Overall survival with KISQALI + AI in 1L postmenopausal patients with HR+/HER2- mBC

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.

> *The **MONALEESA-2 trial** provides evidence of a significant improvement in overall survival with a nonsteroidal aromatase inhibitor plus a CDK4/6 inhibitor in postmenopausal women, as well as impressive median survival to date (63.9 months) among women with HR-positive, HER2-negative advanced breast cancer.*
>
> — Hortobagyi GN, et al

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MONALEESA-2: 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=0.76 (95% CI: 0.63-0.93); *P*=0.008. PFS was the primary end point.

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.

1L=first line; AI=aromatase inhibitor; CDK=cyclin-dependent kinase; HR=hazard ratio; mBC=metastatic breast cancer; OS=overall survival; PFS=progression-free survival.

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TRIAL DESIGN | EFFICACY | LANDMARK SURVIVAL ESTIMATES | SUBGROUP ANALYSES | TIME TO CHEMOTHERAPY | PATIENT DISPOSITION | SUBSEQUENT THERAPIES | SAFETY | CONCLUSION

Trial design

MONALEESA-2 was a randomized, double-blind, placebo-controlled phase III study that assessed the efficacy and safety of KISQALI + letrozole as a first-line treatment for postmenopausal patients with HR+/HER2- mBC[1,2]

- Postmenopausal women with HR+/HER2- mBC
- No prior therapy for advanced disease
- Prior (neo)adjuvant ET allowed
- N=668

- Treatment-free interval >12 months from completion of treatment until randomization required for prior NSAI use

Randomization (1:1)

Stratified by

- Presence/absence of liver/lung metastases

KISQALI (600 mg/day orally)
3 weeks on/1 week off
+
Letrozole (2.5 mg/day)
n=334

Placebo
+
Letrozole (2.5 mg/day)
n=334

Primary end point
- Progression-free survival (locally assessed per RECIST v1.1)

Key secondary end point
- Overall survival

Other secondary end points
- Overall response rate
- Clinical benefit rate
- Safety
- Quality of life

Additional end points
- Time to chemotherapy

> *"Significant improvement in overall survival is one of the primary goals in the treatment of advanced breast cancer, in addition to maintaining or improving quality of life."* — Hortobagyi GN, et al

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.

ET=endocrine therapy; NSAI=nonsteroidal aromatase inhibitor; RECIST=response evaluation criteria in solid tumors.

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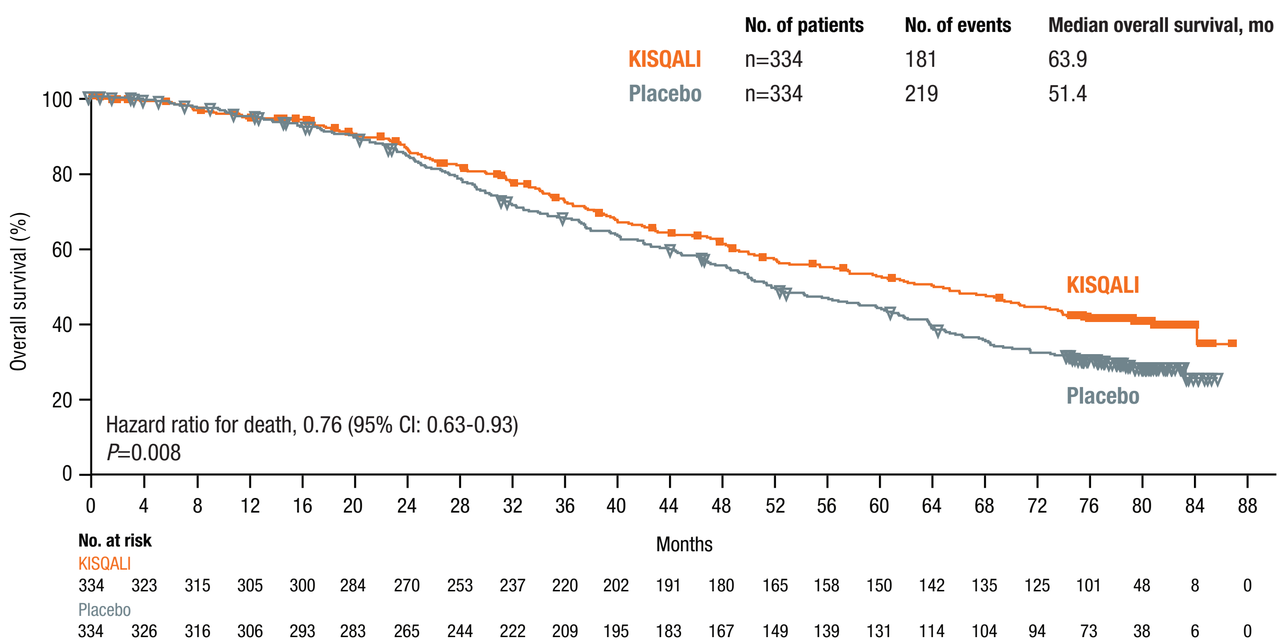
Overall survival with KISQALI + letrozole in 1L postmenopausal patients

At a median follow-up of 80 months

OVERALL SURVIVAL | KISQALI + LETROZOLE[1]



Hazard ratios are based on stratified Cox model.

PFS was the primary end point.[2]

63.9 MONTHS mOS WITH KISQALI + LETROZOLE (95% CI: 52.4-71.0)[1]

>1-YEAR INCREASE IN mOS

"The MONALEESA-2 trial provides…impressive median survival to date (63.9 months) among women with HR-positive, HER2-negative advanced breast cancer." — Hortobagyi GN, et al

IMPORTANT SAFETY INFORMATION (continued)

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. Consultation with a dermatologist is recommended.

mOS=median overall survival.

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Landmark survival estimates

	4-YEAR OS[1]	5-YEAR OS[1]	6-YEAR OS[1]
KISQALI + letrozole n=334	60.9% (95% CI: 55.2%-66.1%)	52.3% (95% CI: 46.5%-57.7%)	44.2% (95% CI: 38.5%-49.8%)
Placebo + letrozole n=334	55.2% (95% CI: 49.5%-60.5%)	43.9% (95% CI: 38.3%-49.4%)	32.0% (95% CI: 26.8%-37.3%)
Landmark survival difference	5.7%	8.4%	12.2%

6-YEAR SURVIVAL LANDMARKS
DIFFERED BY 12%
WITH KISQALI + LETROZOLE VS PLACEBO + LETROZOLE[1]

> *"The Kaplan-Meier analysis shows that the overall survival benefit of ribociclib began to emerge at approximately 20 months and continued to increase with longer follow-up, as indicated by survival at 5 years and 6 years."* — Hortobagyi GN, et al

For overall survival Kaplan-Meier curve, see previous page.

- Statistically significant improvement in overall survival in the ITT population; *P*=0.008 (HR=0.76 [95% CI: 0.63-0.93])[1]

IMPORTANT SAFETY INFORMATION (continued)

Severe cutaneous adverse reactions (continued). 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.

ITT=intent to treat.

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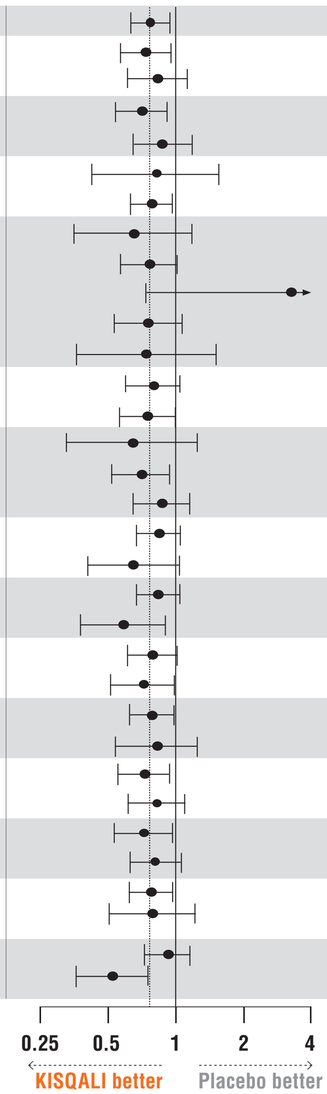
Overall survival benefit across subgroups consistent with results in the overall population

EXPLORATORY SUBGROUP ANALYSES[1]

SUBGROUP		KISQALI + letrozole n/N	KISQALI + letrozole Median OS, mo	Placebo + letrozole n/N	Placebo + letrozole Median OS, mo	Hazard ratio (95% CI)
All patients		181/334	63.9	219/334	51.4	0.76 (0.63-0.93)
ECOG performance status	0	103/204	68.7	135/202	54.3	0.73 (0.56-0.94)
	1	78/130	57.4	84/132	46.8	0.82 (0.60-1.12)
Age	<65 years	100/184	59.7	129/189	46.7	0.69 (0.53-0.90)
	≥65 years	81/150	68.0	90/145	60.4	0.87 (0.64-1.17)
Race	Asian	19/28	51.0	19/23	52.5	0.80 (0.42-1.54)
	Non-Asian	151/281	63.9	184/287	51.4	0.77 (0.62-0.96)
Region	Asia	20/35	65.3	24/33	51.2	0.64 (0.35-1.16)
	Europe	83/150	62.1	101/146	50.3	0.75 (0.56-1.01)
	Latin America	5/7	37.9	4/7	66.3	3.21 (0.73-14.12)
	North America	57/108	68.7	74/121	52.8	0.75 (0.53-1.06)
	Other	16/34	67.3	16/27	58.5	0.73 (0.36-1.50)
Prior chemotherapy	No	91/188	69.5	117/189	58.5	0.78 (0.59-1.03)
	Yes	90/146	52.0	102/145	44.7	0.74 (0.56-0.98)
Prior hormonal agent	NSAI and others	18/30	60.6	18/23	52.5	0.63 (0.32-1.24)
	None	76/158	68.9	103/162	52.8	0.69 (0.52-0.94)
	Tamoxifen	87/146	56.5	98/149	50.1	0.86 (0.64-1.15)
PGR	+	146/271	65.3	171/278	57.5	0.83 (0.66-1.04)
	–	32/55	51.1	41/49	37.7	0.64 (0.40-1.02)
ER + PGR	++	144/269	65.3	170/277	56.9	0.82 (0.66-1.03)
	Other	37/65	55.5	49/57	37.7	0.58 (0.37-0.89)
Number of metastatic sites	<3	115/220	68.0	136/222	56.1	0.78 (0.61-1.00)
	≥3	66/114	55.5	83/112	46.5	0.71 (0.51-0.98)
Liver involvement	No	145/275	68.0	163/262	56.9	0.77 (0.62-0.97)
	Yes	36/59	37.7	56/72	38.1	0.81 (0.54-1.24)
Lung involvement	No	97/181	66.1	119/185	50.5	0.72 (0.55-0.94)
	Yes	84/153	59.7	100/149	52.1	0.81 (0.61-1.09)
Liver or lung involvement	No	80/152	70.5	90/144	52.4	0.71 (0.53-0.96)
	Yes	101/182	55.5	129/190	51.4	0.81 (0.62-1.05)
Bone lesion only metastasis	No	144/265	61.5	172/255	50.3	0.77 (0.61-0.96)
	Yes	37/69	72.6	47/79	56.4	0.78 (0.50-1.21)
De novo	No	134/220	52.4	144/221	51.2	0.91 (0.72-1.15)
	Yes	47/114	NE	75/113	52.8	0.52 (0.36-0.74)



- Randomization was stratified by the presence or absence of liver or lung metastases[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.

ECOG=Eastern Cooperative Oncology Group; ER=estrogen receptor; NE=not estimable; PGR=progesterone receptor.

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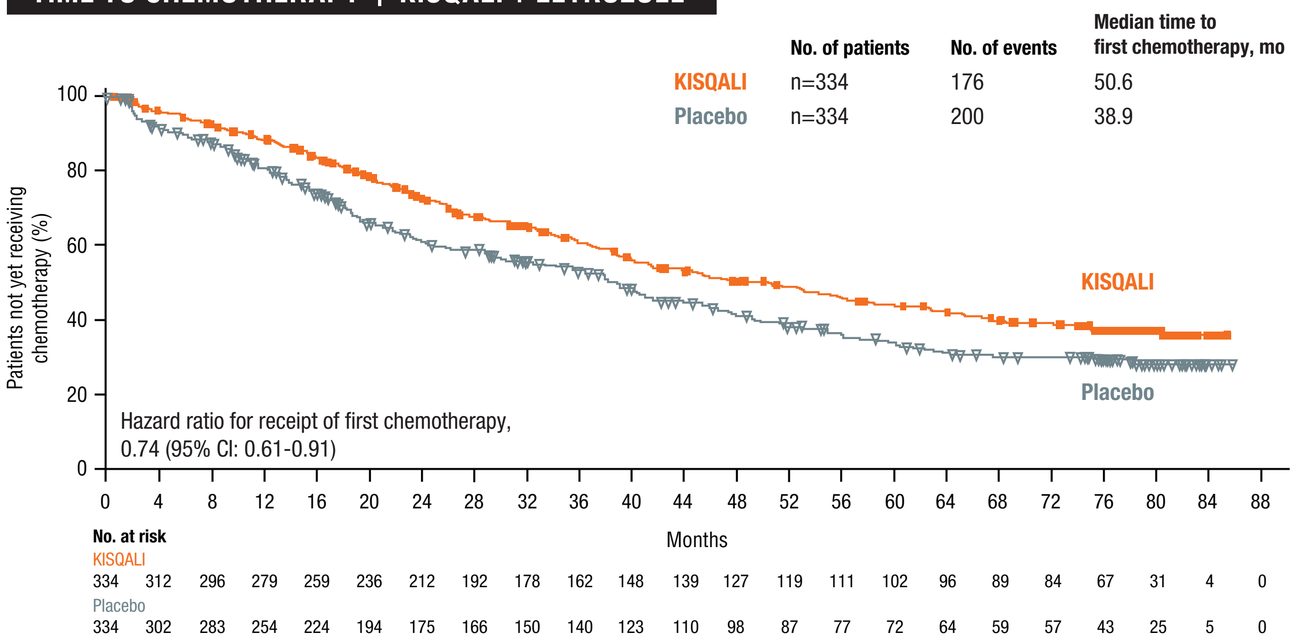
Median time to chemotherapy delayed over 4 years

At a median follow-up of 80 months

TIME TO CHEMOTHERAPY | KISQALI + LETROZOLE[3]



50.6 MONTHS mTTC WITH KISQALI + LETROZOLE[1]

- Time to chemotherapy was an exploratory end point and was defined as the time from randomization to the beginning of the first chemotherapy after discontinuing study treatment[4]
- There was no prespecified statistical procedure controlling for type 1 error

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.

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.

mTTC=median time to chemotherapy.

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Patient disposition

	KISQALI + letrozole[3] (n=334)	Placebo + letrozole[3] (n=334)	All patients[3] (N=668)
Patients treated—no. (%)			
Treatment ongoing	30 (9.0)	17 (5.1)	47 (7.0)
Ended treatment	304 (91.0)	313 (93.7)	617 (92.4)
Reason for end of treatment—no. (%)			
Adverse event	37 (11.1)	9 (2.7)	46 (6.9)
Physician decision	25 (7.5)	20 (6.0)	45 (6.7)
Progressive disease	204 (61.1)	263 (78.7)	467 (69.9)
Protocol deviation	3 (0.9)	1 (0.3)	4 (0.6)
Patient/guardian decision	29 (8.7)	23 (6.9)	52 (7.8)
Death	6 (1.8)	1 (0.3)	7 (1.0)

Four patients in the placebo arm did not receive study treatment.
Treatment ongoing refers to patients continuing study treatment at the time of data cutoff (June 10, 2021).

9% OF PATIENTS REMAINED ON TREATMENT AT THE TIME OF DATA CUTOFF, WITH A MEDIAN FOLLOW-UP OF 80 MONTHS[1,3]

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.

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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Subsequent therapies

	KISQALI + letrozole[3] (n=334)	Placebo + letrozole[3] (n=334)
No. of patients who discontinued study treatment—n (%)	**304 (91.0)**	**317 (94.9)**
Chemotherapy		
Pyrimidine analogues	129 (42.4)	155 (48.9)
Taxanes	100 (32.9)	128 (40.4)
Platinum compounds	30 (9.9)	24 (7.6)
Anthracyclines	55 (18.1)	69 (21.8)
Endocrine therapy		
Aromatase inhibitors	138 (45.4)	138 (43.5)
Exemestane	96 (31.6)	96 (30.3)
Letrozole	64 (21.1)	49 (15.5)
Anastrozole	5 (1.6)	10 (3.2)
Antiestrogens	156 (51.3)	193 (60.9)
Fulvestrant	145 (47.7)	175 (55.2)
Tamoxifen	27 (8.9)	41 (12.9)
Kinase inhibitors	131 (43.1)	147 (46.4)
Everolimus	90 (29.6)	90 (28.4)
Palbociclib	49 (16.1)	100 (31.5)
Ribociclib	14 (4.6)	6 (1.9)
Abemaciclib	8 (2.6)	12 (3.8)
Other		
Alpelisib	11 (3.6)	4 (1.3)

Percentages reported are based on the number of patients who discontinued study treatment. A patient with multiple occurrences is only counted once in the total row.

> *"Although subsequent use of CDK4/6 inhibitors in any line of therapy was more frequent in the placebo group than in the ribociclib group (34.4% vs. 21.7%), the ribociclib group had a significant overall survival benefit."*
>
> — Hortobagyi GN, et al

- Statistically significant improvement in overall survival in the ITT population; *P*=0.008 (HR=0.76 [95% CI: 0.63-0.93])[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%.

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Safety summary

The most common adverse event occurring in at least 15% of patients in any group was neutropenia (63.8% for KISQALI vs 1.2% for placebo).[1,3]

Additional key grade 3/4 adverse events of special interest in the KISQALI and placebo arms were[1]:

- Hepatobiliary toxic effects (14.4% for KISQALI vs 4.8% for placebo)
- Prolonged QT interval (4.5% for KISQALI vs 2.1% for placebo)
- Grade 3 interstitial lung disease/pneumonitis was observed in 2 patients (0.6%) in the KISQALI group and 0 patients in the placebo group

  —There were no grade 4 events or deaths related to interstitial lung disease/pneumonitis in the KISQALI arm

> *"Adverse-event profiles in both trial groups were consistent with previously reported results...no new safety signals were revealed."* — Hortobagyi GN, et al

IMPORTANT SAFETY INFORMATION (continued)

Neutropenia (continued). 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. 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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Unrivaled overall survival data across 3 phase III KISQALI trials

2019:

MONALEESA-7
KISQALI + AI in 1L premenopausal patients

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.

2020:

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

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.

2022:

MONALEESA-2
KISQALI + AI in 1L postmenopausal patients

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.

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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.**

2L=second line.

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KISQALI® ribociclib 200 mg tablets

The only CDK4/6 inhibitor with statistically significant overall survival proven across 3 phase III trials

> *Taken together, the MONALEESA trials of ribociclib have shown a consistent overall survival benefit regardless of accompanying endocrine therapy, line of therapy, or menopausal status.* — Hortobagyi GN, et al

MONALEESA-7
KISQALI + AI in 1L premenopausal patients

At a median follow-up of 54 months (exploratory analysis), median OS was 58.7 months with KISQALI + NSAI + goserelin (95% CI: 48.5-NR) vs 47.7 months with 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. PFS was the primary end point.[5-7]

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

At a median follow-up of 71 months (exploratory analysis), in a 1L subgroup analysis, median OS was 67.6 months (95% CI: 59.6-NR) with KISQALI + fulvestrant 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. PFS was the primary end point.[8-11]

MONALEESA-2
KISQALI + 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 letrozole (95% CI: 47.2-59.7); HR=0.76 (95% CI: 0.63-0.93); *P*=0.008. PFS was the primary end point.[1,2]

Results from the 71-month exploratory analysis from MONALEESA-3 and 54-month exploratory analysis from MONALEESA-7 were not prespecified and were observational in nature; as such, there was no prespecified statistical procedure controlling for type 1 error.

IMPORTANT SAFETY INFORMATION

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

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

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

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References

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