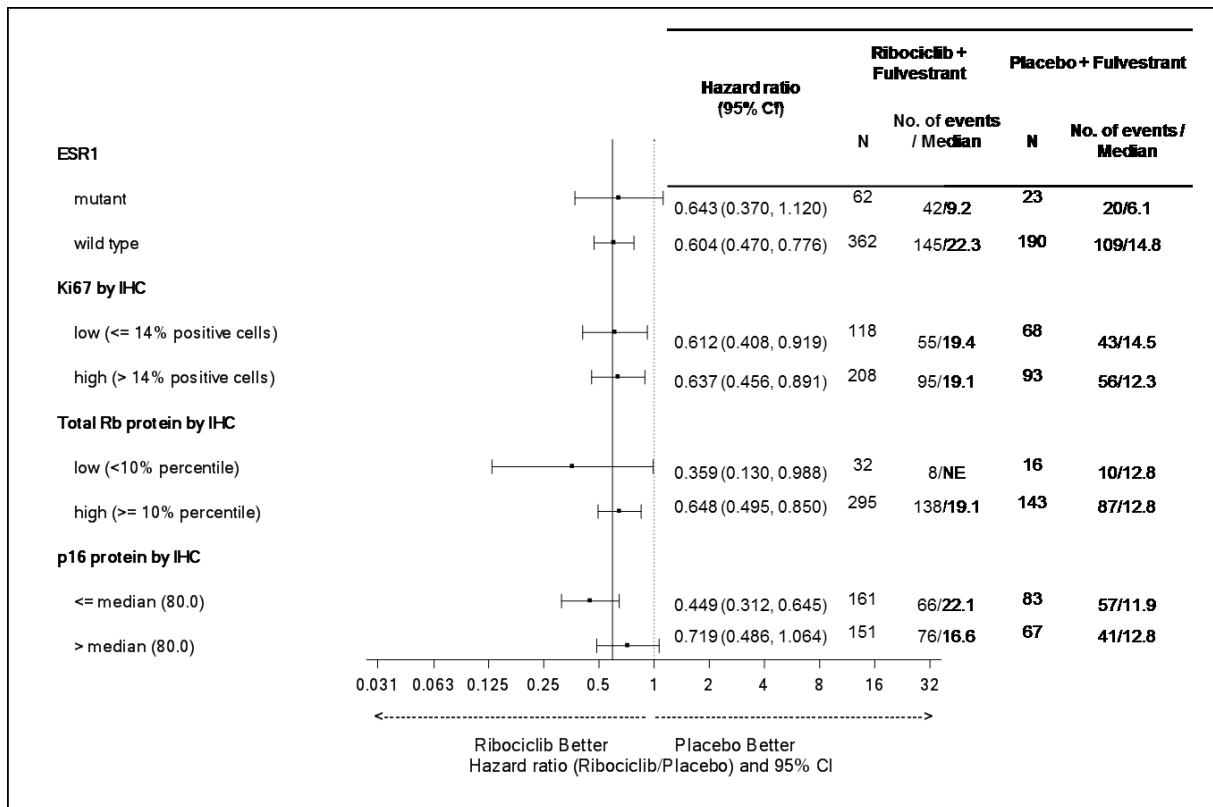Hazard ratio (Ribociclib/Placebo) and 95% CI

[Foot note source: FIR, F2301, Table 4-3 foot note] Previous endocrine therapy (A vs B) is classified as the following using case report form data (CRF):
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 12-9.

Table 12-9   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 [17].

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 12-10 and the Kaplan-Meier curve is provided in Figure 12-14 [34].

Table 12-10   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 12-14   MONALEESA-3 (F2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (03-Jun-19 cut-off)
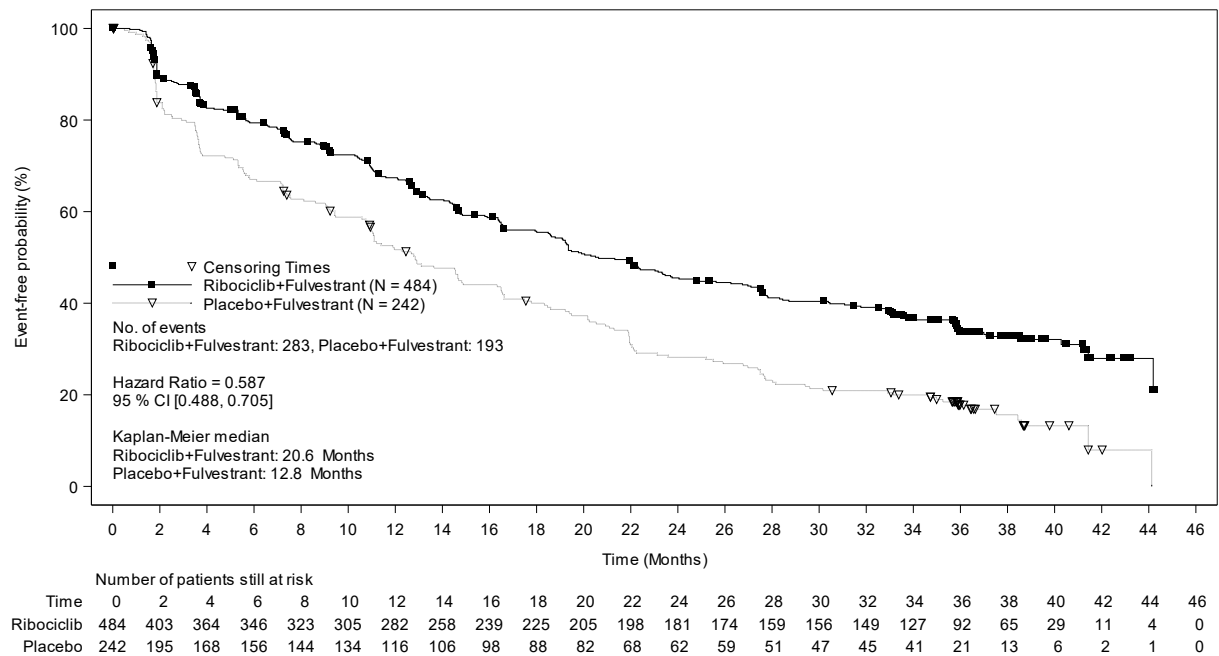
Results were consistent across pre-specified sub-groups of age, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone only metastatic disease. The subgroup analysis based on prior endocrine therapy is presented in Table12-11 [34].

Table 12-11   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 [34].

The OS results from this interim analysis with a 03-Jun-19 cut-off are provided in Table 12-12 and Figure 12-15.

**Table 12-12   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, (NE, 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 12-15   MONALEESA-3 (F2301) Kaplan Meier plot of OS (FAS) (03-Jun-19 cut-off)
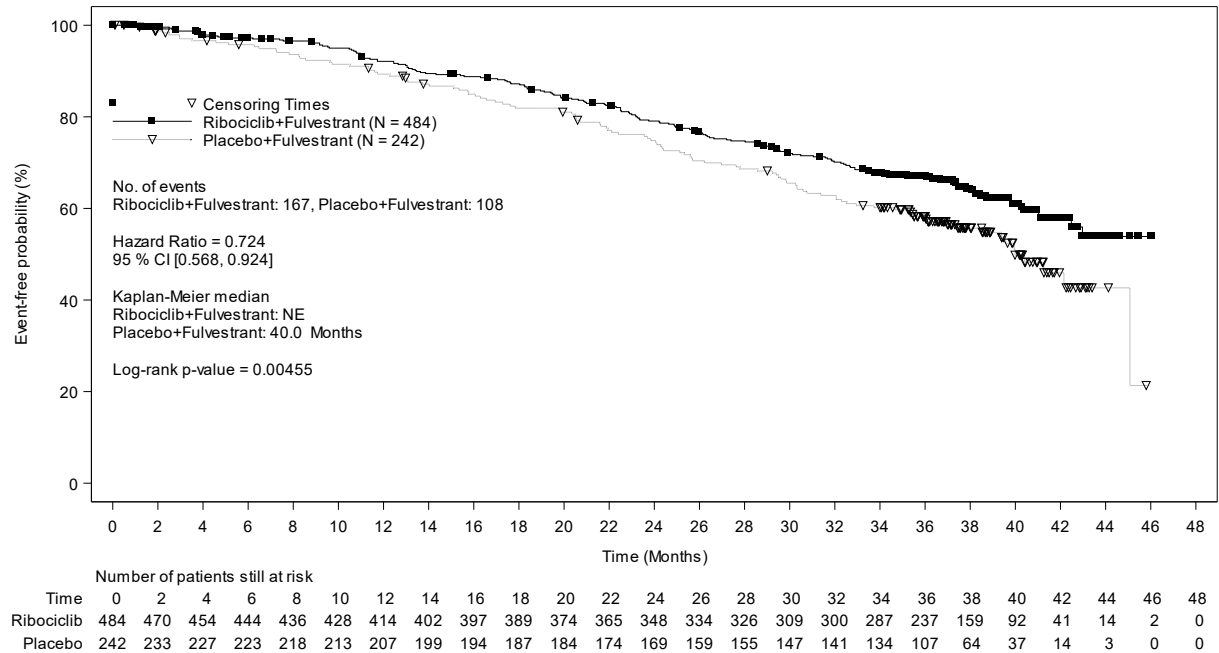
Log-rank test and Cox model are stratified by lung and/or liver metastasis, prior chemotherapy for advanced disease, and endocrine combination partner per IRT

OS results for subgroups analyses are presented in Figures 12-16, 12-17 and 12-18.

Figure 12-16   MONALEESA-3 (F2301) Kaplan Meier plot of OS treatment naïve patients in the metastatic/advanced disease setting (FAS) (03-Jun-19 cut-off)
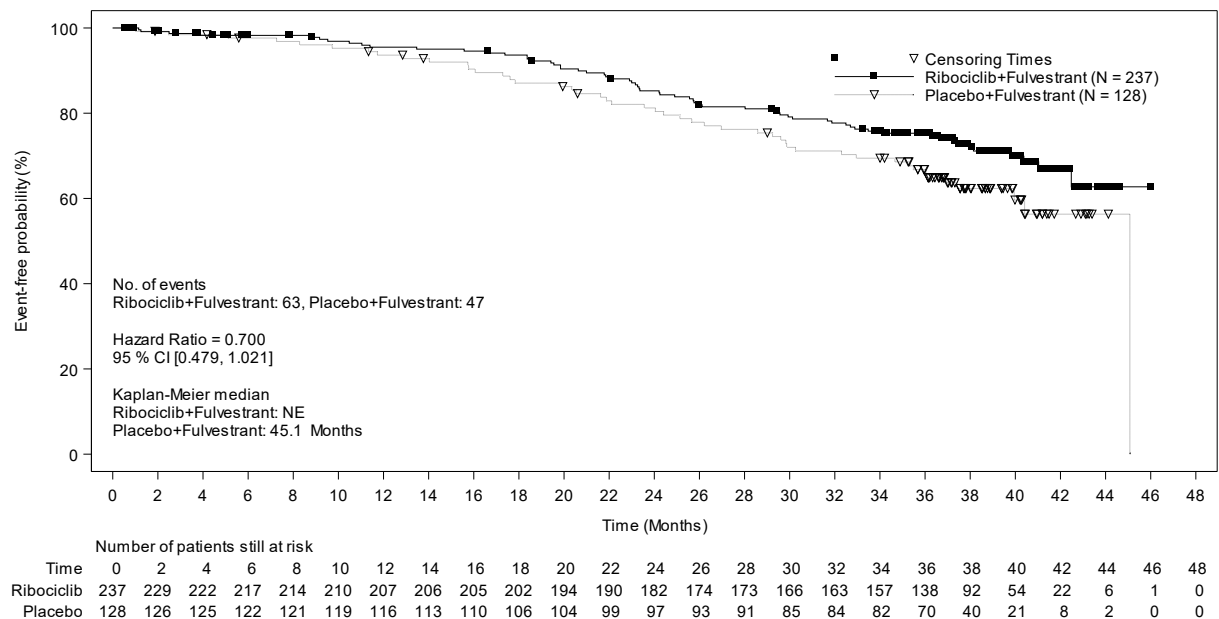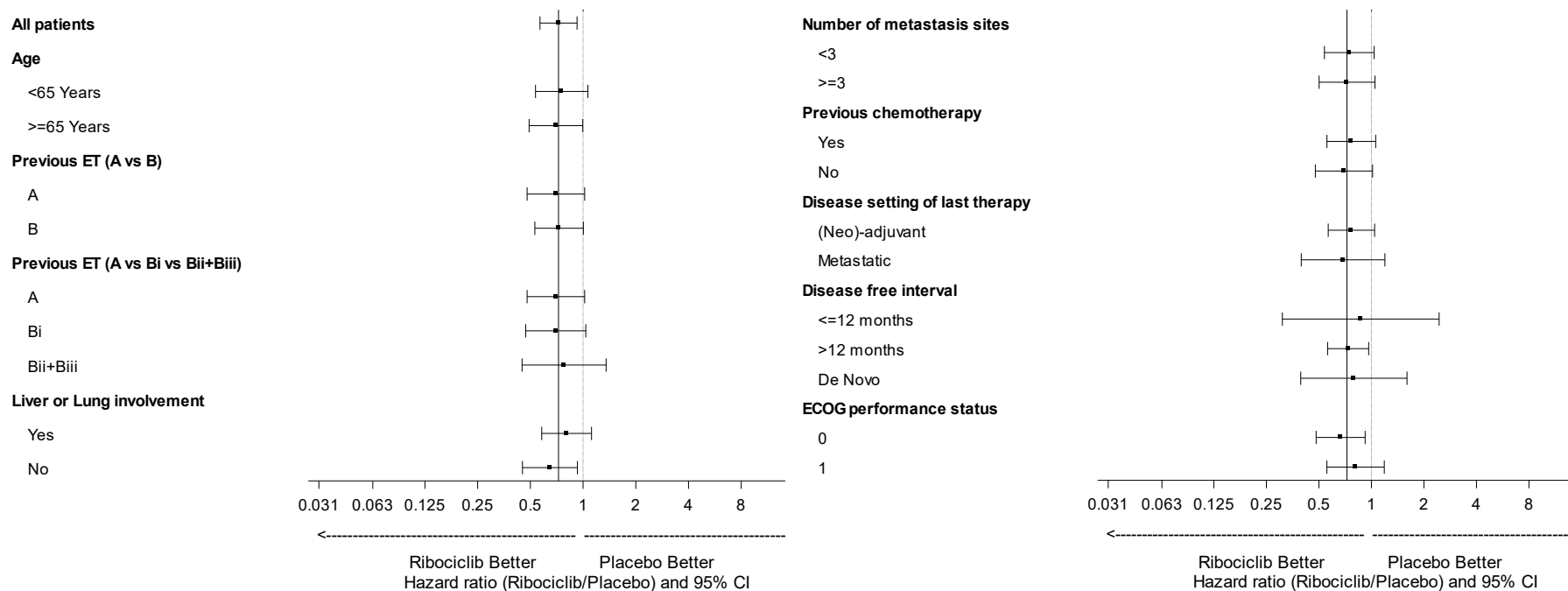
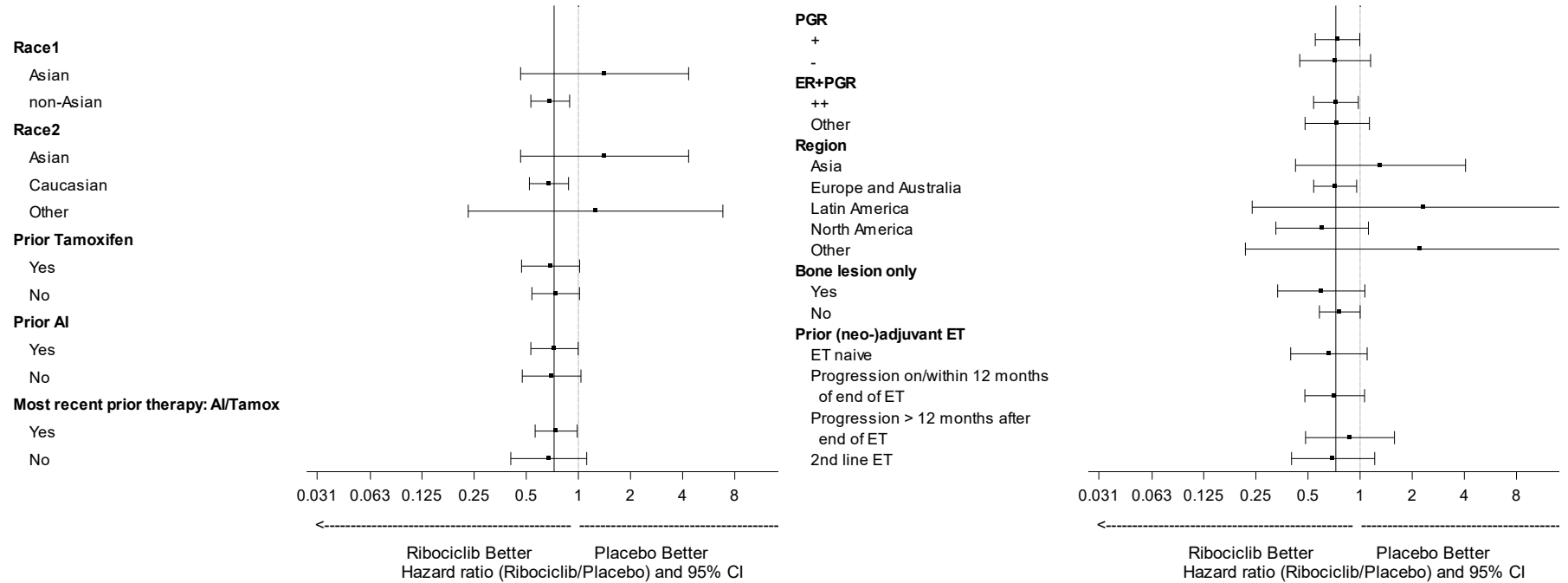*Hazard ratio is based on unstratified Cox model*

Figure 12-17   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)
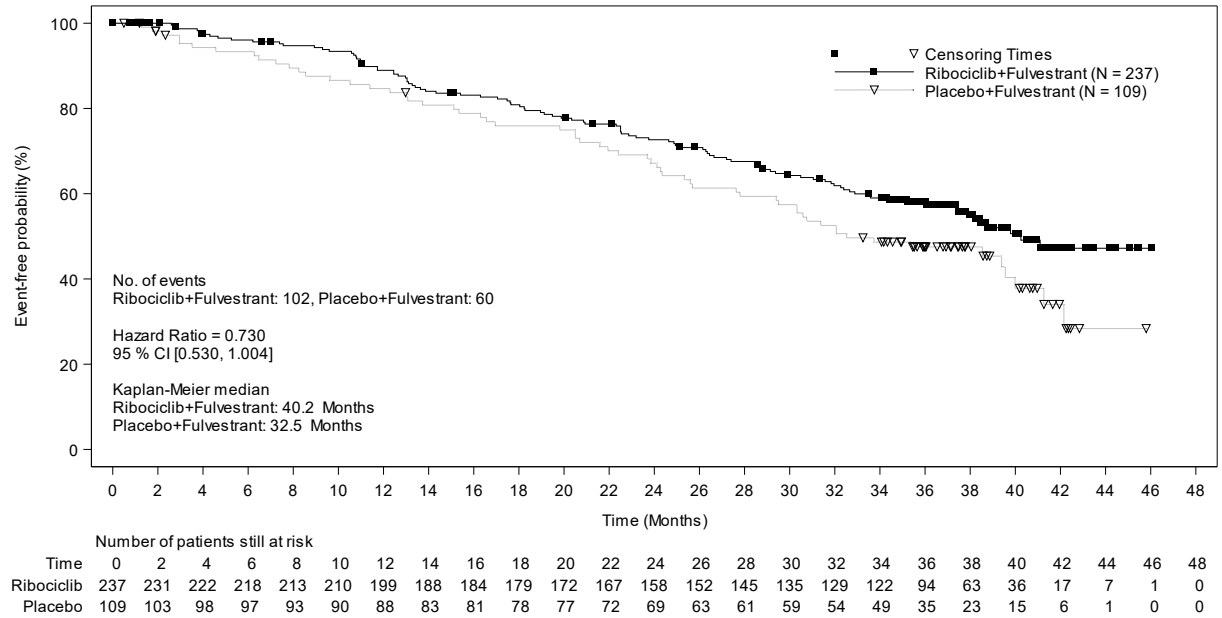
Hazard ratio is based on unstratified Cox model

Figure 12-18   MONALEESA-3 (F2301) Forest plot of OS from sub-group analysis (FAS) (03-Jun-19 cut off)

Race1
  Asian
  non-Asian
Race2
  Asian
  Caucasian
  Other
Prior Tamoxifen
  Yes
  No
Prior AI
  Yes
  No
Most recent prior therapy: AI/Tamox
  Yes
  No

0.031 0.063 0.125 0.25 0.5 1 2 4 8

<-------------------------------- ------------------------------------>
        Ribociclib Better   Placebo Better
        Hazard ratio (Ribociclib/Placebo) and 95% CI

PGR
  +
  -
ER+PGR
  ++
  Other
Region
  Asia
  Europe and Australia
  Latin America
  North America
  Other
Bone lesion only
  Yes
  No
Prior (neo-)adjuvant ET
  ET naive
  Progression on/within 12 months
    of end of ET
  Progression > 12 months after
    end of ET
  2nd line ET

0.031 0.063 0.125 0.25 0.5 1 2 4 8

<-------------------------------- ------------------------------------>
        Ribociclib Better   Placebo Better
        Hazard ratio (Ribociclib/Placebo) and 95% CI

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 [34].

Clinical efficacy in patients with advanced hormone receptor (HR)-positive, HER 2-negative breast cancer (Study CLEE011X2107)

CLEE011X2107 is a phase Ib, multicenter study of the combination of Kisqali and/or alpelisib with letrozole in adult patients with advanced hormone receptor (HR) positive, HER 2-negative breast cancer [8]. The combination of Kisqali 600 mg/day (3-weeks-on and 1 week-off) and letrozole 2.5 mg/day was studied in the dose escalation (previously treated patients (n=19)) and expansion (first line patients (n=28)) of one arm of this study [8].

The data from first-line patients treated with Kisqali 600 mg plus letrozole 2.5 mg demonstrated clinical activity as shown by the ORR and CBR: the ORR was 39.3%, and the CBR was 78.6% [8]. The Kaplan Meier estimate of PFS at 15 months was 57.5% for the expansion phase [8]. Among the 24 patients with measurable disease, the ORR was 45.8% and CBR 79.2% [8].

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 [39,41,42].

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 [41,42].

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) [41,42].

Table 12-13 summarizes the efficacy results in male patients.

Table 12-13   COMPLEEMENT-1 (A2402) 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)*

13   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 [6]. *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 recommended dose of 600 mg. As well, there is potential to induce incidences of PVCs at elevated exposures (approximately 5 fold the anticipated clinical Cmax) [6].

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) [6].

Reproductive toxicity/Fertility

See section 9 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 [6].

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 [6].

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 effects on the uterus/cervix and on the testicular interstitial (Leydig) cell may be related to prolonged hypoprolactinemia secondary to CDK4 inhibition of lactotrophic cell function in the pituitary gland, altering the hypothalamus-pituitary-gonadal axis.

Potential mechanisms for the thyroid findings in males include a rodent-specific microsomal enzyme induction in the liver and/or a dysregulation of the hypothalamus-pituitary-testis-thyroid axis secondary to a persistent on-target hypoprolactinemia.

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.

Considering important differences between rodents and humans with regard to synthesis and role of prolactin, this mode of action is not expected to have consequences in humans [36,37].

14   Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30° C [9].

Information might differ in some countries.

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

15 References

This version of the Core Data Sheet document is without references.