NEW DRUGS

Ribociclib

Aust Prescr 2018;41:172
https://doi.org/10.18773/austprescr.2018.058

Approved indication: breast cancer

Kisqali (Novartis)
200 mg tablets
Australian Medicines Handbook Appendix A

Like palbociclib, ribociclib is a small-molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. It should be used in combination with an aromatase inhibitor such as letrozole and is indicated as an initial endocrine-based therapy for advanced or metastatic breast cancer that is hormone receptor-positive (oestrogen and/or progesterone) and human epidermal growth factor receptor 2 (HER2)-negative.

Inhibiting CDK4 and 6 kinases, which are increased in hormone receptor-positive breast cancers, aims to reduce cell proliferation. The recommended starting dose of ribociclib is 600 mg once daily for 21 days of a 28-day treatment cycle. This is followed by seven days off ribociclib treatment. An aromatase inhibitor should be taken every day of the 28-day cycle.

The approval of ribociclib in Australia is mainly based on a phase 3 randomised controlled trial in 668 postmenopausal women with previously untreated advanced or metastatic hormone receptor-positive and HER2-negative breast cancer.[1,2] Women were randomised 1:1 to ribociclib (600 mg) plus letrozole (2.5 mg) or placebo plus letrozole. After a median follow-up of 26.4 months, median progression-free survival was significantly longer in the ribociclib arm compared with the letrozole-only arm (25.3 vs 16 months).[2] The corresponding overall response rates were 42.5% versus 28.7%. Overall survival rates were not statistically significantly different between the groups. However, the survival data were not mature at this time point.

Adverse events are common with ribociclib – 44.6% of patients needed their dose reduced because of an event and 7.5% had to discontinue treatment permanently. The most common reasons for stopping were elevated liver enzymes and vomiting.

The most frequently reported adverse events with ribociclib are neutropenia (76.9%), nausea (53.3%), fatigue (41.3%), diarrhoea (38.3%), alopecia (34.4%), leucopenia (32.9%), vomiting (33.5%), constipation (27.8%), rash (22.2%) and back pain (24.3%).[2] Neutropenia is often severe (grade 3 or 4) with ribociclib and requires dose interruption. Hepatobiliary toxicity occurred in 24% of patients. In terms of cardiac effects, 7.5% of patients had a prolonged QT interval on at least one occasion and 0.9% had their ribociclib dose adjusted or interrupted because of prolonged QT or syncope.

ECG, complete blood counts, liver function and serum electrolytes should be assessed before treatment is started and in subsequent treatment cycles as dose reduction, interruption or discontinuation may be required.

Ribociclib is contraindicated in patients with corrected QT interval >450 milliseconds or who already have, or are at risk of developing, long QT syndrome. Ribociclib should not be co-administered with drugs that prolong the QT interval as it could have additive effects.

Ribociclib is extensively metabolised and is a substrate of cytochrome P450 (CYP) 3A4, so concurrent use of strong CYP3A4 inhibitors and inducers is not recommended as they may alter ribociclib plasma concentrations. If a strong CYP3A4 inhibitor cannot be avoided, the ribociclib dose should be reduced. Pomegranates and grapefruits (including juice) are not recommended as they inhibit CYP3A enzymes and may increase concentrations of ribociclib. Other foods are not expected to affect ribociclib exposure.

Peak plasma concentrations of ribociclib are reached within 1–4 hours and repeated dosing results in steady-state concentrations after eight days. Ribociclib is extensively metabolised, mainly by CYP3A4. Its half-life is 32 hours and most of the dose is eliminated in the faeces (69.1%) and urine (22.6%). Dose adjustment is not required in mild–moderate renal impairment and ribociclib has not been studied in severe impairment. The ribociclib dose should be adjusted in patients with moderate–severe hepatic impairment.

Ribociclib in combination with letrozole prolonged progression-free survival by 9.3 months compared to letrozole alone in postmenopausal women with advanced or metastatic breast cancer. However, there is not yet evidence that therapy improves overall survival. Myelosuppression and ribociclib's cardiac and hepatic effects can be serious and treatment limiting, and ribociclib has many potential drug interactions.

REFERENCES

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2. Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S, et al. Updated results from MONALEESA-2, a phase III trial of first-line ribociclib plus letrozole versus placebo plus letrozole in hormone receptor-positive, HER2-negative advanced breast cancer. Ann Oncol 2018;29:1541-7. https://doi.org/10.1093/annonc/mdy155

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.

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