Ancona, 07.08.2015

Point-by-point reply to reviewer's comments

Dear Editor,

Please find enclosed the edited manuscript in Word format (ESPS Manuscript NO: 19871).

Title: Medical treatment for Gastro-entero-pancreatic neuroendocrine tumors.

Author: Rossana Berardi, Francesca Morgese, Mariangela Torniai, Agnese Savini, Stefano Partelli, Silvia Rinaldi, Miriam Caramanti, Consuelo Ferrini, Massimo Falconi, Stefano Cascinu

Name of Journal: World Journal of Gastrointestinal Oncology

Reviewer's comment:
The manuscript by Berardi and co-workers is a well written, up-to-date and in-depth review regarding new biological perspectives on medical treatment for gastro-entero-pancreatic neuroendocrine tumors.

Authors' reply
We are grateful for the comment.

Reviewer's comment:
There are some minor comments/suggestions:
The authors should include a short paragraph regarding the classification (especially the WHO 2010 classification) and epidemiology of gastro-entero-pancreatic neuroendocrine tumors.

Authors' reply:
We thank and do agree with the comment. Therefore we have included short paragraphs regarding the WHO 2010 classification and epidemiology of gastro-entero-pancreatic tumors.
Please find below the paragraphs we added in the manuscript.

"Although still considered a rare disease, SEER data showed an increasing incidence in the last three decades up to 3.65/100000 per years[3]. This may be due to a remarkable improvement of diagnostic technique as well as a real change in population demography[4]. GEP-NENs are more

frequently detected in adult population with a median age at diagnosis of 65 years[5], and in about 50% of cases nodal (25%) or distant (25%) metastases are present at the time of diagnosis[3,6]. On the basis of their morphologic features and proliferation index, NENs are currently stratified in two groups, according to WHO 2010 classification criteria[7]: neuroendocrine carcinomas (NECs), G3 tumors with ki67 proliferation index > 20%, and neuroendocrine tumors (NETs), including G1 (ki67 < 3%) and G2 (ki67 between 3 and 20%) neoplasms. Neuroendocrine carcinomas represent a separate cluster in the family of NENs, with specific biological features and a more aggressive behavior, so chemotherapy is currently considered the standard of care in this specific set[8,9]. Conversely well and moderately-differentiated NETs do not represent a single entity and their pathogenesis has become clearer in recent years."

Reviewer's comment:
The authors should include a short paragraph regarding standard chemotherapeutic options for gastro-entero-pancreatic neuroendocrine tumors.

Authors' reply:
We thank the reviewer for the comment. We have included a short paragraph regarding standard chemotherapeutic options for these neoplasms.
Please find below the paragraphs we added in the manuscript.
"CHEMOTHERAPY
Although most of the studies were conducted on a heterogeneous population and the relationship between response rate and proliferation index value is often not clearly defined, chemotherapy should be considered in GEP-NETs treatment, in particular for symptomatic patients, progressive disease, moderated differentiation and more aggressive features. Chemotherapy should also be evaluated when the aim is to obtain a response in case of bulky lesions. However the best sequence for chemotherapy still remains uncertain[14-18].
The most common used chemotherapy schemes include alkylating agents (streptozotocin (STZ), dacarbazine, temozolomide), antimetabolites (5-fluorouracil (5FU), capecitabine) and platinum derivatives.
Temozolomide (TMZ) combined with 5-fluorouracil (5-FU)[19] or capecitabine[20] can represent the regimen of choice in G1 and G2 advanced P-NETs. Retrospective data showed a response rate of 70% and PFS of 18 months of temozolomide and capecitabine combination[20].
Furthermore STZ in association with 5FU is frequently evaluated as a first-line treatment for locally advanced or metastatic P-NETs with response rates ranging from 6 to 40%, with the benefit in progression-free survival (PFS) of 5 – 20 months and with a median survival of 16 – 24 months[19].
Then, oxaliplatin in combination with capecitabine could also be considered for different setting of G1-G2 GEP-NETs[15]. None of small retrospective studies or case reports conducted with other chemotherapy regimens have demonstrated sufficient efficacy in GEP-NETs."

Reviewer's comment:
The authors should include the target for the investigated drugs in tables 1&2.

Authors' reply:
We thank the reviewer for the comment and therefore we have modified tables 1 and 2 including the target for every investigated drug.

Reviewer's comment:
There are some typographical and grammatical errors that should be corrected.

Authors' reply:
We thank the reviewer for the comment and therefore we have corrected the typographical and grammatical errors in the text.

Sincerely yours,

Rossana Berardi, MD

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