

February 7, 2019

Dear Editor-in-Chief,

We thank you for your interest to our article entitled “Management of skin toxicities during panitumumab treatment in metastatic colorectal cancer”.

We answered point by point to the comments of the reviewers and we have taken into account the editor’s queries in the manuscript.

Note that we did not upload a language certificate because the manuscript has been read for English language by an English-native scientist from global Amgen staff (Dr G. Demonty, Regional Medical Director Europe).

One of the authors signed separately the copyright license agreement for geographical reasons.

I look forward to hearing from you.

Sincerely yours,

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Answers to the reviewers

Title: Management of skin toxicities during panitumumab treatment in metastatic colorectal cancer.

By O. Bouché *O et al*

Comments from Reviewer 1

This is a well written and quite interesting manuscript. It provides real-world data regarding skin toxicity after panitumumab therapy; good data are provided regarding the timing of skin reactions, the potential role of prophylactic therapy, the adherence to recommended protocols, other than analysing the impact of such reactions on patients' quality of life. My only concern

is that, considering it is a very peculiar topic, I am not completely sure that the paper completely falls within the scope of World Journal of Gastroenterology.

Response: We thank the reviewer for his/her comments.

Comments from Reviewer 2

This is overall a well-written interesting article. The topic is very hot since immunotherapy is quite effective for many tumor types. Nonetheless, this paper can be improved to address some key points and references. Please improve this paper. The authors did not discuss the influence of environment (including the microbiome) on the adverse effects. It should be discussed. Related to the above point, the authors used all patients in one basket, but there are differences in patients, according to tumor molecular pathology (such as MSI status, KRAS, BRAF, PIK3CA mutations) and environment (including microbiome in gut and tumor/normal tissue). The authors must discuss the recent trend of molecular pathological epidemiology (MPE). MPE is an emerging field that can link environment (including the microbiome), food, and lifestyle to molecular pathologies, disease subtypes, ie, subgroups of patients (even adverse events of treatment) and contribute to biomarker research and precision medicine. Microbiome, lifestyle and diets can help patient's recovery and clinical outcomes. Please discuss MPE. You can find relevant papers easily by net and pubmed search (eg, I see Gut 2011, Annu Rev Pathol 2019, J Pathol online).

Response: We thank the reviewer for his/her encouraging comments and suggestions. We agree with him/her that the environment plays a role on the adverse effects. However, the study protocol was not designed to explore specifically this issue. We pragmatically assessed the rates and the management of skin toxicities associated to panitumumab treatment. It was out of the scope of the study to assess whether some mutations, for example, were more frequently associated to some skin toxicities. We must also underscore that panitumumab treatment is not an immunotherapy. Indeed, panitumumab is a monoclonal antibody that targets EGFR which is not a molecule of the immune system. This is precisely because panitumumab targets EGFR, which is involved in the physiology of epidermidis, that skin toxicities occur. In contrast, pembrolizumab for example that blocks PD-L1 and therefore allows the immune system to destroy cancer cells is considered as an immunotherapy.

Comments from Reviewer 3

Excellent observational study. It could be presumed that EPIDERMAL growth factor receptor inhibitors will have some impact on the skin as EPIDERMAL layer. The methodology is excellent except for antibiotic use. All the queries were put directly in the word document of the manuscript in red because there are no Lines in the manuscript.

Response: We thank the reviewer for his/her comments. We have taken into account the queries in the manuscript.

First comment in Materials and Methods: we have completed the text for indicating that “*A glossary defining precisely the dermatological toxicity was created by the dermatologist of the Scientific Committee and given to the physicians*”.

Second comment in Results (in section “*Preventive and curative treatments of dermatological toxicities*”): The oral antibiotics that have been used were not specifically analyzed. They are generally cyclins (minocycline, tetracycline). We agree with the reviewer that the use of antibiotics as a prophylactic treatment is an issue particularly in terms of bacterial resistance. There is however an expert consensus for prophylactic management (including antibiotics) of skin reactions for all patients treated with EGFR inhibitors (see, for example, Hofheinz et al, Recommendations for the Prophylactic Management of Skin Reactions Induced by Epidermal Growth Factor Receptor Inhibitors in Patients with Solid Tumors. *Oncologist* 2016; 21: 1483).