NEW DRUGS

New drugs

Aust Prescr 2020;43:94–5
https://doi.org/10.18773/austprescr.2020.026
First published 24 April 2020

Abemaciclib

Approved indication: breast cancer

Verzenio (Eli Lilly)

50 mg, 100 mg and 150 mg tablets

Like palbociclib and ribociclib, abemaciclib is a small-molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6. These kinases are involved in cell cycle progression and are often overexpressed in hormone receptor positive (HR+) breast cancers. Blocking them leads to cell cycle arrest, senescence and apoptosis.

Abemaciclib is specifically indicated for HR+/human epidermal growth factor receptor 2 negative (HER2–) locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant. It can be given as initial endocrine-based therapy, or after previous endocrine therapy. In pre- or perimenopausal women, the endocrine therapy should be combined with a luteinising hormone-releasing hormone agonist.

Abemaciclib has been assessed in three clinical trials of women with HR+/HER2– advanced breast cancer: MONARCH 1, 2 and 3 (see Table). MONARCH 1 was a single-arm, phase II trial in women who had failed two endocrine therapies and had already had 1–2 chemotherapy regimens. Women received abemaciclib monotherapy 200 mg twice daily.

At 12 months, the objective response rate was 19.7% (all partial responses), median progression-free survival was six months and the median overall survival was 17.7 months (see Table).[1]

The MONARCH 2 trial was a double-blind, phase III trial in 669 women who had progressed during endocrine therapy but had not received chemotherapy. They were randomised to receive fulvestrant in combination with abemaciclib (150 mg twice daily) or placebo. Median progression-free survival was significantly longer with abemaciclib than with placebo (16.4 vs 9.3 months)[2] as was median overall survival (46.7 vs 37.3 months).[3] The corresponding objective response rates were 35.2% and 16.1%.

MONARCH 3 was another double-blind, phase III trial. The 493 women enrolled had not received previous systemic therapy and most had metastatic disease at baseline. They were randomised to an aromatase inhibitor (anastrozole or letrozole) plus abemaciclib (150 mg twice daily) or placebo. Median progression-free survival was significantly longer with abemaciclib than with placebo (28.2 vs 14.7 months). The corresponding objective response rates were 48.2% versus 34.5%.[4]

The most common adverse effects with abemaciclib include diarrhoea (84.6% of patients), neutropenia (45.1%), nausea (43.5%), infections (43.6%),

Table **Efficacy of abemaciclib in HR+/HER2– advanced breast cancer**

Trial	Daily treatment	No. of patients	ORR	Median progression-free survival	Median overall survival
MONARCH 1[1]	abemaciclib monotherapy	132	19.7%	6 months	17.7 months
MONARCH 2[2,3]	abemaciclib + fulvestrant	446	35.2%	16.4 months	46.7 months
	placebo + fulvestrant	223	16.1%	9.3 months	37.3 months
MONARCH 3[4]	abemaciclib + aromatase inhibitor*	326	48.2.%	28.2 months	–
	placebo + aromatase inhibitor*	162	34.5%	14.7 months	–

* anastrozole or letrozole
HR+ hormone receptor positive
HER2– human epidermal growth factor receptor 2 negative
ORR objective response rate estimated as the total number of complete and partial responses divided by the number of patients

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

fatigue (40.5%), anaemia (30.1%) and vomiting (27.7%). Hair loss occurred in 20.7% women. Hepatotoxicity and venous thromboembolism were also reported in the trials.

Diarrhoea was serious in 11.7% of cases. Onset was 6–8 days after the start of treatment and severe cases lasted for about a week. If this occurs, the abemaciclib dose should be interrupted until symptoms resolve. Fluids and an antidiarrhoeal medicine such as loperamide are recommended.

Neutropenia was serious in 28% of patients who were taking abemaciclib and fulvestrant, and fatal cases have occurred. Onset was a month after the start of treatment. Blood counts should therefore be measured at baseline and then monitored regularly.

Dose reduction or interruption may be required with serious adverse effects such as diarrhoea and haematologic and liver toxicities. As with other drugs in this class, abemaciclib can cause interstitial lung disease. In serious cases, the drug should be permanently discontinued.

The recommended starting dose of abemaciclib is 150 mg twice daily in combination with endocrine therapy. As the drug is metabolised in the liver, the dose should be reduced to one tablet a day in those with severe liver impairment. After oral administration, peak plasma concentrations are reached within eight hours and repeated dosing results in steady-state concentrations after five days. Abemaciclib's elimination half-life is 25 hours and most of the dose is excreted in the faeces.

Abemaciclib is metabolised by cytochrome P450 (CYP) 3A so concurrent use of strong inhibitors (e.g. clarithromycin, itraconazole, ketoconazole) and inducers (e.g. carbamazepine, rifampicin, St John's wort) is best avoided. If co-administration of a strong inhibitor cannot be avoided, the abemaciclib dose should be reduced.

Abemaciclib prolongs progression-free survival when used in combination with fulvestrant or an aromatase inhibitor in women with advanced HR+/HER2– breast cancer. As with palbociclib and ribociclib, diarrhoea is very common and may limit treatment. Severe neutropenia does not seem to be as common with abemaciclib as it was with palbociclib.

T manufacturer provided useful information

REFERENCES

1. Dickler MN, Tolaney SM, Rugo HS, Cortés J, Diéras V, Patt D, et al. MONARCH 1, a phase II study of abemaciclib, a CDK4 and CDK6 inhibitor, as a single agent, in patients with refractory HR+/HER2- metastatic breast cancer. Clin Cancer Res 2017;23:5218-24. https://doi.org/10.1158/1078-0432.CCR-17-0754
2. Sledge GW Jr, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breat cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35:2875-84. https://doi.org/10.1200/JCO.2017.73.7585
3. Sledge GW, Toi M, Neven P, Sohn J, Inoue K, Pivot X, et al. The effect of abemaciclib plus fulvestrant on overall survival in hormone receptor-positive, ERBB2-negative breast cancer that progressed on endocrine therapy – MONARCH 2: a randomized clinical trial. JAMA Oncol 2020;6:116-24. https://doi.org/10.1001/jamaoncol.2019.4782
4. Goetz MP, Toi M, Campone M, Sohn J, Paluch-Shimon S, Huober J, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. J Clin Oncol 2017;35:3638-46. https://doi.org/10.1200/JCO.2017.75.6155

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

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, and the European Medicines Agency.