New drugs

Regorafenib

Approved indication: colorectal cancer
Stirvarga (Bayer)
40 mg tablets
Australian Medicines Handbook section 14.2.3

Regorafenib is indicated for patients with metastatic colorectal cancer who have had previous treatment with multiple regimens (chemotherapy, targeted anticancer therapies). Life expectancy is generally only a few months for these patients.

Regorafenib is a protein kinase inhibitor with a similar structure to sorafenib (Aust Prescr 2006;29:167-71). It is thought to work by inhibiting multiple signalling pathways involved in angiogenesis and tumour growth.

The approval of regorafenib is based on a phase III placebo-controlled trial of 760 adults with progressive colorectal cancer despite treatment. Only patients with a life expectancy of at least three months were enrolled and those with CNS metastases were excluded. Oral regorafenib 160 mg or placebo was given once a day for three weeks of a four-week cycle until disease progressed or patients had unacceptable adverse effects. Although overall survival was approximately six weeks longer with regorafenib than with placebo, progression-free survival was similar between groups. Stable disease was more common with active treatment than with the placebo (41% vs 15%) (see Table).[1]

Adverse effects were very common with regorafenib and many patients had to have their dose modified or interrupted. Over half of the participants had a serious (grade 3 or 4) regorafenib-related event. The most frequently reported serious reactions were hand–foot skin reactions (17%), fatigue (9%), diarrhoea (7%), hypertension (7%), rash (6%) and oral mucositis (3%). Myocardial ischaemia and reversible posterior leukoencephalopathy have also occurred in patients taking regorafenib.

Eight of the 505 patients in the regorafenib group died because of an adverse event. Causes included pneumonia (2 cases), gastrointestinal bleeding (2 cases), intestinal obstruction (1 case), pulmonary haemorrhage (1 case), seizure (1 case) and sudden death (1 case).[1]

Fatal drug-induced liver failure has been reported with regorafenib. Liver function tests are therefore recommended before and during treatment and dose reductions may be needed if liver function declines. There is an increased risk of bleeding so blood counts and coagulation should be monitored, especially in patients receiving concomitant anticoagulants.

Electrolyte abnormalities can occur with this drug and monitoring is recommended during treatment. As with other anti-angiogenic drugs, wound healing may be delayed and regorafenib treatment should be stopped two weeks before surgery.

Regorafenib tablets should be taken with a low fat meal. Following a 160 mg dose, peak plasma concentrations are reached after 3–4 hours. Regorafenib is metabolised in the liver and its elimination half-life is 20–30 hours. The drug and its metabolites are excreted in the faeces (71%) and urine (19%). Close monitoring is recommended with severe renal or hepatic impairment as there is limited drug experience in these patients.

Regorafenib is mainly metabolised via cytochrome (CYP) 3A4 and uridine diphosphate glucuronosyl

Table **Efficacy of regorafenib in metastatic colorectal cancer**[1]

	Treatment	
	Regorafenib + best supportive care	**Placebo + best supportive care**
Number of patients	505	255
Mean duration of treatment	2.8 months	1.8 months
Median overall survival	6.4 months	5 months
Median progression-free survival	1.9 months	1.7 months
Response to treatment	No complete responses 5 partial responses 207 patients (41%) had stable disease	No complete responses 1 partial response 38 patients (15%) had stable disease

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.

transferase UGT1A9. Concomitant use of strong CYP3A4 inhibitors (e.g. clarithromycin, ketoconazole and grapefruit juice) and inducers (e.g. phenytoin, dexamethasone and St John's wort) should be avoided. Regorafenib also inhibits P-glycoprotein so may increase concentrations of concomitant drugs affected by this transporter such as digoxin. Co-administration of regorafenib with antibiotics that affect the gut flora may reduce regorafenib's efficacy.

For patients with metastatic disease who have no other therapeutic options, regorafenib improves survival time by approximately six weeks. Its main effect seems to be to keep the disease stable. However, regorafenib causes considerable adverse affects which are often severe and sometimes fatal.

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REFERENCE *†A

1. Grothey A, Van Cutsem E, Sobrero S, Falcone A, Ychou A, Humblet Y, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-12.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)