Pharmacokinetics partly explains the relationship between carcinoembryonic antigen level and survival of colorectal cancer patients treated with ramucirumab

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Pharmacokinetics partly explains the relationship between CEA level and survival of colorectal cancer patients treated with ramucirumab

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Dear Editors,

Yoshino and colleagues (1) recently reported results from the RAISE trial, in which 1072 metastatic colorectal cancer patients were treated with ramucirumab, a monoclonal antibody targeting vascular endothelial growth factor receptor 2 (VEGF-R2). They observed that low baseline serum levels of carcinoembryonic antigen (CEA) were associated with longer overall (OS) and progression-free (PFS) survivals. However, the authors did not discuss the possible mechanisms behind this association although the published literature may provide an answer.

First, Cohn and colleagues (2), using a subset of 907 patients from the same RAISE trial, observed that both low baseline CEA and high trough serum concentrations (Cmin) of ramucirumab were associated with longer OS and PFS. Second, Caulet and colleagues (3) reported similar results in metastatic colorectal cancer patients treated with bevacizumab, an anti-VEGF monoclonal antibody. These authors indeed reported that high bevacizumab Cmin was associated with longer OS and PFS. In addition, they observed that bevacizumab clearance increased with both high baseline plasma VEGF and high baseline serum CEA levels. The influence of plasma VEGF on bevacizumab clearance may be explained by target-mediated drug disposition, a mechanism frequently reported for monoclonal antibodies (4, 5). Because CEA level increases with tumour burden (6), it may constitute a biomarker of VEGF level in tumour microenvironment, a potent angiogenic factor that also increases with tumour volume (7). The increase of bevacizumab clearance with high serum CEA level, which led to low serum concentrations of bevacizumab, may therefore correspond to an elimination of the monoclonal antibody related to tumour VEGF.

Since VEGF-R2 expression was shown to be directly proportional to colorectal tumour doubling time in a preclinical model of xenografted mice (8) and VEGF-R2 promoter activity was significantly increased during the course of the disease in a mouse model of colitis-associated cancer (9), a positive correlation between tumour burden and amount of VEGF-R2 may reasonably be hypothesized. The association of CEA with both pharmacokinetics of ramucirumab and survival may be similar to bevacizumab. Increased serum CEA levels may represent higher tumour burden and

should therefore correspond to increased VEGF-R2 expression. This may result in increased target-mediated elimination of ramucirumab, leading to underexposure and therefore to decreased clinical efficacy. As for bevacizumab, part of the relationship between serum CEA levels and survival of patients treated with ramucirumab may be explained by an increase in target-mediated disposition of the monoclonal antibody with tumour volume.

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