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Udine, August 2<sup>nd</sup>, 2015

Dear Editor-in-Chief,

We are enclosing in its revised version our invited manuscript entitled '**Treatment-related gastrointestinal toxicities in patients diagnosed with advanced colorectal cancer or pancreatic carcinomas: a critical update**' to be considered for publication in the World Journal of Gastroenterology (ID 00109194).

The manuscript has been modified accordingly to the reviewers' suggestions.

We thank the reviewers for their work and appreciate their comment. Though compelling, the role of cannabinoids (Cannabinoids for medical use: a systematic review and Meta-analysis. Whiting P.F. et al JAMA. 2015;313(24):2456-2473) was not mentioned throughout our manuscript as we mainly focused on the different types and pathogenesis of gastrointestinal toxicities, rather than discussing their specific treatments. As such, should we add a paragraph commenting on the potential anti-emetic activity of cannabinoids, we would have to drastically change the manuscript.

Worldwide, gastrointestinal malignancies remain a significant health problem, with close to 2 million new cases every year. Over the last two decades, while the widespread use of novel therapies has contributed to progressively increase the median survival of gastrointestinal cancer patients, and the availability of additional therapeutic options has created new challenges and generated more complicated treatment algorithms.

Gastrointestinal toxicities (GIT), including oral mucositis, nausea and vomiting, and diarrhea, are common side

effects of chemotherapy and targeted agents in patients with advanced colorectal cancer and pancreatic cancer. Although it is not easy to establish their burden in terms of both patient's quality of life and cancer care costs, the frequency of these toxicities is rapidly growing with a potential negative effect also on patient's outcome, as a result of dose reductions, delays or even discontinuation of effective treatments. Thus, identifying patients at higher risk of developing GIT as well as an optimal management are paramount in order to improve patient's compliance and outcome. In our review we firstly describe the characteristics of treatment-induced GIT, than we discuss the current knowledge on the pathophysiology of these side effects and comment the scales commonly used to assess and grade them. Finally, we provide a critical update on GIT incidence based on the results of key randomized trials conducted in patients with metastatic colorectal cancer and advanced pancreatic cancer.

All authors of this paper have directly contributed to data collection and manuscript drafting. Also, all Authors have read and approved the final version of the manuscript.

We certify that the manuscript represents valid work and that neither this manuscript nor one with substantially similar content under our authorship has been published or is being considered for publication elsewhere.

We thank you for considering our work and look forward for hearing from you at your earliest convenience.

Yours sincerely,

Giuseppe Aprile

first author, on behalf of prof. Stephen Sonis, senior and corresponding author

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