



## Letter to the Editor

# More rationale for optimal sequencing of therapeutic monoclonal antibodies in metastatic colorectal cancer



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Large recent multicentric randomised studies highlight the opportunities offered by a multiple treatment strategy in RAS wild-type metastatic colorectal cancer (mCRC). A review in *the European Journal of Cancer* [1] revealed that the optimal use and sequencing of cytotoxic chemotherapy and targeted agents across multiple lines of treatment for mCRC remain unclear. However, from the recently published randomised phase 2 PRODIGE 18 clinical trial, it appears that continuation of bevacizumab with second-line chemotherapy after progression confers a survival advantage (both overall survival [OS] and progression-free survival [PFS]) as compared with the alternative strategy of switching both the chemotherapy regimen and the targeted therapy [2]. Clearly, adding cetuximab to bevacizumab does not improve survival, and thus, anti-epidermal growth factor receptor (anti-EGFR) antibody plus chemotherapy could be the first treatment of choice followed, at progression, by bevacizumab plus a chemotherapy switch. The biological mechanisms which can sustain this clinical observation are not clearly elucidated, and the purpose of the present letter is to shed some light in this area. Molecular-based explanations have been advocated in the article by Modest et al. [1]. In brief,

preclinical and clinical data reveal an increase of circulating vascular endothelial growth factor-A (VEGF-A) under bevacizumab. This change in VEGF-A concentration may induce resistance to cetuximab by upregulating vascular endothelial growth factor receptor 2 signalling. The alternative, still in line with the optimal cetuximab-bevacizumab sequencing, is a hypothesis considering both bevacizumab and cetuximab outside the strict perimeter of their primary mechanisms of action, i.e. an antiangiogenic effect for the former and EGFR pathway inhibition for the latter. More precisely and importantly, recent experimental and clinical data have revealed that bevacizumab activity, through its interaction with VEGF, may in fact restore endothelial cell diapedesis in favour of tissular diffusion of cytotoxic T lymphocytes instead of regulatory T cells facilitated by the impact of VEGF on endothelial cells [3]. Thus, under bevacizumab treatment, adequate tissular redistribution of beneficial antitumour CD8 T cells is achieved in place of detrimental regulatory T cells. This replenishment of CD8 T cells in breast cancer tumours under bevacizumab treatment has already been demonstrated [4]. A relative abundance of available CD8<sup>+</sup> T cells is thus of prime importance considering the immune-related effect conferred by bevacizumab. This can be conferred by cetuximab as follows: the IgG1 nature of cetuximab enables it to develop antibody-dependent cellular cytotoxicity (ADCC), which was recently highlighted by others and us for its significant contribution to the global action mechanism of

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cetuximab [5]. Of importance is the immune modulation generated by ADCC [5]. In brief, based on preclinical and clinical observations, cetuximab-mediated ADCC, through a natural killer cell release of  $\text{INF}\alpha$ , results in priming of cytotoxic T cells [5]. It is thus conceivable that the beneficial order of cetuximab followed by bevacizumab can be accounted for, bearing in mind the known prognostic importance of cytotoxic T-cell infiltration in metastatic colorectal cancer (mCRC).

In the light of these immunological considerations regarding the cetuximab-bevacizumab association, it is advisable to incorporate immunology-based translational studies in future clinical trials, including investigations into the quality and quantity of immunological cells at both circulating and tumoural levels. In conclusion, these immunological considerations reveal a favourable T-cell profile which can result from the cetuximab-bevacizumab association. In addition, this may constitute a strong argument supporting to combine the cetuximab-bevacizumab sequence with immunotherapy by checkpoint inhibitors. This is noteworthy in the current context of setting immunotherapy-based combination strategies in mCRC.

### Conflict of interest statement

G.M. has received honorarium from Merck, MSD, BMS and Roche.

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