NOVARTIS

KRYXANA™ (ribociclib)
200 mg Film-coated tablets

1 Trade name

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.

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.

3 Indications

Kryxana is (a cyclin-dependent kinase inhibitor, CDKi) indicated for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- letrozole, as an initial endocrine-based therapy in postmenopausal women.
- fulvestrant as an initial endocrine based therapy or after disease progression following endocrine therapy in post-menopausal women.
- non-steroidal aromatase inhibitor in pre- or peri- menopausal women. In pre- or peri-menopausal women, the endocrine therapy should be combined with a luteinizing hormone-releasing hormone (LHRH) agonist.

4 Dosage regimen and administration

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

Dosage regimen

General target population

The recommended dose of Kryxana 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. Kryxana can be taken with or without food (see section 8 Interactions).

The treatment should be continued as long as the patient is deriving clinical benefit from therapy or until unacceptable toxicity occurs.

Kryxana should be used together with 2.5 mg letrozole or another aromatase inhibitor or with 500 mg fulvestrant.

When Kryxana is used in combination with an aromatase inhibitor, the aromatase inhibitor should be taken orally once daily continuously throughout the 28-day cycle. Please refer to the Product Information of the aromatase inhibitor for additional details.

When Kryxana is used in combination with fulvestrant, fulvestrant is administered intramuscularly on days 1, 15 and 29, and once monthly thereafter. Please refer to the Product Information of fulvestrant for additional details.

Treatment of pre- or peri-menopausal women with the approved Kryxana combinations should also include an LHRH agonist in accordance with local clinical practice.

Patients should be encouraged to take their dose at approximately the same time each day, preferably in the morning. If the patients vomits after taking the dose or misses a dose, and additional dose should not be taken that day. The next prescribed dose should be taken at the usual time.

Dose modifications

Management of severe or intolerable adverse drug reactions (ADRs) may require temporary dose interruption, reduction, or discontinuation of Kryxana. If dose reduction is required, the recommended dose reduction guidelines for adverse drug reactions (ADRs) are listed in Table 4-1.

Table 4-1 Dose modification guidelines for adverse drug reactions

	Kryxana	
	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 Kryxana in the management of specific adverse events. 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 Kryxana until recovery to Grade ≤2. Resume Kryxana at the same dose level. If toxicity recurs at Grade 3, interrupt Kryxana dose until recovery to Grade ≤2, then resume Kryxana at the next lower dose level.	Interrupt Kryxana until recovery of neutropenia to Grade ≤2. Resume Kryxana at the next lower dose level.	Interrupt Kryxana until recovery to Grade ≤2. Resume Kryxana at the next lower dose level.
	Perform Complete Blood Counts (CBC) before initiating treatment with Kryxana. After initiating treatment with Kryxana, monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.			
**Grade 3 neutropenia with a single episode of fever >38.3°C or a sustained temperature above 38°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 Kryxana until recovery to ≤baseline Grade, then resume Kryxana at same dose level. If Grade 2 recurs, resume Kryxana at next lower dose level. --- Baseline at Grade 2: No dose interruption.	Interrupt Kryxana until recovery to ≤baseline Grade, then resume at next lower dose level. If Grade 3 recurs, discontinue Kryxana.	Discontinue Kryxana

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 Kryxana.
Perform Liver Function Tests (LFTs) before initiating treatment with Kryxana. After initiating treatment with Kryxana, monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated. If Grade ≥2 abnormalities are observed, more frequent monitoring is recommended.	
**Baseline = prior to treatment initiation.* *Grading according to CTCAE Version 4.03 CTCAE=Common Terminology Criteria for Adverse Events.*	

Table 4-4 Dose modification and management for QT prolongation

ECGs with QTcF >480 ms	1. Interrupt the Kryxana dose 2. If QTcF interval prolongation resolves to <481 ms, resume Kryxana at the next lower dose level; 3. If QTcF interval ≥481 ms recurs, interrupt the Kryxana dose until QTcFinterval resolves to <481 ms; and then resume Kryxana at next lower dose level
ECGs with QTcF >500 ms	If QTcF interval greater than 500 ms on at least 2 separate ECGs: Interrupt Kryxana until QTcF reaches <481 ms then resume Kryxana 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 Kryxana.
Assess ECG prior to initiation of treatment. After initiating treatment with Kryxana, 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.	

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 medical therapy and monitor as clinically indicated.	Interrupt Kryxana until recovery to Grade ≤1, then resume Kryxana at the next lower dose level*.	Discontinue Kryxana

Grading according to CTCAE Version 4.03.
** An individualized benefit-risk assessment should be performed when considering resuming Kryxana*
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 Kryxana dose until recovery to Grade ≤1, then resume Kryxana at the same dose level. If Grade 3 recurs, resume Kryxana at the next lower dose level.	Discontinue Kryxana.
**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 Kryxana with strong CYP3A inhibitors

Concomitant use of Kryxana should be avoided with strong CYP3A inhibitors and an alternative concomitant medication should be considered with low potential for CYP3A inhibition. If a strong CYP3A inhibitor must be co-administered, the Kryxana dose should be reduced to 200 mg once daily. If the strong inhibitor is discontinued, the Kryxana 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. Kryxana has not been studied in breast cancer patients with severe renal impairment (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). A dose adjustment is required in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) and the starting dose of 400 mg is recommended. Kryxana has not been studied in breast cancer patients with moderate and severe hepatic impairment (see section 11 Clinical pharmacology).

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

Pediatric patients

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

Geriatric patients (65 years of age or older)

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

Method of administration

Kryxana should be taken orally once daily at the same time every day, preferably in the morning, with or without food. If the patient vomits after taking the dose or misses a dose, an additional dose should not be taken that day. The next prescribed dose should be taken at the usual time. Kryxana 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.

5 Contraindications

Kryxana 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 Kryxana plus letrozole in phase III clinical study.

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 ≥3 (to normalization or Grade <3) was 12 days in the Kryxana plus any combination treatment group. Severity of neutropenia is concentration dependent. Febrile neutropenia was reported in 1.7% of patients exposed to Kryxana in the phase III clinical studies. 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 Kryxana. CBC should be monitored every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles then as clinically indicated.

Based on the severity of the neutropenia, Kryxana 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 Kryxana dose adjustment is required. In patients who develop Grade 3 neutropenia without fever, the Kryxana dose should be interrupted until recovery to Grade ≤2 and then Kryxana should be resumed at the same dose level. If Grade 3 neutropenia without fever recurs, Kryxana dose should be interrupted until recovery, then Kryxana 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, Kryxana dose should be interrupted until recovery to Grade ≤2, then Kryxana should be resumed at the next lower dose level.

Hepatobiliary toxicity

In the phase III clinical study, increases in transaminases were observed.

Grade 3 or 4 increases in ALT (11.2% vs. 1.7%) and AST (7.8% vs. 2.1%) were reported in the Kryxana 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 Kryxana plus any combination treatment and placebo plus any combination treatment arms respectively.

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

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 level recovered to normal within 154 days; and 2 patients in Study F2301, whose level recovered to normal within 121 and 532 days, respectively, after discontinuation of Kryxana. There were no such cases reported in Study E2301).

LFTs should be performed before initiating therapy with Kryxana. The LFTs should be monitored every 2 weeks for first 2 cycles, at the beginning of each of the subsequent 4 cycles, then as clinically indicated.

Based on the severity of the transaminase elevations, Kryxana 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 increase in total bilirubin (TB) above 2 x ULN: No Kryxana 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, Kryxana dose should be interrupted until values return to ≤baseline Grade, then Kryxana should be resumed at the same dose level. If Grade 2 recurs, then Kryxana 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 Kryxana dose interruption is required.
- In patients who develop Grade 3 (ALT and/or AST elevations of >5 to 20 x ULN), Kryxana dose should be interrupted until values return to ≤baseline Grade, then Kryxana should be resumed at next lower dose level. If Grade 3 recurs, Kryxana should be discontinued.
- In patients who develop Grade 4 (ALT and/or AST elevations of >20 x ULN), Kryxana 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) increase, 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, Kryxana should be discontinued.

QT interval prolongation

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

In 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 Kryxana plus tamoxifen group (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. An increase of >60 ms from baseline in the QTcF interval was observed in 14/87 (16.1%) of patients receiving Kryxana plus tamoxifen and in 18/245 (7.3%) of patients receiving ribociclib plus an NSAI.

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

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 Kryxana therapy.

Kryxana 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 bradyarrhythmias
- Electrolyte abnormalities

Kryxana 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). Based on the findings in MONALEESA-7 (E2301), Kryxana is not recommended for use in combination with tamoxifen (see section 12 Clinical studies).

Based on the observed QT prolongation during treatment, Kryxana 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 Kryxana should be interrupted.
- If QTcF interval prolongation is resolved to <481 ms, Kryxana should be resumed at the next lower dose level.
- If QTcF interval ≥481 ms recurs, Kryxana dose should be interrupted until QTcF interval resolves to <481 ms, then Kryxana 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 Kryxana should be interrupted.
- If QTcF interval prolongation resolves to <481 ms, Kryxana 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, Kryxana should be permanently discontinued.

Reproductive toxicity

Based on animal findings and its mechanism of action, Kryxana can cause fetal harm when administered to a pregnant woman. Women of reproductive potential should be advised to use effective contraception during therapy with Kryxana and for at least 21 days after the last dose (see section 9 Pregnancy, lactation, females and males of reproductive potential).

Severe cutaneous reactions

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

Interstitial Lung Disease (ILD)/Pneumonitis

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

In the three phase III clinical studies, ILD (any Grade 0.3%, including 0.1% Grade 3) was reported in the Kryxana treated group, with no cases in the placebo treated group. Pneumonitis (any Grade 0.6%, vs 0.4%) was reported in the Kryxana and placebo treated groups, respectively, with no grade 3/4 events in either treatment group. Additional cases of ILD/pneumonitis have been observed with Kryxana in the post-marketing setting (see section 7 Adverse drug reactions).

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 Kryxana should be interrupted until recovery to Grade ≤1, and then Kryxana can be resumed at the next lower dose level. For Grade 3 or 4 ILD/pneumonitis Kryxana should be permanently discontinued (see section 4 Dosage regimen and administration).

Soya lecithin

Kryxana contains soya lecithin. Patients who are hypersensitive to peanut or soya should not take Kryxana.

7 Adverse drug reactions

Summary of the safety profile

The overall safety profile of Kryxana reported below is based on the pooled data set of 1065 patients who received Kryxana in combination with endocrine therapy (N=582 in combination with an aromatase inhibitor and N=483 in combination with fulvestrant) in double-blind, placebo-controlled phase III clinical studies (MONALEESA-2, MONALEESA-7-NSAI arm, MONALEESA-3) in HR-positive, HER2-negative advanced or metastatic breast cancer. The median duration of exposure to study treatment across the pooled phase III studies data set was 19.2 months with 61.7% patients exposed for ≥12 months.

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

In the pooled analysis of three phase III studies, on-treatment deathswere reported in 22 patients (2.1%) treated with Kryxana 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 Kryxana 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 hypokalemia and Grade 2 QT prolongation that improved to Grade 1 on the same day, both reported 10 days before the event) 1 (0.1%).

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

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

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 (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

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

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

Adverse drug reactions	Kryxana N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kryxana N=1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
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
Hypophosphatemia	35 (3.3)	12 (1.5)	22 (2.1)	7 (0.9)	Common
Nervous system disorders					
Headache	290 (27.2)	191 (23.3)	7 (0.7)	5 (0.6)	Very common
Dizziness	149 (14.0)	93 (11.4)	2 (0.2)	1 (0.1)	Very common
Vertigo	64 (6.0)	14 (1.7)	2 (0.2)	0	Common
Cardiac disorders					
Syncope	25 (2.3)	13 (1.6)	18 (1.7)	8 (1.0)	Common
Respiratory, thoracic and mediastinal disorders					
Cough	258 (24.2)	152 (18.6)	0	0	Very common
Dyspnoea	155 (14.6)	95 (11.6)	20 (1.9)	8 (1.0)	Very common
Musculoskeletal and connective tissue disorders					
Back pain	256 (24.0)	180 (22.0)	23.0 (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

Adverse drug reactions	Kryxana N=1065 n (%) All Grades	Placebo N=818 n (%) All Grades	Kryxana N=1065 n (%) Grades 3/4	Placebo N=818 n (%) Grades 3/4	Frequency category All Grades
Skin and subcutaneous tissue disorders					
Alopecia	268(25.2)	102 (12.5)	0	0	Very common
Rash[4]	253 (23.8)	81 (9.9)	10 (0.9)	1 (0.1)	Very common
Pruritus	197 (18.5)	57 (7.0)	5 (0.5)	0	Very common
Dry skin	96 (9.0)	23 (2.8)	0	0	Common
Erythema	55 (5.2)	13 (1.6)	2 (0.2)	1 (0.1)	Common
Vitiligo	30 (2.8)	0	1 (0.1)	0	Common
General disorders and administration site conditions					
Fatigue	373 (35.0)	263 (32.2)	23 (2.2)	5 (0.6)	Very common
Peripheral oedema	171 (16.1)	83 (10.1)	2 (0.2)	0	Very common
Pyrexia	168 (15.8)	60 (7.3)	5 (0.5)	1 (0.1)	Very common
Asthenia	161 (15.1)	108 (13.2)	10 (0.9)	3 (0.4)	Very common
Oropharyngeal pain	87 (8.2)	46 (5.6)	0	0	Common
Dry mouth	83 (7.8)	51 (6.2)	1 (0.1)	0	Common
Investigations					
Abnormal liver function tests[5]	216 (20.3)	89 (10.9)	105 (9.9)	17 (2.1)	Very common
Blood creatinine increased	84 (7.9)	20 (2.4)	7 (0.7)	0	Common
Electrocardiogram QT prolonged	73 (6.9)	14 (1.7)	14 (1.3)	2 (0.2)	Common

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

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

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

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

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

Laboratory abnormalities

Clinically relevant abnormalities of routine haematological or biochemical laboratory values from the data set of 3 pooled phase III studies are presented in Table 7-2.

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

Laboratory abnormalities	Kryxana N=1065 n (%) All Grades	Placebo N=818n (%) All Grades	Kryxana 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
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 Kryxana 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 theirs 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
Skin and subcutaneous tissue disorders
Toxic epidermal necrolysis (TEN)

Description of selected adverse drug reactions

Neutropenia

Neutropenia was most frequently reported by laboratory findings in the phase III studies. Based on its severity, neutropenia was managed by laboratory monitoring, dose interruption and/or dose modification. Treatment discontinuation due to neutropenia was low (0.8%) in patients receiving Kryxana 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 Kryxana plus any combination arm vs the placebo plus any combination arm (27.3% vs 19.6%, respectively), with more Grade 3/4 AEs reported in the patients treated with Kryxana plus any combination treatment (13.2% vs. 6.1%, respectively). Dose interruptions and/or adjustments due to hepatotobiliary toxicity events were reported in 12.3% of Kryxana - treated patients, primarily due to ALT increased (7.9%) and/or AST increased (7.3%). Discontinuation of treatment with Kryxana due to abnormal liver function tests, hepatotoxicity occurred in 2.4% and 0.3% of patients, respectively (see section 6 Warnings and precautions).

QT prolongation

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

A central analysis of ECG data (average of triplicate) showed 55 patients (5.2%) and 12 patients (1.5%) with at least one post-baseline QTcF interval >480 m sec for the Kryxana treatment arm and the placebo arm, respectively. Among the patients who had QTcF interval prolongation of >480 ms, the median time to onset was 15 days regardless of the combination and these changes were reversible with dose interruption and/or dose adjustment (see sections 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*. 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. Concomitant use of strong CYP3A inhibitors, including but not limited to clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir, ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, and voriconazole (see section 6 Warnings and precautions) should be avoided. Alternative concomitant medications with low potential to inhibit CYP3A should be considered and patients should be monitored for ADRs *(*see sections 4 Dosage regimen and administration, 6 Warnings and precautions and 11 Clinical Pharmacology).

If co-administration of Kryxana with a strong CYP3A inhibitor cannot be avoided, Kryxana dose should be reduced to 200 mg. However, there are no clinical data with this dose adjustment (see section 4 Dosage regimen and administration). If the strong inhibitor is discontinued, the Kryxana 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 Kryxana-related toxicity, dose should be modified (see section 4 Dosage regimen and administration) or treatment should be interrupted until toxicity is resolved *(*see sections 4 Dosage regimen and administration and 11 Clinical Pharmacology)

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

Medicinal products that may decrease ribociclib plasma concentrations

Co-administration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89%. Avoid concomitant use of strong CYP3A inducers, including but not limited to phenytoin, rifampin, carbamazepine and St John's Wort *(Hypericum perforatum)*. An alternate concomitant medication with no or minimal potential to induce CYP3A should be considered (see sections 6 Warnings and precautions and 11 Clinical pharmacology).

Medicinal products that may have their plasma concentrations altered by ribociclib

Co-administration of midazolam (CYP3A4 substrate) with multiple doses of Kryxana (400 mg) increased the midazolam exposure by 280% (3.80-fold) in healthy subjects, compared with administration of midazolam alone. Simulations using physiologically-based PK (PBPK) models suggested that Kryxana given at the clinically relevant dose of 600 mg is expected to increase the midazolam AUC by 5.2-fold. Therefore caution is recommended when Kryxana is administered with CYP3A substrates with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, may need to be reduced as ribociclib has the potential to increase their exposure (see section 11 Clinical pharmacology).

Co-administration of caffeine (CYP1A2 substrate) with multiple doses of Kryxana (400 mg) increased caffeine exposure by 20% (1.20-fold) in healthy subjects, compared with administration of caffeine alone. At the clinically relevant dose of 600 mg, simulations using PBPK models predicted only weak inhibitory effects of ribociclib on CYP1A2 substrates (<2-fold increase in AUC) (see section 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 (see section 11 Clinical pharmacology).

Drug-food interactions

Kryxana 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 Kryxana film-coated tablet with a high-fat, high-calorie meal had no effect on the rate and extent of absorption of ribociclib (C_{max} GMR: 1.00; 90% CI: 0.898, 1.11; AUC_{inf} GMR: 1.06; 90% CI: 1.01, 1.12 (see section 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). Co-administration of Kryxana with medicinal products that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption was not observed in the population pharmacokinetic analysis nor in simulations using PBPK models (see section 11 Clinical pharmacology).

Anticipated interactions

Anti-arrhythmic medicines and other medicinal products that may prolong the QT interval: Co-administration of Kryxana 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. Kryxana is not recommended for use in combination with tamoxifen (see section 6 Warnings and precautions).

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk summary

Pregnancy status should be verified prior to starting treatment with Kryxana.

Based on findings from animal studies and the mechanism of action, Kryxana can cause fetal harm when administered to a pregnant woman.

There are no available human data informing the drug-associated risk. In animal reproduction studies, administration of ribociclib to pregnant animals during organogenesis resulted in increased incidences of postimplantation loss and reduced fetal weights in rats and increased incidences of fetal abnormalities in rabbits at exposures 0.6 to 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk of major birth defects is 2-4% and of miscariage is 15-20% of clinically recognized pregnancies in the U.S. general populations.

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.

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.

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.

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.

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. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in nursing infants from Kryxana, 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 Kryxana should not breastfeed for at least 21 days after the last dose.

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.

9.3 Females and males of reproductive potential

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

Pregnancy testing

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

Contraception

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

Infertility

A fertility study in 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). There are no clinical data available regarding the effects of Kryxana on fertility. Based on animal studies, Kryxana may impair fertility in males of reproductive potential.

10 Overdosage

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

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).

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.

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. Additionally, the *in vivo* antitumor activity of ribociclib in combination with fulvestrant was assessed in immune-deficient mice bearing the ZR751 ER+ human breast cancer xenografts. The combination of ribociclib and fulvestrant resulted in complete tumor growth inhibition.

Pharmacodynamics (PD)

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

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

Cardiac electrophysiology

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

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.

Absorption

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

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 (C_{max} GMR: 1.00; 90% CI: 0.898, 1.11; AUC_{inf} GMR: 1.06; 90% CI: 1.01, 1.12) (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.

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.

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

Elimination

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

Ribociclib is eliminated mainly via the feces, with a small contribution from the renal route. In 6 healthy male subjects, following a single oral dose of [^{14}C] ribociclib, 91.7% of the total administered radioactive dose was recovered within 21 days; feces was the major route of excretion (69.1%), with 22.6% of the dose recovered in the urine.

Linearity/non-linearity

Ribociclib exhibited slightly over-proportional increases in exposure (C_{max} and AUC) across the dose range of 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.

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.

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. 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).

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 C_{max}; 1.28 for AUC_{inf}) and severe (GMR: 1.32 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment. Based on a population pharmacokinetic analysis that included 160 patients with normal hepatic function and 47 patients with mild hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib, further supporting the findings from the dedicated hepatic impairment study (see section 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.

Geriatric patients

Of 334 patients who received Kryxana in the phase III study (MONALEESA 2, ribocilib plus letrozole arm), 150 patients (44.9%) were ≥65 years of age and 35 patients (10.5%) were ≥75 years of age. Of 483patients who received Kryxana in the phase III study (MONALEESA 3, ribociclib plus fulvestrant arm), 226 patients (46.8%) were ≥65 years of age and 65 patients (13.5%) were ≥75 years of age. No overall differences in safety or effectiveness of Kryxana 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 C_{max} and AUC_{inf} by 1.7-fold and 3.2-fold, respectively, following a single 400 mg ribociclib dose. C_{max} and AUC_{last} for LEQ803 (a prominent metabolite of ribociclib, accounting for less than 10% of parent exposure) decreased by 96% and 98%, respectively. Simulations using PBPK suggested that a moderate CYP3A4 inhibitor (erythromycin) may increase C_{max} and AUC of ribociclib 400 mg single dose by 1.3-fold and 1.9-fold, respectively (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 C_{max} and AUC_{inf} by 81% and 89%, respectively, following a single 600 mg ribociclib dose. LEQ803 C_{max} increased 1.7-fold and AUC_{inf} decreased by 27%, respectively. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease ribociclib single dose C_{max} and AUC by 37% and 60%**,** respectively (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 C_{max} and AUC_{inf} by 2.1-fold and 3.8-fold, respectively. Simulations using PBPK suggested that at a 600 mg ribociclib dose, midazolam C_{max} and AUC may increase 2.4-fold and 5.2-fold, respectively. The effect of multiple doses of ribociclib on caffeine was minimal, with C_{max} decreasing by 10% and AUC_{inf} increasing slightly by 20%. Simulations using PBPK suggested only weak inhibitory effects on CYP1A2 substrates at a 600 mg ribociclib dose (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 (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). Co-administration of ribociclib with medicinal products that elevate the gastric pH was not evaluated in a clinical trial; however, altered ribociclib absorption was not observed in population pharmacokinetic analysis nor in simulations using PBPK models (see sections 4 Dosage regimen and administration and 8 Interactions).

Letrozole: Data from a clinical trial in patients with breast cancer and population PK analysis indicated no drug interaction between ribociclib and letrozole following co-administration of the drugs (see section 8 Interactions).

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

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

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

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

Effect of ribociclib on transporters: *In vitro* evaluations indicated that Kryxana has a low potential to inhibit the activities of the drug transporters P-gp, OATP1B1/B3, OCT1, MATE2K at clinically relevant concentrations. Kryxana may inhibit BCRP, OCT2, MATE1, and human BSEP at clinically relevant concentrations (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 (see section 8 Interactions). Ribociclib is not a substrate for hepatic uptake transporters OATP1B1/1B3 or OCT-1 *in vitro* (see section 8 Interactions).

12 Clinical studies

Study CLEE011A2301 (MONALEESA-2)

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

A total of 668 patients were randomized in a 1:1 ratio to receive either Kryxana 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%)]). Demographics and baseline disease characteristics were balanced and comparable between study arms. Kryxana 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. Patients were not allowed to cross over from placebo to Kryxana during the study or after disease progression.

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

Primary analysis

The primary endpoint for the study was met at the planned interim analysis conducted after observing 80% of the targeted progression-free survival (PFS) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1), based on the investigator assessment in the full population (all randomized patients) and confirmed by a blinder independent central radiological assessment.

The efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kryxana plus letrozole compared to patients receiving placebo plus letrozole in the full analysis set (FAS) (HR = 0.556 with 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 Kryxana plus letrozole. The median PFS was not reached in the Kryxana plus letrozole arm (95% CI: 19.3, NE) at the time of the primary analysis.The median PFS was 14.7 months (95% CI, 13.0, 16.5) for the placebo plus letrozole arm. Results were consistent across the subgroups of age, race, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone only metastasic disease (Figure 12-2).

Progression free survival is summarized in Table 12-1 and the Kaplan-Meier curve for PFS is provided in Figure 12-1. 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). The one-sided stratified log-rank test p-value was 0.002.

Hazard ratios based on a pre-specified subgroup analysis are in favor of the Kryxana 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 boneonly metastasis disease.

Table 12-1 CLEE011A2301 primary efficacy results (PFS) based on investigator radiological assessment (02-Jan-17 cut-off)

	Kryxana 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 Kaplan-Meier plot of PFS based on investigator assessment – Study A2301 (Full analysis set 02-Jan-17 cut-off)

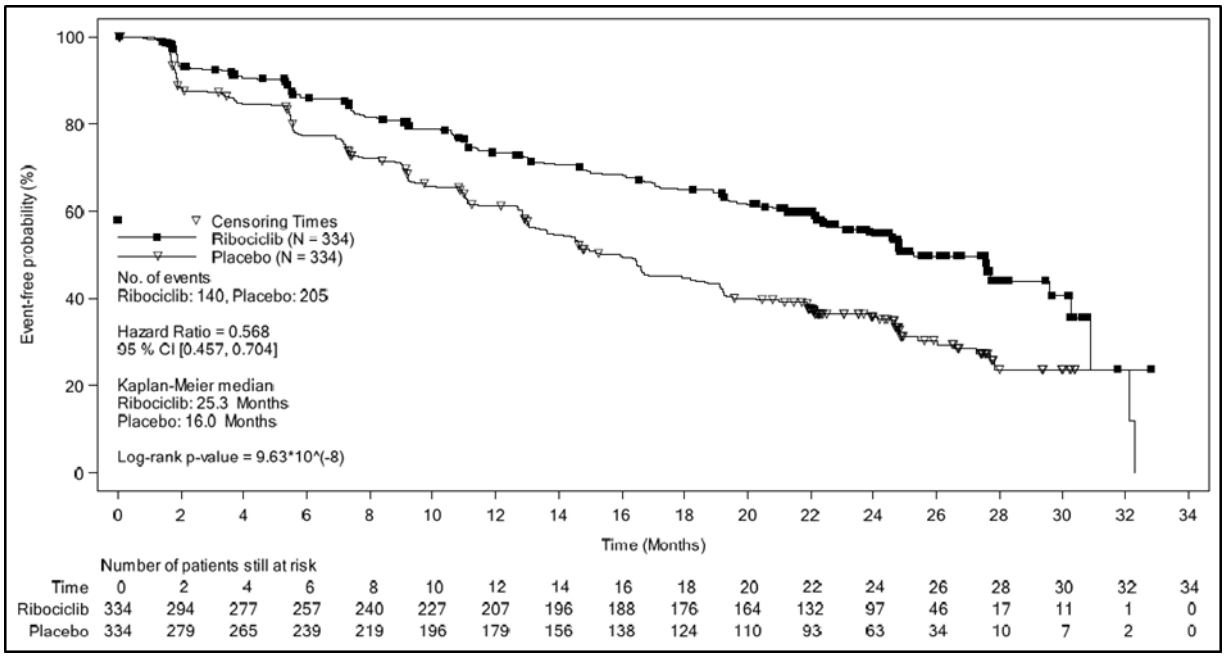
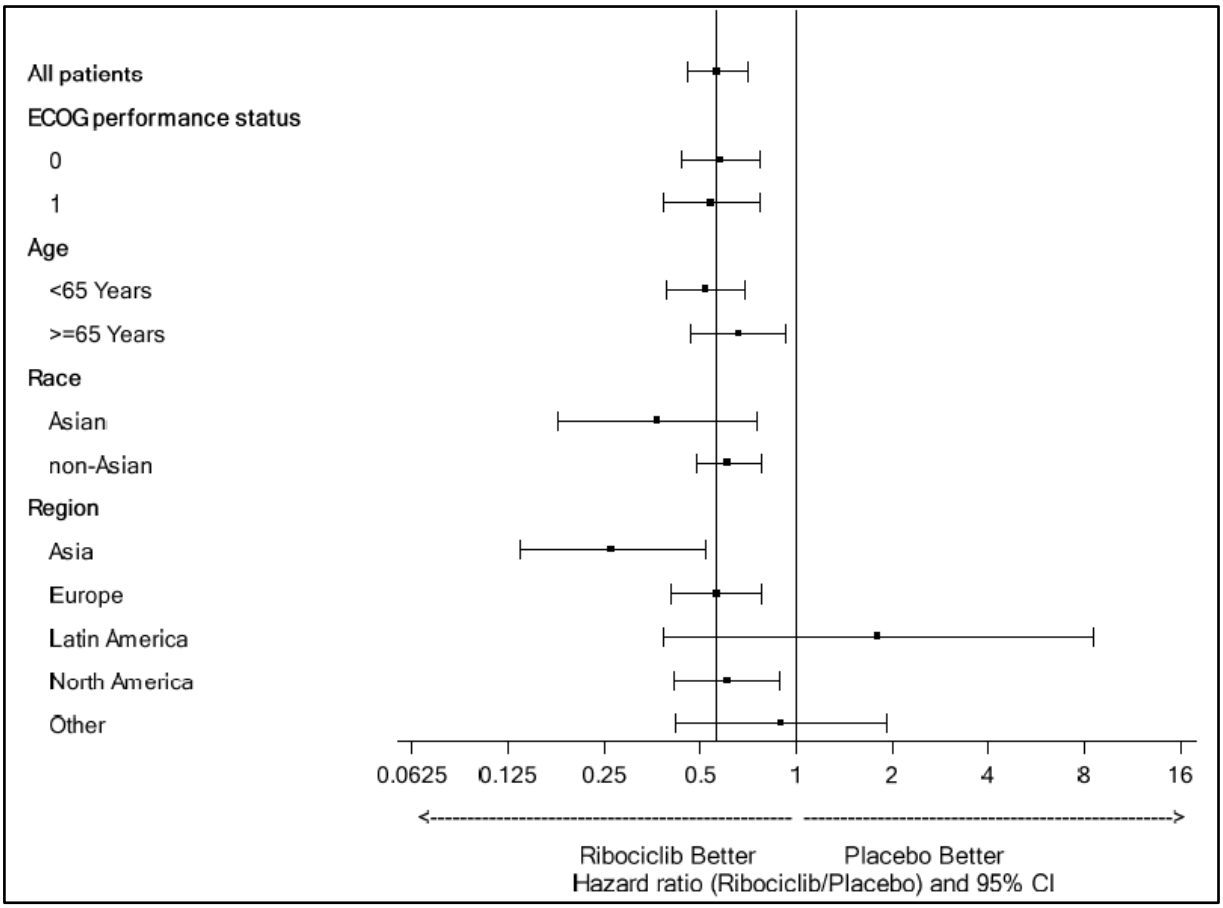
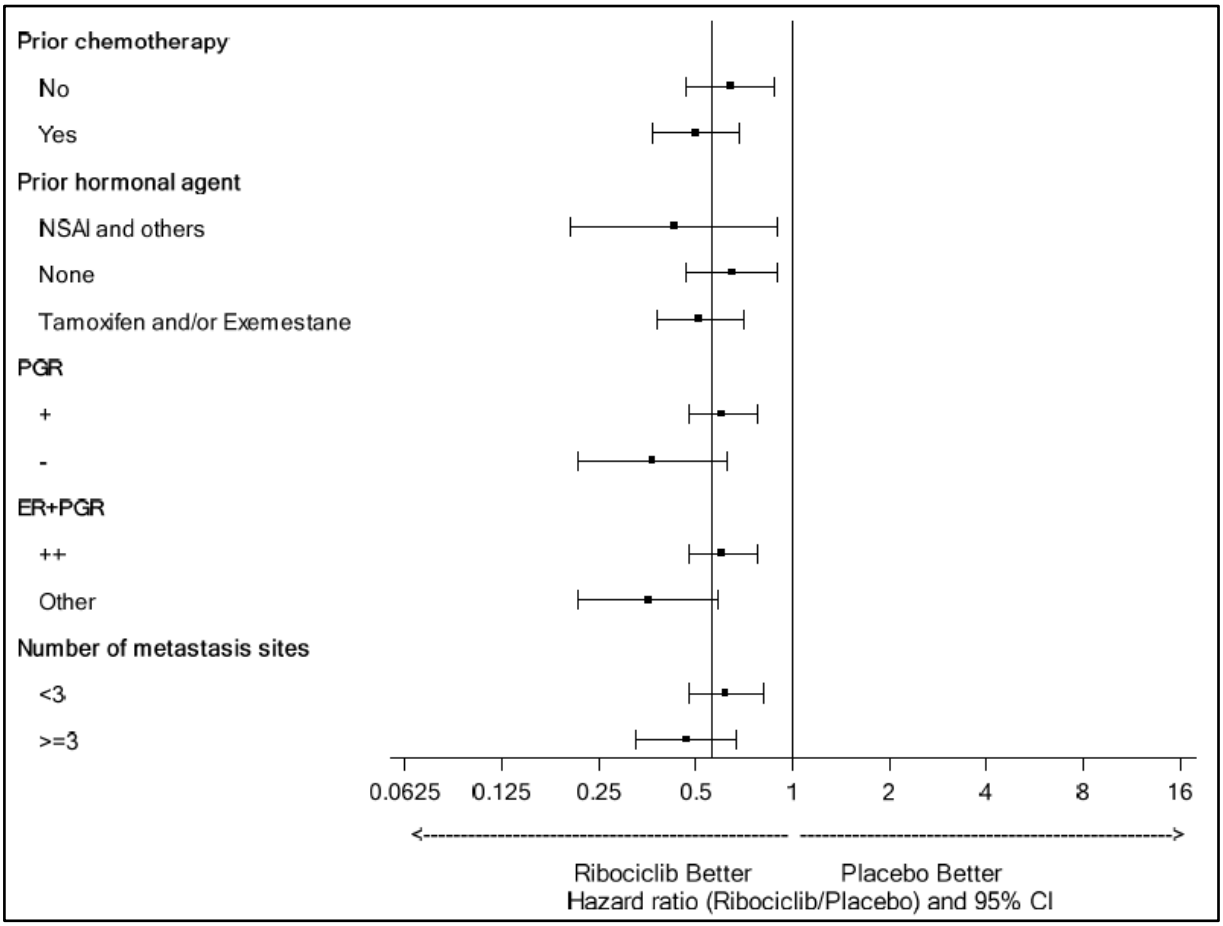
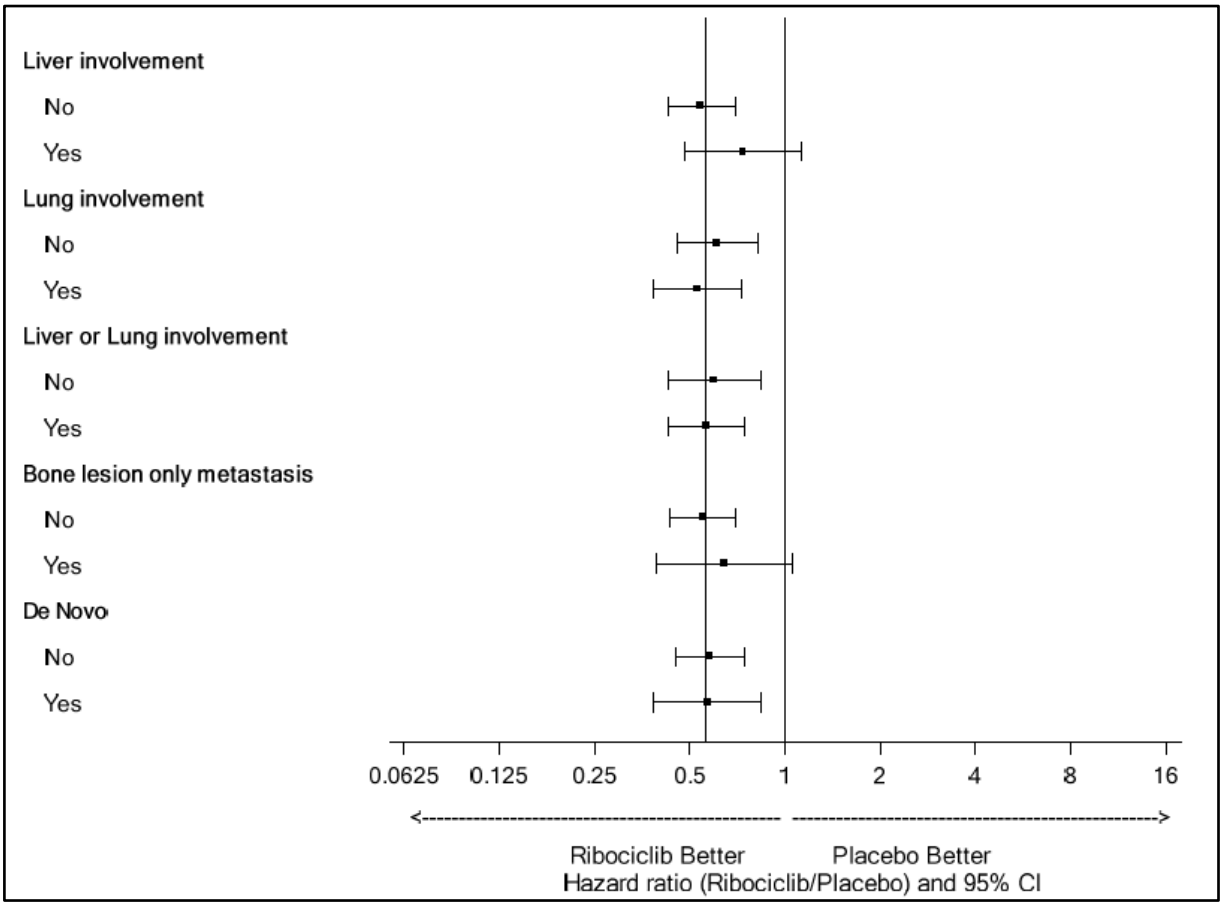
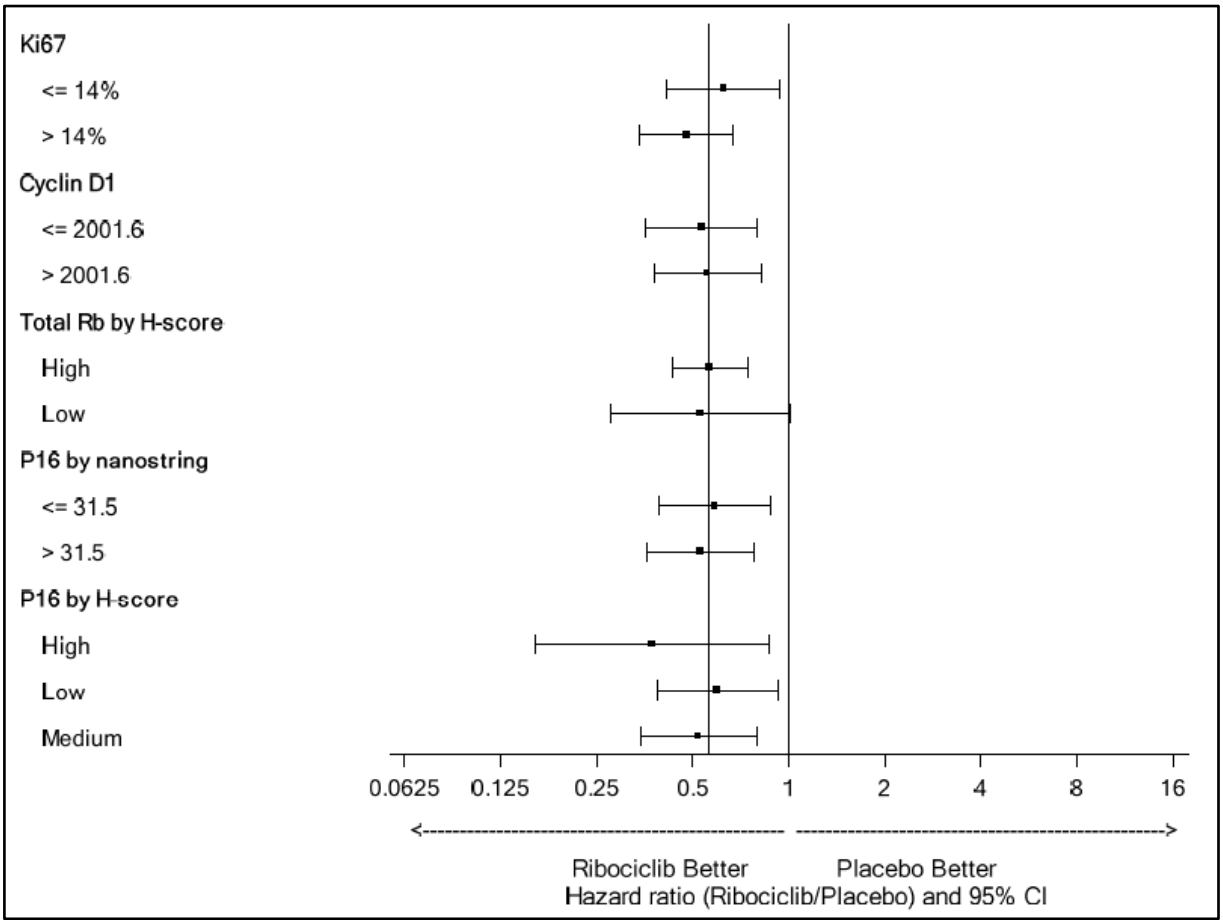


Figure 12-2 Forest plot of PFS based on Investigator review – Study A2301 (Full analysis set) (02-Jan-17 cut-off)




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


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



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

Updated results (02 January 2017 cut-off) for overall response and clinical benefit rates are displayed in Table 12-2.

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

Table 12-2 CLEE011A2301 efficacy results (ORR, CBR) based on investigator assessment (02-Jan-17 cut-off)

Analysis	Kryxana + 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).

OS benefit increased over time, with a 6-year survival rate of 44.2% (38.5, 49.8) for Kryxana vs. 32.0% (26.8, 37.3) for placebo. The median OS was 63.9 months (95% CI: 52.4, 71.0) for the Kryxana 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 Kryxana arm. The exploratory OS results from subgroup analyses demonstrated that the OS benefit was generally consistent across the patient subgroups of prior adjuvant or neoadjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone-only metastatic disease (see Figure 12-6). 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 12-3 and the Kaplan-Meier curve is provided in Figure 12-3.

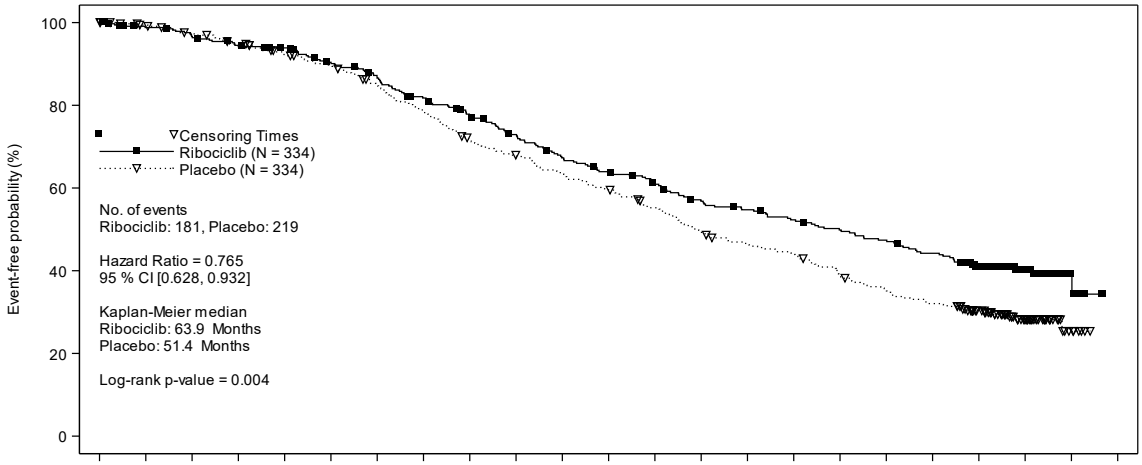
Table 12-3 MONALEESA-2 (A2301) efficacy results (OS) (10-Jun-21 cut-off)

Overall survival, overall study population	Kryxana 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 12-3 MONALEESA-2 (A2301) Kaplan-Meier plot for OS (FAS) (data cutt-off 10-Jun-2021)

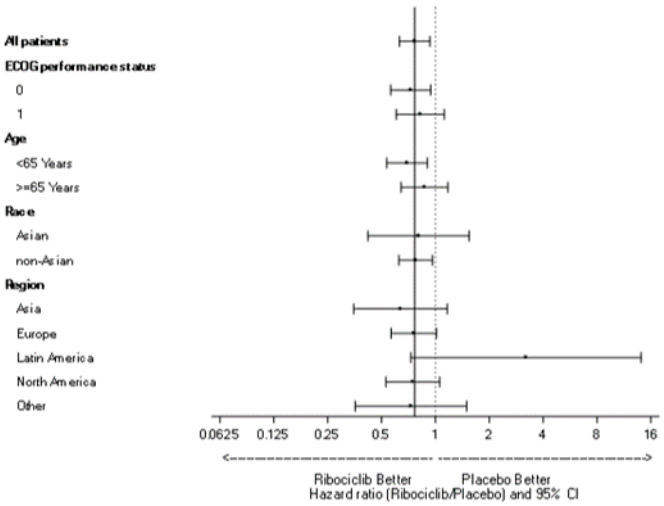


Number of patients still at risk

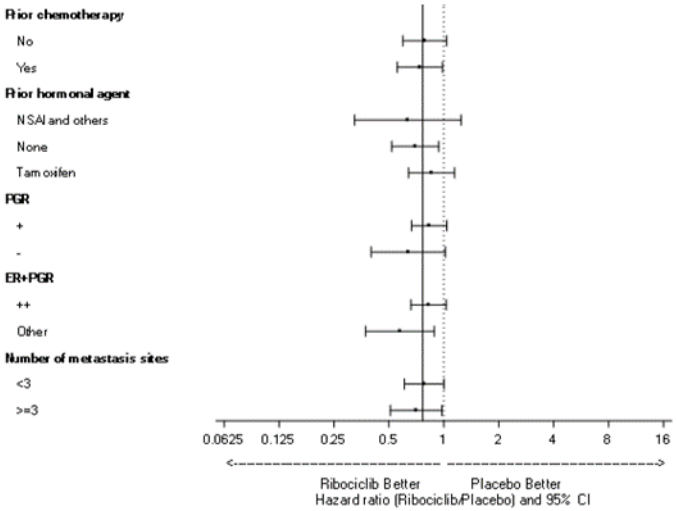
Time	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88
Ribociclib	334	323	315	305	300	284	270	253	237	220	202	191	180	165	158	150	142	135	125	101	48	8	0
Placebo	334	326	316	306	293	283	265	244	222	209	195	183	167	149	139	131	114	104	94	73	38	6	0

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

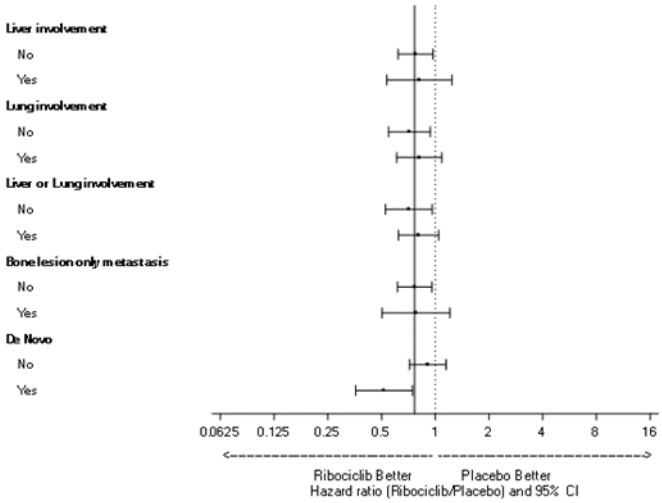
Figure 12-4 MONALEESA-2 (A2301) Forest plot OS from subgroup analysis (FAS) (10-Jun-21 cut off)



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



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



	Hazard ratio (95% CI)	Ribociclib events n/N (%)	Placebo events n/N (%)
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 Kryxana 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 Kryxana arm compared to the placebo arm (HR: 0.742; 95% CI: 0.606, 0.909).

Study CLEE011E2301 (MONALEESA-7)

Kryxana 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 perimenopausal women with hormone receptor (HR)-positive, HER2-negative, advanced breast cancer.

As per study inclusion criteria, pre-menopausal women was defined as an adult female patient (≥18 and <60 y.o.) who had last menstrual period within the last 12 months. If a patient received tamoxifen or toremifene within 14 days before starting the study, or was on treatment induced amenorrhea, the patient's plasma estradiol and follicle stimulating hormone (FSH) must be in the premenopausal range per local normal range. Peri-menopausal status was defined as neither pre- nor post-menopausal.

A total of 672 patients were randomized to receive either Kryxana 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.

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 Kryxana 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 Kryxana during the study or after disease progression. Patients were not allowed to switch between endocrine combination partners.

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. Prior to study entry, of these 672 patients, 14% of patients had received prior chemoterapy for metastatic disease, 32.6% of patients had received chemotherapy in the adjuvant and 18.0% in neo-adjuvant setting; 39.6% had received endocrine therapy in the adjuvant setting and 0.7% in the neoadjuvant setting. In Study E2301 40.2% of patients had *de novo* metastatic disease, 23.7% had bone-only disease, and 56.7% had visceral disease.

Primary analysis

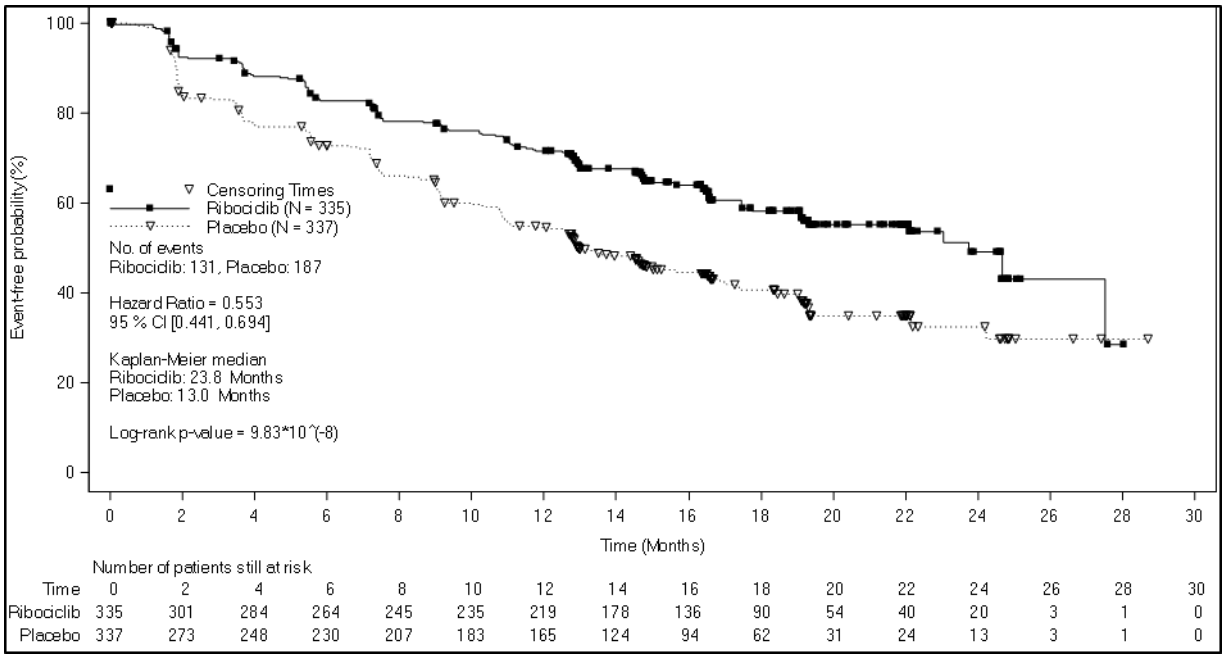
The primary endpoint for the study was met after observing 318 progression-free survival (PFS) events using RECIST v1.1, based on the investigator assessment in the full analysis set (all randomized patients) and confirmed by a blinded independent central radiological assessment of a randomly selected 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.

In the overall study population, the median PFS (95% CI) was 23.8 months (19.2, NE) in the Kryxana plus tamoxifen or NSAI plus goserelin and 13.0 months (11.0, 16.4) in the placebo plus tamoxifen or NSAI plus goserelin [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 12-5. 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).

Overall response rate (ORR) per investigator assessment based on RECISTv1.1 was higher in the Kryxana 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 12-5).

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 Kryxana to tamoxifen or NSAI plus goserelin resulted in delaying time-to-deterioration in the EORTC QLQ-C30 global health scale score compared with placebo plus tamoxifen or NSAI plus goserelin (median not estimable versus 21.2 months; HR: 0.699 [95% CI: 0.533, 0.916]; p=0.004.

Figure 12-5 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 Kryxana or placebo in combination with NSAI plus goserelin, the median PFS (95% CI) was 27.5 months (19.1, NE) in the Kryxana 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 12-3 and the Kaplan-Meier curves for PFS are provided in Figure 12-4. Kryxana is not recommended for use in combination with tamoxifen due to the risk of QTc interval prolongation (see section 6 Warnings and precautions).

Results in the Kryxana 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 12-7).

In the NSAI sub-group, the median time to response (TTR) was not reached in either the Kryxana arm or the placebo arm and the probability of response by 6 months was 34.7% (95% CI: 29.0, 41.1) in the Kryxana 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 Kryxana arm.

In the NSAI sub-group, the median duration of response (DOR) was not reached (95% CI: 18.3 months, NE) in the Kryxana 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 Kryxana arm and 36.4% (95% CI: 25.6, 49.8) in the placebo arm at 12 months.

Table 12-4 MONALEESA-7 (E2301) primary efficacy results (PFS) based on investigator assessment in patients who received NSAI (20-Aug-17 cut-off)

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

CI=confidence interval; N=number of patients; NE = Not estimable.
[a] – PFS based on investigator radiological assessment

Figure 12-6 MONALEESA-7 (E2301) Kaplan-Meier plot of PFS based on investigator assessment in patients who received NSAI (20-Aug-17 cut off)

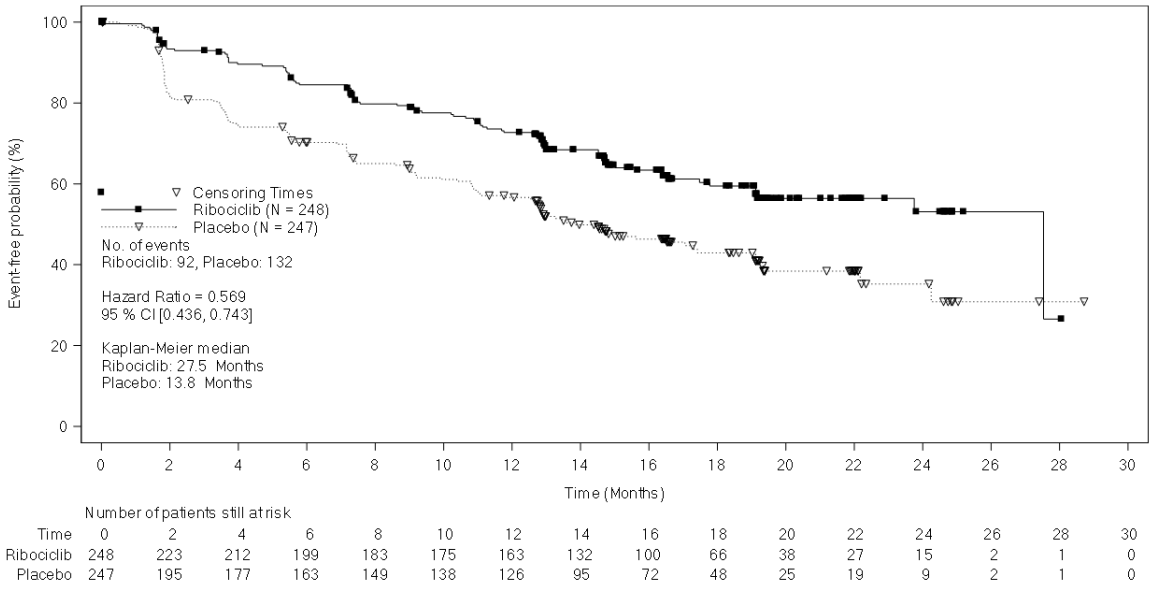


Table 12-5 MONALEESA-7 (E2301) efficacy results (ORR, CBR) based on investigator assessment in patients who received NSAI (20-Aug-17 cut off)

Analysis	Kryxana 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 12-7 MONALEESA-7 (E2301) Forest plot of PFS based on investigator assessment in patients who received NSAI (20-Aug-17 cut off)

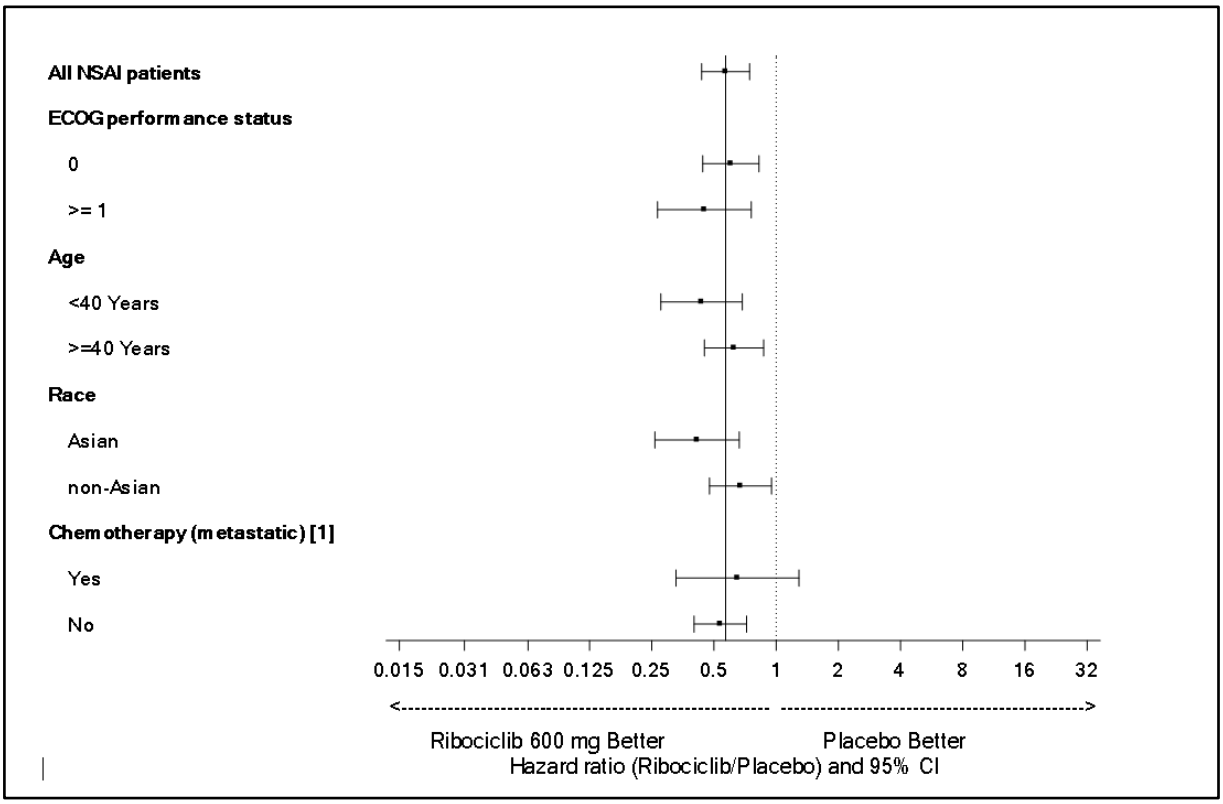


Figure 12-7 MONALEESA-7 (E2301) Forest plot of PFS based on investigator assessment in patients who received NSAI (20-Aug-17 cut off), continued

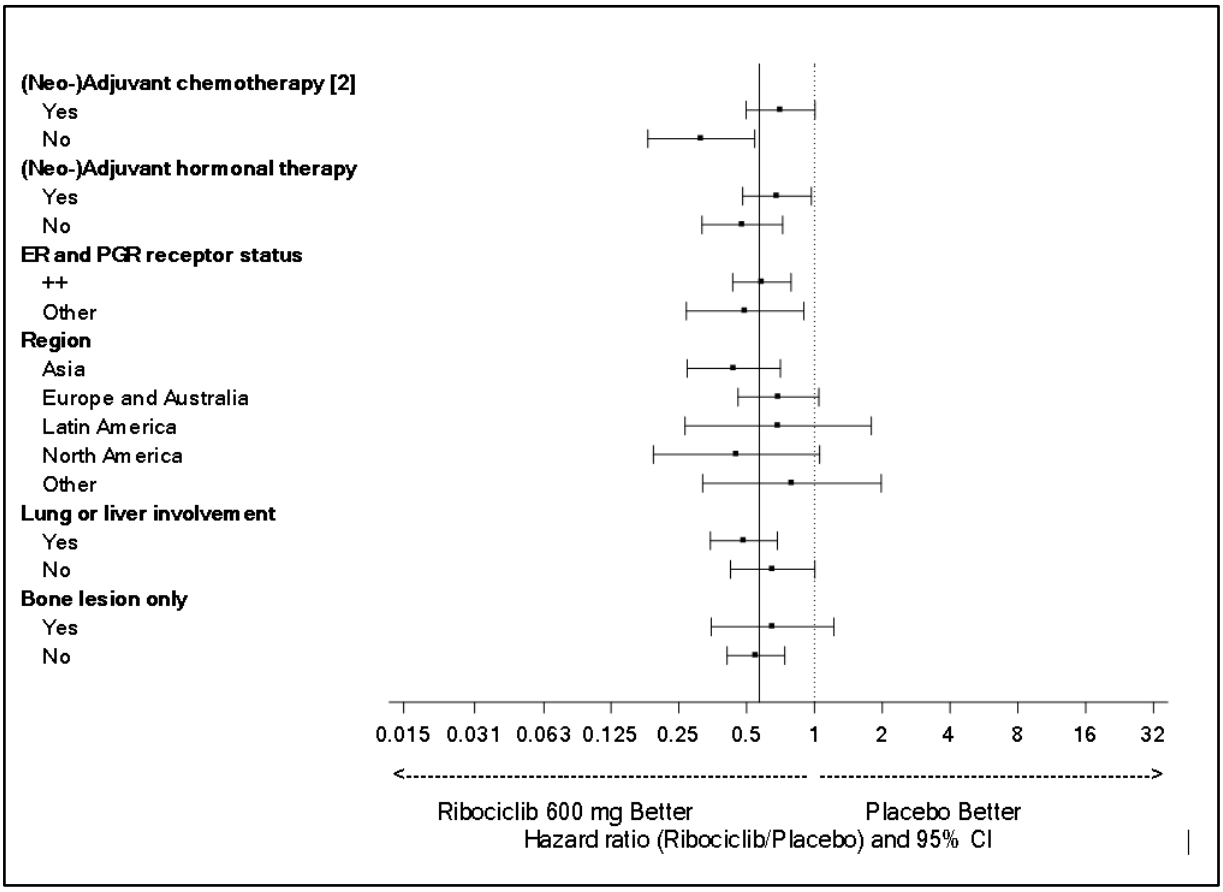


Figure 12-7 MONALEESA-7 (E2301) Forest plot of PFS based on investigator assessment in patients who received NSAI (20-Aug-17 cut off), continued

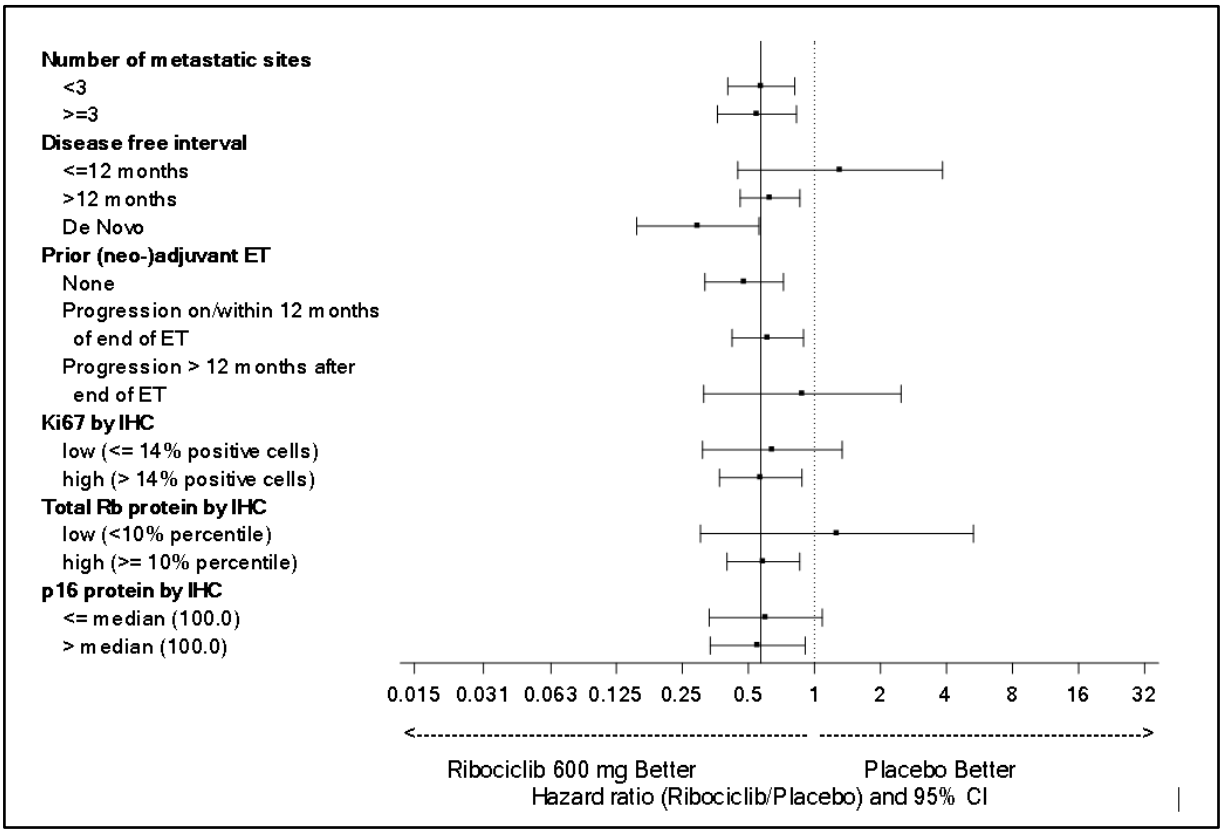
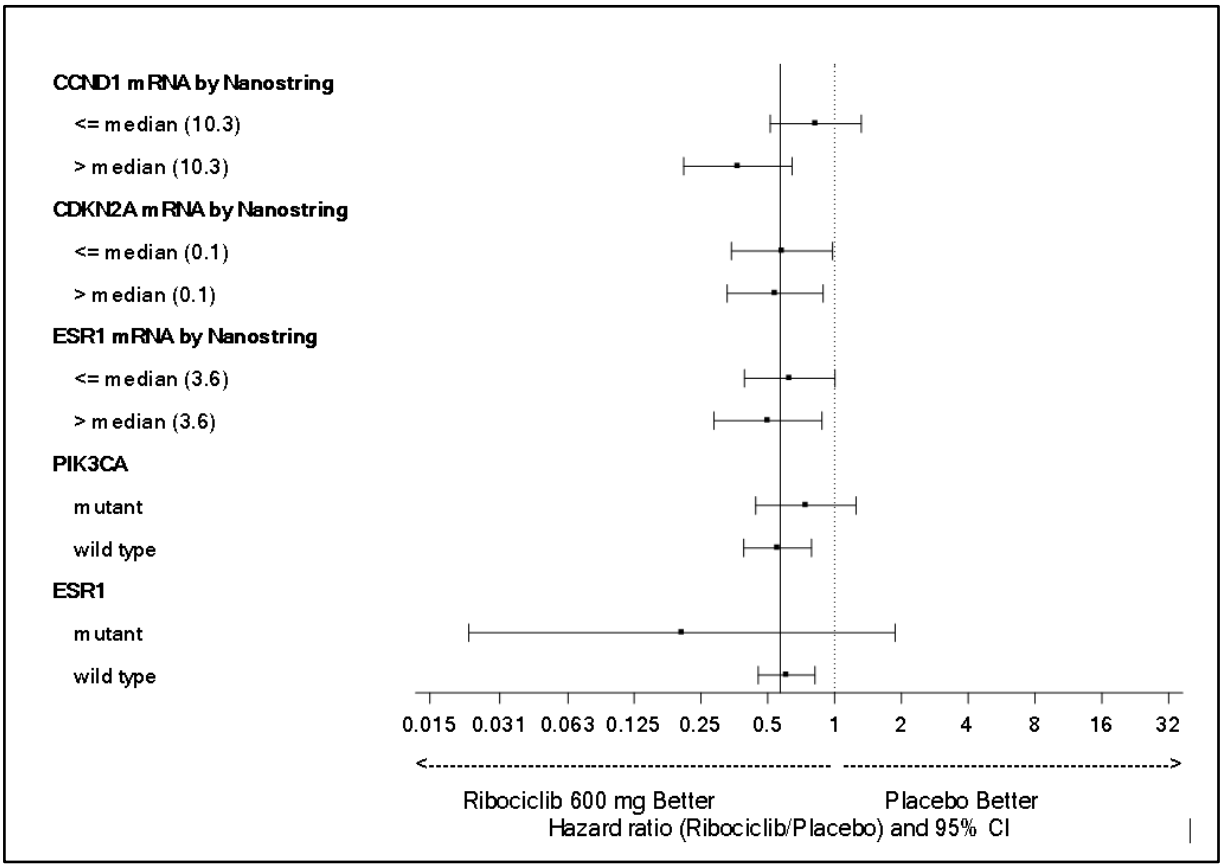


Figure 12-7 MONALEESA-7 (E2301) Forest plot of PFS based on investigator assessment in patients who received NSAI (20-Aug-17 cut off), continued



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 12-6 as well as in Figures 12-8 and 12-9.

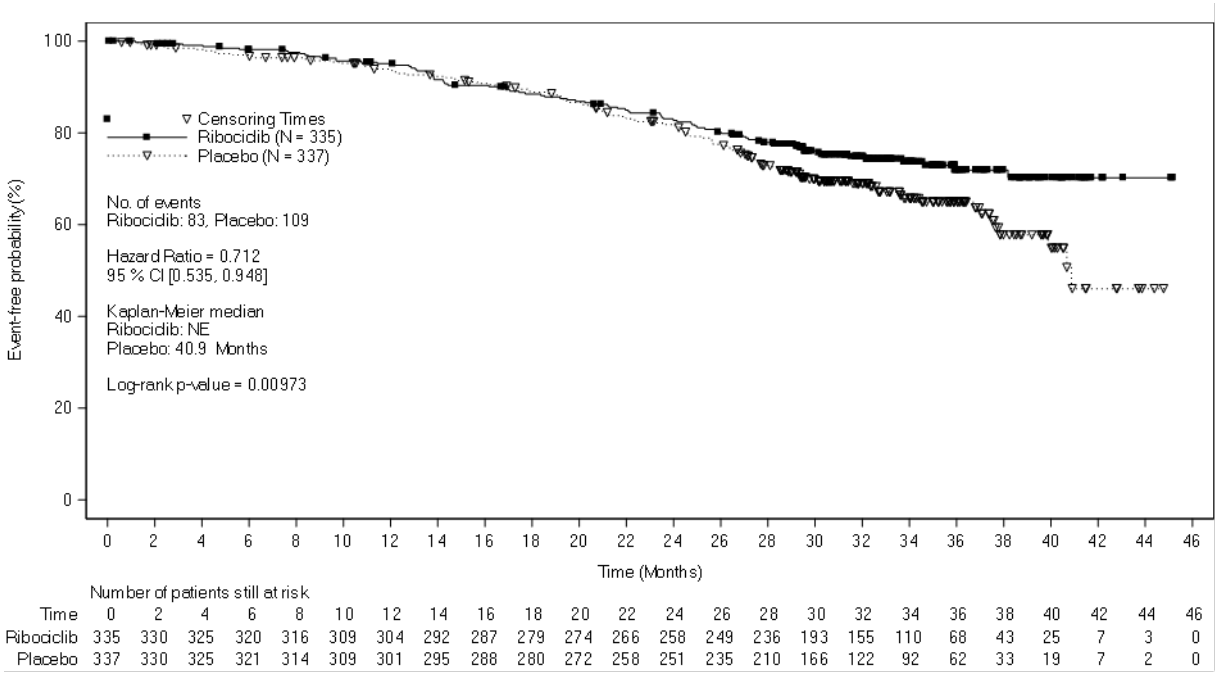
Table 12-6 MONALEESA-7 (E2301) efficacy results (OS) (30-Nov-18 cut-off)

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;

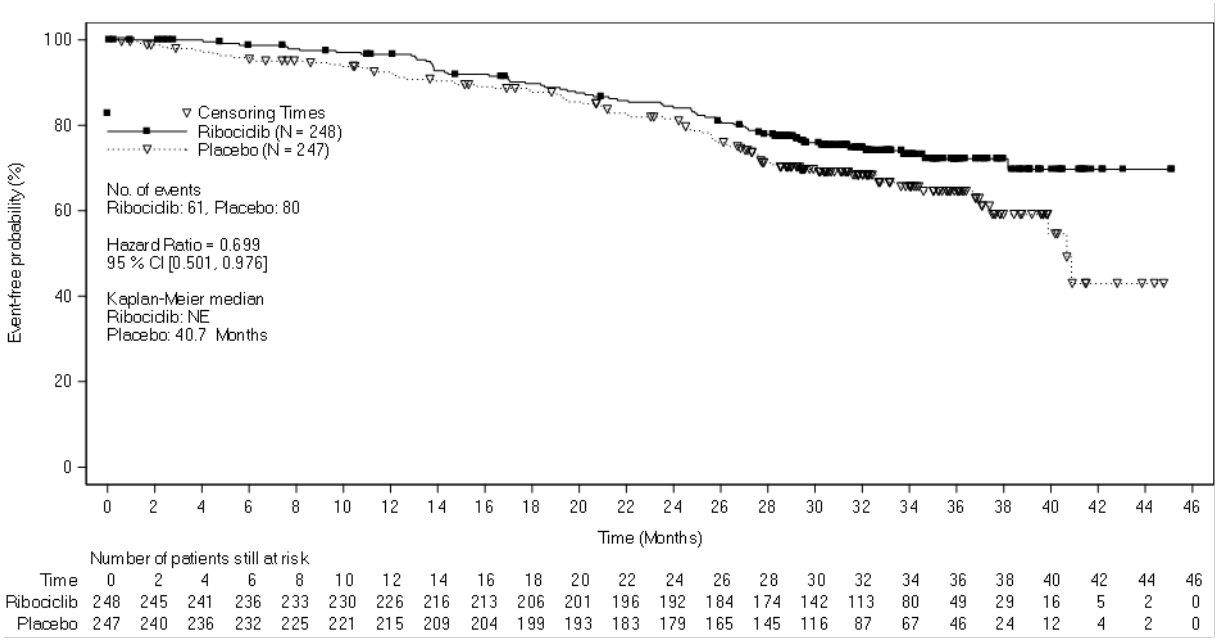
[a]p-value is obtained from the one-sided log-rank test stratified by lung and/or liver metastases, prior chemotherapy for advanced disease, and endocrine partner per IRT

Figure 12-8 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 12-9 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 Kryxana 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 Kryxana 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).

Study CLEE011F2301 (MONALEESA-3)

Kryxana 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.

A total of 726 patients were randomized in a 2:1 ratio to receive either Kryxana 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. Kryxana 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.

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). Prior to study entry 42.7% of patients had received chemotherapy in the adjuvant and 13.1% in the neoadjuvant setting, while 58.5% had received endocrine therapy in the adjuvant and 1.4% in the neoadjuvant setting and 21% had received prior endocrine therapy in the advanced breast cancer setting. In study F2301 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.

Primary analysis

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

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

The primary efficacy results demonstrated a statistically significant improvement in PFS in patients receiving Kryxana 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 Kryxana plus fulvestrant arm. The median (95% CI) PFS was 20.5 months (18.5, 23.5) in the Kryxana 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 12-10 and 12-11 respectively.

Figure 12-10 MONALEESA-3 (F2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (03-Nov-17 cut-off)

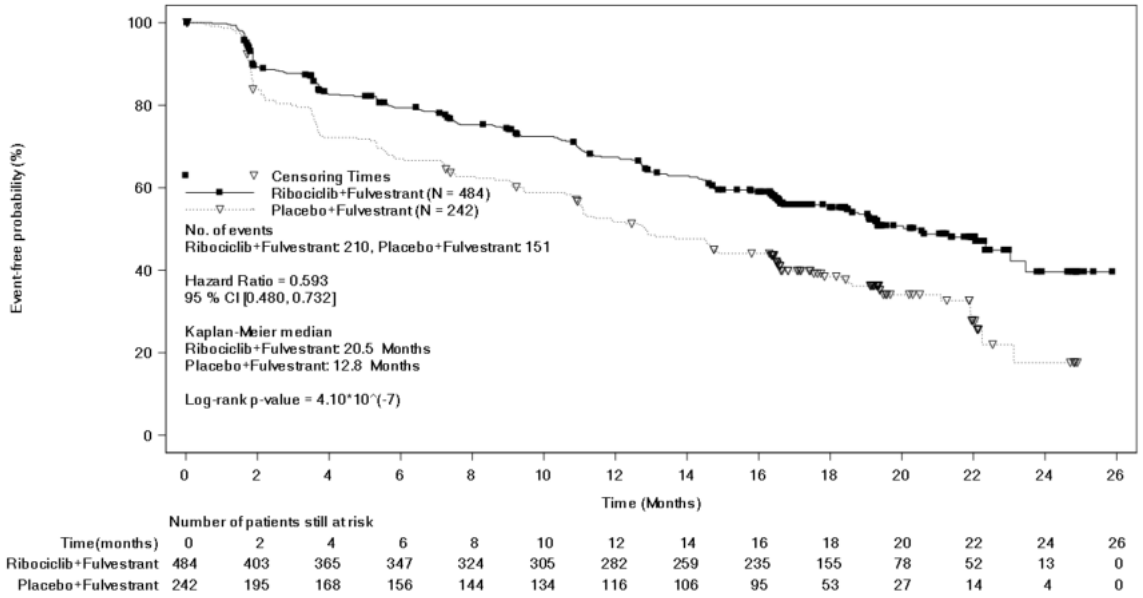


Figure 12-11 MONALEESA-3 (F2301) Forest plot of PFS based on investigator assessment (FAS) (03-Nov-17 cut-off)

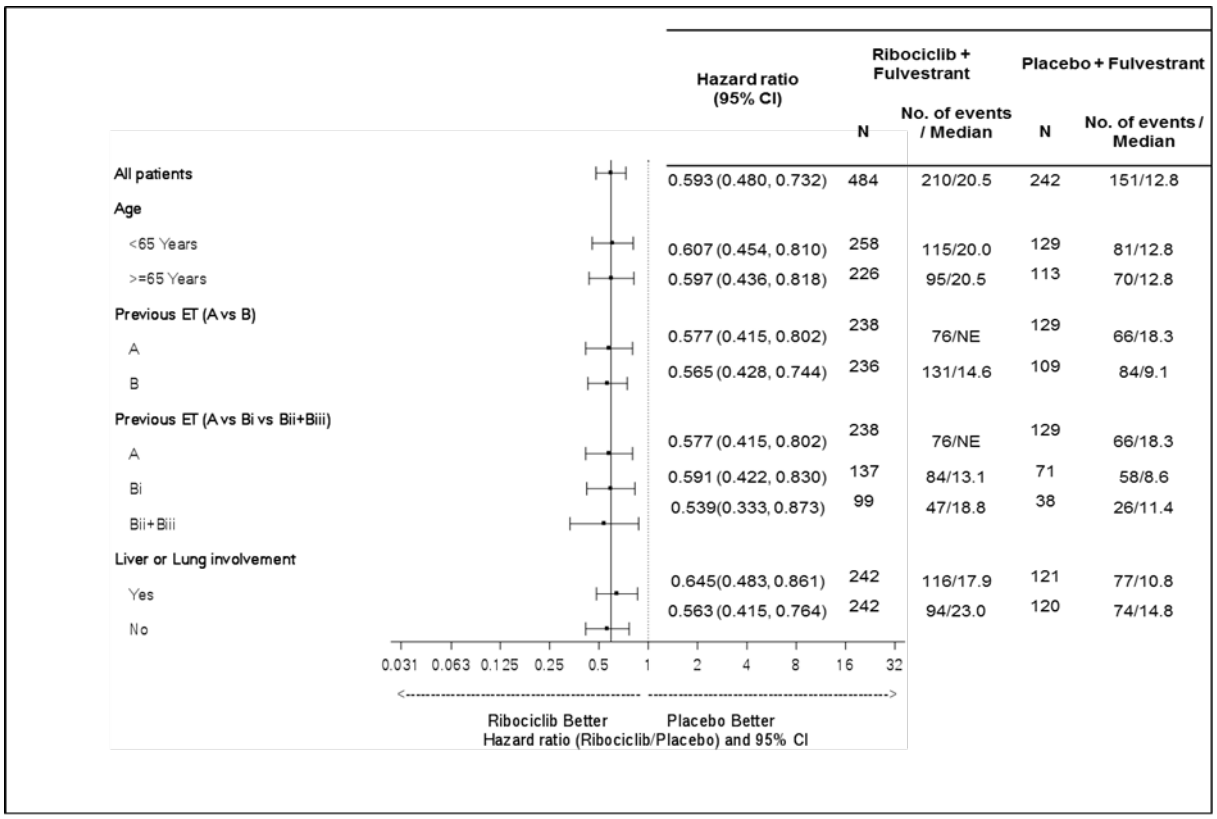


Figure 12-11 MONALEESA-3 (F2301) Forest plot of PFS based on investigator assessment (FAS) (03-Nov-17 cut-off), continued

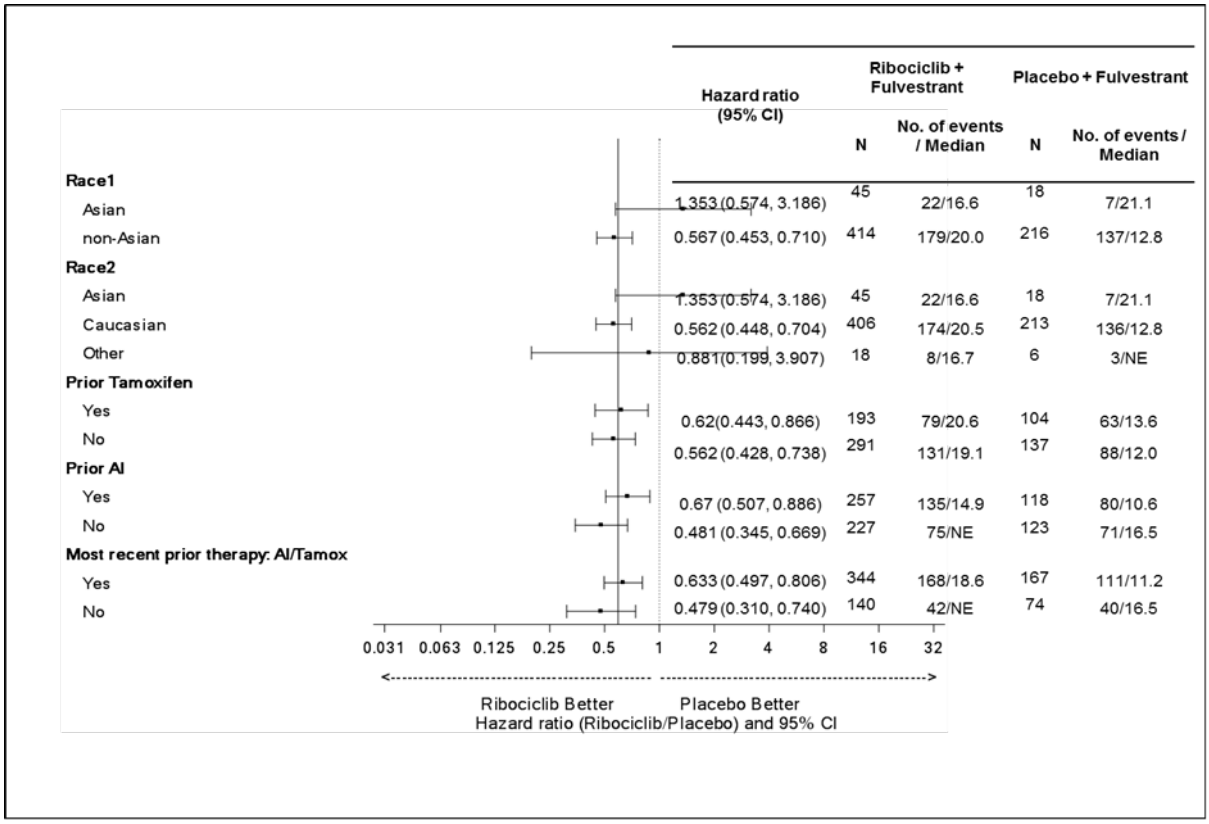


Figure 12-11 MONALEESA-3 (F2301) Forest plot of PFS based on investigator assessment (FAS) (03-Nov-17 cut-off), continued

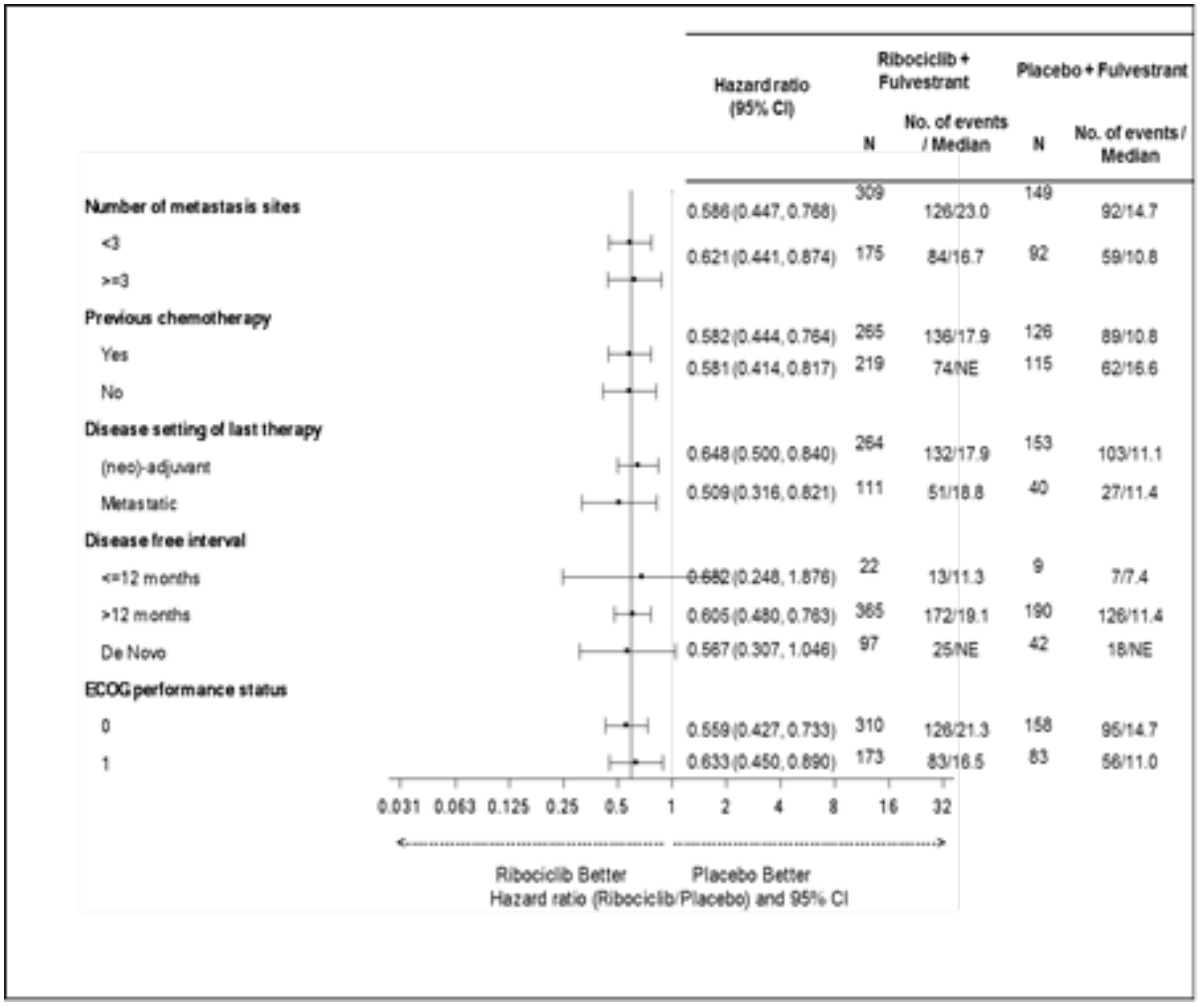


Figure 12-11 MONALEESA-3 (F2301) Forest plot of PFS based on investigator assessment (FAS) (03-Nov-17 cut-off), continued

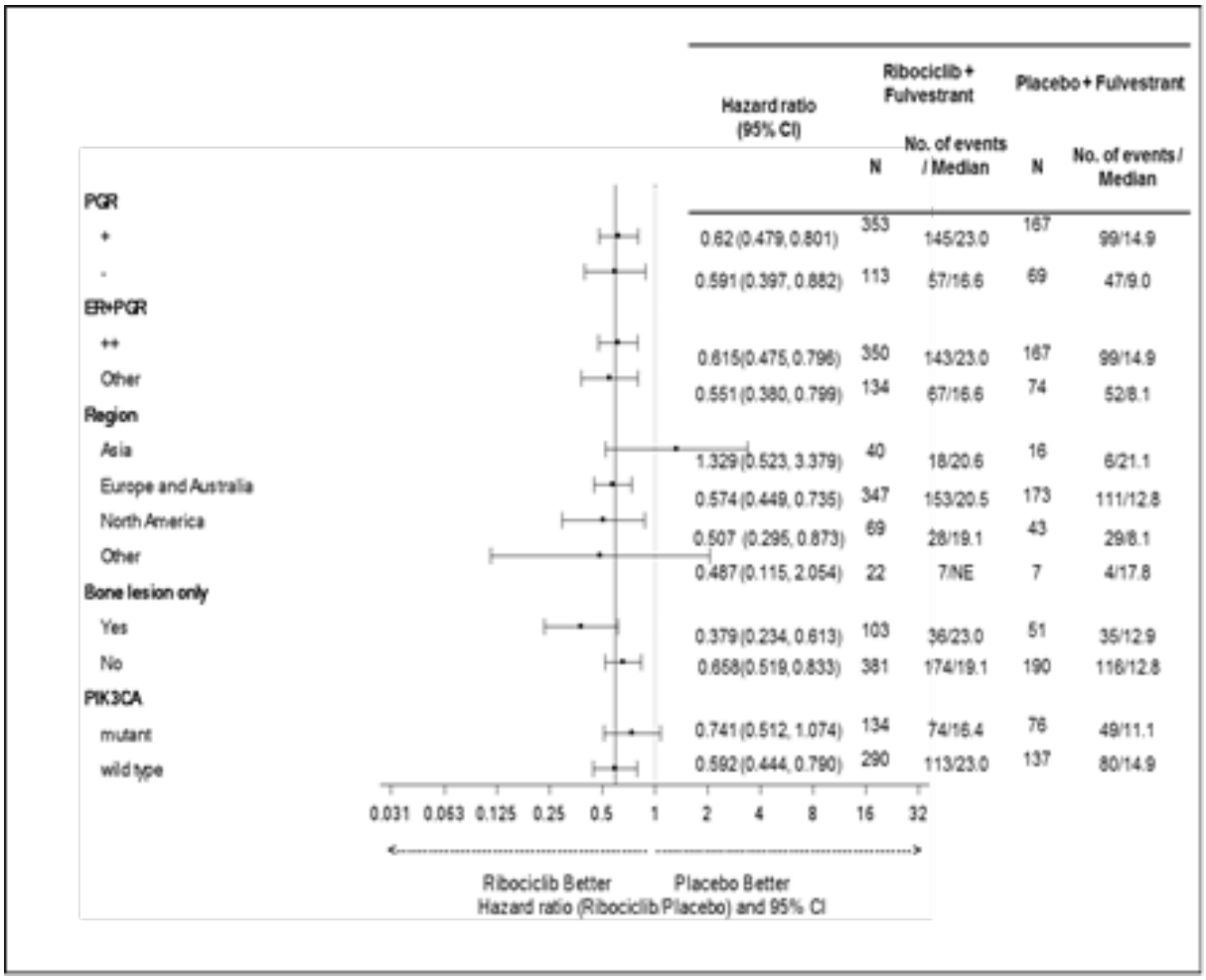


Figure 12-11 MONALEESA-3 (F2301) Forest plot of PFS based on investigator assessment (FAS) (03-Nov-17 cut-off), continued

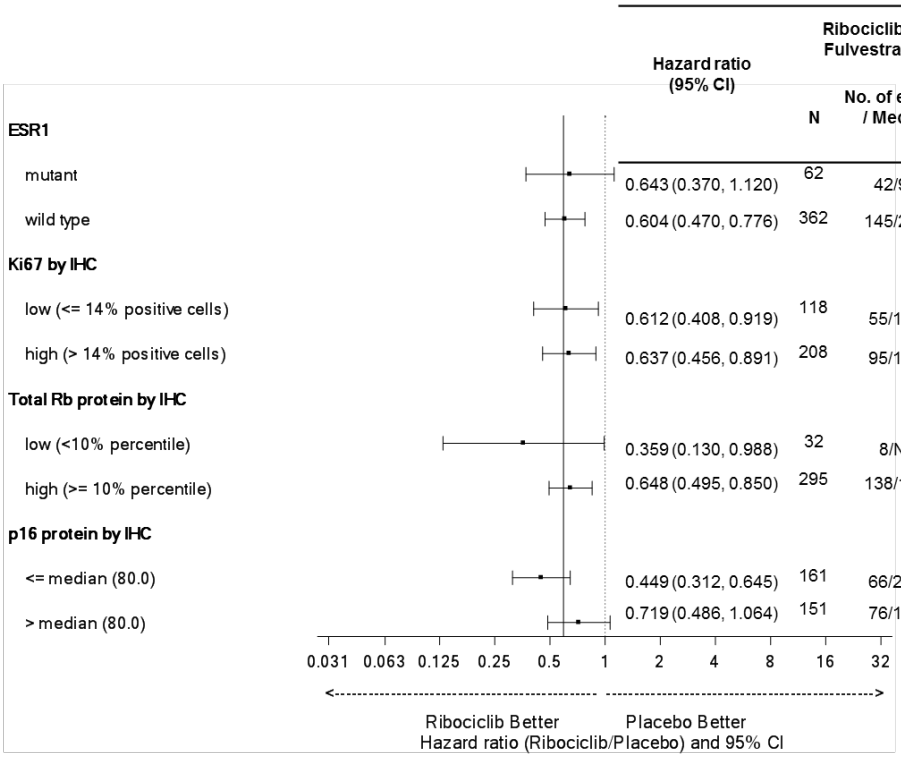
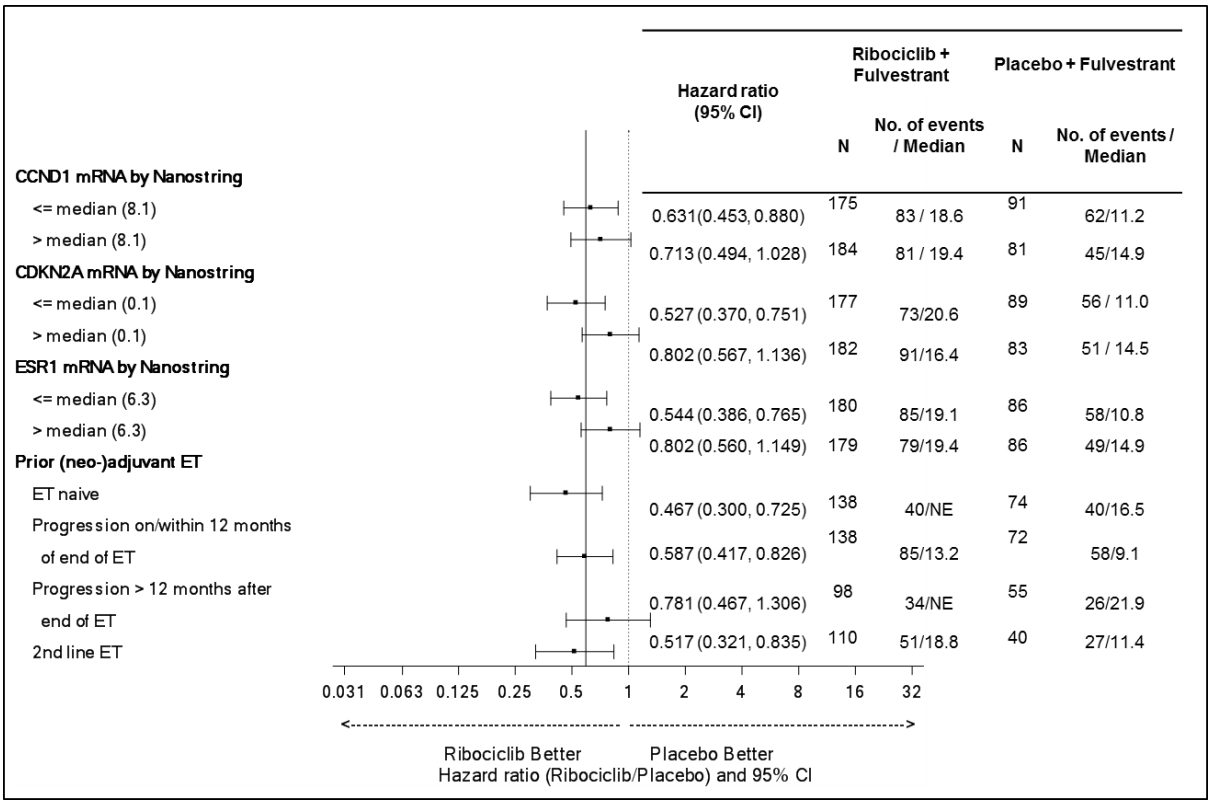


Figure 12-11 MONALEESA-3 (F2301) Forest plot of PFS based on investigator assessment (FAS) (03-Nov-17 cut-off), continued



[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 Kryxana plus fulvestrant arm and in the placebo plus fulvestrant arm is summarized in Table 12-7.

Table 12-7 MONALEESA-3 (F2301) efficacy results (ORR, CBR) based on investigator assessment (03-Nov-17 cut-off)

Analysis	Kryxana 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 Kryxana 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 Kryxana to fulvestrant resulted in delaying TTD in the EORTC QLQ-C30 global health scale score compared with placebo plus fulvestrant, (median not estimable versus 19.4 months; HR: 0.795 [95% CI: 0.602,1.050]; p-value 0.051.

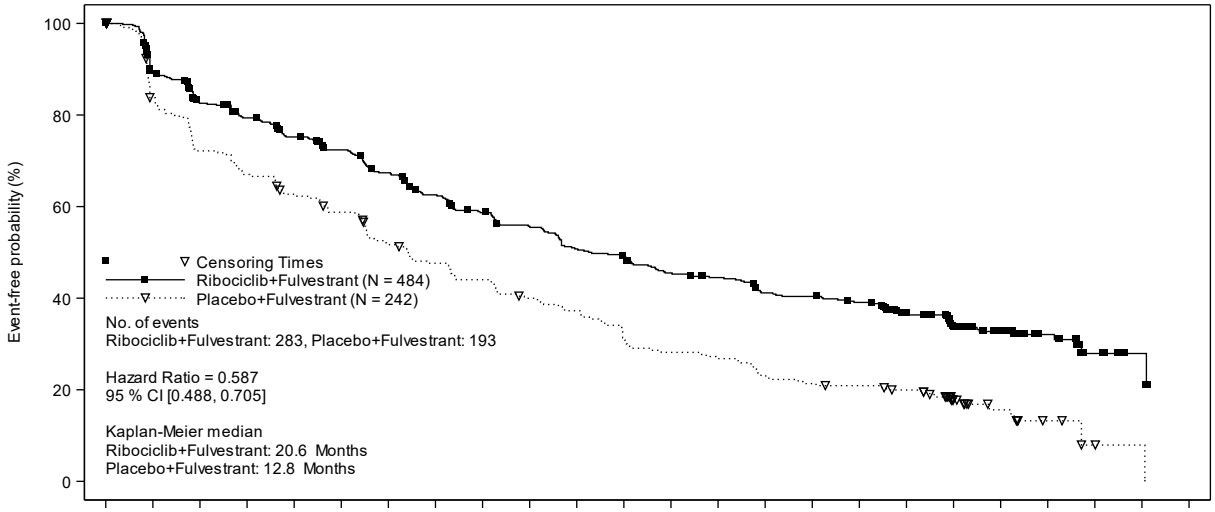
Final OS Analysis

Since the median PFS for first line patients had not been reached at the time of the primary analysis, a descriptive update of primary efficacy results (PFS) was performed at the time of the second OS interim analysis, and the updated PFS results are summarized in Table 12-8 and the Kaplan-Meier curve is provided in Figure 12-12.

Table 12-8 MONALEESA-3 (F2301) primary efficacy results (PFS) based on investigator assessment (03-Jun-19 cut-off)

	Kryxana 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 12-12 MONALEESA-3 (F2301) Kaplan-Meier plot of PFS based on investigator assessment (FAS) (03-Jun-19 cut-off)



Number of patients still at risk

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

Results were consistent across pre-specified sub-groups of age, prior adjuvant or neo-adjuvant chemotherapy or hormonal therapies, liver and/or lung involvement, and bone only metastatic disease. The subgroup analysis based on prior endocrine therapy is presented in Table 12-9.

Table 12-9 MONALEESA-3 (F2301) efficacy results (PFS) for prior endocrine therapy subgroup (03-Jun-19 cut-off)

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

CI=confidence interval

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

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

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

The OS results from this interim analysis with a 03-Jun-19 cut-off are provided in Table 12-10 and Figure 12-13.

Table 12-10 MONALEESA-3 (F2301) efficacy results (OS) (03-Jun-19 cut-off)

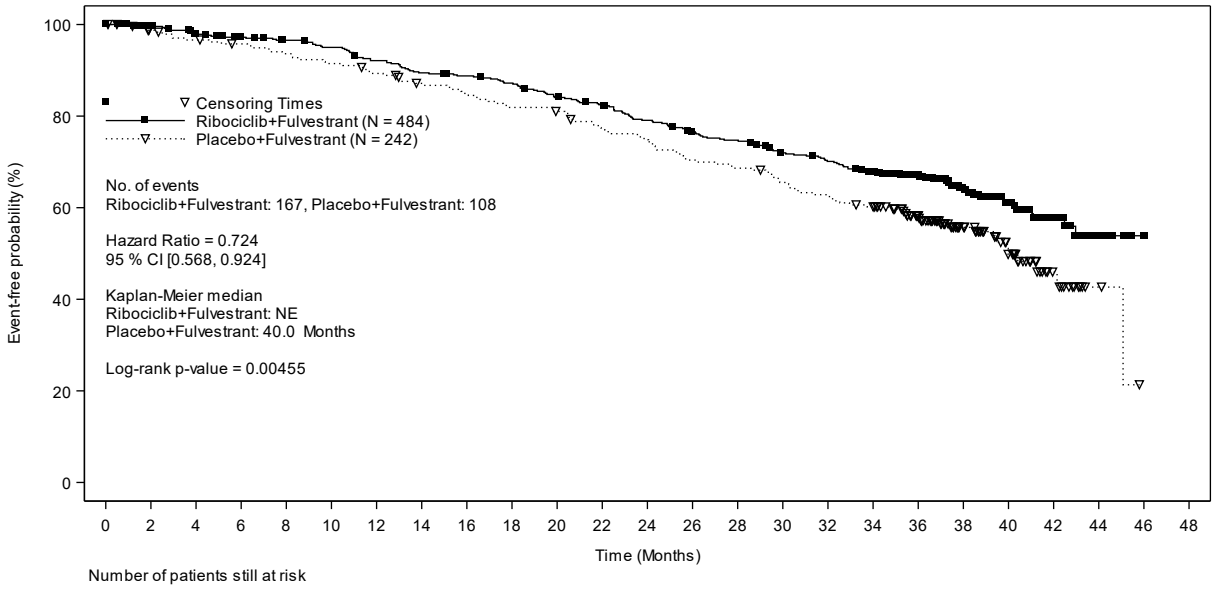
	Kryxana 600 mg	**Placebo**
Overall study population	N=484	N=242
Number of events - n [%]	167 (34.5)	108 (44.6)
Median OS [months] (95% CI)	NE, (NE, NE)	40 (37, NE)
HR (95% CI)	0.724 (0568, 0924)	
p value	0.00455	

- [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 12-13 MONALEESA-3 (F2301) Kaplan Meier plot of OS (FAS) (03-Jun-19 cut-off)



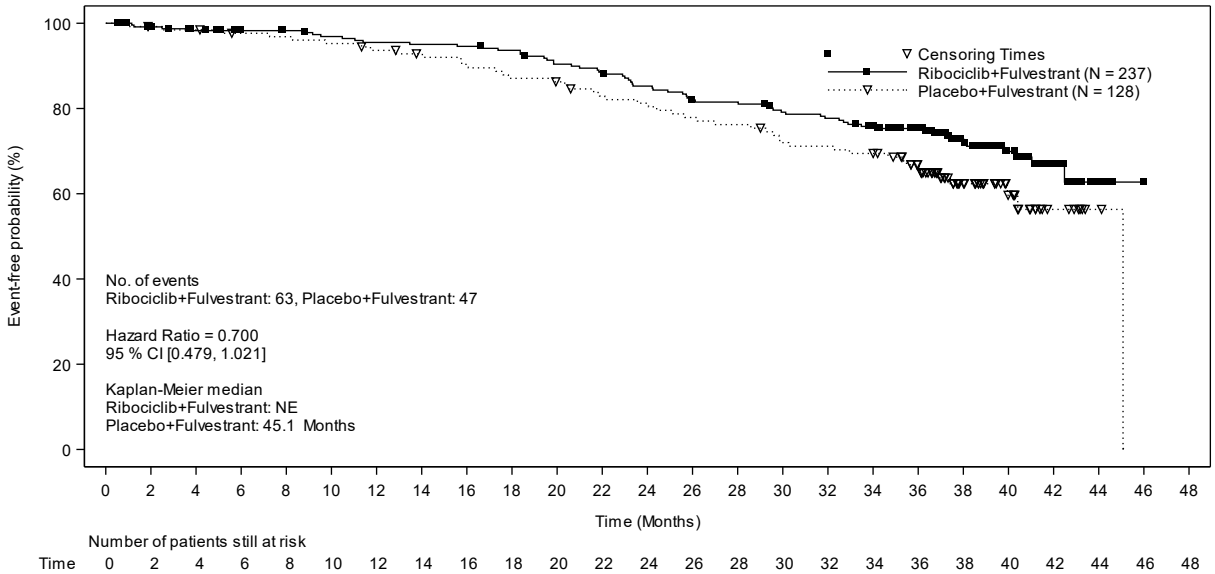
Number of patients still at risk

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

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

OS results for subgroups analyses are presented in Figures 12-14, 12-15 and 12-16.

Figure 12-14 MONALEESA-3 (F2301) Kaplan Meier plot of OS treatment naïve patients in the metastatic/advanced disease setting (FAS) (03-Jun-19 cut-off)

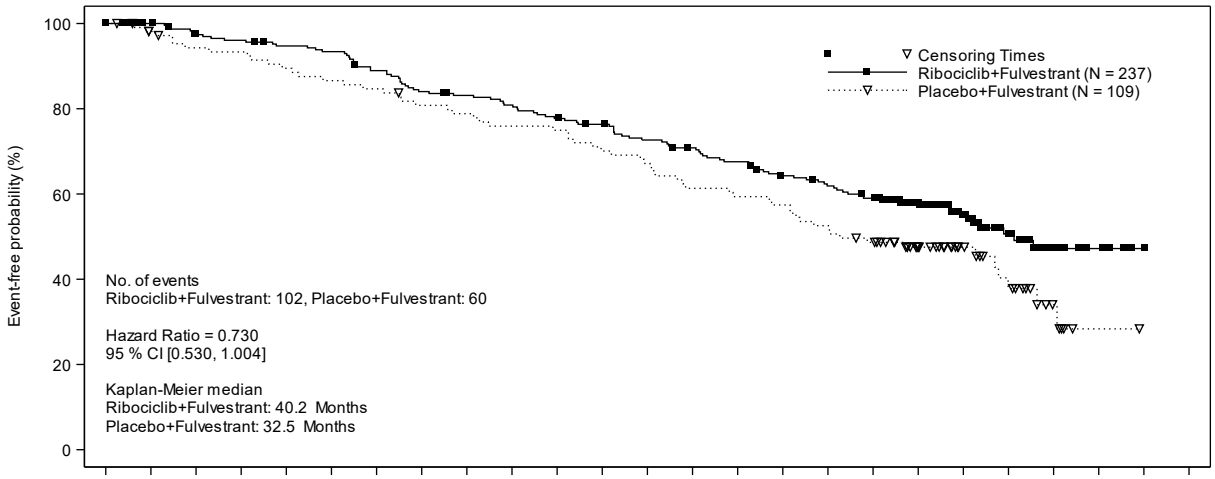


Number of patients still at risk

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

Hazard ratio is based on unstratified Cox model

Figure 12-15 MONALEESA-3 (F2301) Kaplan Meier plot of OS in patients who received up to 1 line of treatment for metastatic/advanced disease setting (FAS) (03-Jun-19 cut-off)



Number of patients still at risk

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

Hazard ratio is based on unstratified Cox model

Figure 12-16 MONALEESA-3 (F2301) Forest plot of OS from sub-group analysis (FAS) (03-Jun-19 cut off)

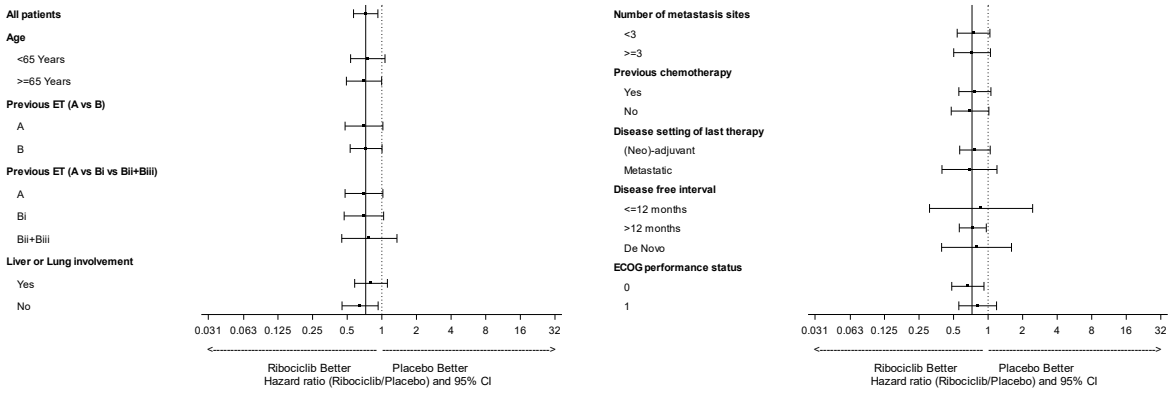
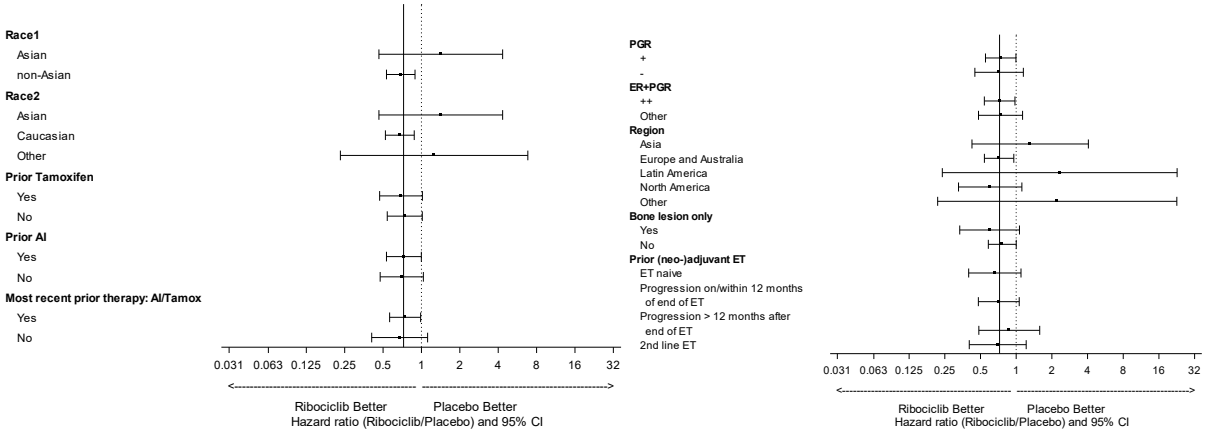


Figure 12-16 MONALEESA-3 (F2301) Forest plot of OS from sub-group analysis (FAS) (03-Jun-19 cut off), continued



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 Kryxana 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 Kryxana arm and 29.4 months (95% CI: 24.1, 33.1) in the placebo arm.

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. *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 C_{max}).

Repeated dose toxicity

Repeated dose toxicity studies (treatment schedule of 3 weeks on/1 week off) in rats up to 27 weeks duration and dogs up to 39 weeks duration, revealed the hepatobiliary system (proliferative changes, cholestasis, sand-like gallbladder calculi, and inspissated bile) as the primary target organ of toxicity of ribociclib. Target organs associated with the pharmacological action of ribociclib in repeat dose studies include bone marrow (hypocellularity), lymphoid

system (lymphoid depletion), intestinal mucosa (atrophy), skin (atrophy), bone (decreased bone formation), kidney (concurrent degeneration and regeneration of tubular epithelial cells) and testes (atrophy). Besides the atrophic changes seen in the testes, which showed a trend towards reversibility, all other changes were fully reversible after a 4-week treatment free period. These effects can be linked to a direct anti-proliferative effect on the testicular germ cells resulting in atrophy of the seminiferous tubules. Exposure to ribociclib in animals in the toxicity studies was generally less than or equal to that observed in patients receiving multiple doses of 600 mg/day (based on AUC).

Reproductive toxicity/Fertility

See section 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.

Phototoxicity

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

Carcinogenesis

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

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

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

The 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 Kryxana 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.

14 Pharmaceutical information

Incompatibilities

Not applicable.

Special precautions for storage

Do not store above 30°C.

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

The expiry date is indicated in the packaging

Pack Size

Box, 1 blister @ 21 film-coated tablets

Reg. No.

HARUS DENGAN RESEP DOKTER

Manufactured by Novartis Pharmaceutical Manufacturing LLC, Ljubljana, Slovenia
For Novartis Pharma AG, Basel, Switzerland
Imported by PT Novartis Indonesia, Jakarta, Indonesia

Leaflet based on CDS 09-May-2022 and RIGHT Choice Study Update and change of DP manufacturer to Novartis Pharmaceutical Manufacturing LLC

KRYXANA™ (ribociclib)
Tablet salut selaput 200 mg

Informasi Produk untuk Pasien

DISETUJUI OLEH BPOM : 09/07/2024 ID : EREG100005VR12300042

Bacalah brosur ini dengan saksama sebelum Anda mengonsumsi Kryxana.

Mohon simpan brosur ini. Anda mungkin akan membutuhkan brosur ini untuk dibaca kembali.

Apabila Anda memiliki pertanyaan lebih lanjut, mohon hubungi dokter, apoteker atau tenaga kesehatan.

Obat ini diresepkan untuk Anda. Jangan gunakan obat ini untuk penyakit lain; jangan berikan obat ini kepada orang lain karena dapat membahayakan meskipun gejala penyakitnya serupa dengan gejala penyakit Anda.

Jika terjadi efek samping yang parah atau Anda mengalami efek samping lain yang tidak tertera pada brosur ini, mohon hubungi dokter, apoteker atau tenaga kesehatan.

Apa isi brosur ini

1 Apakah KRYXANA itu dan apa kegunaannya

Apakah Kryxana itu

Kryxana tablet salut selaput 200 mg mengandung zat aktif ribociclib, yang termasuk ke dalam golongan obat yang disebut sebagai *cyclin dependent kinase (CDK) inhibitors* dan berguna untuk mengobati kanker payudara jenis tertentu.

Apakah kegunaan Kryxana

Kryxana adalah obat yang memerlukan resep dokter, yang digunakan untuk pengobatan *hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative* stadium lanjut atau yang kankernya sudah menyebar ke bagian tubuh lainnya (metastasis). Kryxana digunakan dalam kombinasi dengan obat golongan penghambat aromatase non-steroid, letrozole atau fulvestrant (pada pasien pasca-menopause), dan agonis LHRH (pada pasien pre- atau peri- menopause), sebagai terapi berbasis-hormonal untuk kanker payudara stadium lanjut atau metastatik.

Bagaimana cara kerja Kryxana

Kryxana menghambat kinerja sekelompok enzim yang bernama *cyclin dependent kinases (CDK)* yang berperan dalam memberikan sinyal ke sel kanker untuk tumbuh dan berkembang menjadi sel-sel kanker baru. Dengan menghambat kinerja dari enzim-enzim ini, Kryxana dapat

mengurangi pertumbuhan sel kanker dan menghambat terbentuknya sel-sel kanker baru, dan dapat membunuh sel kanker.

Kryxana harus digunakan secara kombinasi dengan obat golongan penghambat aromatase atau fulvestrant atau agonis LHRH.

Pada wanita pre- atau peri-menopause, Kryxana harus digunakan bersamaan dengan obat lain dari golongan agonis LHRH (*luteneizing hormone-releasing hormone*).

Tanyakan kepada dokter, apoteker atau tenaga kesehatan, jika Anda memiliki pertanyaan terkait cara kerja Kryxana atau mengapa Anda diresepkan obat ini.

2 Apa yang harus Anda ketahui sebelum dan selama mengonsumsi Kryxana

Ikuti petunjuk dari dokter Anda secara saksama. Informasi yang Anda dapatkan dari dokter mungkin berbeda dengan informasi umum yang tertera pada brosur ini.

Jangan mengonsumsi Kryxana

Jika Anda alergi (hipersensitif) terhadap ribociclib atau kandungan lain yang terdapat pada obat ini.

Jika Anda merasakan kemungkinan terjadi alergi, mintalah anjuran dari dokter Anda.

Perhatian dan Peringatan

Jika salah satu kondisi di bawah ini terjadi pada Anda, beritahukan kepada dokter atau Apoteker sebelum Anda mengonsumsi Kryxana:

- Jika Anda mengalami demam, radang tenggorokan atau sariawan di mulut akibat infeksi (merupakan gejala akibat kadar sel darah putih yang rendah).
- Jika Anda memiliki masalah pada hati atau pernah mengalami penyakit pada hati sebelumnya.
- Jika Anda mengalami gangguan jantung atau gangguan detak jantung, seperti detak jantung yang tidak teratur, termasuk kondisi yang disebut dengan sindrom perpanjangan QT (*QT interval prolongation*), kadar kalium, magnesium, kalsium atau fosfor yang rendah dalam darah Anda.
- Jika Anda sedang hamil, mungkin sedang hamil, atau berencana untuk hamil (lihat bagian Kehamilan dan Menyusui).
- Jika Anda sedang menyusui atau berencana untuk menyusui (lihat bagian Kehamilan dan Menyusui).
- Jika Anda sedang mengonsumsi obat-obatan atau supplemen lain (lihat bagian “Mengonsumsi obat-obatan lain”). (Interaksi Obat)

Segera beritahukan dokter atau apoteker jika Anda mengalami gejala ini pada saat pengobatan dengan Kryxana:

- Demam, meriang, lemah dan sering terjadi infeksi dengan gejala seperti radang tenggorokan atau sariawan pada mulut (hal ini mungkin disebabkan dari kadar sel darah putih yang

rendah). **Segera beritahukan dokter Anda jika Anda mengalami gejala baru atau perburukan kondisi.**

- Kelelahan, kulit kekuningan dan gatal atau jika bagian putih pada mata Anda berwarna kekuningan, mual atau muntah, hilang nafsu makan, nyeri pada bagian kanan atas perut (abdomen), air kemih berwarna gelap atau coklat, atau Anda mudah mengalami memar atau pendarahan (hal ini mungkin merupakan gejala adanya masalah pada hati). **Segera beritahukan dokter Anda jika Anda mengalami gejala baru atau perburukan kondisi.**
- Nyeri atau rasa tidak nyaman pada dada, perubahan detak jantung (lebih cepat atau lebih lambat), keringat berlebihan, perasaan melayang, pusing, bibir kebiruan, napas tersengal-sengal, bengkak pada kaki (udem) atau bengkak pada kulit (hal ini mungkin merupakan gejala masalah pada jantung). **Segera beritahukan dokter Anda jika Anda mengalami gejala baru atau perburukan kondisi.**
- Kombinasi dari beberapa gejala berikut: ruam, kulit kemerahan, pecah-pecah pada bibir, mata atau mulut, pengelupasan kulit, demam tinggi, gejala seperti flu dan pembesaran kelenjar getah bening (hal ini mungkin merupakan gejala reaksi kulit serius). **Segera beritahukan dokter Anda jika Anda mengalami gejala baru atau perburukan kondisi.**
- Sesak napas, batuk dan napas tersengal-sengal (hal ini mungkin merupakan gejala reaksi paru serius). **Segera beritahukan dokter Anda jika Anda mengalami gejala baru atau perburukan kondisi.**

Dokter Anda mungkin akan menghentikan sementara atau mengurangi dosis atau menghentikan secara permanen pengobatan Anda dengan Kryxana.

Pemantauan selama pengobatan dengan Kryxana

Anda akan di tes darah secara rutin sebelum dan selama pengobatan dengan Kryxana untuk memantau fungsi hati Anda (pemantauan kadar transaminase dan bilirubin), jumlah sel darah (sel darah putih, sel darah merah dan trombosit), elektrolit (termasuk kalium, kalsium, magnesium dan fosfat). Aktivitas jantung Anda juga akan dimonitor sebelum dan selama pengobatan melalui tes electrokardiogram (EKG). Hasil tes dapat dipengaruhi oleh pengobatan dengan Kryxana. Jika diperlukan, dokter mungkin dapat menghentikan sementara atau mengurangi dosis Kryxana sampai terjadi perbaikan pada fungsi hati, sel darah, elektrolit atau aktivitas jantung Anda.

Dokter Anda juga dapat memutuskan untuk menghentikan secara permanen pengobatan Anda dengan Kryxana.

Pasien usia lanjut (usia 65 tahun keatas)

Anda dapat menggunakan Kryxana dengan dosis yang sama seperti pada pasien dewasa jika Anda berusia 65 tahun keatas.

Anak-anak dan remaja (di bawah usia 18 tahun)

Kryxana tidak diperuntukan bagi anak-anak dan remaja di bawah usia 18 tahun.

Mengonsumsi obat-obatan lain (interaksi dengan obat lain termasuk vaksin dan produk biologis)

Sebelum mengonsumsi Kryxana, beritahukan dokter atau apoteker jika Anda sedang atau pernah mengonsumsi obat-obatan lain, termasuk obat-obatan dan suplemen yang dapat dibeli tanpa resep dokter, karena mungkin terjadi interaksi dengan Kryxana. Khususnya jika Anda mengonsumsi obat-obatan berikut:

- Beberapa obat-obatan yang digunakan untuk mengobati infeksi. Termasuk obat-obatan yang digunakan untuk mengobati infeksi jamur, seperti ketoconazole, itraconazole, voriconazole or posaconazole, atau obat-obatan yang digunakan untuk mengobati infeksi bakteri tertentu, seperti telithromycin, clarithromycin, ciprofloxacin, levofloxacin dan azithromicyn.
- Beberapa obat-obatan yang digunakan untuk mengobati HIV/AIDS seperti ritonavir, saquinavir, indinavir, lopinavir, nelfinavir, telaprevir dan efavirenz.
- Beberapa obat-obatan yang digunakan untuk menggobati kejang (obat anti epilepsi) seperti karbamazepin, fenitoin, rifampin dan midazolam.
- *St. John's Wort*, bahan herbal yang digunakan untuk mengobati depresi dan kondisi lain (juga dikenal sebagai *Hypericum Perforatum*)
- Beberapa obat-obatan yang digunakan untuk mengobati masalah detak jantung seperti amiodarone, disopyramide, procainamide, quinidine dan sotalol.

Kryxana dapat meningkatkan atau menurunkan kadar obat-obat lain dalam darah termasuk obat dan suplemen yang tidak memerlukan resep dokter dan/atau obat-obat herbal. Pastikan Anda menginformasikan kepada dokter Anda riwayat pengobatan Anda sebelumnya, termasuk pengobatan herbal yang Anda lakukan sebelum mengonsumsi Kryxana.

Anda juga harus memberitahukan dokter Anda jika Anda sedang mengonsumsi Kryxana dan jika Anda diresepkan obat baru yang belum pernah Anda konsumsi sebelumnya selama pengobatan dengan Kryxana.

Tanyakan kepada dokter atau apoteker jika Anda tidak yakin apakah obat-obatan yang Anda konsumsi termasuk obat-obatan yang tertera diatas.

Mengonsumsi Kryxana bersamaan dengan makanan dan minuman (interaksi dengan makanan dan minuman)

Anda harus mengonsumsi Kryxana pada waktu yang sama setiap hari, dianjurkan di pagi hari. Kryxana bisa dikonsumsi bersamaan atau tanpa makanan.

Anda tidak boleh mengonsumsi *grapefruit* atau meminum *grapefruit juice* selama pengobatan dengan Kryxana karena dapat mempengaruhi cara Kryxana diproses di dalam tubuh Anda dan mungkin menurunkan kadar Kryxana dalam darah yang menyebabkan Kryxana menjadi kurang efektif.

Kehamilan dan Menyusui

Jika Anda sedang hamil atau menyusui, mungkin sedang hamil, atau berencana hamil, mintalah anjuran dari dokter atau apoteker sebelum mengonsumsi obat ini.

Dokter Anda akan mendiskusikan dengan Anda terkait resiko yang mungkin terjadi jika Anda mengonsumsi Kryxana selama kehamilan atau menyusui.

Pasien wanita yang mungkin hamil

Kryxana dapat membahayakan bagi janin. Jika Anda mungkin hamil (dalam usia subur), dokter Anda akan memastikan bahwa Anda tidak sedang hamil sebelum memulai pengobatan. Gunakan metode kontrasepsi yang paling efektif selama pengobatan dan setidaknya 21 hari setelah selesai pengobatan. Tanyakan kepada dokter Anda terkait metode kontrasepsi yang efektif.

Menggunakan kendaraan atau mesin

Pengobatan dengan Kryxana mungkin menyebabkan efek samping lemah dan lesu. Oleh karena itu, Anda harus berhati-hati bila berkendaraan atau menggunakan mesin selama pengobatan Anda.

3 Bagaimana cara mengonsumsi Kryxana

Anda harus mengonsumsi Kryxana sesuai petunjuk dokter atau apoteker. Dokter atau apoteker akan memberitahukan berapa tablet yang harus ada konsumsi dan pada hari apa saja Anda harus mengonsumsi obat tersebut. Tanyakan kembali kepada dokter atau apoteker jika Anda tidak yakin. Anda tidak boleh merubah dosis atau jadwal pengobatan tanpa berkonsultasi terlebih dahulu dengan dokter Anda.

Jangan melebihi dosis yang direkomendasikan oleh dokter Anda.

Berapa banyak Kryxana yang harus Anda konsumsi

- Dosis awal Kryxana umumnya 600 mg (3 tablet 200 mg) sekali sehari. Dokter Anda akan memberitahukan berapa banyak tepatnya jumlah tablet Kryxana yang harus Anda konsumsi.
- Kryxana harus dikonsumsi pada waktu dan jam yang sama setiap harinya (diutamakan dikonsumsi di pagi hari) dari hari ke-1 sampai hari ke-21 dari siklus 28 hari.
- Dokter Anda juga akan menginformasikan berapa dosis aromatase inhibitor atau fulvestran atau agonis LHRH yang harus Anda konsumsi dan kapan Anda harus mengonsumsinya.

Sangatlah penting untuk mengikuti rekomendasi dari dokter Anda. Jika Anda mengalami efek samping, dokter mungkin akan menganjurkan dosis yang lebih rendah atau menganjurkan Anda untuk melewatkan dosis atau menghentikan pengobatan.

Kapan Anda mengonsumsi Kryxana

Kryxana harus dikonsumsi pada waktu dan jam yang sama setiap harinya untuk memudahkan anda mengingat kapan Anda harus meminum obat, dianjurkan dikonsumsi pada pagi hari.

Bagaimana cara mengonsumsi Kryxana

Kryxana harus ditelan langsung (tablet tidak boleh di kunyah, dihancurkan atau dibelah sebelum ditelan). Anda tidak boleh mengonsumsi tablet jika pecah, retak atau tidak utuh.

Berapa lama Anda harus mengonsumsi Kryxana

Kryxana dikonsumsi sekali sehari dari hari ke-1 sampai hari ke-21 dari siklus 28 hari. Lanjutkanlah mengonsumsi Kryxana selama dianjurkan dokter Anda.

Pengobatan dengan Kryxana merupakan pengobatan jangka panjang, yang dapat berlangsung selama berbulan-bulan atau bertahun-tahun. Dokter Anda akan memonitor kondisi Anda secara rutin untuk melihat apakah pengobatan tersebut memberikan efek yang diharapkan.

Jika Anda memiliki pertanyaan terkait durasi pengobatan dengan Kryxana, tanyakan kepada dokter atau apoteker.

Apabila Anda mengonsumsi Kryxana lebih dari yang seharusnya

Apabila Anda tidak sengaja mengonsumsi terlalu banyak tablet Kryxana, atau ada orang lain yang tidak sengaja mengonsumsi obat Anda, segera hubungi dokter atau rumah sakit terdekat. Tunjukan kemasan Kryxana. Tindakan medis mungkin diperlukan.

Apabila Anda lupa mengonsumsi Kryxana

Apabila Anda lupa mengonsumsi Kryxana, jangan mengonsumsi dosis ganda untuk menutupi dosis yang telah Anda lewatkan. Minumlah dosis selanjutnya sesuai jadwal pengobatan Anda.

Apabila Anda berhenti mengonsumsi Kryxana

Menghentikan pengobatan dengan Kryxana dapat menyebabkan perburukan kondisi Anda. Jangan menghentikan pengobatan kecuali atas anjuran dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut terkait penggunaan Kryxana, tanyakan kepada dokter atau apoteker Anda.

4 Efek samping yang mungkin terjadi

Seperti halnya semua obat, pasien yang diobati dengan Kryxana mungkin mengalami efek samping, meskipun tidak terjadi pada semua pasien.

Beberapa efek samping yang mungkin serius

Jika anda mengalami efek samping serius, **hentikan pengobatan dan segera beritahukan kepada dokter Anda.**

Sangat umum: *dapat memengaruhi lebih dari 1 per10 orang*

- Demam, keringat dingin atau meriang, batuk, gejala seperti flu, kehilangan berat badan, napas tersengal-sengal, adanya darah pada dahak, bagian tubuh terasa panas atau nyeri, diare atau sakit perut, atau merasa kelelahan (merupakan gejala infeksi)

- Demam, radang tenggorokan, sariawan pada mulut yang disebabkan oleh infeksi (merupakan tanda rendahnya kadar leukosit atau limfosit, yang merupakan jenis sel darah putih)
- Hasil tes darah yang abnormal yang memberitahukan kondisi hati Anda (hasil tes fungsi hati yang abnormal).

Umum: *dapat memengaruhi hingga 1 per 10 orang*
- Pendarahan atau memar spontan (tanda rendahnya kadar trombosit atau sel darah merah)
- Radang tenggorokan atau sariawan pada mulut dengan demam setidaknya 38,3°C atau demam di atas 38°C selama lebih dari 1 jam dengan/atau tanpa infeksi *(febrile neutropenia)*
- Penurunan kadar kalium dalam darah, yang dapat mengakibatkan gangguan detak jantung.
- Pingsan
- Detak jantung tidak teratur (perubahan aktivitas ritmik pada jantung)
- Gangguan hati (hepatotoksisitas)

Tidak Umum: *dapat memengaruhi hingga 1 per 100 orang*
- Infeksi serius, dengan percepatan detak jantung, sesak napas atau napas tersengal-sengal, demam, dan menggigil (sepsis, tanda-tanda infeksi dalam darah, boleh jadi mengancam jiwa)

Frekuensi tidak diketahui: *frekuensi tidak dapat diestimasi dari data yang tersedia*
- Reaksi kulit parah termasuk kombinasi dari: ruam, kulit kemerahan, pecah-pecah pada bibir, mata atau mulut, pengelupasan kulit, demam tinggi, gejala seperti flu dan pembesaran kelenjar getah bening (*toxic epidermal necrolysis (TEN)*).
- Pembengkakan paru, yang dapat menyebabkan napas tersengal-sengal atau sesak napas. Jika parah, dapat mengancam jiwa (*interstitial lung disease (ILD)*/pneumonitis).

Efek samping lain yang mungkin terjadi

Efek samping lain yang mungkin terjadi termasuk daftar di bawah ini. Jika salah satu dari efek samping ini terjadi pada Anda dan menjadi parah, beritahukan kepada dokter, apoteker atau tenaga kesehatan.

Sangat umum: *dapat memengaruhi lebih dari 1 per 10 orang*
- Lemah, lesu, kulit pucat (tanda rendahnya kadar sel darah merah)
- Radang tenggorokan, meler, hidung tersumbat, bersin-bersin, nyeri pada pipi atau kening dengan atau tanpa demam, batuk, serak, kehilangan suara (gejala infeksi saluran pernapasan)
- Nyeri pada saat buang air kecil atau sering buang air kecil (infeksi saluran kemih)
- Penurunan nafsu makan
- Sakit kepala
- Pusing
- Batuk
- Napas tersengal-sengal
- Nyeri punggung

- Mual
- Diare
- Muntah
- Susah buang air besar (konstipasi)
- Nyeri perut (nyeri abdomen)
- Luka atau sariawan pada mulut disertai pembengkakan pada gusi *(stomatitis)*
- Perut tidak enak, masalah pencernaan (dispepsia)
- Kerontokan atau penipisan rambut *(alopecia)*
- Ruam
- Gatal *(pruritus)*
- Kelelahan *(fatigue)*
- Pembengkakan pada tangan, pergelangan atau kaki (udem perifer)
- Demam *(pyrexia)*
- Lesu *(asthenia)*

Umum: *dapat memengaruhi hingga 1 per 10 orang*

- Nyeri abdomen, mual, muntah, diare, perut bengkak atau kembung, dan merasa tidak enak badan (tanda-tanda radang selaput lambung – gastroenteritis)
- Mata berair
- Mata kering
- Penurunan kadar kalsium dalam darah, yang kadang menyebabkan kram
- Penurunan kadar fosfat dalam darah
- Sensasi kehilangan keseimbangan (vertigo)
- Rasa tidak enak pada mulut *(dysgeusia)*
- Kulit kering
- Kulit kemerahan (eritema)
- Kehilangan pigmen warna kulit bebercak-bercak (vitiligo)
- Radang tenggorokan (*oropharyngeal pain)*
- Mulut kering
- Gangguan fungsi ginjal (dilihat dari kadar kreatinin dalam darah).

Selama pengobatan dengan Kryxana, Anda juga mungkin mengalami efek samping yang terlihat dari gangguan pada hasil tes darah yang memberikan dokter Anda informasi terkait fungsi tubuh Anda:

Sangat umum:

- Kadar enzim berikut ini dapat meninggi:
  - Alanin aminotransferase (ALT) dan/atau aspartat aminotransferase (AST) (enzim-enzim yang menunjukkan fungsi hati)

- Kadar kreatinin dapat meninggi
- Rendahnya kadar sel darah berikut:
  - Jumlah leukosit, neutrofil, limfosit, trombosit
- Rendahnya kadar hemoglobin, gula darah, fosfor, albumin dan kalium.

Umum:

- Kadar bilirubin dalam darah dapat meninggi.

5 Cara Penyimpanan Kryxana

- Jauhkan obat dari penglihatan dan jangkauan anak-anak.
- Jangan mengonsumsi obat setelah tanggal kedaluarsa yang tercantum pada kotak obat
- Simpan dengan menggunakan kemasan aslinya.
- Simpan pada suhu tidak lebih dari 30°C.

Jangan mengonsumsi obat ini jika Anda melihat kerusakan atau tanda perusakan pada kemasan.

Tanyakan kepada apoteker terkait cara pembuangan obat-obatan yang sudah tidak Anda gunakan lagi.

6. Informasi lebih lanjut

Apakah kandungan Kryxana

Zat aktif dari Kryxana adalah ribociclib

Kandungan lain dari Kryxana yaitu:

Tablet inti: *Microcrystalline cellulose; low-substituted hydroxypropylcellulose; crospovidone (Type A); colloidal silicon dioxide; magnesium stearate.*

Bahan penyalut: *polyvinyl alcohol (partially hydrolysed); titanium dioxide (E171); iron oxide black (E172); iron oxide red (E172); talc: lecithin (soy) (E322); xanthan gum.*

Bagaimana bentuk dan isi Kryxana

Kryxana dipasarkan dalam bentuk tablet salut selaput dalam blister aluminium.

Tablet salut selaput berwarna ungu terang keabuan, tidak berbelah, bulat, melengkung dengan tepi lebih tipis, dan memiliki cetakan “RIC” dan “NVR” pada masing-masing sisi.

Setiap tablet salut selaput mengandung 200 mg ribociclib, sebagai garam *succinate*.

Kemasan

Dus, 1 blister @ 21 tablet salut selaput

No. Reg.

HARUS DENGAN RESEP DOKTER

Produsen Obat

Diproduksi oleh Novartis Pharmaceutical Manufacturing LLC, Ljubljana, Slovenia
Untuk Novartis Pharma AG, Basel, Swiss
Diimpor oleh PT Novartis Indonesia, Jakarta, Indonesia

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