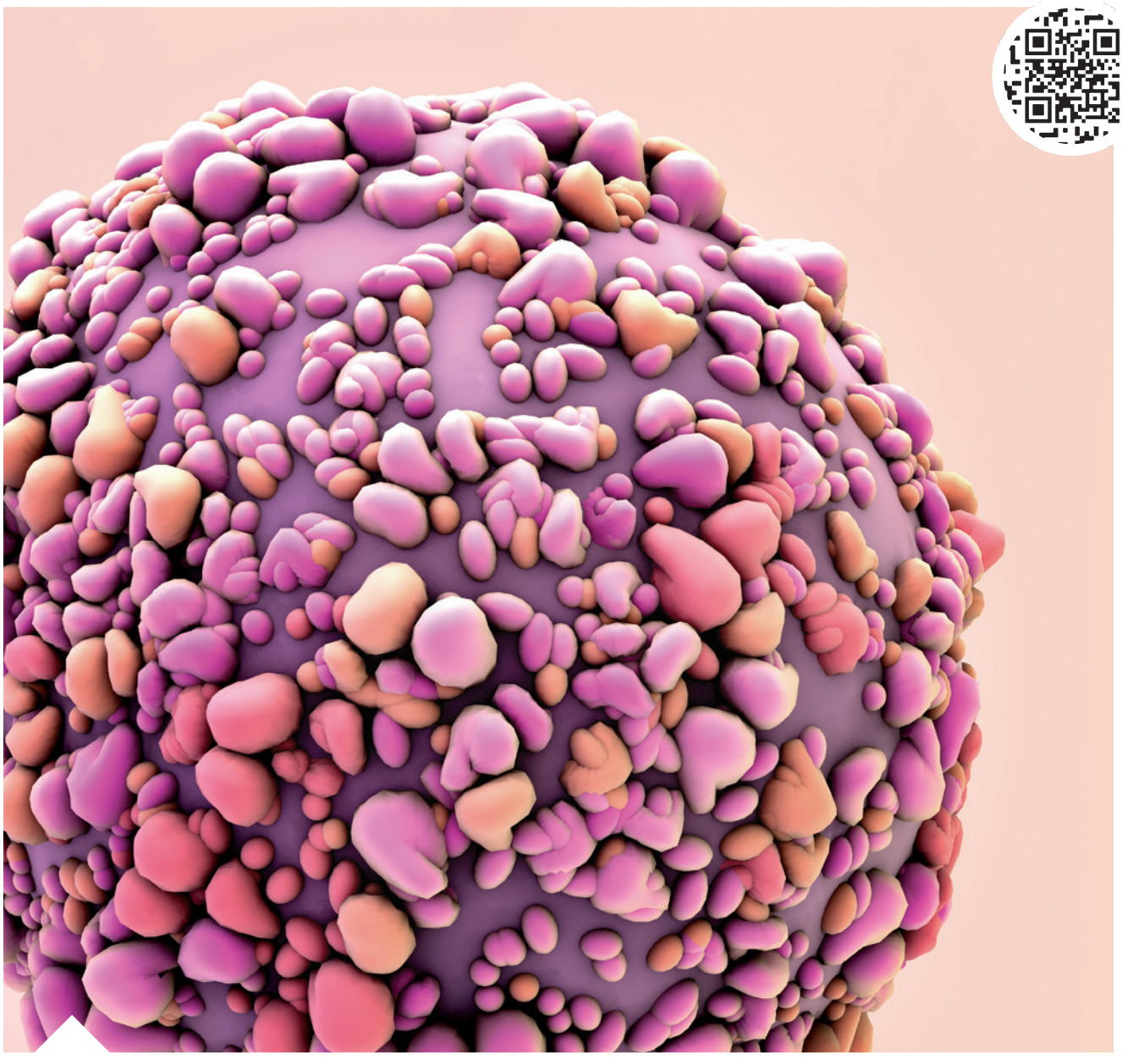
Health Monitor®

# Clinician Update

## Metastatic Breast Cancer

Scan here for a behind-the-scenes look at the case study on p. 29



# TARGETED THERAPIES: How kinase inhibitors are changing the paradigm of care

Today, recent options allow more tailored treatment after resistance to endocrine therapy occurs. Here's what to know about a key class that targets the kinase pathway.

**The landscape of breast cancer treatment has changed dramatically** in recent years, giving oncologists and their patients new choices and increased optimism. These advancements have included more options for treating hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (mBC), a type that becomes more difficult to treat as the disease progresses.[1]

"Historically, endocrine therapy has served as the foundation of treatment for HR+/HER2- mBC, exploiting the tumor's reliance on hormonal pathways for proliferation," explains Francisco J. Esteva, MD, PhD, Chief, Division of Hematology and Medical Oncology, Lenox Hill Hospital, New York. "Yet the challenge of overcoming resistance to endocrine therapy—whether inherent or developed—persists."

*Continued on p. 4* ►

Illustration by Anna Godeassi

Illustration by Anna Godeassi

## A new reality: longer progression-free and overall survival

Fortunately, a new age of precision medicine has begun thanks to the next generation of therapeutics, enabling more targeted and less toxic treatments.[1,2] A major advance has been the arrival of cyclin-dependent kinase (CDK)4/6 inhibitors.

"The introduction of CDK4/6 inhibitors, used in tandem with aromatase inhibitors or fulvestrant, marks a critical evolution in treatment, demonstrably enhancing progression-free survival and, according to certain randomized clinical trials, even overall survival," Dr. Esteva says. "The availability of CDK4/6 inhibitors has significantly altered the front-line treatment approach for postmenopausal women diagnosed with HR+/HER2- mBC." In fact, a recent review showed that among patients with HR+/HER2- mBC, median overall survival (OS) increased by nearly 25% following the emergence of these novel therapies.[3]

## Advantages of CDK4/6 inhibitors

CDK4/6 enzymes play an important role in the proliferation of cancer cells distinct from endocrine pathways such as those of aromatase inhibitors. "These innovative agents impede the activity of CDK 4 and 6, crucial proteins in cell cycle progression," he says, ultimately stalling tumor proliferation in synergy with aromatase inhibitors, which target cancer growth driven by estrogen. It is this dual-mechanism strategy that markedly enhances response rates and treatment outcomes.

Extensive research shows CDK4/6 inhibitors have several advantages over conventional therapies, including:[1,2]

- ***Lower risk of developing resistance.*** The molecular pathway they target is crucial for the survival and growth of tumors, making it more difficult for cancer cells to build resistance.
- ***Improved tolerability.*** Compared with conventional chemotherapy, using these targeted therapies lessens the risk of toxicity and minimizes off-target effects.
- ***Oral administration.*** Taking oral agents like CDK4/6 inhibitors is more convenient for patients versus intravenous treatment, such as chemotherapy.
- ***Less invasive.*** CDK4/6 inhibitors are a more appealing option for patients who may not be good candidates for more invasive treatments, such as surgery or radiation therapy.

> "IN CLINICAL PRACTICE, I ADVOCATE FOR STARTING TREATMENT WITH BOTH AN AROMATASE INHIBITOR AND A CDK4/6 INHIBITOR, BARRING ANY CONTRAINDICATIONS TO THIS COMBINATION, TO MAXIMIZE THERAPEUTIC BENEFIT FROM THE OUTSET."
>
> — Francisco J. Esteva, MD, PhD

## Proven benefits in first-line therapy

The NCCN Guidelines recommend using CDK4/6 inhibitors, in combination with an aromatase inhibitor or fulvestrant, for first-line therapy in pre- and postmenopausal women with HR+/HER2- mBC.[4] This recommendation is based on placebo-controlled clinical trials that showed unprecedented survival rates with certain agents in the class.

"I tend to use the CDK4/6 inhibitors that have demonstrated benefit in overall survival in the primary analysis of large, randomized studies, which are ribociclib and abemaciclib," says Nicholas P. McAndrew, MD, MSCE, Assistant Clinical Professor of Medicine, Division of Hematology/Oncology, at UCLA David Geffen School of Medicine. He notes that palbociclib has not demonstrated the same degree of benefit in OS in either the early or advanced settings as has been reported with other CDK4/6 inhibitors, which is why he favors the other options. These preferences are consistent with NCCN Guidelines, which designate ribociclib plus an aromatase inhibitor or fulvestrant, or abemaciclib plus fulvestrant, as category 1 recommendations for first-line therapy of HR+/HER2- mBC.[4]

"When first-line studies show a greater than 1-year absolute improvement in OS with the addition of ribociclib or abemaciclib and with the majority of patients having manageable toxicities with stable quality-of-life indices, it's difficult not to include these agents in the first-line setting," Dr. McAndrew explains.

For example, the phase 3 Monaleesa-2 trial evaluated the safety and efficacy of ribociclib in combination with the aromatase inhibitor letrozole as first-line systemic therapy among postmenopausal patients with HR+/HER2- advanced (recurrent or metastatic) breast cancer. With a median follow up of 6.6 years, combination therapy showed a significant benefit with a median OS of 63.9 months among patients who received ribociclib plus letrozole, compared with 51.4 months among those who received letrozole alone. The risk for death in the trial was reduced by 24% in the ribociclib group.[5]

Likewise, final results from the phase 3 Monarch-3 trial in postmenopausal women with HR+/HER2- advanced breast cancer showed that after a median follow-up of 8.1 years, median OS was 66.8 months among patients who received abemaciclib

Illustration by Anna Godeassi

plus an aromatase inhibitor compared with 53.7 months for those who received aromatase inhibitor therapy alone. According to the study authors, this represented a meaningful clinical benefit despite not reaching statistical significance for OS (statistical significance for progression-free survival was reached in an earlier interim analysis of the trial).[6]

In contrast to these studies, the Monaleesa-7 trial included pre- and perimenopausal women—the first study to include patients in this younger population. After 42 months, OS was 70.2% among patients who received ribociclib-based therapy compared with 46.0% among those who received endocrine therapy alone.[7]

In addition, a recent meta-analysis bolsters the evidence for using these agents: In a review of 41 randomized clinical trials—including 17 in the first-line setting—researchers found that ribociclib and abemaciclib (plus endocrine therapy) yielded the best survival outcomes across trials.[8]

## Effective for a wide range of patients

"The tolerability of CDK4/6 inhibitors presents a broad therapeutic window for diverse patient profiles," says Dr. Esteva. He notes that ideal candidates are those who haven't yet undergone endocrine therapy for their metastatic condition as well as patients experiencing a recurrence after a period of remission following adjuvant endocrine therapy. "In clinical practice, I advocate for starting treatment with both an aromatase inhibitor and a CDK4/6 inhibitor, barring any contraindications to this combination, to maximize therapeutic benefit from the outset," Dr. Esteva says. "This approach underscores the shift towards more aggressive first-line treatments in the management of this cancer subtype, aiming to use the full potential of current therapeutic advancements."

Dr. McAndrew agrees, noting that many patients do not have issues with tolerability with CDK4/6 inhibitors. "Because of the improved survival seen with certain CDK4/6 inhibitors, most patients can tolerate—and are motivated to tolerate—these agents in the first-line setting," he says. If side effects are a concern for patients, he suggests prioritizing ribociclib-based therapy. "Generally, ribociclib does not carry some of the gastrointestinal side effects that are commonly seen with abemaciclib, and it is easier to dose-reduce [to improve tolerability]," he says. "Hence, I tend to prefer ribociclib, especially in premenopausal women given the data from Monaleesa-7." For patients who do experience side effects that may compromise adherence, clinical trials suggest that palbociclib plus fulvestrant may be an option for minimizing intolerable adverse effects experienced with other CDK4/6 inhibitors.[8]

In addition, patients with visceral metastases may also benefit from this class, as data have consistently demonstrated benefit with CDK4/6 inhibitor therapy, notes Dr. McAndrew. For example, a recent phase II trial showed that patients treated with ribociclib plus endocrine therapy had fewer adverse events and significantly longer progression-free survival compared with those treated with combination chemotherapy.[9]

*—by Morgan Meissner*

"THE TOLERABILITY OF CDK4/6 INHIBITORS PRESENTS A BROAD THERAPEUTIC WINDOW FOR DIVERSE PATIENT PROFILES."

—Francisco J. Esteva, MD, PhD

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Illustration by stournsaeh / Getty images

PRACTICE PEARLS

# Improving breast cancer outcomes for **BLACK WOMEN**

**While Black women have a 4% lower incidence of breast cancer** compared with White women, they are 41% more likely to die from the disease. What's more, despite recent advances in imaging, genomic testing and treatment, the mortality rate has remained the same for a decade.[1,2]

"You still see disparities across all stages of the cancer continuum, from access to screening and early and appropriate treatment to novel treatment, clinical trials, prevention and end-of-life care," explains Andrea Silber, MD, Clinical Professor of Medical Oncology at Yale School of Medicine and Assistant Clinical Director for Diversity and Health Equity at Yale Cancer Center. "And there's literature to show that with stage 4 breast cancer, Black women do worse, regardless of stage of initial diagnosis and insurance status—and it's not all due to delay of diagnosis."

Less understood is why Black women experience these devastating numbers and how clinicians, researchers and policymakers can address the factors that contribute to this and other healthcare inequities. "Despite the identification of disparities, this increase in mortality in women of color has not been erased," says Dr. Silber. "That

is something terrible, but it's also an opportunity to think about what kinds of interventions might make a difference."

On her part, Dr. Silber has thought a lot about how best to treat and care for these patients. "I hold the belief that everyone who comes into a therapeutic setting—oncologists *and* patients—has the best intentions," notes Dr. Silber. "But that doesn't mean they have the best tools or the best understanding."

While many problems are systemic and require changes in healthcare policy and research, there is still much oncology professionals can do to help improve outcomes in Black women. Here, Dr. Silber offers practical strategies to achieve that goal.

### Establish trust and listen with empathy.

Dr. Silber says that it can be as simple as establishing a good rapport from the very first visit: introducing yourself to a patient, learning their name and sharing yours, and looking at the patient rather than focusing on a computer. "We can't let some of the technology we have stop the things that allow us to be perceived as caring, empathetic, kind human beings, particularly if someone is from a different background," says Dr. Silber, adding that hiring a more diverse workforce in healthcare would also be helpful. "With how our society has treated people of color and people with lower incomes, we need to meet the person where they are and treat people with respect."

Illustration by stournsaeh / Getty images

### Discuss implications of the patient's cancer diagnosis for her family and friends.

Dr. Silber acknowledges that it may seem a clinician's opportunity to talk about breast cancer prevention has passed by the time a Black patient is diagnosed, but she sees it differently. "When you're caring for women of color, there's a generational component to your care as an oncologist. The patient may have daughters, she may have sisters, she may have communities," Dr. Silber explains. "If I'm seeing someone with stage 3 cancer, there may not be a role for prevention for that patient, but there may be for her daughter," she notes. "You're not taking care of tumor cells; you're taking care of women with cancer…and your role is amplified throughout those layers of family and community."

Therefore, it's crucial to have conversations that include discussion about genetic testing, the need for early and regular mammography for family members and friends, and whether there's a history of cancer in the family, notes Dr. Silber. "In many Black communities, people may not know their family history or their genetics," she says. Dr. Silber says these conversations are important opportunities for oncologists, stressing that it could be as simple as saying to a patient, "It's important for you to share your diagnosis with your family, because that could be helpful, even lifesaving, for another family member."

> "I HOLD THE BELIEF THAT EVERYONE WHO COMES INTO A THERAPEUTIC SETTING—ONCOLOGISTS *AND* PATIENTS—HAS THE BEST INTENTIONS. BUT THAT DOESN'T MEAN THEY HAVE THE BEST TOOLS OR THE BEST UNDERSTANDING."
>
> —Andrea Silber, MD

Another issue: Not all oncologists are aware that subsets of breast cancer are associated with different risk factors in Black women, says Dr. Silber. For instance, premenopausal Black women with triple-negative breast cancer (TNBC), an aggressive type, don't have the same risk factors as non-Black women.[3] "Early pregnancy is not protective, for example, and while breastfeeding can reduce the risk of TNBC, women of color have previously been disincentivized from breastfeeding," says Dr. Silber. That means there's an opportunity to educate these patients on how TNBC differs from other types and the implications for her family.

### Plan ahead for certain side effects.

According to Dr. Silber, "Black women are more likely to have neuropathy associated with taxanes, a common chemotherapeutic in early- and late-stage breast cancer," she says. "So if someone has neuropathy, the doctor may say, 'Oh, we can't give you that dose, we'll have to stop chemotherapy early,'" which may raise her risk for recurrence and reduce her chances of treatment response. In such cases, docetaxel, which is associated with a lower rate of neuropathy, may be a better choice for initial therapy.

In addition, dermatologic side effects of chemotherapy differ for Black women receiving treatment for human epidermal growth factor receptor 2-positive (HER2+) breast cancer versus White women.[4] For example, Black women are more likely to develop nail changes and hyperpigmentation from drug-related rashes. Dr. Silber advises working with a dermatologist to help manage these problems.

Also disheartening: The long-disproved myth that Black people experience less pain than White people persists, which may result in undertreatment of cancer pain.[5] Be sure to ask them about their pain level—say, on a scale of 1 (little pain) to 10 (extreme pain)—and map out pain management strategies according to the level of their pain. ►

"BLACK WOMEN ARE LESS LIKELY TO BE TREATED ACCORDING TO GUIDELINES. AND THERE'S LITERATURE TO SHOW THAT WITH STAGE 4 BREAST CANCER, BLACK WOMEN DO WORSE, REGARDLESS OF STAGE OF DIAGNOSIS AND INSURANCE STATUS."
—Andrea Silber, MD

**Help with the logistics of treatment.**

Of course, even the best treatment isn't ideal if it's not feasible for the patient to adhere to the regimen. "Giving someone chemotherapy and being able to give someone all the planned chemotherapy are not the same things," Dr. Silber notes. "A patient may skip chemo appointments because she doesn't have transportation or childcare that enables her to be there. I don't like looking just at adherence; that's kind of like blaming the patient. We need to look at what we as oncologists can do to make things better. If I say to someone that this regimen is once a week and they say they can't do it, is there a similar regimen we can follow?"

Another solution to logistical issues: Connect them with a patient navigator. Research shows that patient navigation represents an important evidence-based intervention to help mitigate some of the racial disparities. This type of care coordination uses a variety of health workers, including lay community health workers who are connected to the healthcare team to help patients overcome barriers to cancer care.[6]

**Consult educational resources.**

It can be overwhelming to think about tackling the disparities in care for Black women with breast cancer. However, there are resources that can help. The African American Breast Cancer Alliance (*aabcainc.org*), which offers educational programs, is a useful site for both clinicians and patients. "No one thinks they're being racist," notes Dr. Silber. "But we may spend time talking to a Black woman about something that really applies to White women."

**Discuss clinical trials.**

In a 2023 study of racial and ethnic inequities in oncology trial participation from 2017 to 2022, which included patients with metastatic breast cancer, the number of Black women participating was significantly lower (4.4%) compared with White women (6.3%).[7] Dr. Silber gives one example of how this may occur: Black women participating in breast cancer trials may start with lower white blood cell (WBC) counts. If a trial has a minimum WBC baseline required for participation, the investigators may need to withhold treatment for a time to get the patient's count up. "I've found this to be a real barrier to putting Black women in clinical trials, even though the neutropenia is not clinically significant and not associated with increased infection," says Dr. Silber. It's important to be up to date on clinical trials and how Black women can access them. In addition to *clinicaltrials.gov*, organizations that provide clinical trial information for Black women include Carebox (*connect.careboxhealth.com*) and TOUCH, the Black Breast Cancer Alliance (*touchbbca.org*).

*—by Lorie Parch*

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# KISQALI—the only CDK4/6 inhibitor to achieve statistically significant overall survival in a broad range of patients across 3 phase III trials


**KISQALI + AI postmenopausal patients**
MONALEESA-2

**KISQALI + fulvestrant postmenopausal patients**
MONALEESA-3

**KISQALI + AI premenopausal patients**
MONALEESA-7

1L refers to patients with mBC.

**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]

**MONALEESA-3** was a randomized, double-blind, placebo-controlled phase III study of KISQALI + fulvestrant (n=484) vs placebo + fulvestrant (n=242) for the treatment of postmenopausal patients with HR+/HER2- mBC who have received no or only 1 line of prior ET for advanced disease. OS was a secondary end point; PFS was the primary end point. 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.[1,4-6]

**MONALEESA-7** was a randomized, double-blind, placebo-controlled phase III study of KISQALI + ET (NSAI or tamoxifen) + goserelin vs placebo + ET (NSAI or tamoxifen) + goserelin (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), 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.[1,7-10]

**Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.**

# KISQALI showed a tolerable safety profile with adverse reactions that were transient, manageable, and reversible

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

**ADVERSE REACTIONS OCCURRING IN ≥10% AND ≥2% HIGHER THAN PLACEBO[1]**

| | KISQALI + LETROZOLE n=334 | | PLACEBO + LETROZOLE n=330 | |
|---|---|---|---|---|
| | Grade 3 or 4 | All grades | Grade 3 or 4 | All grades |
| Vomiting | 3.6% | 29% | 0.9% | 16% |
| Decreased appetite | 1.5% | 19% | 0.3% | 15% |
| Back pain | 2.1% | 20% | 0.3% | 18% |
| Nausea | 2.4% | 52% | 0.6% | 29% |
| Fatigue | 2.4% | 37% | 0.9% | 30% |
| Urinary tract infection | 0.6% | 11% | 0% | 8% |
| Headache | 0.3% | 22% | 0.3% | 19% |
| Insomnia | 0.3% | 12% | 0% | 9% |
| Dyspnea | 1.2% | 12% | 0.6% | 9% |
| Diarrhea | 1.2% | 35% | 0.9% | 22% |
| Constipation | 1.2% | 25% | 0% | 19% |
| Stomatitis | 0.3% | 12% | 0% | 7% |
| Abdominal pain | 1.2% | 11% | 0% | 8% |
| Rash | 0.6% | 17% | 0% | 8% |
| Pruritus | 0.6% | 14% | 0% | 6% |
| Pyrexia | 0.3% | 13% | 0% | 6% |
| Alopecia | 0% | 33% | 0% | 16% |
| Edema peripheral | 0% | 12% | 0% | 10% |

**LABORATORY ABNORMALITIES OCCURRING IN ≥10% OF PATIENTS[1]**

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

- Dose reductions due to ARs occurred in 45% of patients receiving KISQALI plus letrozole
- Permanent discontinuations due to AEs: 7.5% with KISQALI + letrozole; 2.1% with placebo + letrozole[3]
- 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

## 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.

KISQALI® ribociclib 200 mg tablets

# KISQALI demonstrated a consistent safety profile across multiple phase III clinical trials

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

**ADVERSE REACTIONS OCCURRING IN ≥10% AND ≥2% HIGHER THAN PLACEBO[1]**

| | KISQALI + FULVESTRANT n=483 | | PLACEBO + FULVESTRANT n=241 | |
|---|---|---|---|---|
| | Grade 3 or 4 | All grades | Grade 3 or 4 | All grades |
| Infections | 4.6% | 42% | 1.7% | 30% |
| Dyspnea | 1.4% | 15% | 1.7% | 12% |
| Nausea | 1.4% | 45% | 0.8% | 28% |
| Vomiting | 1.4% | 27% | 0% | 13% |
| Abdominal pain | 1.4% | 17% | 0.8% | 13% |
| Diarrhea | 0.6% | 29% | 0.8% | 20% |
| Constipation | 0.8% | 25% | 0% | 12% |
| Rash | 0.8% | 23% | 0% | 8% |
| Pruritus | 0.2% | 20% | 0% | 7% |
| Decreased appetite | 0.2% | 16% | 0% | 13% |
| Dizziness | 0.2% | 13% | 0% | 8% |
| Pyrexia | 0.2% | 11% | 0% | 7% |
| Cough | 0% | 22% | 0% | 15% |
| Alopecia | 0% | 19% | 0% | 5% |
| Edema peripheral | 0% | 15% | 0% | 7% |

**LABORATORY ABNORMALITIES OCCURRING IN ≥10% OF PATIENTS[1]**

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

- Infections included urinary and respiratory tract infections, gastroenteritis, and sepsis (1%)
- Dose reductions due to ARs: 32% with KISQALI + fulvestrant
- Permanent discontinuations due to AEs: 8.5% with KISQALI + fulvestrant; 4.1% with placebo + fulvestrant[4]
- 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

## MONALEESA-7: KISQALI + AI in 1L premenopausal patients

**ADVERSE REACTIONS OCCURRING IN ≥10% AND ≥2% HIGHER THAN PLACEBO[1]**

| | KISQALI + NSAI + GOSERELIN n=248 | | PLACEBO + NSAI + GOSERELIN n=247 | |
|---|---|---|---|---|
| | Grade 3 or 4 | All grades | Grade 3 or 4 | All grades |
| Infections | 1.6% | 36% | 0.4% | 24% |
| Arthralgia | 0.8% | 34% | 1.2% | 29% |
| Rash | 0.4% | 17% | 0% | 9% |
| Pyrexia | 0.8% | 17% | 0% | 7% |
| Nausea | 0% | 32% | 0% | 20% |
| Alopecia | 0% | 21% | 0% | 13% |
| Constipation | 0% | 16% | 0% | 12% |
| Cough | 0% | 15% | 0% | 10% |
| Pain in extremity | 0% | 10% | 1.2% | 8% |
| Stomatitis | 0% | 10% | 0.4% | 8% |
| Pruritus | 0% | 11% | 0% | 4% |

**LABORATORY ABNORMALITIES OCCURRING IN ≥10% OF PATIENTS[1]**

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

- Infections included urinary and respiratory tract infections, gastroenteritis, and sepsis (<1%)
- Dose reductions due to ARs: 33% for patients taking KISQALI + NSAI + goserelin
- Permanent discontinuations due to AEs in the ITT population: 4% with KISQALI + ET (NSAI or tamoxifen) + goserelin; 3% with placebo + ET (NSAI or tamoxifen) + goserelin[7]
- **KISQALI is not indicated for concomitant use with tamoxifen**
- 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

# More medical experts are endorsing KISQALI as their first-line CDK4/6 inhibitor, and with favorable coverage, more HCPs can adopt it in their practice

## NCCN CATEGORY 1 UPDATE

National Comprehensive Cancer Network® (NCCN®) **now differentiates ribociclib (KISQALI®) as the only Category 1 Preferred 1L treatment option** in combination with an AI for patients with HR+/HER2- mBC.[11]

There is controversy on the choice of CDK4/6i as there are no head-to-head comparisons between the agents and there are some differences in the study populations in the phase III randomized studies.

NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

## 9 out of 10

**patients have favorable coverage for KISQALI for all approved indications[12]**

Unrestricted or single-step edit coverage from MMIT data as of July 2023.

**Novartis also offers multiple financial assistance options for eligible patients.**

# Join the growing number of HCPs who have made KISQALI their CDK4/6 inhibitor of choice

## 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.

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.

**Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.**

KISQALI® ribociclib 200 mg tablets

## Explore the data

### IMPORTANT SAFETY INFORMATION (continued)

**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.

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.

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.

**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.

### 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.

**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.

**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.**

1L=first line; 2L=second line; AE=adverse event; AI=aromatase inhibitor; ALT=alanine aminotransferase; AR=adverse reaction; AST=aspartate aminotransferase; CBC=complete blood count; CDK4/6i=cyclin-dependent kinase 4/6 inhibitor; ECG=electrocardiogram; ET=endocrine therapy; GGT=gamma-glutamyl transferase; HR=hazard ratio; ILD=interstitial lung disease; ITT=intent to treat; LFT=liver function test; mBC=metastatic breast cancer; mOS=median overall survival; NR=not reached; NSAI=nonsteroidal aromatase inhibitor; OS=overall survival; PFS=progression-free survival; SCAR=severe cutaneous adverse reaction.

**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.** 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 **5.** Data on file. CLEE011F2301 ad hoc OS analysis. Novartis Pharmaceuticals Corp; 2022. **6.** 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 **7.** 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 **8.** Lu YS, Im SA, 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 **9.** Data on file. CLEE011E2301. Novartis Pharmaceuticals Corp; 2020. **10.** 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 **11.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.1.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed January 29, 2024. To view the most recent and complete version of the guideline, go online to NCCN.org. **12.** Data on file. Kisqali MMIT data July 2023. Novartis Pharmaceuticals Corp; 2023.

**Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.**

NOVARTIS

KISQALI® ribociclib 200 mg tablets

**Novartis Pharmaceuticals Corporation**
East Hanover, New Jersey 07936-1080



3/24

382054

**KISQALI® (ribociclib) tablets, for oral use**
**Initial U.S. Approval: 2017**

**BRIEF SUMMARY: Please see package insert for full prescribing information.**

## 1 INDICATIONS AND USAGE

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.

## 4 CONTRAINDICATIONS

None.

## 5 WARNINGS AND PRECAUTIONS

### 5.1 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 (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.6% of KISQALI-treated patients had ILD/pneumonitis of any grade, 0.4% had Grade 3 or 4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported *[see Adverse Reactions (6.2)]*.

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 recurrent symptomatic or severe ILD/pneumonitis *[see Dosage and Administration (2.2) in the full prescribing information]*.

### 5.2 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 *[see Adverse Reactions (6.2)]*.

If signs or symptoms of severe cutaneous reactions occur, interrupt KISQALI until the etiology of the reaction has been determined *[see Dosage and Administration (2.2) in the full prescribing information]*. 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.

### 5.3 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner *[see Clinical Pharmacology (12.2) in the full prescribing information]*. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4 *[see Dosage and Administration (2.2) in the full prescribing information, Drug Interactions (7.4)]*.

Across MONALEESA-2, MONALEESA-7, and MONALEESA-3 in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor or fulvestrant, 15 out of 1054 patients (1.4%) had a > 500 ms post-baseline QTcF value, and 61 out of 1054 patients (6%) had a > 60 ms increase from baseline in QTcF intervals.

These ECG changes were reversible with dose interruption and the majority occurred within the first four weeks of treatment. There were no reported cases of Torsades de Pointes.

In MONALEESA-2, on the KISQALI plus letrozole treatment arm, there was one (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 *[see Adverse Reactions (6)]*.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 ms. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI therapy *[see Dosage and Administration (2.2) in the full prescribing information]*.

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 QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval.

### 5.4 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 plus placebo subgroup compared with the non-steroidal aromatase inhibitors (NSAIs) plus 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 *[see Clinical Pharmacology (12.2) in the full prescribing information]*.

### 5.5 Hepatobiliary Toxicity

In MONALEESA-2, MONALEESA-7 and MONALEESA-3, increases in transaminases were observed. Across all studies, Grade 3 or 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 for the KISQALI plus aromatase inhibitor or fulvestrant treatment group. The median time to resolution to Grade ≤ 2 was 21 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than two 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 first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated *[see Dosage and Administration (2.2) in the full prescribing information]*.

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 5 (Dose Modification and Management for Hepatobiliary Toxicity) *[see Dosage and Administration (2.2) in the full prescribing information]*. Recommendations for patients who have elevated AST/ALT Grade ≥ 3 at baseline have not been established.

### 5.6 Neutropenia

In MONALEESA-2, MONALEESA-7, and MONALEESA-3, neutropenia was the most frequently reported adverse reaction (75%), and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 62% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade ≥ 2 neutropenia was 17 days. The median time to resolution of Grade ≥ 3 (to normalization or Grade < 3) was 12 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. Febrile neutropenia was reported in 1.7% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. 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 subsequent 4 cycles, and as clinically indicated.

Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 6 *[see Dosage and Administration (2.2) in the full prescribing information]*.

### 5.7 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 ribociclib 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 (AUC). 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 *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1) in the full prescribing information]*.

## 6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1)]*
- Severe Cutaneous Adverse Reactions *[see Warnings and Precautions (5.2)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.3, 5.4)]*
- Hepatobiliary Toxicity *[see Warnings and Precautions (5.5)]*
- Neutropenia *[see Warnings and Precautions (5.6)]*

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to KISQALI in 1065 patients in MONALEESA-2, MONALEESA-7, and MONALEESA-3. Among these patients who received KISQALI, 76% were exposed for 6 months or longer and 62% were exposed for greater than one year. In this pooled safety population, the most common (≥ 20%) adverse reactions, including laboratory abnormalities, were leukocytes decreased (95%), neutrophils decreased (93%), hemoglobin decreased (68%), lymphocytes decreased (66%), aspartate aminotransferase increased (55%), gamma glutamyl transferase increased (53%), alanine aminotransferase increased (52%), infections (47%), nausea (47%), creatinine increased (42%), fatigue (35%), platelets decreased (34%), diarrhea (33%), vomiting (29%), headache (27%), constipation (25%), alopecia (25%), cough (24%), rash (24%), back pain (24%), and glucose serum decreased (20%).

MONALEESA-2: KISQALI in Combination with Letrozole
*Postmenopausal Women with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy*

The safety of KISQALI was evaluated in MONALEESA-2, a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole *[see Clinical Studies (14) in the full prescribing information]*. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥ 12 months.

Serious adverse reactions occurred in 21% of patients who received KISQALI plus letrozole. Serious adverse reactions in ≥1 % of patients receiving KISQALI plus letrozole included abdominal pain (1.5%), vomiting (1.5%), constipation (1.2%), nausea (1.2%), anemia (1.2%), febrile neutropenia (1.2%), dyspnea (1.2%), and alanine aminotransferase increased (1.2%).

Permanent discontinuation of both KISQALI and letrozole due to an adverse reaction occurred in 7% of patients. Permanent discontinuation of KISQALI alone occurred in of 7% of patients. Adverse reactions which resulted in permanent discontinuation of both KISQALI and letrozole in ≥ 2% of patients were alanine aminotransferase increased (5%), aspartate aminotransferase increased (3%), and vomiting (2%).

Dosage interruptions of both KISQALI and letrozole due to an adverse reaction occurred in 71% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients included neutropenia (39%), neutrophils decreased (12%), vomiting (6%), nausea (5%), alanine aminotransferase increased (5%), and leukocytes decreased (5%).

Dose reductions of KISQALI due to an adverse reaction occurred in 45% of patients receiving KISQALI plus letrozole. Adverse reactions which required dose reductions in ≥ 2% of patients included neutropenia (24%), neutrophils decreased (8%), and alanine aminotransferase increased (3%).

Antiemetics and antidiarrheal medications were used to manage symptoms as clinically indicated.

The most common (≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) adverse reactions, including laboratory abnormalities, were neutrophils decreased, leukocytes decreased, hemoglobin decreased, nausea, lymphocytes decreased, alanine aminotransferase increased, aspartate aminotransferase increased, fatigue, diarrhea, alopecia, vomiting, platelets decreased, constipation, headache, and back pain.

Table 8 summarizes the adverse reactions in MONALEESA-2.

**Table 8: Adverse Reactions (≥ 10% and ≥ 2% Higher Than Placebo Arm) in MONALEESA-2**

| Adverse reaction | KISQALI + Letrozole (n = 334) | | Placebo + Letrozole (n = 330) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| **Gastrointestinal disorders** | | | | |
| Nausea[1] | 52 | 2.4 | 29 | 0.6 |
| Diarrhea[1] | 35 | 1.2 | 22 | 0.9 |
| Vomiting[1] | 29 | 3.6 | 16 | 0.9 |
| Constipation[1] | 25 | 1.2 | 19 | 0 |
| Stomatitis[1] | 12 | 0.3 | 7 | 0 |
| Abdominal pain[1] | 11 | 1.2 | 8 | 0 |
| **General Disorders and administration-site conditions** | | | | |
| Fatigue | 37 | 2.4 | 30 | 0.9 |
| Pyrexia[1] | 13 | 0.3 | 6 | 0 |
| Edema peripheral[1] | 12 | 0 | 10 | 0 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Alopecia[1] | 33 | 0 | 16 | 0 |
| Rash[1] | 17 | 0.6 | 8 | 0 |
| Pruritus[1] | 14 | 0.6 | 6 | 0 |
| **Nervous system disorders** | | | | |
| Headache[1] | 22 | 0.3 | 19 | 0.3 |
| Insomnia[1] | 12 | 0.3 | 9 | 0 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Back pain[1] | 20 | 2.1 | 18 | 0.3 |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite[1] | 19 | 1.5 | 15 | 0.3 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Dyspnea[1] | 12 | 1.2 | 9 | 0.6 |
| **Infections and infestations** | | | | |
| Urinary tract infections[1] | 11 | 0.6 | 8 | 0 |

Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[1]Only includes a Grade 3 adverse reaction.

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-2 receiving KISQALI plus letrozole included interstitial lung disease (0.3%), lung infiltration (0.3%), pneumonitis (0.3%), and pulmonary fibrosis (0.6%). Table 9 summarizes the laboratory abnormalities in MONALEESA-2.

**Table 9: Select Laboratory Abnormalities (≥ 10%) in Patients in MONALEESA-2 Who Received KISQALI Plus Letrozole**

| Laboratory abnormality | KISQALI + Letrozole (n = 334) | | Placebo + Letrozole (n = 330) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| **Hematology** | | | | |
| Leukocytes decreased | 93 | 34 | 29 | 1.5 |
| Neutrophils decreased | 93 | 60 | 24 | 1.2 |
| Hemoglobin decreased | 57 | 1.8 | 26 | 1.2 |
| Lymphocytes decreased | 51 | 14 | 22 | 3.9 |
| Platelets decreased | 29 | 0.9 | 6 | 0.3 |
| **Chemistry** | | | | |
| Alanine aminotransferase increased | 46 | 10 | 36 | 1.2 |
| Aspartate aminotransferase increased | 44 | 7 | 32 | 1.5 |
| Creatinine increased | 20 | 0.6 | 6 | 0 |
| Phosphorous decreased | 13 | 5 | 4 | 0.6 |
| Potassium decreased | 11 | 1.2 | 7 | 1.2 |

MONALEESA-7: KISQALI in Combination with an Aromatase Inhibitor
*Pre/perimenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy*

The safety of KISQALI was evaluated in MONALEESA-7, a clinical study of 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus a NSAI or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus

goserelin *[see Clinical Studies (14) in the full prescribing information]*. The median duration of exposure on the KISQALI plus a NSAI arm was 15.2 months with 66% of patients exposed for ≥ 12 months. The safety data reported below are based on 495 pre/perimenopausal patients receiving KISQALI plus NSAI plus goserelin or placebo plus NSAI plus goserelin.

Serious adverse reactions occurred in 17% of patients who received KISQALI plus NSAI plus goserelin. Serious adverse reactions in ≥ 1% of patients receiving KISQALI plus NSAI plus goserelin included drug-induced liver injury (1.6%), abdominal pain (1.2%), dyspnea (1.2%), febrile neutropenia (1.2%), and back pain (1.2%).

Permanent discontinuation of both KISQALI and NSAI due to an adverse reaction occurred in 3% of patients. Permanent discontinuation of KISQALI alone occurred in of 3% of patients. Adverse reactions which resulted in permanent discontinuation of both KISQALI and NSAI in ≥ 2% of patients were alanine aminotransferase increased (2%), and aspartate aminotransferase increased (2%).

Dosage interruptions of KISQALI plus NSAI plus goserelin due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients included neutropenia (41%), neutrophils decreased (26%), and leukocytes decreased (6%).

Dose reductions of KISQALI due to an adverse reaction occurred in 33% of patients receiving KISQALI plus NSAI plus goserelin. Adverse reactions which required dose reductions in ≥ 2 % of patients included neutropenia (17%), neutrophils decreased (5%), and alanine aminotransferase increased (2%).

The most common (≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) adverse reactions, including laboratory abnormalities, were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, infections, arthralgia, alanine aminotransferase increased, nausea, platelets decreased, and alopecia.

Table 10 summarizes the adverse reactions in MONALEESA-7.

**Table 10: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher Than Placebo Arm in MONALEESA-7 (NSAI) (All Grades)**

| Adverse reaction | 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[1;2] | 36 | 1.6 | 24 | 0.4 |
| **Musculoskeletal and connective tissue disorders** | | | | |
| Arthralgia[2] | 34 | 0.8 | 29 | 1.2 |
| **Gastrointestinal disorders** | | | | |
| Nausea[2] | 32 | 0 | 20 | 0 |
| Constipation[2] | 16 | 0 | 12 | 0 |
| Stomatitis[2] | 10 | 0 | 8 | 0.4 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Alopecia[2] | 21 | 0 | 13 | 0 |
| Rash[2] | 17 | 0.4 | 9 | 0 |
| Pruritus[2] | 11 | 0 | 4 | 0 |
| **General disorders and administration-Site Conditions** | | | | |
| Pyrexia[2] | 17 | 0.8 | 7 | 0 |
| Pain in extremity[2] | 10 | 0 | 8 | 1.2 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough[2] | 15 | 0 | 10 | 0 |

Abbreviation: NSAI, non-steroidal aromatase inhibitor.
Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[1]Infections: urinary tract infections, respiratory tract infections, gastroenteritis, sepsis (< 1%).
[2]Only includes a Grade 3 adverse reactions.

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-7 receiving KISQALI plus NSAI included thrombocytopenia (9%), dry skin (9%), oropharyngeal pain (7%), dyspepsia (5%), lacrimation increased (4%), dry eye (4%), vitiligo (3%), hypocalcemia, (2%), blood bilirubin increased (1%), syncope (0.4%), and pneumonitis (0.4%).

**Table 11: Select Laboratory Abnormalities (≥ 10%) in Patients in MONALEESA-7 Who Received KISQALI Plus NSAI Plus Goserelin**

| Laboratory abnormality | KISQALI + NSAI + Goserelin (n = 248) | | Placebo + NSAI + Goserelin (n = 247) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| **Hematology** | | | | |
| Leukocytes decreased | 93 | 36 | 30 | 0.8 |
| Neutrophils decreased | 92 | 63 | 27 | 2.4 |
| Hemoglobin decreased | 84 | 2.4 | 51 | 0.4 |
| Lymphocytes decreased | 55 | 14 | 18 | 2.8 |
| Platelets decreased | 26 | 0.4 | 9 | 0.4 |
| **Chemistry** | | | | |
| Gamma-glutamyl transferase increased | 42 | 7 | 42 | 9 |
| Aspartate aminotransferase increased | 37 | 4.8 | 35 | 1.6 |
| Alanine aminotransferase increased | 33 | 6 | 31 | 1.6 |
| Phosphorous 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 |

MONALEESA-3: KISQALI in Combination with Fulvestrant
*Postmenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy or After Disease Progression on Endocrine Therapy*

The safety of KISQALI was evaluated in MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant *[see Clinical Studies (14) in the full prescribing information]*. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months.

Serious adverse reactions occurred in 29% of patients who received KISQALI plus fulvestrant. Serious adverse reactions in ≥ 1% of patients receiving KISQALI plus fulvestrant included pneumonia (1.9%), nausea (1.4%), vomiting (1.4%), anemia (1.2%), dyspnea (1.2%), neutropenia (1.2%). One case (0.2%) of fatal adverse reaction (pneumonia) occurred in patients who received KISQALI plus fulvestrant.

Permanent discontinuation of both KISQALI and fulvestrant due to an adverse reaction occurred in 8% of patients. Permanent discontinuation of KISQALI alone occurred in of 9% of patients. Adverse reactions which resulted in permanent discontinuation of both KISQALI and fulvestrant in ≥ 2% of patients were alanine aminotransferase increased (5%), and aspartate aminotransferase increased (3%).

Dosage interruptions of KISQALI plus fulvestrant due to an adverse reaction occurred in 72% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients included neutropenia (40%), neutrophils decreased (13%), alanine aminotransferase increased (8%), aspartate aminotransferase increased (8%), and leukocytes decreased (5%).

Dose reductions of KISQALI due to an adverse reaction occurred in 32% of patients receiving KISQALI plus fulvestrant. Adverse reactions which required dose reductions in ≥ 2% of patients included neutropenia (15%), and neutrophils decreased (3%).

The most common (≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) adverse reactions, including laboratory abnormalities, were leukocytes decreased, neutrophils decreased, lymphocytes decreased, creatinine increased, hemoglobin decreased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, nausea, alanine aminotransferase increased, infections, platelets decreased, diarrhea, vomiting, constipation, glucose serum decreased, cough, rash, and pruritus.

Table 12 summarizes the adverse reactions in MONALEESA-3.

**Table 12: Adverse Reactions (≥ 10% and ≥ 2% Higher Than Placebo Arm) in MONALEESA-3**

| Adverse reaction | KISQALI + Fulvestrant (n = 483) | | Placebo + Fulvestrant (n = 241) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| **Gastrointestinal disorders** | | | | |
| Nausea[2] | 45 | 1.4 | 28 | 0.8 |
| Diarrhea[2] | 29 | 0.6 | 20 | 0.8 |
| Vomiting[2] | 27 | 1.4 | 13 | 0 |
| Constipation[2] | 25 | 0.8 | 12 | 0 |
| Abdominal pain[2] | 17 | 1.4 | 13 | 0.8 |
| **Infections and infestations** | | | | |
| Infections[1;2;3] | 42 | 4.6 | 30 | 1.7 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Rash[2] | 23 | 0.8 | 8 | 0 |
| Pruritus[2] | 20 | 0.2 | 7 | 0 |
| Alopecia[2] | 19 | 0 | 5 | 0 |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Cough[2] | 22 | 0 | 15 | 0 |
| Dyspnea | 15 | 1.4 | 12 | 1.7 |
| **Metabolism and nutrition disorders** | | | | |
| Decreased appetite[2] | 16 | 0.2 | 13 | 0 |
| **General disorders and administration-site Conditions** | | | | |
| Edema peripheral[2] | 15 | 0 | 7 | 0 |
| Pyrexia[2] | 11 | 0.2 | 7 | 0 |
| **Nervous system disorders** | | | | |
| Dizziness[2] | 13 | 0.2 | 8 | 0 |

Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[1]Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (1%).
[2]Only include a Grade 3 adverse reactions.
[3]Includes the following fatal adverse reactions: pneumonia (n = 1).

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-3 receiving KISQALI plus fulvestrant included thrombocytopenia (9%) dry skin (8%), dysgeusia (7%), dry mouth (5%), vertigo (5%), dry eye (5%), lacrimation increased (4%), erythema (4%), hypocalcemia (4%), blood bilirubin increased (1%), syncope (1%), interstitial lung disease (0.4%), pneumonitis (0.4%), hypersensitivity pneumonitis (0.2%), and acute respiratory distress syndrome (0.2%).

**Table 13: Select Laboratory Abnormalities (≥ 10%) in Patients in MONALEESA-3 Who Received KISQALI Plus Fulvestrant**

| Laboratory abnormality | KISQALI + Fulvestrant (n = 483) | | Placebo + Fulvestrant (n = 241) | |
|---|---|---|---|---|
| | All Grades (%) | Grade 3 or 4 (%) | All Grades (%) | Grade 3 or 4 (%) |
| **Hematology** | | | | |
| Leukocytes decreased | 95 | 26 | 26 | 0.4 |
| Neutrophils decreased | 92 | 53 | 21 | 0.8 |
| Lymphocytes decreased | 69 | 16 | 35 | 4.1 |
| Hemoglobin decreased | 60 | 4.3 | 35 | 2.9 |
| Platelets decreased | 33 | 1.9 | 11 | 0 |
| **Chemistry** | | | | |
| Creatinine increased | 65 | 1 | 33 | 0.4 |
| Gamma-glutamyl transferase increased | 52 | 8 | 49 | 10 |
| Aspartate aminotransferase increased | 50 | 7 | 43 | 2.9 |
| Alanine aminotransferase increased | 44 | 11 | 37 | 1.7 |
| Glucose serum decreased | 23 | 0 | 18 | 0 |
| Phosphorous decreased | 18 | 4.6 | 8 | 0.8 |
| Albumin decreased | 12 | 0 | 8 | 0 |

COMPLEEMENT-1: KISQALI in Combination with Letrozole and Goserelin or Leuprolide
*Men with HR-positive, HER2-negative Advanced Breast Cancer for Initial Endocrine-Based Therapy*

The safety of KISQALI in combination with letrozole was evaluated in men (n = 39) in an open-label, multicenter clinical study for the treatment of adult patients with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease (COMPLEEMENT-1) *[see Clinical Studies (14) in the full prescribing information]*.

The median duration of exposure to KISQALI was 20.8 months (range, 0.5 to 30.6 months).

Other adverse reactions occurring in men treated with KISQALI plus letrozole and goserelin or leuprolide were similar to those occurring in women treated with KISQALI plus endocrine therapy.

### 6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of KISQALI. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Respiratory disorders:* Interstitial lung disease/pneumonitis

*Skin and Subcutaneous Tissue Disorders:* Stevens-Johnson Syndrome (SJS), Toxic epidermal necrolysis (TEN), Drug-induced hypersensitivity syndrome (DiHS)/Drug reaction with eosinophilia, and systemic symptoms (DRESS)

## 7 DRUG INTERACTIONS

### 7.1 Drugs That May Increase Ribociclib Plasma Concentrations

CYP3A4 Inhibitors

Coadministration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib exposure in healthy subjects by 3.2-fold *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid concomitant use of strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, and voriconazole) and consider alternative concomitant medications with less potential for CYP3A inhibition.

If coadministration of KISQALI with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KISQALI to 400 mg once daily *[see Dosage and Administration (2.2) in the full prescribing information]*.

Instruct patients to avoid grapefruit or grapefruit juice, which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib *[see Patient Counseling Information (17) in the full prescribing information]*.

### 7.2 Drugs That May Decrease Ribociclib Plasma Concentrations

CYP3A4 Inducers

Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89% *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid concomitant use of strong CYP3A inducers and consider an alternate concomitant medication with no or minimal potential to induce CYP3A (e.g., phenytoin, rifampin, carbamazepine, and St. John's wort (Hypericum perforatum).

### 7.3 Effect of KISQALI on Other Drugs

CYP3A Substrates with Narrow Therapeutic Index

Coadministration of midazolam (a sensitive CYP3A4 substrate) with multiple doses of KISQALI (400 mg) increased the midazolam exposure by 3.8-fold in healthy subjects, compared with administration of midazolam alone *[see Clinical Pharmacology (12.3) in the full prescribing information]*. KISQALI given at the clinically relevant dose of 600 mg is predicted to increase the midazolam AUC by 5.2-fold. Therefore, caution is recommended when KISQALI is administered with CYP3A substrates with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

### 7.4 Drugs That Prolong the QT Interval

Avoid coadministration of KISQALI with medicinal products with a known potential to prolong QT, such as antiarrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine, and sotalol), and other drugs that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide, and ondansetron) *[see Warnings and Precautions (5.3), Clinical Pharmacology (12.2) in the full prescribing information]*.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in the full prescribing information]*.

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

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

Data

*Animal Data*

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, 300 mg/kg/day resulted in reduced maternal body weight gain and reduced fetal weights accompanied by skeletal changes related to the lower fetal weights. There were no significant effects on embryo-fetal viability or fetal morphology at 50 or 300 mg/kg/day.

In rabbits at doses ≥ 30 mg/kg/day, there were adverse effects on embryo-fetal development, including increased incidences of fetal abnormalities (malformations and external, visceral, and skeletal variants) and fetal growth (lower fetal weights). These findings included reduced/small lung lobes, additional vessel on the descending aorta, additional vessel on the aortic arch, small eyes, diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes, reduced/small accessory lung lobe, extra/rudimentary 13$^{th}$ ribs, misshapen hyoid bone, bent hyoid bone alae, and reduced number of phalanges in the pollex. There was no evidence of increased incidence of embryo-fetal mortality. There was no maternal toxicity observed at 30 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures (AUC) were approximately 0.6 and 1.5 times, respectively, the exposure in patients at the highest recommended dose of 600 mg/day.

### 8.2 Lactation

Risk Summary

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed infant or on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from KISQALI, advise lactating women not to breastfeed while taking KISQALI and for at least 3 weeks after the last dose.

Data

In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 3.56-fold higher in milk compared to maternal plasma.

### 8.3 Females and Males of Reproductive Potential

Based on animal studies and mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to starting treatment with KISQALI.

Contraception

*Females*

Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with KISQALI and for at least 3 weeks after the last dose.

Infertility

*Males*

Based on animal studies, KISQALI may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

### 8.4 Pediatric Use

The safety and efficacy of KISQALI in pediatric patients has not been established.

### 8.5 Geriatric Use

Of 334 patients who received KISQALI in MONALEESA-2, 150 patients (45%) were ≥ 65 years of age and 35 patients (11%) were ≥ 75 years of age. Of 484 patients who received KISQALI in MONALEESA-3, 226 patients (47%) were ≥ 65 years of age and 65 patients (14%) were ≥ 75 years of age. Of 248 patients who received KISQALI in MONALEESA-7, no patients were ≥ 65 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and younger patients.

### 8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). A reduced starting dose of 400 mg is recommended in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) *[see Dosage and Administration (2.2) in the full prescribing information]*. Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for $C_{max}$; 1.28 for $AUC_{inf}$) and severe (GMR: 1.32 for $C_{max}$; 1.29 for $AUC_{inf}$) hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

### 8.7 Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild (60 mL/min/1.73 $m^2$ ≤ estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 $m^2$) or moderate (30 mL/min/1.73 $m^2$ ≤ eGFR < 60 mL/min/1.73 $m^2$) renal impairment. Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 $m^2$), a starting dose of 200 mg is recommended. KISQALI has not been studied in breast cancer patients with severe renal impairment *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3) in the full prescribing information]*.

## 10 OVERDOSAGE

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

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Illustration by Sandra Dionisi

PATIENT ENGAGEMENT

# Helping patients stay **active** and **engaged** in life

Research confirms that patients who exercise, stay socially connected and continue their favorite activities respond better to therapy and have a more satisfying quality of life. Here are ways to encourage patients to thrive despite living with advanced cancer.

CONTINUED ON NEXT PAGE

**Though outcomes can vary from patient to patient,** research advancements continue to improve outcomes for patients living with metastatic breast cancer (mBC). In fact, one study found that the 5-year survival rate more than doubled over a 20-year period, while data from the National Cancer Institute showed that some patients with mBC lived 10 or more years beyond the date of their initial diagnosis.[1,2] Yet there's one crucial thing patients can do to enhance their treatment plan: maximize their enjoyment of living longer with advanced cancer.

"The more patients can live a regular life—working, engaged in hobbies, exercising, spending time with friends and family—the more mBC can be seen as a chronic disease rather than a terminal one," says Jules Cohen, MD, a breast cancer specialist at Stony Brook Cancer Center in New York. He notes that both the longevity and quality of life of patients with mBC can potentially be improved if they're encouraged to stay active, whether that means physically, mentally or socially. Here are ways to help your patients thrive throughout their cancer journey.

## Educate them on the benefits of regular physical activity.

Research proves there are many advantages of daily movement—and experts confirm they've seen the positive results firsthand in their patients with mBC. Two of the major benefits:

***More independence and a longer life.*** According to Dr. Cohen, patients with mBC who lead a sedentary life—such as spending a lot of time sleeping or needing substantial help with their daily activities—typically have a more limited life expectancy. However, he says, "Patients who are active, ambulatory and independent tolerate treatment well, receive the lion's share of the benefit and live for a prolonged period of time."

For example, a study in *Cancer Nursing* reported that regular exercise significantly improved survival outcomes.[3] Specifically, participants with advanced breast cancer who engaged in moderate physical activity for 1 or more hours a day had an increased likelihood of survival—with a 23% decreased risk of mortality—compared with those who exercised less than 1 hour a day. In addition, a study in *Scientific Reports* found that moderate or vigorous levels of physical activity (as self-defined by patients) were associated with better overall survival in patients with mBC.[4]

***Improvements in pain and fatigue.*** Patients with mBC often experience a range of symptoms and side effects, including fatigue, pain, weakness, loss of cardiopulmonary function, difficulty walking and increased frailty. The good news: "Engaging in exercise or physical activity can improve those symptoms," says Amber Dzbynski, OT, a certified oncology rehabilitation therapist at Mercy Medical Center in Baltimore. "It can also improve range of motion and improve quality of life." For example, a 2023 study of patients with mBC found that those who performed aerobic exercise just twice a week while undergoing treatment reported fewer side effects.

## SOURCES OF SOCIAL SUPPORT

**METAvivor:**
A national support group that can connect patients with mBC with a variety of support groups nationwide. Patients can review their options at *metavivor.org/support/finding-a-support-program.*

**CancerCare:**
Offers a free, 15-week support group led by an oncology social worker for patients with mBC. Patients can register at *cancercare.org.*

**National Breast Cancer Foundation:**
Hosts a monthly virtual support group for patients at any stage of disease. A support group leader facilitates the meeting to encourage a healthy dialogue and patient education. To find out more, patients can visit *nationalbreastcancer.org/breast-cancer-support-groups*.


Illustration by Stephanie Dalton Cowan

## Connect them with experts in oncology rehab.

Stress to patients that exercise should be done according to their ability and strength, says Dzbynski. She cautions that patients undergoing treatment for mBC shouldn't push themselves too much initially. "Your body needs to heal from treatment," she says. "The more patients push themselves, the more exhausting the chronic fatigue can be."

> "ENGAGING IN A HOBBY GIVES PATIENTS SOMETHING OTHER THAN THEIR HEALTH AND CANCER TO FOCUS ON."
>
> —Amber Dzbynski, OT

Therefore, Dzbynski emphasizes that patients should work with all members of their cancer care team—or be referred to an expert in oncology rehabilitation—to design an individualized exercise regimen that will incorporate the types of physical activity, with the appropriate intensity and frequency, that makes the most sense for a patient's particular needs while still remaining beneficial. "Not all trainers at a gym have that knowledge, so starting with the cancer care team or specialized rehab is the best avenue," says Dzbynski. ►

**Reframe "exercise" as doing enjoyable activities.**

While "moderate or vigorous" physical activity may sound daunting to patients with mBC, the types of moderate activity participants chose in the *Cancer Nursing* study included less-strenuous options, such as walking at a moderate pace, doing yoga and hobbies like gardening for an average of an hour a day—so remind patients that, while an hour is the goal, they don't have to achieve that amount every day of the week.[3] In addition, patients can mix and match activities and spread the time throughout the day—such as taking a 30-minute walk in the morning and a yoga class in the evening—according to their abilities and interests.

**Encourage them to engage in hobbies.**

Not surprisingly, a recent study on depression in patients with mBC undergoing chemotherapy found that mental health issues are common.[5] The results showed that the incidence of depression, anxiety and stress among mBC patients were 52.3%, 60.2% and 36.9%, respectively.

One of the best ways patients can boost their mood: "Engaging in a hobby gives patients something other than their health and cancer to focus on," Dzbynski says. "Patients don't have much control over their cancer, but hobbies are something they can control."

For instance, a study in *BMC Complementary Medicine and Therapies* found that yoga had a positive impact on levels of anxiety and depression.[6] Additionally, gardening, knitting and Tai Chi have been found to improve mood.[7] Advising patients to choose a hobby that aligns with their lifestyle and interests can encourage and motivate them to focus on something they enjoy rather than on their disease.

**Help them find the right social support.**

According to a study in the *Journal of Research in Medical Sciences,* belonging to a peer support group improves quality of life among patents with breast cancer.[8] The study authors found that vitality, social functioning and mental health were all higher in the peer-support group than in the control group.

However, while patients can find fellowship and comfort in actively engaging in online communities of others with mBC, Dr. Cohen cautions that patients should steer clear of groups that are dominated by angry and resentful people. Doing some research beforehand is important since not all groups will be helpful for all patients. A patient can start by attending one virtual or in-person meeting to determine if it's a good fit for them. (For organizations that offer support groups, see box on p. 26.)

*–by Cathy Garrard*

"PATIENTS WHO ARE ACTIVE, AMBULATORY AND INDEPENDENT TOLERATE TREATMENT WELL, RECEIVE THE LION'S SHARE OF THE BENEFIT AND LIVE FOR A PROLONGED PERIOD OF TIME."
—Jules Cohen, MD

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**PATIENT:** MEREDITH, 60, HAD A 10-YEAR HISTORY OF HR+ BREAST CANCER. SHE CAME TO SEE ME AFTER A RECENT DIAGNOSIS OF METASTATIC DISEASE.

# "Targeted therapy allows Meredith to travel and enjoy retirement"


PHYSICIAN:

**Maryam Lustberg, MD, MPH**

*Director of the Center for Breast Cancer and Chief of Breast Medical Oncology at Yale School of Medicine*


Illustration by Juhee Kim

**History:**

When I first saw Meredith, she told me she'd not been feeling herself for about 6 months. Before then, she had felt in good health. I learned that 10 years prior, she'd been treated for early-stage HR+ breast cancer that was treated with lumpectomy, radiation and 5 years of aromatase inhibitor therapy.

She explained that a month before consulting me, she had felt increased lower back pain after doing yardwork and took OTC medications. However, when her symptoms did not improve, she saw her PCP who ordered testing. Test results revealed that Meredith had bone metastasis in her mid-back. A bone biopsy confirmed a secondary recurrence of her primary breast cancer and showed invasive ductal carcinoma, nuclear grade 1, ER-positive (100%), PR-positive (90%), HER2-low (1+ IHC), Ki-67 10%. Additionally, osseous hypermetabolic foci of activity was noted in multiple levels of the thoracic spine and her right acetabulum. There was no evidence of metastatic involvement in other organs.

Meredith was understandably shocked to receive the news of a breast cancer recurrence. She felt she had done everything right and thought she was "done" with breast cancer after finishing her earlier multiple treatments. We discussed that although curative intent was not likely with this diagnosis, there were excellent treatment options available.

**Initiating treatment:**

We discussed treatment options and I recommended ribociclib and aromatase inhibitor therapy (letrozole) based on the findings of the published clinical trial MONALEESA-2. Since she has osseous metastasis, I also recommended bone modifying therapy with zoledronic acid. Meredith and I spoke about potential symptoms like hot flashes, arthralgias, vaginal dryness and mood changes. I counseled her on potential fatigue and toxicities, such as cytopenia, liver function abnormalities and QTc prolongation due to ribociclib.

Once on therapy, we monitored for adverse effects by obtaining a baseline EKG along with blood work, which was repeated every 2 weeks for the first 2 cycles. After 1 cycle, Meredith was noted to have increased prolongation of QTc but she had no other toxicities. We then dose-reduced ribociclib to 400 mg a day from 600 mg a day. After this first dose reduction she did not experience additional QTc prolongation and had no other drug-related toxicities.

Throughout treatment, Meredith has had minimal fatigue. Following 3 cycles of treatment, PET CT confirmed significant reduction in hypermetabolic activity in her bones. I've since encouraged her to be active, live her life as before and try to incorporate regular exercise like walking into her daily routine. Meredith is now busy with her usual activities—chasing after her grandkids and traveling the world—and fatigue is not limiting her. She is doing great and says she is living with her metastatic breast cancer diagnosis while focusing on what she enjoys—on her own terms.

**Considerations:**

This case shows how targeted therapies like CDK4/6 inhibitors have revolutionized the way we treat HR+ breast cancer. In the case of ribociclib, the Monaleesa-2 trial confirmed the agent's efficacy for improving overall survival and quality of life in postmenopausal women. This case and the use of cutting-edge therapies also show how, with dedicated research, we will continue to strive for and find new agents for metastatic breast cancer as we work toward a cure.

**NEW!**

**KOL ON DEMAND VIDEO**

Scan here for more insight on Meredith's case.

# Q&A

*Insight on metastatic breast cancer management*

Illustration by sv_sunny/ Getty images

## Options for older and premenopausal women

**Q: What advances have been made in treating typically underrepresented age groups?**

**A:** The good news is, more and more patients, certainly in our health system, are amenable to joining clinical trials. Participation was about 4% when I came to Barnabas, it's now about 21% enrollment. Clinical trials are making all the difference because we do put older patients in trials as well as premenopausal women. And we want different races and ethnicities, because they may have different responses or different side effects. For example, the I-SPY 2 trial has been an enormous success. In this trial, there is no placebo—everyone gets treatment. It used to be that no one over age 70 got treatment, but I now have an 85-year-old in treatment. It really has more to do with biological age than chronological age.

Premenopausal women have other worries: dying and leaving their children, future fertility, relationships, working, losing insurance; it's a very different mindset for these women, which by the way is a growing population. We now have a lot of options to help figure out what will work 10, 20, 30 years from now.

We are evolving in both of these age groups. We try to personalize and strategize care for the cancer and for the needs of that patient, and trials like I-SPY 2 and others help us categorize and offer different options we might not have had before.

*–**M. Michele Blackwood, MD,** Chief of Breast Surgery; Rutgers Cancer Institute of New Jersey; Medical Director at The Center for Breast Health and Disease Management at Barnabas Health Ambulatory Care Center*

## Addressing sexual concerns

**Q: Research suggests providers may not bring up sexual concerns. How do you address this topic?**

**A:** Breast cancer poses significant challenges, with one of the most prominent being its impact on sexual function. Sexual health may be affected at any stage, from the diagnosis through treatment and beyond. Chemotherapy, endocrine therapy, surgeries and radiation can profoundly influence a woman's sexual well-being, contributing to sexual difficulties reported by about 50% of breast cancer survivors. Addressing sexual concerns in breast cancer care is critical, as healthcare providers often lack awareness or knowledge about the necessity of discussing these issues. Patients may feel fear or embarrassment, hindering open communication.

I prioritize creating a comfortable, nonjudgmental environment during consultations, encouraging patients to share intimate concerns. I initiate conversations about sexual health, emphasizing its integral role in overall well-being. By employing patient-friendly language and asking open-ended questions, I allow patients to express themselves freely. I educate them on how treatments may impact sexual function and stress that changes are common. A multidisciplinary approach involving counselors and physical therapists is essential for comprehensive support. After understanding patients' concerns, I discuss potential solutions, including referrals to a specialist or support group. I also offer printed materials that patients can take home to further educate themselves on managing sexual concerns. In addition, I regularly revisit the topic and empower patients to advocate for their own sexual health by asking questions, expressing concerns and actively participating in their care.

*–**Arya Mariam Roy, MD,** Roswell Park Comprehensive Cancer Center, Buffalo, NY*

## Managing common comorbidities

**Q: What are common comorbidities in patients with metastatic breast cancer and how can they be managed?**

**A:** Patients with metastatic breast cancer frequently encounter comorbid conditions that can significantly impact their treatment and quality of life. Prevalent among patients with metastatic breast cancer are bone metastasis–related conditions, with osteoporosis and fractures being common complications. These conditions require comprehensive management, often involving medications like bisphosphonates or denosumab to strengthen bones, alongside lifestyle modifications aimed at minimizing fracture risk.

Cardiovascular disease is another significant comorbidity requiring careful management. Effective control of cardiovascular disease involves a multifaceted strategy that addresses underlying risk factors like hypertension, diabetes and hyperlipidemia. Management typically includes medication, dietary adjustments and physical activity to reduce cardiovascular risk and enhance patient well-being.

Frequently, anemia and fatigue contribute to diminished vitality and quality of life in these patients. Treatment focuses on nutritional support, erythropoiesis-stimulating agents and iron supplementation aimed at reducing symptoms and improving energy levels.

Also common among patients with metastatic breast cancer are depression and anxiety, which impacts their treatment experience and mental health. Addressing psychological concerns is crucial to the care of patients with advanced cancer. Through counseling; participation in support groups; and medication, when necessary, these conditions may be alleviated.

These treatment strategies underscore the importance of a holistic care approach to enhancing the quality of life for patients with metastatic breast cancer.

*–**Francisco J. Esteva, MD, PhD,** Chief, Division of Hematology and Medical Oncology, Lenox Hill Hospital, New York, NY*

"CLINICAL TRIALS ARE MAKING ALL THE DIFFERENCE BECAUSE WE NOW PUT OLDER PATIENTS IN TRIALS AS WELL AS PREMENOPAUSAL WOMEN."
—M. Michele Blackwood, MD

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Health Monitor

# Clinician Update

DECISION TOOL

## HR+/HER2- METASTATIC BREAST CANCER:

# Considerations for CDK4/6 inhibitor therapy

**Combining a CDK4/6 inhibitor with endocrine therapy is the standard first-line treatment for hormone receptor–positive (HR+)/HER2-negative (HER2-) metastatic breast cancer. However, there is no one-size-fits-all approach when it comes to selecting the best agent for an individual patient, as there are no clearcut biomarkers to predict benefit and no published head-to-head trials between CDK4/6 inhibitors. Therefore, the decision rests on clinical judgment, patient characteristics and other factors. When using CDK4/6 inhibitors, here are some important considerations to keep in mind:**

### GUIDING PRINCIPLES:

1. Incorporate patient preference based on shared decision-making.
2. Employ the regimen with a demonstrated benefit in overall survival while taking all other factors into consideration.

### KEY CONSIDERATIONS WHEN INDIVIDUALIZING THERAPY:

**Patient-specific factors such as:**

- Age
- Menopausal status
- Frailty
- Metastatic site(s)
- Presence of certain comorbidities, such as QTc abnormalities and liver abnormalities, that increase the risk of serious complications

**Treatment-related factors such as:**

- Response to prior therapies
- Tolerability of common side effects, including nausea, diarrhea, fatigue and hematologic abnormalities
- Ease of dosing and dose reduction
- Practical considerations, such as access, cost and scheduling

**Source:** National Cancer Institute at the National Institutes of Health (*cancer.gov*).