Ribociclib: another CDK inhibitor hits the mark in breast cancer

This spring, the US Food and Drug Administration approved a second cyclin-dependent kinase (CDK) inhibitor for the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced/metastatic breast cancer in combination with aromatase inhibitors (AIs).[1] The drug, ribociclib, joins palbociclib as the second drug in this class, which targets key regulators of the mammalian cell cycle and can help to overcome resistance to endocrine therapy–like AIs, a standard front-line treatment option in this group of patients. Palbociclib (Ibrance) was approved last year in combination with the AI letrozole, which was recently expanded to include its use in combination with all AIs, the same indication for which ribociclib received approval.

The ribociclib approval was based on the results of a phase 3, randomized, double-blind, placebo-controlled, international clinical trial called MONALEESA-2.[2] The trial, conducted in 29 countries, compared the effects of ribociclib plus letrozole with letrozole plus placebo in 668 postmenopausal women with locally confirmed, HR-positive, HER2-negative, recurrent or metastatic breast cancer.

Patients had not received previous systemic therapy for advanced disease, had measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1), had an Eastern Cooperative Oncology Group performance status of 0 or 1 (range, 1-5; 0, fully active and 5, dead), and had adequate bone marrow and organ function.

Patients were excluded if they had received previous CDK4/6 therapy, any previous systemic chemotherapy, endocrine therapy for advanced disease, previous neoadjuvant or adjuvant therapy with any nonsteroidal AI (unless they had been disease free for more than 12 months), and had inflammatory breast cancer, central nervous system metastases, history of cardiac disease or dysfunction, or impaired gastrointestinal function that alters drug absorption.

Patients were treated with ribociclib at a dose of 600 mg daily on a 3-weeks-on, 1-week-off schedule in 28-day cycles or placebo, which were combined with letrozole at a dose of 2.5 mg a day on a continuous schedule. Randomization was stratified according to the presence or absence of liver or lung metastases and treatment was continued until disease progression, unacceptable toxicity, death or discontinuation of treatment. Dose reductions of ribociclib were allowed, to manage adverse events (AEs), but treatment crossover was not permitted.

Tumor assessments were performed at screening, every 8 weeks during the first 18 months, every 12 weeks thereafter until disease progression, and at the end of treatment, and were assessed by an independent review committee. The baseline characteristics of the patient population were well balanced; patients had a median age of 62 years, all were HR positive except 1 patient who was HER2 positive.

The trial was ended prematurely after an initial interim analysis demonstrated a significant benefit in favor of ribociclib in the primary endpoint, progression-free survival (PFS). Over a median duration of follow-up of 15.3 months, the median PFS was not yet reached in the ribo-

What's new, what's important

Ribociclib is a CDK inhibitor used with AIs to treat postmenopausal women with advanced/metastatic HR-positive, HER2-negative breast cancer. It was approved based on phase 3 data from the MONALEESA-2 trial that compared ribociclib+letrozole with letrozole alone in 668 women. The trial was ended prematurely after an interim analysis showed a significant PFS benefit with ribociclib. Over a median 15.3 months of follow-up, the median PFS was not reached with ribociclib, compared with 14.7 months with placebo. After another 11 months, median PFS was 25.3 months with ribociclib and 16 months with placebo (a 44% reduction in the risk of progression or death). ORRs were 52.7% (ribociclib) and 37.1% (placebo); OS data were immature.

The recommended dose is 600 mg orally once daily for 21 days, with 7 days off treatment. The frequency and severity of AEs were higher with ribociclib, the most common including neutropenia, nausea, fatigue, diarrhea, leukopenia. The most common grade 3/4 AEs with ribociclib were neutropenia, leukopenia, abnormal liver function tests, lymphopenia, and vomiting.

Ribociclib carries warnings about QT interval prolongation, hepatobiliary toxicity, and neutropenia. ECGs and electrolytes should be monitored before starting therapy and repeated during therapy. Liver function tests should also be done before and during treatment. Women should be warned of the risk of fetal harm and need for contraception.

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ciclib arm, compared with 14.7 months in the placebo arm (hazard ratio, 0.556; $P < .0001$). In a subsequent analysis with 11 months of additional follow-up, the median PFS was 25.3 months in the combination arm, compared with 16 months in the placebo arm, which translated into a 44% reduction in the risk of disease progression or death. The PFS benefit with ribociclib was observed across all preplanned subgroup analyses. The objective response rates were 52.7% in the ribociclib arm, compared with 37.1% in the placebo arm, but overall survival data were immature.

The frequency and severity of AEs were increased in the combination arm; most common were neutropenia, nausea, fatigue, diarrhea, leukopenia, alopecia, vomiting, constipation, headache, and back pain. The most common grade 3 or 4 AEs experienced with ribociclib were neutropenia, leukopenia, abnormal liver function tests, lymphopenia, and vomiting.

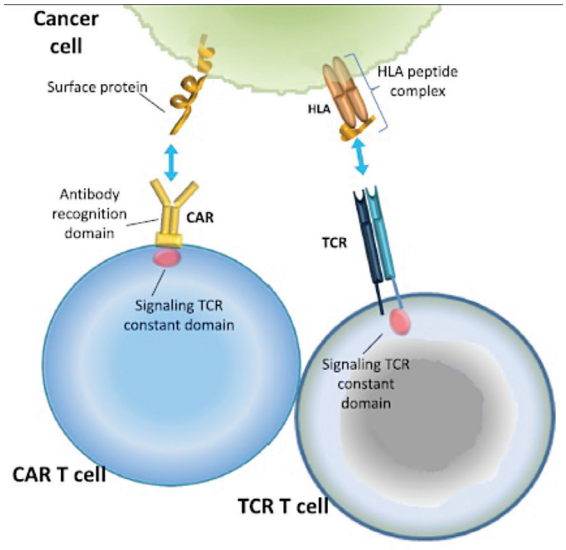
Ribociclib is accompanied by warnings and precautions about QT interval prolongation, hepatobiliary toxicity, and neutropenia. Clinicians are advised to monitor electrocardiograms and electrolytes before the start of ribociclib therapy and to begin treatment only in patients with QTcF values <450 ms and in whom electrolyte abnormalities have been corrected. ECG should be repeated at around day 14 of the first cycle, the beginning of the second cycle, and as deemed clinically necessary.

Liver function tests should be performed before starting treatment, every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. For aspartate aminotransferase (AST) and/

Mechanism of action: ribociclib

Tackling resistance to endocrine therapy

Ribociclib joins the first member of this drug class, palbociclib, in securing FDA approval for the treatment of hormone receptor (HR)-positive advanced/metastatic breast cancer. These drugs target the cyclin-dependent kinases (CDK) 4 and 6, serine/threonine protein kinases whose activity is regulated by their association with regulatory subunits, in this case cyclin D1 and the CDK inhibitor p16.



The cyclin-dependent kinases, CDK4 and CDK6, and their regulator cyclin D1, play a key role in the regulation of a particularly important step in the cell cycle at which the cell commits to proceeding through the cell cycle regardless of external signals. CDK4 and 6 are downstream targets of estrogen receptor activation and their dysregulation is commonly observed in hormone receptor-positive breast cancer, in which it is thought to be an important mechanism of resistance to endocrine therapy, making these proteins attractive therapeutic targets. Reproduced with permission. Aleem E et al. Targeting cell cycle regulators in hematologic malignancies. Front Cell Dev Biol. 2015;3(article 16). doi: 10.3389/fcell.2015.00016.

In order to replicate themselves, mammalian cells proceed through a highly regulated series of steps, known as the cell cycle. CDKs form part of the molecular machinery that controls the cell cycle and, in the case of CDK4/6, they regulate a particularly important step in the cycle, known as the restriction point. Beyond this point, the cell proceeds through the G1 phase and transitions into the S phase, and commits to progressing through the rest of the cell cycle regardless of external signals.

Dysregulation of CDK4/6 and the proteins that regulate their activity is commonly observed in cancer, as a means of driving uncontrolled cell proliferation, a hallmark of cancer, through unchecked entry into the cell cycle. For example, the gene that encodes the p16 protein is the most frequently deleted in human cancer. Since these proteins are kinases, they are readily druggable with small molecule inhibitors, and offer an attractive target for cancer therapy.

This is particularly true in the up to 75% of breast cancers that are driven by activation of HRs, because CDK4/6 is a downstream target of the estrogen receptor (ER). Therefore, dysregulation of the ER in breast cancer drives aberrant CDK4/6 activity and sustained activation of the cell cycle; overexpression of CDK4 and CDK6 and amplification of the cyclin D1 gene (*CCND1*) are frequently encountered in HR-positive breast cancers.

Increased CDK4/6 activity has also been shown to be associated with resistance to endocrine therapy, the standard of care for patients with HR-positive breast cancer. Combining CDK inhibitors like ribociclib with aromatase inhibitors (AIs), a preferred endocrine therapy in postmenopausal women with breast cancer that is HR-positive, but does not express the human epidermal growth factor receptor 2 (HER2), could help to overcome this resistance. Indeed, clinical trials like MONALEESA-2 demonstrate that the combination of CDK inhibitors and AIs has synergistic anticancer activity and helps to prolong survival beyond that which can be achieved with AIs on their own.

or alanine aminotransferase (ALT) levels greater than 3-5 times the upper limit of normal (ULN, grade 2), ribociclib should be interrupted until recovery to baseline or lower. For levels >5-20 times the ULN (grade 3) or recurring grade 2 increases, treatment should be interrupted until recovery to baseline or lower and then resumed at the next lowest dose level. Treatment with ribociclib should be discontinued in the event of recurring grade 3 elevations or for AST/ALT elevations >3 times ULN in combination with total bilirubin >2 times ULN.

Complete blood counts should be performed before starting treatment and monitored every 2 weeks for the first 2 cycles, at the beginning of each of the 4 subsequent cycles, and as clinically needed. If absolute neutrophil counts are 500-1,000 mm^3 (grade 3), treatment should be discontinued until recovery to grade 2 or lower. If grade 3 neutropenia recurs or for grade 3 febrile neutropenia or grade 4 neutropenia, treatment should resume at a lower dose level upon recovery to grade 2 or lower.

Pregnant women and those of reproductive age should be warned of the risk of fetal harm and the need for effective contraception during treatment and for at least 3 weeks after the last dose. Ribociclib is marketed as Kisqali by Novartis.

References

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3. Horobagyi GN, Stemmer SN, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med. 2016;375:1738-1748.