

## **INTEGRATE: A phase 2 study of regorafenib in advanced oesophago-gastric cancer**

The INTEGRATE trial is helping answer an important health question. It has provided evidence that a new treatment, regorafenib, acts against the tumour and is safe. We are now confident that it can be used in a larger trial investigating survival.

We appreciate the part played by our volunteer participants. This may help to improve the medical treatment of patients in the future. Here is a summary of the trial and results.

### **What was the trial about?**

The trial was part of the search for better treatments for cancer of the lower oesophagus and stomach.

Regorafenib (Stivarga) is a new biological treatment that was already in use to act against the growth of colon tumours and GISTs (gastrointestinal stromal tumours). INTEGRATE tested the effect on stomach tumours.

The trial was a phase 2 trial, a small trial designed to test the drug's safety and effect on the tumour. We recruited 152 patients from Australia, New Zealand, Korea and Canada.

Patients were randomly allocated to regorafenib or a placebo tablet. The randomisation system was set up to allocate two-thirds of patients to the trial drug and one-third to placebo.

Four out of five patients were men. All patients had advanced disease that had come back after chemotherapy. They took the tablets for 21 days in each month. Whether patients were on the new drug or the placebo, they all had the usual supportive care by their oncologists and other health professionals.

### **How was the effect of treatment measured?**

During the trial, the size of the tumour was measured from scans, and changes were noted. These were classified as complete response (all visible tumour disappeared), partial response (at least 50% of the tumour disappeared), stable disease, or progressive disease (a 50% increase in the tumour). Another important measure was progression-free survival—that is, the time between the participant's entry into the trial until the disease became worse.

The drug was considered to have benefited a patient if at 8 weeks there was no evidence of the disease becoming worse and the scans showed improvement or stable disease.

Adverse events—that is, symptoms and abnormal test results that may or may not have been related to the treatment—were recorded and classified.

The doctors and other trial investigators did not know which treatment a patient was getting.

### **Was the new treatment better?**

Regorafenib was shown to benefit people with advanced oesophago-gastric cancer. Of the patients taking regorafenib, 46% had no growth in their tumour at 8 weeks, compared with 18% taking placebo.

The average progression-free survival was 11 weeks for patients taking regorafenib and 4 weeks for those on placebo. That is, the treatment delayed the growth of the disease by nearly 2 months on average and longer for many. The average overall survival was also better in the regorafenib group.

The effect of the drug was greater in Korea than in Australia, New Zealand and Canada combined, but

the reason for this is not yet clear. Otherwise, the drug's effect was similar in different groups, such as by age or sex or how far the cancer had spread. This is a substantial benefit at a time when most other treatment options have been used.

### What were the side-effects of the treatment?

Doctors and most patients considered that the treatment was well tolerated. The most common problems were fatigue and loss of appetite, both occurring in about a third of patients. The rates of these side-effects were similar in people taking the active drug and those taking placebo. This suggests they were probably due to the cancer itself rather than the treatment.

Rashes, abnormal liver tests and high blood pressure were more common in the regorafenib patients. 14% of the regorafenib patients (but none of the placebo patients) stopped treatment because of illness or side-effects.

### Were there any serious side-effects?

About 10% of patients taking regorafenib had serious high blood pressure or liver toxicity. This rate was expected for this type of drug.

### What does this mean for trial patients?

Patients taking the new treatment had on average several extra weeks when their disease improved or did not get worse.

Those taking the placebo had the opportunity to transfer to the drug if their disease became worse during the trial. About half of the placebo patients went on to take regorafenib.

### How will the results help future patients?

It appears that future patients with oesophago-gastric cancer may safely benefit from regorafenib. A larger trial (a phase 3 trial) is needed to confirm this. Such a trial would measure improvement in survival due to the drug.

### What will the researchers do next?

The blood samples and tumour tissue provided by INTEGRATE patients will be used, with their permission, to look for individual biological differences that might have affected a patient's progress.

The next step will be for the group to consider the design for a phase 3 trial and seek funds for this.

### Where can I find out more about the trial?

Talk with your GP or oncologist. Also, the results have been presented at a conference

[meetinglibrary.asco.org/content/140049-158](http://meetinglibrary.asco.org/content/140049-158)

and published in a scientific journal

Pavlikis N, and others. Regorafenib for the treatment of advanced gastric cancer (INTEGRATE): a multinational placebo-controlled phase II trial. *Journal of Clinical Oncology*. Published online 22 Jun 2016. [Link to summary](#)

#### Australian Cancer Trials

[www.australiancancertrials.gov.au](http://www.australiancancertrials.gov.au)

#### Trial registration

[www.anzctr.org.au](http://www.anzctr.org.au)

Registered number ACTRN12612000239864

---

The sponsor was the the Australasian Gastro-Intestinal Trials Group (AGITG). The study was funded by Bayer AG, maker of regorafenib, and was coordinated by the NHMRC Clinical Trials Centre

Drs Pavlikis, Kang, Bang, Tebbutt and Zalberg have received research funding or have had advisory roles for Bayer. All other authors have no relationship with Bayer. Full disclosures are listed with the results at [meetinglibrary.asco.org/content/140049-158](http://meetinglibrary.asco.org/content/140049-158) (see link, 'Abstract disclosures').

Results of any clinical trial do not represent complete knowledge about treatment. Patients should not change their therapy on their understanding of the results.