



# INTEGRATE phase II trial: regorafenib vs. placebo in pretreated metastatic gastric cancer patients – is there anything new?

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Gastric cancer ranks among the most frequent cancers and the third leading cause of cancer mortality in both sexes worldwide (1,2). Unfortunately in western Countries the majority of gastric tumours are diagnosed in an advanced stage, when outcome remains disappointing. In this setting chemotherapy still represents the standard of care with the notable exception of trastuzumab use in HER-2 over-expressing tumours (3-7). Recent progresses in the molecular characterization of gastric adenocarcinomas opened new insight for new treatment possibilities to be hopefully explored in the near future (8). Along with these potential treatment opportunities, targeting tumour angiogenesis still represents a therapeutic alternative deserving further clinical development despite the discouraging results from initial trials investigating the role of the anti-VEGF-A monoclonal antibody, bevacizumab (9-11). In fact more recently the use of ramucirumab (an anti-VEGFR-2 monoclonal antibody) demonstrated to improve the clinical outcome of metastatic gastric cancer patients failing first-line treatment, thus becoming one of the possible standard treatments in this setting (12-15).

Consistently with these findings, results from a Chinese phase III study suggested that apatinib, a VEGFR-2 tyrosine kinase inhibitor, might represent an effective second-line treatment thus reinforcing the hypothesis that tumour angiogenesis is a relevant therapeutic target for these patients (16). In this clinical scenario, Pavlakis and co-workers presented the results of the INTEGRATE trial a phase II randomised trial comparing regorafenib to placebo in metastatic gastric cancer patients refractory to one or two previous lines of treatment (17). The trial objective

was to evaluate the clinical activity of regorafenib, an oral multikinase inhibitor that blocks the activity of several protein kinases, including kinases involved in tumour angiogenesis (VEGFR1, VEGFR2, VEGFR3, TIE2), oncogenesis (KIT, RET, RAF-1, BRAF) and in the tumour microenvironment (PDGFR, FGFR).

Primary endpoint was PFS, secondary endpoint included objective tumour response, clinical benefit status at two months, overall survival (OS), toxicity and quality of life. The study included a preplanned stratification for several covariates in order to define their role in the prediction of clinical outcome. Eligible patients were recruited from four Countries (Australia, New Zealand, Canada and South Korea). Ninety-seven patients were recruited in experimental arm, 50 patients in the control arm. More than half of the patients (58%) received either regorafenib or placebo as III line treatment, whereas the remaining patients received treatment as II line therapy. Most of the patients had ECOG PS 0 or 1. Nearly half of the patients (48%) in the experimental group had neutrophil-lymphocyte ratio (NLR)  $\geq 3$  (58% in the placebo group), 42% of the patients in the experimental group had VEGF-A  $>0.14$  pg/mL (46% in the placebo group), 38% had an esophagogastric junction primary tumour. Median age was 63, 36% of the patients in the experimental group were South Korean (38% in the placebo group), 64% were from other Countries (62% in the placebo group). The trial reached its primary endpoint, patients in the regorafenib arm showed in fact an improved median PFS (2.6 *vs.* 0.9 months; HR 0.40;  $P < 0.001$ ). An OS trend in favour of the regorafenib arm was also reported, although

**Table 1** Survival outcomes in phase II–III main studies in pretreated patients with gastric cancer

| Trial design | Treatment                            | OS (months)        | HR   | P value | References |
|--------------|--------------------------------------|--------------------|------|---------|------------|
| Phase III    | Irinotecan/Docetaxel; BSC            | (6.5/5.2) 5.3; 3.8 | 0.65 | 0.007   | (12)       |
| Phase III    | Docetaxel; BSC                       | 5.2; 3.6           | 0.67 | 0.01    | (13)       |
| Phase III    | Ramucirumab; BSC                     | 5.2; 3.8           | 0.77 | 0.047   | (14)       |
| Phase III    | Ramucirumab + paclitaxel; paclitaxel | 9.6; 7.4           | 0.80 | 0.017   | (15)       |
| Phase III    | Apatinib; BSC                        | 6.5; 4.7           | 0.71 | 0.0149  | (16)       |
| Phase II     | Regorafenib; BSC                     | 5.8; 4.5           | 0.74 | 0.14    | (17)       |

BSC, best supportive care; OS, overall survival; HR, hazard ratio.

this was not statistically significant (5.8 *vs.* 4.5 months; HR 0.74;  $P=0.147$ ). No statistically significant differences were reported in both response rate and in the quality of life score. Findings from the study suggested that baseline NLR might have an independent prognostic role for OS and PFS (respectively HR 1.82,  $P=0.001$  and HR 1.56,  $P=0.01$ ), whereas basal VEGF-A plasmatic levels did not correlated with outcome. Although patients from South Korea performed globally better, the PFS advantage for regorafenib treatment was consistent across the different patients' subgroups. The analysis of patients' characteristics in the Integrate trial underscored, once again, clinical-pathological and disease-management differences between Asian and Caucasian gastric cancer patients. Compared to patients from Western Countries less South Korean patients had an esophagogastric junction primary tumour (4%), NLR and VEGF-A plasma concentrations were lower. On the contrary the numbers of previous lines for advanced disease were higher in the South Korean patients (83% *vs.* 43%).

Although the Integrate trial had an undiscussed biological and clinical credibility in suggesting that regorafenib might have an interesting clinical activity in pre-treated advanced gastric cancer patients, several weaknesses in the trial design prevent us to draw definitive conclusions. The choice of a placebo standard arm in this setting is in fact particularly questionable. On the contrary according to current evidence second line treatment in refractory GC should be considered the standard approach in fit patients. Along with irinotecan and taxanes, ramucirumab either alone or in combination with paclitaxel represent the gold standard in good PS patients undergoing PD after first line treatment (Table 1).

These observations make study findings less interpretable and exclusively exploratory, especially when we consider the toxicity profile of regorafenib, which although manageable and apparently not affecting quality of life, should be

carefully considered in the planning of a treatment strategy.

Unfortunately these questions about the use of regorafenib in the second-line treatment of gastric cancer patients are not likely to be answered in future trials. On the basis of the PFS advantage reported in the INTEGRATE phase II trial the authors designed the INTEGRATE II phase III trial (18). The Integrate II trial mostly differs from the phase II study in the primary endpoint (OS) and study population (adults with metastatic or locally recurrent gastro-oesophageal cancer failing or intolerant to two lines of prior anti-cancer therapy).

To date regorafenib cannot be considered a valid approach in the second line for gastric cancer patients; however findings from the Integrate trial represent a very strong basis for further trial. These results along with those deriving from trials analyzing the blockade of mechanisms related to the PD-1/PD-L1 and CTLA-4 pathways will help us designing a more efficient and more targeted treatment strategy for these patients (19-21).

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