

Reply to Editors/Reviewers

Reviewer #1:

"It was with great interest that I read the very thorough review titled "Therapeutic strategies for gastro-entero-pancreatic neuroendocrine neoplasms: state-of-the-art and future perspectives". The incidence of neuroendocrine neoplasms is increasing as well as treatment options so therefore this manuscript is very timely. The outline was put together well but have several comments that should be addressed prior to acceptance. 1. There are multiple references to NEN, NET and NEC. This can be confusing for a non-neuroendocrine specialist. Please either define the differences or keep to NET (G1, G2, G3) or NEC (Poorly differentiated G3). "

- Re. Thanks for the comment. In the Introduction of this modified version of the manuscript, page 6 lines 9-page 7 line 2, we have added a detailed explanation of this terminology. We hope these sentences have now clarified the definitions.

"2. Under small bowel NETs page 13, please include that echos are checked to evaluate for carcinoid heart disease. 3. Page 16 under future perspectives and open questions the author should consider emphasizing the only studies showing benefit for adjuvant therapy were in the setting of PD NECs, not WD. 4. Page 19. A reference is needed when discussing prophylactic octreotide for carcinoid crisis. 5. Page 22. Side effects of lanreotide may also include hypoglycemia, abdominal pain and diarrhea. 6. Page 28. Would consider adding other SSTR imaging such as octreoscan and Cu64 DOTATATE. 7. Page 28. A reference is needed about high renal toxicity with Y90 PRRT. 8. Page 29. Please include the updated NETTER1 analysis from ASCO 2021. 9. Page 32. Would consider adding data presented at NANETS 2020 about Pb 212. 10. Page 41. The NCT #00869050 does NOT describe the trial that is discussed. This NCT # corresponds to a single arm phase 2 trial."

- Re. Following your suggestions, the text has been modified accordingly, and the references updated.

"11. Would consider adding a section to discuss surufatinib. SANET-P and SANET-EP studies."

- Re. Thanks for the suggestion. A paragraph has been added on page 36.

"12. Please spell check as there are multiple typos and grammatical errors throughout the manuscript."

- Re. In agreement with your recommendation, a new language revision of the manuscript has been performed.

Reviewer #2:

“This review provided an overview of the available treatments for GEP-NENs, and discussed future perspectives and new frontiers regarding the therapeutic approach of GEP-NENs. However, there are several deficiencies that need to be addressed. 1. The manuscript is too long, more than 20,000 words. The language should be more refined and some unimportant parts should be deleted. 2. Future perspectives and open questions of each section are not novel and deep enough. The authors should be added some creative opinions and prospects about the future research.”

- Re. Thank you for the comments. In this new version of the manuscript, the text has been shortened (actually 12716 words), and a new language revision has been performed.

“ 3. I recommend the authors to add a table to summarize some important clinical trials for the treatment of GEP-NENs in this manuscript.”

- Re. In agreement with your recommendation, a table reporting the open clinical trials cited in the manuscript has now been added (Supplementary Table 1).