July 30, 2014

Stephen C Strom
Saleh A Naser
Andrzej S Tarnawski
Damian Garcia-Olmo
Editors-in-Chief
World Journal of Gastroenterology
e-Submission

Dear Drs. Strom, Naser, Tarnawski, and Olmo:

My co-authors and I received a minor revision decision regarding our manuscript, titled "Appropriateness of Systemic Treatments in Unresectable Metastatic Well-Differentiated Pancreatic Neuroendocrine Tumors" (Manuscript # 10314), submitted for publication in *World Journal of Gastroenterology*. We have addressed each comment raised by the two reviewers and made clarifications in the manuscript as requested. Our specific responses to the reviewers' comments are attached below. In response to the reviewers' comments, we have specified the sections for our corresponding revisions in the manuscript and quoted the text where reviewers' comments were addressed. In the body of the manuscript, we have used track-changes and highlighted the edited and new text.

My co-authors and I would like to sincerely thank the *World Journal of Gastroenterology* Editors-In-Chief and the reviewers for their review of our manuscript.

Thank you for your time and consideration. We look forward to your decision.

Sincerely,

Dasha Cherepanov, Ph.D.
Associate Director, Outcomes Research
Partnership for Health Analytic Research
LLC, 280 S. Beverly Drive, Suite 404, Beverly Hills, CA 90212
Phone: 310 858-9555; Fax: 310 858-9552; Email: dasha@PHARLLC.com

RESPONSE TO REVIEWERS

Manuscript number: #10314

Title: Appropriateness of Systemic Treatments in Unresectable Metastatic Well-Differentiated Pancreatic Neuroendocrine Tumors

REVIEWER 00068107 Comments

1. **[Reviewer Comment] The manuscript has the novelty and innovation for the conclusion that using the RAND/UCLA modified Delphi process, physician experts obtained consensus on the appropriateness of various medical therapies in unresectable metastatic well-differentiated PNETs.**

[Authors' response] We thank this reviewer for the thorough review of our manuscript and recommendation to accept our manuscript for priority publishing in the *World Journal of Gastroenterology (WJG).*

REVIEWER 02439777 Comments

2. **[Reviewer Comment] There is nothing new in this review article compared to NCCN guideline or NANETs guideline for W/D PNETs. Since there is not enough evidence for appropriate treatment of metastatic W/D PNETs until now, physicians refer to expert-based recommendation or slightly different guidelines for each country. Authors organized the appropriate treatment based on expert panels; so I would like to say this review article is meaningful.**

[Authors' response] We thank this reviewer for the detailed review and comments about our manuscript and for recommending priority publishing in *WJG,* pending minor revisions. We also thank this reviewer for confirming that our expert consensus results correspond with the recommendations reported in the NCCN and NANETS guidelines but also offer a meaningful contribution to the literature.

3. **[Reviewer Comment] The well-differentiation PNETs are classified as G1, G2, and G3 based on 2010 WHO classification. However, these terms are not used in this paper. Please explain about this.**

[Authors' response] The current paper is a part of a larger study which also included the treatment consensus elicitation from the panel in patient scenarios with well-differentiated midgut or non-midgut NETs (recently published in Strosberg et al. *Pancreas* 2013). Altogether 10 key stratifying variables (listed in Table 1) were used to construct detailed patient scenarios which were used to produce appropriateness ratings from the panelists. Hence, a total of 606 unique patient scenarios (202 in PNETS and 404 in midgut/non-midgut NETS) were ranked by each of the panelists, which was a time consuming and labor intensive process.

Given the authors' prior extensive experience with conducting Delphi panels, we conducted extensive cognitive interviews with physician experts to arrive at the 10 most key stratifying variables, such that the resultant total number of patient scenarios capture the range of patient

experience but are still manageable and feasible to be reviewed and ranked by the panelists. However, we do agree that by not including other unique patient scenarios, such as further classification of differentiation of NETs in our study is a limitation.

Hence, we have included the following statement in the Discussion section:

> "Future research should consider collecting treatment appropriateness ratings from physician experts on additional unique PNET patient scenarios not considered in this study, such as patients scenarios with moderately differentiated (intermediate grade or G2) PNETs and poorly differentiated (high grade or G3) PNETs.[35, 36]"

We have also included the following 2 additional references (#36 and #37) for this statement (which were used by the WHO report mentioned by this reviewer, available at: http://www.carcinoid.com/health-care-professional/neuroendocrine-tumors-classification.jsp):

> 36. Klimstra DS, Modlin IR, Coppola D, Lloyd RV, Suster S. The pathologic classification of neuroendocrine tumors: a review of nomenclature, grading, and staging systems. *Pancreas.* 2010;39:707-712 [PMID: 20664470 DOI: 10.1097/MPA.0b013e3181ec124e.]
>
> 37. Strosberg JR, Nasir A, Hodul P, Kvols L. Biology and treatment of metastatic gastrointestinal neuroendocrine tumors. *Gastrointest Cancer Res.* 2008;2:113-125 [PMID: 19259290]

4. **[Reviewer Comment] Authors mentioned only 'appropriate' in the result. It would be great to describe some distinct disagreement in between panels in the discussion.**

[Authors' response] We have included minimal discussion of "disagreement" in this study since only "agreement" is typically reported and discussed in Delphi panel studies. This is because "agreement" yields consensus statements while areas of "disagreement" yield inconclusive or unknown results. Hence, "disagreement" is not typically reported and discussed since no conclusions can be drawn based on such data.

Furthermore, there were very low levels of disagreement in our study, as indicated in the Consensus Results section in the Results and in Table 2:

> "The proportion for which there was disagreement decreased from 13.2% (26 scenarios) before the meeting to 0.99% (2 scenarios) after."

We have also emphasized this in the Discussion section:

> "The panel developed a number of consensus statements with very low levels of disagreement."

There were only two specific scenarios with "disagreement," indicated in the Supplemental Digital Content tables (attached at the end of the manuscript) and shown as panel median ratings color-coded in black font and highlighted in yellow:

- First-line treatment in PNETs with cytotoxic chemotherapy in a patient whose primary problem is uncontrolled tumor-related symptoms.

- Second-line treatment of PNETs with increased dose/ frequency of octreotide-LAR to 30 mg every 3 weeks in a patient whose primary problem is radiographic progression and who had previously responded to a lower dose/frequency of octreotide-LAR.