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Towards shedding some light on regorafenib treatment in refractory metastatic colorectal cancer

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Blocking angiogenesis has been shown to boost biological activity of antineoplastic agents in the treatment of metastatic colorectal cancer (mCRC). Combinations of chemotherapy backbones with antiangiogenic antibody constructs with a double antineoplastic and antiangiogenic spectrum of action are in routine clinical practice of mCRC[1–6] Regorafenib is an oral tyrosine kinase inhibitor (TKI) that targets proliferative, angiogenic and stromal tyrosine kinases that showed for the very first time that this approach leads to a significantly improved OS in chemo-refractory mCRC, after a series of clinical trials exploring other drugs from the same family such as sunitinib, sorafenib, pazopanib, brivanib, cediranib, vatalanib or nintedanib have failed.[7–15] However, like happened to antiangiogenic antibody constructs, the lack of predictive or response markers seriously jeopardises regorafenib's clinical use in unselected populations of patients. Hence, a significant number of unfruitful efforts have been conducted towards the identification of predictive or surrogate molecular and radiological markers of response, without bringing any significant change to the current panorama of regorafenib therapeutics in mCRC.[16–18]

Trying to shed some light on the issue, Martinelli and collaborators report in this edition of *ESMO Open*, data from a retrospective single institution analysis of 123 patients treated with regorafenib and compare clinical and molecular landscapes of a subset of long-term and short-term survivors. In line to what is seen in the pivotal trials of regorafenib in mCRC, the work by Martinelli *et al* found that those patients in their cohort with better performance status, lung-limited disease and slower tumour growth kinetics benefited more from regorafenib. Likewise they did not find any concrete molecular alteration in the 146 genes that could be related to response or resistance to treatment. Nonetheless when they looked at the best and worst responder molecular landscapes, Martinelli and colleagues interestingly found that HER2 gene alterations (one gene mutation and two amplifications) were more frequent in three poor responders, whereas GAS6 amplifications as well as SMAD4 mutations were detected as determinants of high epithelial-mesenchymal transition (EMT) activity in two long responder patients. The reported results, though coming from a small series of patients, acquire external validity once aligned with those reported by other groups. While HER signalling activation has been shown as a resistance-conferring mechanism to other mTKI and monoclonal antibodies' antineoplastic effects,[19] tumours with predominant EMT have been identified as the most favourable subgroup for regorafenib activity when the Consensus Molecular Subtype transcriptomic classification of CRC was retrospectively applied to stratify patients in one of the phase III trials exploring regorafenib.[16]

Therefore, experimental approaches like the one reported by Martinelli and colleagues are promising and have great potential implications in a context highly eager for biomarkers of response. The phase III CORRECT trial, exploring regorafenib, reported 6.4 months of OS for regorafenib versus 5.0 for placebo (HR 0.77; 95% CI 0.64 to 0.94; one-sided p=0.0052) granting thereby the approval of regorafenib in refractory mCRC.[20] Nevertheless, the secondary endpoint, median progression-free survival of 1.9 months for regorafenib and 1.7 months for placebo did not reflect a benefit for a 51% risk reduction of progression (HR 0.49; 95% CI 0.42–0.58; p<0.0001). This fact was

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better reflected by the Kaplan-Meier curves, demonstrating that only every second patient benefited from regorafenib treatment and thus arguing in favour of the necessity to find predictive biomarkers of response. This absence of biomarkers acquires special importance in light of the different tolerability profile showed by regorafenib, which clearly jeopardised regorafenib's implantation as a standard of care for chemorefractory mCRC patients. Trifluridine/tipiracil presented a similar to regorafenib magnitude of benefit compared with control in its clinical trials; however, its toxicity profile accounts for a better acceptance on the oncological community given the lack of biomarkers of response to both drugs.

Hence, more works like that presented by Martinelli and colleagues are needed to better define the use of regorafenib and improve the therapeutic situation of this drug. The used black and white approach based on looking for comparative genomics in best and in poor responders has been validated in a significant number of other studies proving very useful to intensify signals for hypothesis generation when a predominant biomarker is not in place and only a limited series of patients are available. However as previously said, works like Martinelli *et al* could only be considered as hypothesis-generating studies that need a well-established prospective validation in a longer series of patients before seeing their findings used to improve the usage of regorafenib in the treatment of refractory mCRC. Meanwhile, sequencing and selection of salvage treatment in patients with mCRC continues to be molecular unselected.

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