Answering Reviewers

Dear editors and reviewers，

   Thank you for your letter and your comments. Those comments are all valuable and very helpful for revising and improving our minireview. We have addressed the comments raised by the reviewers, revised the manuscript, and would like to resubmit it for your consideration. Further language polishing was performed by a professional English language editing company. Point to point responses to the reviewers' comments are listed clearly in this letter.
   We hope that the revised manuscript is now acceptable for publication in the journal of WJG.
   Thank you again for your consideration.

Best Regards,

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Reviewer #1:

Scientific Quality: Grade D (Fair)
Language Quality: Grade B (Minor language polishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: Nevertheless, patients with G3 NETs or Ki-67 <55% (mostly well differentiated) were far less responsive to the treatment than those with NEC or Ki-67 ≥ 55% (mostly poorly differentiated). The G3 NET and NEC patients had an objective response rate (ORR) of less than 17% and 35-70%, a median progression free survival (mPFS) of 2.4-4 mo and 5.0 mo and a mOS of 17 mo and 99 mo, respectively[8-10]. mOS - is it median overall survival? Please avoid abreviations without full meaning.

Reply: We apologize for the poor language and some non-standard abbreviations in the manuscript. The abreviation "mOS" means median overall survival, which was defined in the last sentence of the first paragraph in the "INTRODUCTION" section. We carefully checked and revised the inappropriate abbreviations throughout the

manuscript, then resubmitted the revised manuscript to a professional English language editing company for language correction. We really hope that the flow and language level have been substantially improved.

Regarding scientific quality, G3 GEP-NET related data were objectively and carefully selected for analysis from a number of immunotherapy studies on NENs. Due to the fact that many prospective clinical trials in the field of NENs have not yet produced final results the patient population included is complex, data heterogeneity is inevitable. Most of the prospective studies are still ongoing. We are sorry that the heterogeneity of clinical trial data can not be avoided. We sincerely hope that the revised manuscript will be to your satisfaction.

Reviewer #2:

Scientific Quality: Grade A (Excellent)
Language Quality: Grade A (Priority publishing)
Conclusion: Accept (General priority)
Specific Comments to Authors: This paper is a well-written and very informative mini-review regarding immunotherapy to G3 PNET. I believe that it will be of great help to clinicians as it summarizes various clinical trials and treatments well. One thing I would like to suggest is the following: Due to the high medical cost of immunotherapy, pre-treatment evaluation including MSI-H, PDL-1 expression, and TMB are recommended to predict treatment response, therefore it would be good to describe various pre-treatment tests (NGS, IHC) for immunotherapy and predictive factors for good responder.

Reply: Thank you very much for your approval and praise of this manuscript. We quite agree with your suggestion, so we have added a column entitled *Predictive biomarkers for Immunotherapies* in the revised manuscript. We will be happy to edit the text further based on helpful comments from the reviewers.

Predictive biomarkers for immunotherapies

The potential of a given patient with G3 GEP-NET to respond to immunotherapies is still largely unknown. NETs can be considered as immunologically "cold" due to their lack of immunoactive cellular components,

low tumor antigens, etc[1, 2].

Immunohistochemical assessment of PD-L1 expression and its role in predicting response to ICIs is an incredibly hot topic. However, in the KEYNOTE-28 study, pNETs with positive PD-L1 expression achieved a low ORR of 6.3%[3]. In the KEYNOTE-158 study, all the 4 GEP-NET patients who achieved PR had negative PD-L1 expression[4]. Besides, in a joint analysis of two prospective, non-randomized trials, no difference in DCR, PFS, or OS was observed between the PD-L1-negative and -positive groups with G3 NENs[5]. In contrast, in the phase Ib trial of toripalimab in the treatment of patients with NENs (Ki-67 ≥ 10%) described above, patients with PD-L1 expression ≥ 10% had better ORR than those with PD-L1 < 10% (50.0% vs. 10.7%, P=0.019)[6]. Therefore, it appears that considering merely the negative or positive expression of PD-L1 is insufficient for identifying GEP-NET patients who may benefit from ICIs and that quantifying PD-L1 expression appears to be more significant. Furthermore, only 10% of tumors expressed PD-L1 in a large cohort of 136 patients with G3 GEP-NENs and those tumoral cells with positive PD-L1 were all in poorly differentiated cases[7]. Therefore, it is necessary to combine PD-L1 with other predictive biomarkers to better predict the population that may benefit from immunotherapy.

For other biomarkers, both high tumor mutational burden (TMB-H) and microsatellite instability-high (MSI-H) / deficient mismatch repair protein (dMMR) are independent adverse prognostic factors for NENs[8] and also have an important predictive value. Wang et al.[9] reported that 50% of the 18 Chinese patients with NETs had TMB-H. In a NET cohort analyzed by Patel et al.[10], found no difference in the PD-L1 positivity rate between G3 and G1/G2 tumors, while the TMB-H rate was significantly higher in G3 NENs independent of tumor origin. Large samples of clinical and genomic data demonstrated that TMB-H was associated with increased survival in patients treated with ICI across various cancer types[11]. Duan et al.[12] discovered that half of pNEN patients had decreased expression of mismatch repair protein

(MMR), another important biomarker. Venizelos et al.[13] recently reported that MSI occurred in only 5.3% (8/152) of GEP-NEC patients and 3.4% (1/29) of G3 GEP-NET patients.

Pre-treatment assessment of one or more of these biomarkers provides a new perspective for screening good responders to immunotherapy.

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