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Translated from ***Rev Prescrire*** **June 2015; 35 (380): 413**

regorafenib (STIVARGA°) and gastrointestinal stromal tumours after treatment failure

Radiological improvement but major adverse effects

● ***Regorafenib*** **had no impact on overall survival in a placebo-controlled trial in 199 patients, but adverse effects were frequent and serious. Symptomatic care is a more reasonable choice.**

Imatinib, an inhibitor of various tyrosine kinases, prolongs survival by a few years in patients with inoperable or metastatic gastrointestinal stromal tumours. *Sunitinib*, another tyrosine kinase inhibitor, is an option if *imatinib* fails. Tailored symptomatic treatment is an alternative (1).

Regorafenib (Stivarga°, Bayer Pharma) inhibits tyrosine kinases involved in angiogenesis and tumour growth (2). It has been authorised for patients with unresectable or metastatic gastrointestinal stromal tumours after failure of *imatinib* and *sunitinib*.

No proven survival advantage. Clinical evaluation of *regorafenib* in this setting is based on a randomised, double-blind, placebo-controlled trial in 199 patients who also received symptomatic treatment (3-5).

Median survival was similar in the two groups, about 17 months (3). Interpretation of this result is difficult as 85% of patients in the placebo group received *regorafenib* when their cancer progressed (3,4). The median time to death or radiological progression (blinded assessment by an independent committee) was 4.8 months in the *regorafenib* group versus 0.9 months in the placebo group (p <0.0001) (3,4).

Frequent and often serious adverse effects. The known adverse effects of *regorafenib* are frequent, often severe and sometimes fatal, including: liver damage; bleeding; hypertension, ischaemic heart disease, cardiac arrhythmia; mucocutaneous damage, including palmoplantar erythrodysaesthesia and mucositis; gastrointestinal perforation and fistulae; infections; hypothyroidism; multiorgan hypersensitivity reactions (DRESS); and leukoencephalopathy (2,5,6). *Regorafenib* interacts with many other drugs (2).

This trial provided no additional information on the adverse effect profile of *regorafenib* (3). Serious adverse effects occurred in 61% of patients in the *regorafenib* group and 14% of those in the placebo group. Most of these effects consisted of palmoplantar erythrodysesthesia, hypertension or diarrhoea. Trial investigators attributed three deaths to *regorafenib*: one due to cardiac arrest, one due to acute liver failure, and one due to azotaemia and metabolic acidosis (3).

In practice. In patients with unresectable or metastatic gastrointestinal stromal tumours in whom *imatinib* and *sunitinib* have failed, the only proven advantage of *regorafenib* is that it delays radiological progression by about 4 months. *Regorafenib* has no proven impact on overall survival. This improvement in a surrogate endpoint is outweighed by very frequent and often severe adverse effects, resulting in an unfavourable harm-benefit balance.

It is more reasonable to propose symptomatic care rather than expose patients to the adverse effects of *regorafenib*.

regorafenib tablets

STIVARGA°

• **40 mg** of *regorafenib* per tablet

cytotoxic drug; inhibitor of multiple tyrosine kinases

■ **New indication:** "*(...) treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumors (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib*". [EU centralised authorisation]

Selected references from Prescrire's literature search.

In response to our request for information, Bayer Healthcare provided us with no documentation on its product.

1- Prescrire Editorial Staff "Imatinib and inoperable or metastatic gastrointestinal stromal tumours. Longer follow-up confirms the overall survival benefit" *Prescrire Int* 2011; **20** (114): 61-63.
2- Prescrire Editorial Staff "Regorafenib. Metastatic colorectal cancer in treatment failure: may prolong survival by a few weeks" *Prescrire int* 2014; **23** (145): 8-11.
3- EMA - CHMP "Extension of indication variation assessment report for Stivarga. EMEA/H/C/002573/II/0001" 26 June 2014: 62 pages.
4- Demetri GD et al. "Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib: an international, multicentre, prospective, randomised, placebo-controlled phase 3 trial (GRID)" *Lancet* 2013 ; **381** (9863): 17 pages.
5- European Commission "SPC-Stivarga" 16 December 2014: 25 pages.
6- Prescrire Editorial Staff "Regorafenib: Dress" *Prescrire Int* 2015; **24** (156): 20-21.