Editorial: Advanced Colorectal Cancer: Clinico-Pathological and Molecular Factors with Prognostic Importance, and Potential Predictive Markers of Response to Modern Systemic Treatments

In Western countries, approximately 20% of patients with colorectal cancer (CRC) present advanced disease stage at diagnosis [1-3]. The standard approach for advanced CRC with inoperable metastasis has been systemic treatment with chemotherapy for over 40 years, followed by combinations with oxaliplatin and irinotecan, that increased both response rates and overall survival (OS), and finally with the addition of monoclonal antibodies with anti-angiogenic or anti-EGFR effect [4-6]. Despite the improvement in modern chemotherapeutic and targeted agents, the long-term survival of patients with stage IV CRC is uncommon, with a poor 5-year survival rate (<15 %) [7]. Surgery remains an important treatment option for advanced CRC, especially since it offers a curative option for select groups: patients with metastatic disease confined to a single organ, patients with a local recurrence only or patients with limited intra-abdominal disease. In such cases, an aggressive and multimodal management integrating both surgical resection and systemic chemotherapy treatment allows achieving long-term surviving rates of 50% [8]. However, in most cases of CRCm, treatment is palliative rather than curative, and the main objectives are to prolong overall survival (OS) and maintain quality of life for as long as possible. Different clinical and pathological characteristics have been proposed as prognostic factors for patients with unresectable CRCm undergoing first line systemic chemotherapy, such as the presence of peritoneal carcinomatosis, number of metastatic locations, elevated tumour markers in serum, or the site of primary tumour [9-11]. However, to date there is no reliable strategy for predicting the survival of individual patients undergoing modern chemotherapy. This has led to an increased interest in identifying prognostic factors that could permit more accurate patient stratification. Regarding to clinical and pathological factors that might have a prognostic role, there are several retrospective studies published to date that have provided conflicting results. Further efforts should be made to study the associations between prognostic factors and CRC biological behaviour.

The first biomarker incorporated into clinical practice was the analysis of mutations in *KRAS* exon 2 (codon 12/13) as an established predictor of lack of response to the anti-*EGFR* monoclonal antibodies Cetuximab and Panitumumab in patients with metastatic colorectal cancer [12, 13]. Kirsten-ras (*KRAS*) is a proto-oncogene encoding a small 21 kD guanosine triphosphate/guanosine diphosphate binding protein involved in regulation of cellular response to many extracellular stimuli [14]. Mutations within *KRAS* abrogating GTP-ase activity and resulting in activation of *RAS/RAF* signaling are found in 35% to 42% of CRCs and are thought to occur early in CRC carcinogenesis. Activating mutation in other members of the *RAS* oncogene family (*KRAS* exons 2, 3 and 4, and *NRAS* exons 2, 3 and 4) have been also described, although they are much less frequent. *NRAS* appears in about 2% of patients with advanced CRC [15]. The presence of less frequent *KRAS* mutations and *NRAS* mutations has recently been related as well with a lack of benefit from anti-*EGFR* therapies [16]. The evaluation of an extended panel of *RAS* mutations can better define the patient population that is likely to benefit from anti-*EGFR* therapy. Thus, testing *RAS*-status is nowadays a routine procedure worldwide, and has been incorporated in clinical practice as a predictive biomarker to decide first line treatment for patients with advanced CRC.

In the other hand, Bevacizumab a monoclonal antibody against VEGF was the first inhibitor of angiogenesis approved for the treatment of advanced CRC in combination with chemotherapy based on the survival benefit observed in clinical trials. The search for molecular markers capable of predicting patients' prognosis and the response to anti-angiogenic treatments has increased. Attempts have been made without success to relate several molecular markers with tumour response to the treatment with bevacizumab; therefore, currently it is not possible to predict in advance which patients will benefit from this treatment [17]. *VEGFR-2/KDR* is the main receptor of the vascular endothelial growth factor (*VEGF*) and is frequently over-expressed in CRC. Several authors have linked this over-expression with a significant increase in tumour vasculature and an increase in the metastatic capacity of the tumours [18]. The binding of *VEGF* to *VEGFR-2/KDR* leads to the phosphorylation and activation of a signalling pathway that stimulates the proliferation, migration and inhibition of apoptosis and maturing of endothelial cell vascular structures [19, 20]. *VEGF* is an important regulator of physiologic and pathologic angiogenesis, and it is over-expressed in many different tumour types. It has been described how *RAS* pathway signaling increases *VEGF* expression and repress negative regulators of angiogenesis, suggesting that *RAS* aberrations could modulate the tumour response to anti-angiogenic therapies [21-23]. It is controversial whether *KRAS* mutations, independently of the use of anti-*EGFR* therapies, have a prognostic role in CRC [24, 25]. Different studies published to the date have not been conclusive, even among several large studies [26, 27], and the role of *KRAS* and *NRAS* mutational status as a predictor of outcome of oxaliplatin-based chemotherapy and bevacizumab remains uncertain.

BRAF mutations occur in 5 -15 % of metastatic CRC [28]. This mutation has been found to be a poor prognostic factor in multiple clinical trials and more frequently is associated with adverse histological features and poorly differentiated morphology [29-31]. *BRAF* mutant metastatic CCR group could benefit of an aggressive and targeted therapy. During the last years a significant progress has been made in the investigation and identification of biomarkers candidates to predict response to new therapeutic strategies. The FIRE-3 clinical trial results suggest that patients with right-colon cancer seem to benefit less from treatment with anti-*EGFR* drugs [32], in addition, this patients are more likely to present *BRAF* mutations and microsatellite instability (MSI). This data are specially relevant, since tumours with MSI are associated with lymphocytic infiltration and *PD-1* and *PDL-1* over-expression, and there is preliminary evidence from phase I clinical trials showing encouraging responses of these tumours to anti-*PD-1* monoclonal antibodies, and suggest that this specific subgroup of patients might benefit from immune targeted approaches [33-35]. Other important potential predictive markers include *HER2* amplification, *ALK* and *ROS1* rearrangements or cMET amplifications. All of them might have a role in the tumour resistance to anti-*EGFR* therapies, but they also represent a challenging opportunity for the development of targeted therapy in advanced CRC. *HER2* amplification is present in approximately 3% of patients and in these tumours responses to anti-*HER2* therapies have been observed in xenograft models [36] and humans [37]; ALK-fusions and *cMET* amplification have also been observed in a small proportion of patients (1 and 2% respectively), but both biological abnormalities could predict the success of targeted therapies witch warrantees the investigation of the effectiveness of this pathways inhibition in advanced CRC [38, 39].

In conclusion the improvement of patient's outcomes that we have observed in the last years, has been leaded by a better molecular understanding of CRC, what has allowed for a better patient prognostication and for the application of precision medicine in their treatment. Nowadays it is mandatory before deciding ours patient's treatment the evaluation for *RAS* and *BRAF* status, and to integrate this information with classical variables such as Performance Status, age and goal of treatment to select the optimal therapy for the patient. The future advances in the treatment of advanced CRC will come from the development of novel therapies for *RAS*-mutated tumours, and from the identification of subgroups of patients with molecular abnormalities suitable to be treated with targeted therapies such as *BRAF*, *PIK3CA* mutations, *HER2* amplification or MSI.

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