TRANSLATIONAL PROGRAM OF THE PHASE II MEDITREME TRIAL: IDENTIFICATION OF PROGNOSTIC FACTORS FOR RESPONSE TO DURVALUMAB AND TREMELIMUMAB IN COMBINATION WITH FOLFOX IN METASTATIC COLORECTAL CANCER

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Background Single agent PD-1/PD-L1 inhibition are not effective in metastatic colorectal cancer with microsatellite stable tumors. However, signal of efficacy was shown using combination of anti-PD-L1 and anti-CTLA-4 in multitreated patients and the combination with FOLFOX regimen could lead to a potential positive effect on antitumor immune response. We report here the immune response observed following immunomonitoring of patients before and during MEDITREME trial.

Methods MEDITREME was a single arm phase II trial which aimed at evaluating efficacy and safety of mFOLFOX in combination with durvalumab and tremelimumab. We studied the phenotypic and functional immune response at inclusion and after 15 days (C2), 5 (C5) and 12 (C12) weeks of treatment by flow cytometry and the specific T response by ELISPOT. These immune parameters could be linked to survival data (RECIST criteria, progression free-survival) to highlight factors that may be prognostic of treatment response. One patient with a complete response allowed further a more detailed analysis of antitumoral immune response by single cell (sc) RNA- and TCR-sequencing, ELISPOT and flow cytometry analyses of the blood and tumor infiltrated immune cells.

Results Computational cytometry analyses showed that high baseline levels of Th2, Tc2 and PDL1+ MDSC were associated with non-responder patients. Conversely, a high baseline level of activated T cells secreting IFN γ and TNF α and a high level of activated T cells expressing ICOS and high level of CD45RA+ Treg after a treatment cycle were associated with responder patients. Concerning specific T cells response, TERT response at C2 and C5 was associated with responder patients and with high PFS. ScRNA sequencing performed on CD8 cells isolated from blood and tumor samples from the patient with a complete response showed an accumulation of polyfunctional CD8 T cells in tumor with high level of expression of effector cytokine and cytotoxic molecules. TCR sequencing analysis underlined the expansion of multiple clonotypes in TILs with some similarity between clone found in TILs and blood at the time of surgery. Moreover, we showed that only in TILs and blood at surgery charged multiple TCR clones predicted to recognize similar antigen. Finally, we generated the 14 predicted CD8 neoantigen peptides thanks to tumor exome sequencing and found that blood T cells and TILs response against neoantigens.

Conclusions Immunomonitoring has allowed us to associate peripheral immune parameters with treatment efficacy. ScRNA sequencing underlines the ability of the treatment to induce a specific immune response against neoantigens in a complete responder patient.

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Trial Registration ClinicalTrials.gov Identifier: NCT03202758

Ethics Approval

Eudra-CT registration number 2016-005006-19