Unraveling immune complexity in metastatic colorectal cancer: a step towards the development of circulating immune biomarkers

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Abstract

Metastatic colorectal cancer currently represents a major therapeutic challenge due to the lack of response to immunotherapies.

Clinical efficacy and safety of AVE, CET and IRI have previously been reported for the treatment of refractory MSS mCRC. Here, we aim to characterize the systemic immune response and investigate its potential role in response to immunotherapy.

MSS, chemo refractory (anti-EGFR refractory if RAS wild-type) mCRC patients were enrolled (RAS wild-type: 28 patients, RAS mutated: 27 patients) and treated with CET and IRI from week 1 (W1) and AVE from W3. Clinical objectives, including safety and efficacy were previously reported. Using high-dimensional flow cytometry and FlowJo™, peripheral blood mononuclear cells were characterized for immune populations' phenotypes (including B, T, natural killer (NK) and myeloid cell populations) and proportions. Modifications of immune cells proportions were analysed over time (sequential blood samples were collected at W0, W3, and W11) and correlated with response, progression-free survival (PFS) and overall survival (OS) of included patients. P-values were calculated using the Wilcoxon test.

Of the 55 treated patients, 148 blood samples (W0: 55, W3: 53, W11: 40) were available for flow cytometry analyses. Overall, B, T, NK, and myeloid cell populations remained stable over time and were not associated with clinical efficacy. Some T and NK cell subpopulations showed variations. Regardless of RAS mutational status, a decrease of TH17 frequency over time was associated with PFS ≤ 6 months, OS ≤ 12 months and tumour growth. At baseline, a lower frequency of circulating NKT cells was associated with tumour response, and an increase of NKT cell frequency over time was associated with tumour response, PFS > 6 months and OS > 12 months. Circulating NKT cells, and more specifically NKT CD8+ cells were also associated with intra tumoral CD3+ and CD8+ infiltration. Proteomic and transcriptomic analyses could further help to decipher patients according to survival and reveal importance of immune signalling activation.

Independently of RAS mutational status, modifications of TH17 and NKT cell frequencies in MSS mCRC patients' blood included in the AVETUXIRI trial seems to be associated with tumour response and patients' survival after treatment.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.