QT prolongation and ECG testing with KISQALI: Perceptions and facts

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

Indications

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

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

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.

Across clinical trials in patients with advanced or metastatic breast cancer treated with KISQALI in combination with an aromatase inhibitor or fulvestrant ("KISQALI treatment groups"), 1.6% of patients treated with KISQALI 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 been observed in the postmarketing setting, with fatalities reported.

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Treatment decisions greatly impact your patients' lives

Informing yourself about QT prolongation with KISQALI allows you to give your patients the best possible care

Many factors are weighed when deciding on a treatment for your patients with HR+/HER2- mBC. One of those factors may be cardiotoxicity. For KISQALI, the only cardiotoxicity reported in the Prescribing Information is QT prolongation. And while QT prolongation is a serious consideration, understanding the facts around this adverse reaction may help inform your treatment decision and support your overall experience with KISQALI.[1]

Read on to get all the facts.

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, median OS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004.[1-3]

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

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 treatment with KISQALI immediately and evaluate the patient. Permanently discontinue treatment with KISQALI in patients with recurrent symptomatic or severe 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.

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Perception #1

QT prolongation is a common problem with KISQALI

Click to reveal the fact

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

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. Consultation with a dermatologist is recommended.

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. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation. Across KISQALI treatment groups, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms increase from baseline in QTcF intervals. These electrocardiogram (ECG) changes were reversible with dose interruption and most occurred within the first 4 weeks of treatment. No cases of torsades de pointes were reported. In MONALEESA-2, on 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.

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Perception #1

QT prolongation is a common problem with KISQALI

Fact:

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

In a pooled analysis across 3 phase III trials of 1054 pre- and postmenopausal patients treated with KISQALI + an AI or fulvestrant[1]:

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

6.0% (61/1054) experienced a >60 ms increase from baseline in QTcF interval

There were no reported cases of torsades de pointes.[1]

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner.[1]

In MONALEESA-2, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation.[1]

The average incidence of QTcF >480 ms across all 3 trials was 5.4% for patients taking KISQALI[4-6]

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

IMPORTANT SAFETY INFORMATION (continued)

QT interval prolongation (continued). Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of treatment, at the beginning of each of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting therapy with KISQALI.

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Perception #2

Severe QT prolongation with KISQALI is very common

Click to reveal the fact

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

IMPORTANT SAFETY INFORMATION (continued)

QT interval prolongation (continued). Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong the QT interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval.

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Perception #2

Severe QT prolongation with KISQALI is very common

(QTcF >500 ms or >60 ms change from baseline)

Fact:

For those patients who experienced QT prolongation, the incidence of severe cases was low

Incidence of severe QT prolongation in patients receiving KISQALI[4-6]

	>500 ms postbaseline QTcF value	>60 ms increase from baseline in QTcF intervals
MONALEESA-2: KISQALI + AI in 1L postmenopausal patients	<1% (2/334)	3% (10/334)
MONALEESA-3: KISQALI + fulvestrant in 1L/2L postmenopausal patients	2% (8/483)	7% (31/483)
MONALEESA-7: KISQALI + AI in 1L premenopausal patients	NOT REPORTED	7% (18/245)

In MONALEESA-2, in the KISQALI + AI treatment arm, there was 1 (0.3%) case of sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-3 or MONALEESA-7.[1]

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

IMPORTANT SAFETY INFORMATION (continued)

Increased QT prolongation with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF increase from baseline was ≥10 ms higher in the tamoxifen + placebo subgroup compared with the non-steroidal 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.

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Perception #3

QT prolongation with KISQALI is irreversible

Click to reveal the fact

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

IMPORTANT SAFETY INFORMATION (continued)

Hepatobiliary toxicity. Across KISQALI treatment groups, increases in transaminases were observed. Across all trials, grade 3/4 increases in alanine aminotransferase (ALT) (11% vs 2.1%) and aspartate aminotransferase (AST) (8% vs 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 92 days and median time to resolution to grade ≤2 was 21 days for the KISQALI treatment groups.

In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than 3 times the upper limit of normal (ULN) and total bilirubin greater than 2 times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

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Perception #3

QT prolongation with KISQALI is irreversible

Fact:

QT prolongation with KISQALI is reversible

ECG changes in patients were manageable and reversible with dose interruption and reduction[1]

DOSE MODIFICATION AND MANAGEMENT FOR QT PROLONGATION	
ECGs with QTcF >480 ms	Interrupt KISQALI treatment • If QTcF prolongation resolves to <481 ms, resume treatment at the next lower dose level; • If QTcF ≥481 ms recurs, interrupt dose until QTcF resolves to <481 ms, then resume KISQALI at next lower dose level
ECGs with QTcF >500 ms	Interrupt KISQALI treatment if QTcF >500 ms • If QTcF prolongation resolves to <481 ms, resume treatment at the next lower dose level Permanently discontinue KISQALI if QTcF interval prolongation is either >500 ms or >60 ms change from baseline AND associated with any of the following: torsades de pointes, polymorphic ventricular tachycardia, unexplained syncope, or signs/symptoms of serious arrhythmia

In case of QTcF prolongation at any given time during treatment, more frequent ECG monitoring is recommended.[1]

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

IMPORTANT SAFETY INFORMATION (continued)

Hepatobiliary toxicity (continued). Perform liver function tests (LFTs) before initiating therapy with 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. Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.

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Perception #4

ECG testing must continue for the duration of therapy and is an added complication

Click to reveal the fact

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

IMPORTANT SAFETY INFORMATION (continued)

Neutropenia. Across KISQALI treatment groups neutropenia was the most frequently reported adverse reaction (AR) (75%), and a grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 62% of patients in the KISQALI treatment groups. Among the patients who had grade 2, 3, or 4 neutropenia, the median time to grade ≥2 was 17 days. The median time to resolution of grade ≥3 (to normalization or grade <3) was 12 days in the KISQALI treatment groups. Febrile neutropenia was reported in 1.7% of patients in the KISQALI treatment groups. Treatment discontinuation due to neutropenia was 1%.

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.

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Perception #4

ECG testing must continue for the duration of therapy and is an added complication

Fact:

Testing is straightforward, with only 3 ECGs required, all within the first 30 days of treatment*

ECGs are only required during the first 30 days*— when the majority of QT prolongation cases occurred in clinical trials[1]

ECG MONITORING		
Baseline		✓
Cycle 1	Day 14	✓
Cycle 2	Day 1	✓ (final scheduled)

Monitoring requirements based on a 28-day treatment cycle.

*Additional monitoring may be required as clinically indicated.

- **KISQALI should only be initiated in patients with QTcF <450 ms. In case of QTcF prolongation during therapy, more frequent monitoring is recommended**

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

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. In animal reproduction studies, administration of KISQALI to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve. 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.

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Optimizing patients' cardiovascular health when considering KISQALI

Considerations prior to initiating therapy

Patients may have multifactorial baseline cardiac issues or cardiovascular risk factors that can be managed. If baseline cardiovascular conditions can be managed and patients are not on medications that prolong the QT interval, treatment with KISQALI may be considered where appropriate.[1]

- Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:
  - —long QT syndrome
  - —uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
  - —electrolyte abnormalities
- KISQALI should only be initiated in patients with QTcF <450 ms
- Monitor serum electrolytes prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any electrolyte abnormalities prior to treatment

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

Select drugs that prolong the QT interval

- Avoid using KISQALI with drugs known to prolong the QT interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval[1]
  - —Antiarrhythmic medicines (including, but not limited to, amiodarone, disopyramide, procainamide, quinidine, and sotalol)
  - —chloroquine
  - —clarithromycin
  - —methadone
  - —ondansetron
  - —pimozide
  - —halofantrine
  - —haloperidol
  - —moxifloxacin
  - —bepridil
  - —grapefruit or grapefruit juice

IMPORTANT SAFETY INFORMATION (continued)

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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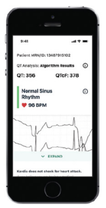
ECG testing made accessible

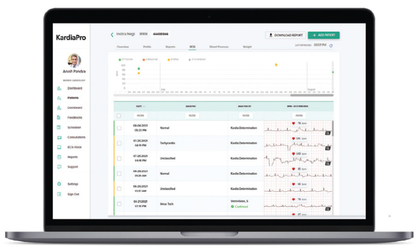
The KISQALI ECG Device Monitoring Program can provide you with an AliveCor® KardiaMobile 6L ECG device so you and your patients can receive their ECG testing in seconds in your office or at home.

For in-office readings, use the **KardiaStation Professional app** to record an ECG with the KardiaMobile 6L



The KardiaStation Professional app is available for download on Android™ and iOS devices.

Use the **KardiaPro web-based portal** to access QTcF results from in-office and at-home readings



Limitations apply. KISQALI ECG Device Monitoring Program is only permitted to be used for monitoring or evaluating a patient for the current or potential administration of ribociclib. The equipment or services are not permitted to be used for any purpose outside of the scope of the program. You must not bill any entity or person for any equipment or services relating to the provision or interpretation of the ECG. In the event that you fail to abide by the rules of the KISQALI ECG Device Monitoring Program, your participation in the program may be terminated or modified at any time without prior notice, and you may be subject to additional remedies. Additional terms and conditions apply.

Sunshine Act costs may apply.

Watch this informative video to learn about the AliveCor® KardiaMobile 6L ECG device and how to use it

If you are unable to perform ECGs in-office, contact Novartis Oncology about the ECG Device Monitoring Program

In a clinical trial, increased QT prolongation was observed with concomitant use of tamoxifen. **KISQALI is not indicated for concomitant use with tamoxifen.**[1]

IMPORTANT SAFETY INFORMATION

Warnings and precautions with KISQALI include interstitial lung disease/pneumonitis, severe cutaneous adverse reactions, QT interval prolongation, increased QT prolongation with concomitant use of tamoxifen, hepatobiliary toxicity, neutropenia, and embryo-fetal toxicity.

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References

1L=first line; 2L=second line; AI=aromatase inhibitor; CYP3A=cytochrome P450, family 3, subfamily A; ECG=electrocardiogram; HR=hazard ratio; mBC=metastatic breast cancer; OS=overall survival; PFS=progression-free survival; QTcF=QT interval corrected by Fridericia's formula.

References: 1. Kisqali. Prescribing information. Novartis Pharmaceuticals Corp. **2.** 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 **3.** 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 **4.** Hortobagyi GN, Stemmer SM, Burris HA, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. *Ann Oncol.* 2018;29(7):1541-1547. **5.** 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 **6.** 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

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