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 erythrodysesthesia and mucositis; gastrointestinal perforation and fistulae; infections; hypothyroidism; multorgan 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 benefit 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.

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**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]