In Reply

We thank Fazio and Milione [1] for their comment on our position paper recently published in ***The Oncologist*** [2]. As highlighted in our paper, evidence-based medicine in response to chemotherapy is lacking, and the choice of the best therapeutic option remains a challenge. Fazio and Milione described in their letter that the main primary localization of a well-differentiated grade 3 neuroendocrine tumor (NET G-3) is the pancreas. They identified in their retrospective cohort that the incidence of pancreatic NET G-3 is 42% of all NET G-3 (10 out of 24). Similarly, in our position paper, we stressed that the main localizations of NET G-3 are the pancreas, the stomach, and the colon.

In addition, we factually reported that there is no validated phase III study on NET G-3 and there are no prospective data ongoing on the targeted therapy efficacy. Furthermore, we agree with their comment that in "low" NET G-3, the proven efficacy of targeted therapy should be evaluated and that in some cases such therapy, either everolimus or sunitinib, should be considered. Fazio and Milione believe that somatostatin receptor-targeted treatments might have a therapeutic efficacy in NET G-3. In 2016, the NETTER-1 phase III study validated the efficacy of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera, Advanced Accelerator Applications, Saint-Genis-Pouilly, France) in patients with inoperable, progressive, somatostatin receptor-positive midgut grade 1–2 neuroendocrine tumor. The NETTER-1 study presented as an inclusion criterion patients with a Ki-67 level below 20. No data on the "aggressive" grade 2 NET subgroup treated in the NETTER-1 study that helped to propose ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate in NET G-3 have been published. Moreover, it has been reported that patients with pancreatic tumors had higher rates of positive somatostatin receptor scintigraphy (46%), lower rates of Ki-67 (70% with Ki-67 $<$55%), and longer overall survival. Such data pave the way for an evaluation in NET G-3 with a Ki-67 below 55% of the efficacy of the ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate (Lutathera). Finally, the 2016 European Neuroendocrine Tumor Society (ENETS) guidelines state that chemotherapy as first-line treatment with a temozolomide plus capecitabine or streptozotocin plus 5-fluorouracil regimen [3] appears as the recommended option in NET G-3.

As stressed by Milione et al. in a recent review, there is a clinicopathologic heterogeneity of NET G-3 that deserves specific clinical trials [4]. Cell differentiation and Ki-67 level appear as the key points in the management of NET G-3 with a Ki-67 cut-off.

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