January 7, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7006-review.doc).

Title: Colorectal cancer and immunity : what we know and perspectives

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7006

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated
Table 1 is formated in three-line table
Figure 1 and figure 2 have been removed and uploaded separately in .ppt format according to your recommendation
Manuscript was reviewed by a native-speaker of English

2 Revision has been made according to the suggestions of the reviewer and have been underlined in the manuscript.

Reviewer 1:

(1) "Please always quote the references. Some statements concerning other studies have not been quoted"

Response: References have been added (46, 48, 59, 60, 61)

(2) "TILs" should be spelled out the first time

Response: we spelled it (page 9)

(3) "In the same paragraph the authors stated "The prognostic value of Tregs in CRC is still controversial… …there is considerable evidence that Tregs are associated with a poor outcome in CRC." The two are contradictory.

Response: According to your recommendation we removed the contradictory sentence " The prognostic value of Tregs in CRC is still controversial", and we added " This difference may be related to the heterogeneity of methods for characterization and quantification of Tregs and the use of more reliable techniques such as flow cytometry have shown the deleterious role of Tregs." (page 12) to explain the controversial datas.

Reviewer 2:

(1) "I would consider focussing on the therapeutic aspects more."

Response: To date there is no validated immunotherapy strategies. We did a review of trials but we do not have more data on current therapeutic trials.

(2) "perhaps some emphasis on biomarkers to guide clinical management"

There is no validated immune parameter as a biomarker in clinical practice. Even Immune infiltrate, which is the most validated, is not yet used in daily practice. In order to clarify this point we added: However, other teams have not confirmed these results yet and major information are lacking in this large retrospective series such as age, MSI status or the use of adjuvant therapy. Despite these

promising results, there is still no immune quantification test in routine practice to use immune infiltrate to guide our therapeutic strategies. This underlines the difficulty to find a standardized and reproducible test that complies with daily practice. Such tests should be of particular interest for clinicians, especially for stage II patients for whom the indication for adjuvant treatment is more controversial. (page 11). We therefore did not want to emphasis on biomarkers which are not used in daily clinical practice.

But in order to be more exhaustive, we added data on myeloid derived suppressor cells (MDSC):

Myeloid-derived suppressor cells (MDSC) are immunosuppressive cells. As Tregs, they contribute to the immune tolerance by inhibiting the function of CD8(+) T cells. The prognostic value of MDSC is not well known, but they are thought to be deleterious, as elimination of MDSC in mouse tumor models was shown to enhance antitumor responses, resulting in tumor regression [61]. (page 13)

Others immune mechanisms could be induced by cytotoxic chemotherapy. It has been shown in murine model that 5-Fluorouracil could lead to a decrease of MDSC in the spleen and tumors in vivo, combinate to a T cell-dependent antitumor responses [61], but the therapeutic impact is not well established. page 14)

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Simon PERNOT (MD) and Julien Taieb (MD, PhD)
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