MONALEESA Clinical Trial Program

Breast Cancer Franchise

The breadth and innovation associated with the MONALEESA clinical trial program are emblematic of Novartis' deep and longstanding commitment to all patients with advanced or metastatic breast cancer

With more than **2,000 patients enrolled across three trials**, the MONALEESA clinical trial program is the largest industry-sponsored Phase III registration program researching a CDK4/6 inhibitor in HR+/HER2- advanced breast cancer[1]

MONALEESA-7 was the first and only Phase III trial entirely dedicated to evaluating a CDK4/6 inhibitor in **premenopausal women** with HR+/HER2- advanced breast cancer[2]

MONALEESA-3 is the only randomized Phase III trial to study a **CDK4/6 inhibitor plus fulvestrant** in the first-line setting showing efficacy in patients with de novo advanced breast cancer and those who had not received adjuvant therapy in more than a year[3]

	MONALEESA-2	MONALEESA-7	MONALEESA-3
About the Trial	• Kisqali + letrozole vs letrozole alone as first-line treatment for postmenopausal women with HR+/HER2- advanced breast cancer • 668 women enrolled[4]	• Kisqali + aromatase inhibitor + goserelin vs endocrine therapy + goserelin alone as first-line treatment for premenopausal women with HR+/HER2- advanced breast cancer • 672 women enrolled[2]	• Kisqali + fulvestrant vs fulvestrant alone as first- or second-line treatment* for postmenopausal women with HR+/HER2- advanced breast cancer • 726 women enrolled[3]
Efficacy Results	• Kisqali plus letrozole significantly prolonged PFS compared to letrozole alone[4] • Median PFS[4]: » 25.3 months for Kisqali plus letrozole vs » 16.0 months for letrozole alone » HR=0.568 (95% CI: 0.457-0.704; p<0.0001)	• Kisqali + aromatase inhibitor + goserelin significantly prolonged PFS compared to aromatase inhibitor + goserelin alone[2] • Median PFS[2]: » 27.5 months for Kisqali combination therapy vs » 13.8 months for aromatase inhibitor + goserelin » HR=0.569 (95% CI: 0.436-0.743; p<0.0001)	• Kisqali + fulvestrant significantly prolonged PFS compared to fulvestrant alone[3] • Median PFS[3]: » 20.5 months for Kisqali + fulvestrant vs » 12.8 months for fulvestrant alone » HR=0.593 (95% CI: 0.480-0.732; p<0.0001) • Median PFS as first-line therapy[3]: » Not reached for Kisqali + fulvestrant vs » 18.3 months for fulvestrant alone » HR=0.577 (95% CI: 0.415-0.802; p<0.0001)
Safety Results	• Most common grade 3/4 adverse events (AEs) for Kisqali + letrozole vs letrozole alone[4]: » Neutropenia (62.0% vs 1.2%) » Leukopenia (21.3% vs .9%) • Discontinuation rate due to AEs: 8.1% (Kisqali plus letrozole) vs 2.4% (letrozole alone)[4]	• Most common grade 3/4 AEs for Kisqali combination therapy vs endocrine therapy + goserelin[2]: » Neutropenia (60.6% vs 3.6%) » Leukopenia (14.3% vs 1.2%) • Discontinuation rate due to AEs: 3.6% (Kisqali combination therapy) vs 3.0% (endocrine therapy + goserelin alone)[2]	• Most common grade 3/4 AEs for Kisqali + fulvestrant vs fulvestrant alone[3]: » Neutropenia (53.4% vs 0.0%) » Leukopenia (14.1% vs 0.0%) • Discontinuation rate due to AEs: 8.5% (Kisqali + fulvestrant) vs 4.1% (fulvestrant alone)[3]

**First-line setting includes de novo patients and those whose disease relapsed >12 months since end of neo(adjuvant) endocrine therapy; second-line setting includes patients who relapsed <12 months since end of neo(adjuvant) endocrine therapy and received up to one line of prior endocrine therapy for advanced disease*

***MONALEESA-7 also evaluated Kisqali + tamoxifen + goserelin compared to tamoxifen + goserelin alone. These data are not being evaluated by health authorities*

In the European Union, Kisqali is not indicated in combination with an aromatase inhibitor and goserelin as first-line treatment for premenopausal women with HR+/HER2- advanced breast cancer. Kisqali is not indicated in combination with fulvestrant as first- or second-line therapy for postemenopausal women with HR+/HER2- advanced breast cancer.

Please see Important Safety Information on the following page.

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Important Safety Information from the Kisqali EU SmPC

The most common ADRs and the most common grade 3/4 ADRs (reported at a frequency ≥20% and ≥2% respectively) for which the frequency for Kisqali plus letrozole exceeds the frequency for placebo plus letrozole were blood and lymphatic system disorders (including abnormally low neutrophil and white blood cell count), headache, back pain, nausea, fatigue, diarrhea, vomiting, constipation, hair loss and rash and abnormally low levels of neutrophils or white blood cells, abnormal liver function tests (increased alanine and aspartate aminotransferase), abnormally low lymphocyte count, low levels of phosphate, vomiting, nausea, fatigue and back pain, respectively. Low levels of neutrophils was the most commonly seen severe adverse event; fever in addition to a low neutrophil count was reported in 1.5% of patients.

Kisqali can cause serious side effects such as a significant decrease in neutrophil count, abnormal liver function tests and may have an effect on the electrical activity of the heart known as QT/QTc interval prolongation, which could lead to disturbances in heart rhythm. As a precaution, patients should have complete blood counts, liver function, and serum electrolyte levels measured prior to starting treatment as well as during treatment with Kisqali. Patients should also have their heart activity checked before and monitored during treatment.

The efficacy and safety of ribociclib have not been studied in patients with critical visceral disease.

The use of Kisqali with medicinal products known to prolong QTc interval or strong CYP3A4 inhibitors should be avoided as this may lead to prolongation of the QT/QTc interval. If treatment with a strong CYP3A4 inhibitor cannot be avoided, the Kisqali dose should be reduced. Concomitant administration with other medicines that could affect cardiac repolarization or prolong the QT/QTc interval should be taken into account prior to and during treatment with Kisqali. Patients taking sensitive CYP3A4 substrates with narrow therapeutic index should use caution because of the increased risk of adverse events that may occur if these medications are co-administered with Kisqali.

Kisqali contains soya lecithin and therefore it should not be taken by patients who are allergic to peanut or soya.

Animal studies suggest that Kisqali may cause fetal harm in pregnant women. Therefore, as a precaution, women of childbearing potential should use effective contraception while receiving Kisqali during treatment and up to 21 days after stopping treatment. Women should not breast feed for at least 21 days after the last dose of Kisqali. Kisqali may affect fertility in males.

Please see full Prescribing Information for Kisqali, available at **www.kisqali.com**.

References:

1. Novartis data on file.
2. Tripathy D, Im SA, 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. The Lancet Oncology 2018.
3. Slamon, J et al. Ribociclib (RIB) + fulvestrant (FUL) in postmenopausal women with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC): Results from MONALEESA-3. Journal of Clinical Oncology 2018.
4. Hortobagyi G, Stemmer S, Burris H, 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. Annals of Oncology 2018.

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