Confident care: Effective management of adverse reactions with dose modifications

DID YOU KNOW?

- The majority of **adverse reactions** with KISQALI were **manageable and reversible**[1]
- The **survival benefits** observed with KISQALI were **maintained in patients requiring dose reductions**[2]
- In MONALEESA-2, managing adverse reactions with dose reductions **helped patients stay on therapy an average of 6.5 months longer** than those without dose reductions[3]
- **KISQALI is the only CDK4/6 inhibitor** that offers **one tablet strength for straightforward dose reductions**[4]

MONALEESA-2, a phase III study of KISQALI + AI vs placebo + AI in 1L postmenopausal patients: At a median follow-up of 80 months, median OS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with placebo + letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004. OS was a secondary end point; PFS was the primary end point.[4-6]

In a post hoc analysis, at a median follow-up of 80 months, median OS was 66.0 months (95% CI: 57.6-75.7) for patients with ≥1 dose reduction vs 60.6 months (95% CI: 42.5-79.2) for patients without dose reduction; 62.6% of patients (209/334) had ≥1 dose reduction. Efficacy in the placebo comparator arms was not assessed and should be interpreted with caution.[2,3,5]

Permanent discontinuations in MONALEESA-2: 7% with KISQALI + letrozole.[4]

Dose modification of KISQALI is recommended based on individual safety and tolerability.[4]

Please see page 6 for additional safety information.

Indications

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

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy

IMPORTANT SAFETY INFORMATION

Interstitial lung disease/pneumonitis. Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors.

In patients with advanced or mBC (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.6% of patients had ILD/pneumonitis of any grade, 0.4% had grade 3/4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have occurred in the postmarketing setting, some resulting in death.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

Effective management of adverse reactions: Neutropenia case study

Meet Angela, a financial professional who enjoys staying active and having brunch with friends.

Patient portrayal.

ANGELA'S CLINICAL EVALUATION

Age	45
Menopausal status	Premenopausal
ECOG PS	1
Clinical considerations	• At 32, was diagnosed with early breast cancer and underwent a lumpectomy followed by 3 years of adjuvant therapy • 12 years later, her cancer returned in both breasts with metastatic bone lesions • Family history of breast cancer (mother was diagnosed with early breast cancer at 42) • Treatment: KISQALI + NSAI + goserelin

MONITORING RESULTS

- CBC with differential on Day 14 of Cycle 1 revealed ANC of 450/mm^3 (**grade 4 neutropenia**=ANC <500/mm^3)
- Afebrile with no signs/symptoms of infection

COURSE OF ACTION

- Dose interrupted
- Two weeks after dose interruption, CBC with differential revealed ANC of 1200/mm^3
- Because neutrophil count recovered to grade <2 (ANC >1000/mm^3), KISQALI resumed at reduced dose of 400 mg daily

For patients who experience neutropenia:

Median time to onset of grade ≥2: 17 days
Median time to resolution of grade ≥3: 12 days

Click here for more detailed information about dose adjustments and managing neutropenia

IMPORTANT SAFETY INFORMATION (continued)

Interstitial lung disease/pneumonitis (continued). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue KISQALI in patients with severe ILD/pneumonitis or any recurrent symptomatic ILD/pneumonitis.

Severe cutaneous adverse reactions. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KISQALI.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

Effective management of adverse reactions: QT prolongation case study

Meet Elena, an art teacher who enjoys nourishing her body and mind with water aerobics and Sunday dinners with her family.

Patient portrayal.

ELENA'S CLINICAL EVALUATION

Age	59
Menopausal status	Postmenopausal
ECOG PS	1
Clinical considerations	• Primary care physician noticed a lump while doing a routine checkup and referred Elena to an oncologist • Recently diagnosed with de novo HR+/HER2- mBC • Treatment: KISQALI + AI

MONITORING RESULTS

- Baseline QTcF: 435 ms
- Cycle 1 Day 14 QTcF: 485 ms (**grade 2 QT prolongation**)

COURSE OF ACTION

- Dose interrupted
- Elena's third ECG reported a QTcF of 450 ms, allowing the patient to restart treatment at 400 mg because QTcF prolongation resolved to <481 ms

KISQALI has been shown to prolong the QT interval, but the incidence was low

1.4% (15/1054) had a >500 ms postbaseline QTcF value

5.8% (61/1054) experienced a >60 ms increase from baseline in QTcF interval

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner.[4]

Click here for more detailed information about dose adjustments and managing QT prolongation

IMPORTANT SAFETY INFORMATION (continued)

Severe cutaneous adverse reactions (continued). If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life-threatening cutaneous reactions during KISQALI treatment.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

KISQALI maintained overall survival in patients requiring dose reductions across 3 phase III trials

	mOS for patients with ≥1 dose reduction	mOS for patients without dose reductions
MONALEESA-2: 62.6% of patients (209/334) had ≥1 dose reduction[2,3]	**66.0 months** (95% CI: 57.6-75.7)	**60.6 months** (95% CI: 42.5-79.2)
	HR=0.87 (95% CI: 0.65-1.18)	
MONALEESA-3: 40.7% of patients (197/484) had ≥1 dose reduction[7,8]	**NOT REACHED** (95% CI: 43-NR)	**NOT REACHED** (95% CI: 41.1-NR)
	HR=0.88 (95% CI: 0.64-1.21)	
MONALEESA-7: 40.7% of patients (101/248) had ≥1 dose reduction[8,9]	**NOT REACHED** (95% CI: NR-NR)	**NOT REACHED** (95% CI: NR-NR)
	HR=0.79 (95% CI: 0.46-1.36)	

Results are based on a post hoc analysis; efficacy in the placebo comparator arms was not assessed and should be interpreted with caution.

In the MONALEESA trials, the efficacy of KISQALI was maintained regardless of dose reduction

MONALEESA-2 was a randomized, double-blind, placebo-controlled, phase III study of KISQALI + letrozole (n=334) vs placebo + letrozole (n=334) in postmenopausal patients with HR+/HER2- mBC who received no prior therapy for advanced disease. OS was a secondary end point; PFS was the primary end point. At a median follow-up of 80 months, mOS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with placebo + letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004.[4-6]

MONALEESA-3 was a randomized, double-blind, placebo-controlled, phase III study of KISQALI + fulvestrant (n=484) vs placebo + fulvestrant (n=242) in postmenopausal patients with HR+/HER2- mBC who received no or only 1 line of prior ET for advanced disease. OS was a secondary end point; PFS was the primary end point. In an exploratory analysis of a 1L subgroup of patients receiving KISQALI + fulvestrant (n=237) or placebo + fulvestrant (n=128), at a median follow-up of 71 months mOS was 67.6 months with KISQALI + fulvestrant (95% CI: 59.6-NR) vs 51.8 months with placebo + fulvestrant (95% CI: 40.4-61.2); HR=0.673 (95% CI: 0.504-0.899). At a median follow-up of 39 months, statistical significance was established for overall survival in the ITT population; HR=0.724 (95% CI: 0.568-0.924); *P*=0.00455. Results from the 71-month analysis were not prespecified and were observational in nature; as such, there was no prespecified statistical procedure controlling for type 1 error.[4,10-12]

MONALEESA-7 was a randomized, double-blind, placebo-controlled, phase III study of KISQALI + ET (NSAI or tamoxifen) + goserelin (n=335) vs placebo + ET (NSAI or tamoxifen) + goserelin (n=337) (ITT) in premenopausal patients with HR+/HER2- mBC who received no prior ET for advanced disease. **KISQALI is not indicated for concomitant use with tamoxifen.** Efficacy results are from a prespecified subgroup analysis of 495 patients who received KISQALI (n=248) or placebo (n=247) with an NSAI + goserelin and were not powered to show statistical significance. OS was a secondary end point; PFS was the primary end point. At a median follow-up of 54 months (exploratory analysis), mOS was 58.7 months with KISQALI + NSAI + goserelin (95% CI: 48.5-NR) vs 47.7 months with placebo + NSAI + goserelin (95% CI: 41.2-55.4); HR=0.798 (95% CI: 0.615-1.035). At a median follow-up of 35 months, statistical significance was established for overall survival in the ITT population; HR=0.71 (95% CI: 0.54-0.95); *P*=0.00973. Results from the 54-month analysis were not prespecified and were observational in nature; as such, there was no prespecified statistical procedure controlling for type 1 error.[4,13-16]

IMPORTANT SAFETY INFORMATION (continued)

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner.

Avoid KISQALI in patients who are at significant risk of developing torsades de pointes (TdP), including those with:

- congenital long QT syndrome;
- uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism;
- electrolyte abnormalities;
- taking drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

Only KISQALI offers single-strength tablets for simple dose reductions

Dose reductions with KISQALI mean no need for new mid-cycle prescriptions or additional costs[4]

Starting dose	1st reduction	2nd reduction
3 TABLETS (600 mg)	2 TABLETS (400 mg)	1 TABLET (200 mg)

- KISQALI is given as 600 mg (3 x 200-mg tablets) orally, once daily (3 weeks on, 1 week off) with either:
  - An AI once daily (continuously); in men and premenopausal women, an LHRH agonist should also be administered according to current clinical practice guidelines; or
  - Fulvestrant 500 mg intramuscularly on Days 1, 15, and 29, and once monthly thereafter; in men and premenopausal women, an LHRH agonist should also be administered according to current clinical practice guidelines
- Patients should continue treatment until disease progression or unacceptable toxicity
- Dose adjustments for adverse reactions should be made in a stepwise order by reducing the number of tablets taken
- If dose reduction below 200 mg/day is required, discontinue treatment
- Dose modification of KISQALI is recommended based on individual safety and tolerability
- KISQALI can be taken with or without food

"...the single-tablet strength allows for simple dose adjustments, and to me, that is game changing."

—Nick McAndrew, MD
University of California, Los Angeles

This health care professional has been compensated by Novartis Pharmaceuticals Corporation.

IMPORTANT SAFETY INFORMATION (continued)

QT interval prolongation (continued). Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation.

In patients with advanced or mBC (MONALEESA-2, MONALEESA-3, and MONALEESA-7) who received 600 mg KISQALI plus NSAI or fulvestrant, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first 4 weeks of KISQALI. There were no reported cases of torsades de pointes. In MONALEESA-2, in the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3.

Perform electrocardiogram (ECG) in all patients prior to starting KISQALI. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of KISQALI, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

KISQALI + letrozole safety profile

MONALEESA-2: KISQALI + letrozole in 1L postmenopausal patients

ADVERSE REACTIONS OCCURRING IN ≥10% AND ≥2% HIGHER THAN PLACEBO[4]

	KISQALI + letrozole (n=334)		Placebo + letrozole (n=330)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
GASTROINTESTINAL DISORDERS				
Nausea	52	2.4*	29	0.6*
Diarrhea	35	1.2*	22	0.9*
Vomiting	29	3.6*	16	0.9*
Constipation	25	1.2*	19	0
Stomatitis	12	0.3*	7	0
Abdominal pain	11	1.2*	8	0
GENERAL DISORDERS AND ADMINISTRATION-SITE CONDITIONS				
Fatigue	37	2.4	30	0.9
Pyrexia	13	0.3*	6	0
Peripheral edema	12	0	10	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Alopecia	33	0	16	0
Rash	17	0.6*	8	0
Pruritus	14	0.6*	6	0
NERVOUS SYSTEM DISORDERS				
Headache	22	0.3*	19	0.3*
Insomnia	12	0.3*	9	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Back pain	20	2.1*	18	0.3*
METABOLISM AND NUTRITION DISORDERS				
Decreased appetite	19	1.5*	15	0.3*
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS				
Dyspnea	12	1.2*	9	0.6*
INFECTIONS AND INFESTATIONS				
Urinary tract infection	11	0.6*	8	0

- Dose reductions due to ARs: 45% with KISQALI + letrozole
- Permanent discontinuations: 7% with KISQALI + letrozole
- The most common ARs (≥20% on the KISQALI arm and ≥2% higher than placebo), including laboratory abnormalities, were decrease in neutrophils, decrease in leukocytes, decrease in hemoglobin, nausea, decrease in lymphocytes, increase in ALT, increase in AST, fatigue, diarrhea, alopecia, vomiting, decrease in platelets, constipation, headache, and back pain
- Fatal ARs occurred in 1.8% of patients who received KISQALI. Fatal ARs in ≥0.1% of patients receiving KISQALI included acute respiratory failure (0.6%), acute myocardial infarction, sudden death (with grade 3 hypokalemia and grade 2 QT prolongation), unknown cause, and pneumonia (0.3% each)
- ARs in patients with visceral metastases receiving KISQALI were consistent with ARs in those without visceral metastases[17]

The majority of adverse reactions with KISQALI were manageable and reversible

Grading according to CTCAE version 4.03.
*Only includes grade 3 ARs.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

KISQALI + letrozole safety profile (continued)

MONALEESA-2: KISQALI + letrozole in 1L postmenopausal patients

LABORATORY ABNORMALITIES OCCURRING IN ≥10% OF PATIENTS[4]

	KISQALI + letrozole (n=334)		Placebo + letrozole (n=330)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
HEMATOLOGY				
Leukocyte count decreased	93	34	29	1.5
Neutrophil count decreased	93	60	24	1.2
Hemoglobin decreased	57	1.8	26	1.2
Lymphocyte count decreased	51	14	22	3.9
Platelet count decreased	29	0.9	6	0.3
CHEMISTRY				
ALT increased	46	10	36	1.2
AST increased	44	7	32	1.5
Creatinine increased	20	0.6	6	0
Phosphorus decreased	13	5	4	0.6
Potassium decreased	11	1.2	7	1.2

- Patients may require dose interruption, reduction, or discontinuation for ARs. Monitoring should include pulmonary symptoms, ECGs, serum electrolytes, LFTs, and CBCs. See Warnings and Precautions for risk of ILD/pneumonitis, SCARs, QT prolongation, hepatobiliary toxicity, neutropenia, and embryo-fetal toxicity
- ARs in patients with visceral metastases receiving KISQALI were consistent with ARs in those without visceral metastases[17]

The majority of adverse reactions with KISQALI were manageable and reversible

IMPORTANT SAFETY INFORMATION (continued)

Increased QT prolongation with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen. Avoid use of tamoxifen with KISQALI. In MONALEESA-7, the observed mean QTcF increase from baseline was >10 ms higher in the tamoxifen + placebo subgroup compared with the nonsteroidal aromatase inhibitor (NSAI) + placebo subgroup. In the placebo arm, an increase of >60 ms from baseline occurred in 6/90 (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%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

KISQALI + fulvestrant safety profile

MONALEESA-3: KISQALI + fulvestrant in 1L/2L postmenopausal patients

ADVERSE REACTIONS OCCURRING IN ≥10% AND ≥2% HIGHER THAN PLACEBO[4]

	KISQALI + fulvestrant (n=483)		Placebo + fulvestrant (n=241)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
GASTROINTESTINAL DISORDERS				
Nausea	45	1.4‡	28	0.8‡
Diarrhea	29	0.6‡	20	0.8‡
Vomiting	27	1.4‡	13	0
Constipation	25	0.8‡	12	0
Abdominal pain	17	1.4‡	13	0.8‡
INFECTIONS AND INFESTATIONS				
Infections*†	42	4.6‡	30	1.7‡
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Rash	23	0.8‡	8	0
Pruritus	20	0.2‡	7	0
Alopecia	19	0	5	0
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS				
Cough	22	0	15	0
Dyspnea	15	1.4	12	1.7
METABOLISM AND NUTRITION DISORDERS				
Decreased appetite	16	0.2‡	13	0
GENERAL DISORDERS AND ADMINISTRATION-SITE CONDITIONS				
Peripheral edema	15	0	7	0
Pyrexia	11	0.2‡	7	0
NERVOUS SYSTEM DISORDERS				
Dizziness	13	0.2‡	8	0

- Dose reductions due to ARs: 32% with KISQALI + fulvestrant
- Permanent discontinuations: 8% with KISQALI + fulvestrant
- The most common ARs (≥20% on the KISQALI arm and ≥2% higher than placebo), including laboratory abnormalities, were decrease in leukocytes, decrease in neutrophils, decrease in lymphocytes, increase in creatinine, decrease in hemoglobin, increase in gamma-glutamyl transferase, increase in AST, nausea, increase in ALT, infections, decrease in platelets, diarrhea, vomiting, constipation, decrease in glucose serum, cough, rash, and pruritus
- Fatal ARs occurred in 1.2% of patients who received KISQALI. Fatal ARs in ≥0.1% of patients receiving KISQALI included cardiac failure, ventricular arrhythmia, pneumonia, acute respiratory distress, pulmonary embolism, and hemorrhagic shock (0.2% each)
- ARs in patients with visceral metastases receiving KISQALI were consistent with ARs in those without visceral metastases[17]

The majority of adverse reactions with KISQALI were manageable and reversible

Grading according to CTCAE version 4.03.
*Infections included urinary and respiratory tract infections, gastroenteritis, and sepsis (1%).
†Includes the following fatal adverse reactions: pneumonia (n=1).
‡Only includes grade 3 ARs.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

KISQALI + fulvestrant safety profile (continued)

MONALEESA-3: KISQALI + fulvestrant in 1L/2L postmenopausal patients

LABORATORY ABNORMALITIES OCCURRING IN ≥10% OF PATIENTS[4]

	KISQALI + fulvestrant (n=483)		Placebo + fulvestrant (n=241)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
HEMATOLOGY				
Leukocyte count decreased	95	26	26	0.4
Neutrophil count decreased	92	53	21	0.8
Lymphocyte count decreased	69	16	35	4.1
Hemoglobin decreased	60	4.3	35	2.9
Platelet count decreased	33	1.9	11	0
CHEMISTRY				
Creatinine increased	65	1	33	0.4
GGT increased	52	8	49	10
AST increased	50	7	43	2.9
ALT increased	44	11	37	1.7
Glucose serum decreased	23	0	18	0
Phosphorus decreased	18	4.6	8	0.8
Albumin decreased	12	0	8	0

- Patients may require dose interruption, reduction, or discontinuation for ARs. Monitoring should include pulmonary symptoms, ECGs, serum electrolytes, LFTs, and CBCs. See Warnings and Precautions for risk of ILD/pneumonitis, SCARs, QT prolongation, hepatobiliary toxicity, neutropenia, and embryo-fetal toxicity
- ARs in patients with visceral metastases receiving KISQALI were consistent with ARs in those without visceral metastases[17]

The majority of adverse reactions with KISQALI were manageable and reversible

IMPORTANT SAFETY INFORMATION (continued)

Hepatotoxicity. In patients with advanced or mBC, drug-induced liver injury and increases in transaminases occurred with KISQALI.

In patients with advanced or mBC (MONALEESA-2, MONALEESA-7, and MONALEESA-3) treated with KISQALI, grade 3 or 4 increases in ALT and AST occurred in 11% and 8%, respectively. Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 92 days for the KISQALI plus aromatase inhibitor or fulvestrant treatment arms. The median time to resolution to grade ≤2 was 21 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment arms. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST >3x the ULN and total bilirubin >2x the ULN, with normal alkaline phosphatase, in the absence of cholestasis (Hy's Law) occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI.

Perform liver function tests (LFTs) before initiating KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

KISQALI + NSAI + goserelin safety profile

MONALEESA-7: KISQALI + NSAI + goserelin in 1L premenopausal patients

ADVERSE REACTIONS OCCURRING IN ≥10% AND ≥2% HIGHER THAN PLACEBO[4]

	KISQALI + NSAI + goserelin (n=248)		Placebo + NSAI + goserelin (n=247)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
INFECTIONS AND INFESTATIONS				
Infections*	36	1.6†	24	0.4†
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS				
Arthralgia	34	0.8†	29	1.2†
GASTROINTESTINAL DISORDERS				
Nausea	32	0	20	0
Constipation	16	0	12	0
Stomatitis	10	0	8	0.4†
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
Alopecia	21	0	13	0
Rash	17	0.4†	9	0
Pruritus	11	0	4	0
GENERAL DISORDERS AND ADMINISTRATION-SITE CONDITIONS				
Pyrexia	17	0.8†	7	0
Pain in extremity	10	0	8	1.2†
RESPIRATORY, THORACIC, AND MEDIASTINAL DISORDERS				
Cough	15	0	10	0

- Dose reductions due to ARs: 33% with KISQALI + NSAI + goserelin
- Permanent discontinuations: 3% with KISQALI + NSAI + goserelin
- The most common ARs (≥20% on the KISQALI arm and ≥2% higher than placebo), including laboratory abnormalities, were decrease in leukocytes, decrease in neutrophils, decrease in hemoglobin, decrease in lymphocytes, increase in gamma-glutamyl transferase, increase in AST, infections, arthralgia, increase in ALT, nausea, decrease in platelets, and alopecia
- ARs in patients with visceral metastases receiving KISQALI were consistent with ARs in those without visceral metastases[17]

The majority of adverse reactions with KISQALI were manageable and reversible

Grading according to CTCAE version 4.03.
*Infections included urinary and respiratory tract infections, gastroenteritis, and sepsis (<1%).
†Only includes grade 3 ARs.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

KISQALI + NSAI + goserelin safety profile (continued)

MONALEESA-7: KISQALI + NSAI + goserelin in 1L premenopausal patients

LABORATORY ABNORMALITIES OCCURRING IN ≥10% OF PATIENTS[4]

	KISQALI + NSAI + goserelin (n=248)		Placebo + NSAI + goserelin (n=247)	
	All grades (%)	Grade 3 or 4 (%)	All grades (%)	Grade 3 or 4 (%)
HEMATOLOGY				
Leukocyte count decreased	93	36	30	0.8
Neutrophil count decreased	92	63	27	2.4
Hemoglobin decreased	84	2.4	51	0.4
Lymphocyte count decreased	55	14	18	2.8
Platelet count decreased	26	0.4	9	0.4
CHEMISTRY				
GGT increased	42	7	42	9
AST increased	37	4.8	35	1.6
ALT increased	33	6	31	1.6
Phosphorus decreased	14	1.6	11	0.8
Potassium decreased	11	1.2	14	1.2
Glucose serum decreased	10	0.4	10	0.4
Creatinine increased	8	0	2	0

- Patients may require dose interruption, reduction, or discontinuation for ARs. Monitoring should include pulmonary symptoms, ECGs, serum electrolytes, LFTs, and CBCs. See Warnings and Precautions for risk of ILD/pneumonitis, SCARs, QT prolongation, hepatobiliary toxicity, neutropenia, and embryo-fetal toxicity
- ARs in patients with visceral metastases receiving KISQALI were consistent with ARs in those without visceral metastases[17]

The majority of adverse reactions with KISQALI were manageable and reversible

IMPORTANT SAFETY INFORMATION (continued)

Neutropenia. KISQALI causes concentration-dependent neutropenia. In patients with advanced or mBC (MONALEESA-2, MONALEESA-7, and MONALEESA-3) who received KISQALI plus NSAI or fulvestrant, 75% had neutropenia, 62% had grade 3/4 decrease in neutrophil count (based on laboratory findings), and 1.7% had febrile neutropenia. The median time to grade ≥2 neutropenia was 17 days. The median time to resolution of grade ≥3 neutropenia to grade <3 was 12 days. Treatment discontinuation due to neutropenia was required in 1% of patients.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

Please see additional Important Safety Information throughout and click here for full Prescribing Information for KISQALI.

KISQALI® ribociclib 200 mg tablets

KISQALI single-strength tablets make dose adjustments

SIMPLE & CONVENIENT

Dose reductions with KISQALI mean no need for new mid-cycle prescriptions or additional costs

- The majority of **adverse reactions** with KISQALI were **manageable and reversible**[1]
- The **survival benefits** observed with KISQALI were **maintained in patients requiring dose reductions**[2]
- In MONALEESA-2, managing adverse reactions with dose reductions **helped patients stay on therapy an average of 6.5 months longer** than those without dose reductions[3]
- **KISQALI is the only CDK4/6 inhibitor** that offers **one tablet strength for straightforward dose reductions**[4]

MONALEESA-2, a phase III study of KISQALI + AI vs placebo + AI in 1L postmenopausal patients: At a median follow-up of 80 months, median OS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with placebo + letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004. OS was a secondary end point; PFS was the primary end point.[4-6]

In a post hoc analysis, at a median follow-up of 80 months, median OS was 66.0 months (95% CI: 57.6-75.7) for patients with ≥1 dose reduction vs 60.6 months (95% CI: 42.5-79.2) for patients without dose reduction; 62.6% of patients (209/334) had ≥1 dose reduction. Efficacy in the placebo comparator arms was not assessed and should be interpreted with caution.[2,3,5]

Permanent discontinuations in MONALEESA-2: 7% with KISQALI + letrozole.[4]

Dose modification of KISQALI is recommended based on individual safety and tolerability.[4]

Please see page 6 for additional safety information.

IMPORTANT SAFETY INFORMATION (continued)

Embryo-fetal toxicity. Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose.

Adverse reactions. Most common (incidence ≥20%) adverse reactions include infections, nausea, fatigue, diarrhea, vomiting, headache, constipation, alopecia, cough, rash, and back pain.

Laboratory abnormalities. Across clinical trials of patients with advanced or metastatic breast cancer, the most common laboratory abnormalities reported in the KISQALI arm (all grades, pooled incidence ≥20%) **were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, AST increased, gamma-glutamyl transferase increased, ALT increased, creatinine increased, platelets decreased, and glucose serum decreased.**

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Important Safety Information

Indications

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

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy

IMPORTANT SAFETY INFORMATION

Interstitial lung disease/pneumonitis. Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors.

In patients with advanced or mBC (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.6% of patients had ILD/pneumonitis of any grade, 0.4% had grade 3/4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have occurred in the postmarketing setting, some resulting in death.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue KISQALI in patients with severe ILD/pneumonitis or any recurrent symptomatic ILD/pneumonitis.

Severe cutaneous adverse reactions. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KISQALI.

If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life-threatening cutaneous reactions during KISQALI treatment.

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner.

Avoid KISQALI in patients who are at significant risk of developing torsades de pointes (TdP), including those with:

- congenital long QT syndrome;
- uncontrolled or significant cardiac disease, recent myocardial infarction, heart failure, unstable angina, bradyarrhythmias, uncontrolled hypertension, high degree atrioventricular block, severe aortic stenosis, or uncontrolled hypothyroidism;
- electrolyte abnormalities;
- taking drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval.

Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation.

In patients with advanced or mBC (MONALEESA-2, MONALEESA-3, and MONALEESA-7) who received 600 mg KISQALI plus NSAI or fulvestrant, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms QTcF increase from baseline. QTcF prolongation was reversible with dose interruption. The majority of QTcF prolongation occurred within the first 4 weeks of KISQALI. There were no reported cases of torsades de pointes. In MONALEESA-2, in the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3.

Perform electrocardiogram (ECG) in all patients prior to starting KISQALI. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of KISQALI, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI.

Increased QT prolongation with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen. Avoid use of tamoxifen with KISQALI. In MONALEESA-7, the observed mean QTcF increase from baseline was >10 ms higher in the tamoxifen + placebo subgroup compared with the nonsteroidal aromatase inhibitor (NSAI) + placebo subgroup. In the placebo arm, an increase of >60 ms from baseline occurred in 6/90 (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%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI.

Hepatotoxicity. In patients with advanced or mBC, drug-induced liver injury and increases in transaminases occurred with KISQALI.

In patients with advanced or mBC (MONALEESA-2, MONALEESA-7, and MONALEESA-3) treated with KISQALI, grade 3 or 4 increases in ALT and AST occurred in 11% and 8%, respectively. Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 92 days for the KISQALI plus aromatase inhibitor or fulvestrant treatment arms. The median time to resolution to grade ≤2 was 21 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment arms. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST >3x the ULN and total bilirubin >2x the ULN, with normal alkaline phosphatase, in the absence of cholestasis (Hy's Law) occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI.

Perform liver function tests (LFTs) before initiating KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation.

Neutropenia. KISQALI causes concentration-dependent neutropenia. In patients with advanced or mBC (MONALEESA-2, MONALEESA-7, and MONALEESA-3) who received KISQALI plus NSAI or fulvestrant, 75% had neutropenia, 62% had grade 3/4 decrease in neutrophil count (based on laboratory findings), and 1.7% had febrile neutropenia. The median time to grade ≥2 neutropenia was 17 days. The median time to resolution of grade ≥3 neutropenia to grade <3 was 12 days. Treatment discontinuation due to neutropenia was required in 1% of patients.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

Embryo-fetal toxicity. Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose.

Adverse reactions. Most common (incidence ≥20%) adverse reactions include infections, nausea, fatigue, diarrhea, vomiting, headache, constipation, alopecia, cough, rash, and back pain.

Laboratory abnormalities. Across clinical trials of patients with advanced or metastatic breast cancer, the most common laboratory abnormalities reported in the KISQALI arm (all grades, pooled incidence ≥20%) **were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, AST increased, gamma-glutamyl transferase increased, ALT increased, creatinine increased, platelets decreased, and glucose serum decreased.**

Please click here for full Prescribing Information for KISQALI.

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Abbreviations and references

Abbreviations: 1L=first line; 2L=second line; AI=aromatase inhibitor; ALT=alanine aminotransferase; ANC=absolute neutrophil count; AR=adverse reaction; AST=aspartate aminotransferase; CBC=complete blood count; CDK=cyclin-dependent kinase; CTCAE=Common Terminology Criteria for Adverse Events; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ET=endocrine therapy; GGT=gamma-glutamyl transferase; HR=hazard ratio; ILD=interstitial lung disease; ITT=intent to treat; LFT=liver function test; LHRH=luteinizing hormone-releasing hormone; mBC=metastatic breast cancer; mOS=median overall survival; NR=not reached; NSAI=nonsteroidal aromatase inhibitor; OS=overall survival; PFS=progression-free survival; PS=performance status; QTcF=QT interval corrected by Fridericia's formula; SCAR=severe cutaneous adverse reaction.

References: 1. Data on file. CLEE011A2301. Novartis Pharmaceuticals Corp; 2016. **2.** Data on file. ML2 OS by dose reduction. Novartis Pharmaceuticals Corp; 2021. **3.** Data on file. CLEE011A2301 additional analysis. Novartis Pharmaceuticals Corp; 2021. **4.** Kisqali. Prescribing information. Novartis Pharmaceuticals Corp. **5.** Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med.* 2022;386(10):942-950. doi:10.1056/NEJMoa2114663 **6.** Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med.* 2016;375(18):1738-1748. doi:10.1056/NEJMoa1609709 **7.** Data on file. CLEE011F2301 additional analysis. Novartis Pharmaceuticals Corp; 2020. **8.** Data on file. OS by dose reduction poster. Novartis Pharmaceuticals Corp; 2020. **9.** Data on file. CLEE011E2301 additional analysis. Novartis Pharmaceuticals Corp; 2020. **10.** Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: MONALEESA-3. *J Clin Oncol.* 2018;36(24):2465-2472. doi:10.1200/JCO.2018.78.9909 **11.** Neven P, Fasching PA, Chia S, et al. Updated overall survival from the MONALEESA-3 trial in postmenopausal women with HR+/HER2− advanced breast cancer receiving first-line ribociclib plus fulvestrant. *Breast Cancer Res.* 2023;25(1):103. doi:10.1186/s13058-023-01701-9 **12.** Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med.* 2020;382(6):514-524. doi:10.1056/NEJMoa1911149 **13.** Tripathy D, Im S-A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19(7):904-915. doi:10.1016/S1470-2045(18)30292-4 **14.** Lu Y-S, Im S-A, Colleoni M, et al. Updated overall survival of ribociclib plus endocrine therapy versus endocrine therapy alone in pre- and perimenopausal patients with HR+/HER2- advanced breast cancer in MONALEESA-7: a phase III randomized clinical trial. *Clin Cancer Res.* 2022;28(5):851-859. doi:10.1158/1078-0432.CCR-21-3032 **15.** Data on file. CLEE011F2301. Novartis Pharmaceuticals Corp; 2021. **16.** Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med.* 2019;381(4):307-316. doi:10.1056/NEJMoa1903765 **17.** Yardley DA, Yap YS, Azim HA, et al. Pooled exploratory analysis of survival in patients with HR+/HER2− advanced breast cancer and visceral metastases treated with ribociclib + endocrine therapy in the MONALEESA trials. Poster presented at: ESMO Congress 2022; September 9-13, 2022; Paris, France. Poster 205P.

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