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# Comment on: "Exploring the best treatment options for BRAF-mutant metastatic colon cancer"

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An interesting and particularly welcome article by Taieb et al.[1] describes treatment options for the management of bad-prognosis colorectal cancer (CRC) patients harbouring BRAF-mutated tumours. The current and future therapeutic strategies for this category of patients are based on well-established and complex preclinical data to which the authors paid insufficient attention.

One of the major advances in BRAF-mutated CRC is the setting of BRAFi–MEKi combinations. Of importance, although not discussed by the authors, this association of a BRAFi with a MEKi was dictated by the fact that BRAFi can induce neoplasia, most often cutaneous squamous cell carcinoma.[2] This effect is attributed predominantly to paradoxical ERK activation (the ability of BRAFi to stimulate RAF signalling in BRAF wt condition, thus activating ERK and stimulating proliferation).[3] Figure 1 of the paper[1] makes no mention of this tissue-specific molecular aspect, which is important not only for mechanistic reasons, but is also of therapeutic interest since BRAFi, which evades paradoxical MAPK pathway activation, is currently in clinical development.[4] Moreover, a definition of a paradox index has been set for BRAFi (vemurafenib, dabrafenib and encorafenib, PLX8394) as a means of quantifying a therapeutic window of high clinical efficacy (at least in BRAF-mutant melanoma cells) with minimal paradoxical ERK activation.[5]

The authors did mention another level of the underlying molecular complexity, i.e. the interruption by MEKi of negative feedback of ERK signalling at the initiation steps of MAPKinase signalling.[6] This explains why, in the case of colorectal cancer cells and not melanoma cells (deprived of EGFR signalling), the addition of EGFRi is a necessary complement to the BRAFi–MEKi association. When advocating EGFRi in CCR, and more broadly, the use of monoclonal antibodies, the respective order of application of cetuximab versus bevacizumab is still a matter of debate. Cetuximab is an IgG1 and this characteristic confers to the drug the capacity to develop the clinically important mechanism of antibody-dependent cellular cytotoxicity (ADCC). ADCC was recently highlighted by others and us for its significant contribution to the global action mechanism of cetuximab.

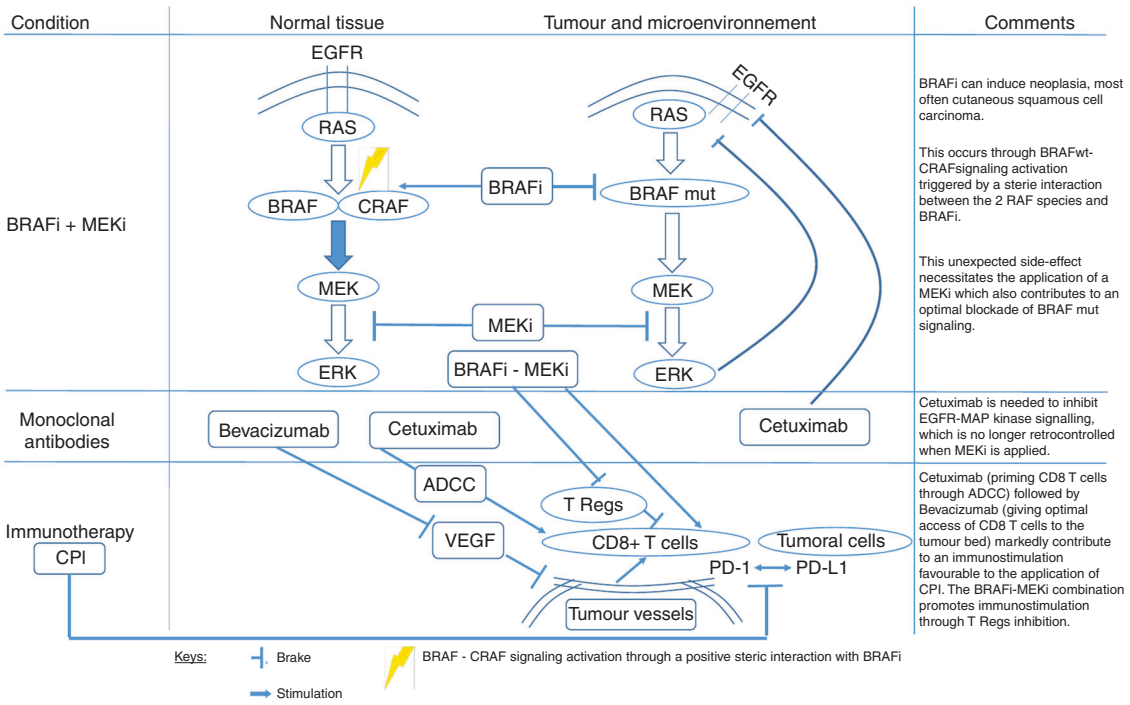


**Fig. 1** BRAF - mutated metastatic CRC: molecular bases for an optimal combination BRAFi - MEKi - cetuximab - bevacizumab - CPI.

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Of importance is the immune modulation generated by ADCC.[7] In brief, based on preclinical and clinical observations, cetuximab-mediated ADCC, through natural killer-cell release of INFα, results in priming of cytotoxic T cells.[7] Recent experimental and clinical data have revealed that bevacizumab, through its interaction with VEGF, may in fact restore normal endothelial cell diapedesis. This results in favourable tissular diffusion of cytotoxic T lymphocytes instead of regulatory T cells, the diffusion of which is facilitated by the deleterious impact of VEGF on endothelial cells.[8] Thus, under bevacizumab treatment, adequate tumoural tissue redistribution of beneficial antitumour CD8 T cells is achieved in place of detrimental regulatory T cells. This background may support recent clinical results regarding the optimal order for cetuximab (priming CD8 T cells) versus bevacizumab (allowing optimal access of CD8 T cells to the tumoural bed) in first-line metastatic CRC[9] and strengthens combination strategies also including immunotherapy by checkpoint inhibitors in unstable microsatellite BRAF-mutated CRC patients. The fact that BRAF + MEK inhibition positively affects the tumour microenvironment and immune modulation is thus a strong argument in favour of adding immunotherapy in the context of the cetuximab–BRAFi–MEKi/bevacizumab combination with attention being paid to an optimal sequencing. The included figure recapitulates the molecular mechanisms considered above and seeks to clarify the particularly complex background-sustaining treatment options for metastatic BRAF-mutated CRC.

## AUTHOR CONTRIBUTIONS

G.M. and J.G. made substantial contributions to study conception and design. GM. and J.G. were involved in drafting the paper. All authors contributed to and approved all drafts.

## ADDITIONAL INFORMATION

**Ethics approval and consent to participate** This project did not constitute research. Therefore, ethics committee approval was not required.

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