Regression of advanced neuroendocrine tumors among patients receiving placebo

Dear Editor,

The management of advanced well-differentiated or moderately differentiated neuroendocrine tumors (NETs) is challenging. These tumors, in fact, have a heterogeneous clinical behavior, many of them having an indolent disease course and some of them depicting an aggressive pattern. Few NETs may even undergo spontaneous remission, but this phenomenon has never been quantified and characterized. In this study, we performed a literature-based meta-analysis of all prospective randomized trials in which an active experimental treatment was compared with a placebo control arm and estimated the pooled rate of tumor shrinkage in placebo-treated patients. Our analysis clearly showed that a subset of NET patients attained a tumor shrinkage greater than 10% from baseline upon placebo, and this proportion was similar across the examined studies.

In the last few years, six randomized placebo-controlled trials have demonstrated that molecularly targeted therapies, such as somatostatin analogs (SSA) (Rinke et al. 2009, Caplin et al. 2014), everolimus (Pavel et al. 2011, Yao et al. 2011, 2016) and sunitinib (Raymond et al. 2011), are efficacious in prolonging progression-free survival among patients with gastroenteropancreatic (GEP) or pulmonary NETs. Two of these agents have also shown a marginal effect on overall survival (Raymond et al. 2011, Yao et al. 2011).

A true placebo was the selected control arm in five of these trials, whereas the control arm consisted of placebo plus an SSA in one trial enrolling patients with carcinoid syndrome-related NETs (Pavel et al. 2011).

The antitumor activity of novel molecularly targeted agents is commonly depicted by the waterfall plots, which report the percent change from baseline in size of target lesions on an individual basis. These graphics reveal that the patient subset with stable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) is quite heterogeneous; a group of them showing a modest increase in tumor size of less than 20% and another group showing a tumor shrinkage of less than 30%.

Interestingly, a tumor shrinkage has been detected in a non-negligible proportion of cases in the placebo arm of randomized trials recruiting patients with a diagnosis of NET from different sites, suggesting that these tumors may undergo spontaneous regression.

This phenomenon was repeatedly described in several malignancies in the past and has been recently systematically reviewed by Ghatalia et al. (2016). These authors identified 61 randomized studies with placebo or no active treatment as the control arm and reported a pooled overall response rate (ORR) of 1.95% (95% CI: 1.53–2.48%) and a disease control rate (DCR) of 32.33% (95% CI: 27.21–37.9%) in the control arm. In the meta-analysis by Ghatalia and coworkers, which also included two pancreatic NET trials, only partial or complete response according to RECIST or WHO criteria was considered a measure of tumor shrinkage (Ghatalia et al. 2016).

To better estimate the occurrence of spontaneous tumor regression in NETs, we performed a literature-based meta-analysis of the five prospective randomized trials with a true placebo control arm (Table 1). Eligible patients had pathologically confirmed well-differentiated NET (grade 1 or grade 2 according to the 2010 WHO classification), with unresectable locally advanced or metastatic disease. The primary tumor origin was the pancreas in two of the examined studies (Raymond et al. 2011, Yao et al. 2011), the pancreas, midgut or hindgut in one study (Caplin et al. 2014), the lung or gastrointestinal tract in one study (Yao et al. 2016) and the midgut in one study (Rinke et al. 2009) (Table 1). Data on ORR according to RECIST or WHO criteria were obtained from the text or tables, whereas the rates of tumor shrinkage were extracted from the published waterfall plots with Engauge Digitizer, v.9.5 software. The change in the size of target lesions was reported in waterfall plots for each
patient before crossover from placebo to the experimental therapy in trials where crossover was permitted. We used a random-effects model with a generic inverse-variance approach to estimate the study endpoints.

The pooled estimate of ORR among 531 NET patients in the placebo arm of five randomized trials was 1.52% (95% CI 0.73–3.16%) and was consistent across all studies ($I^2 = 0\%$, $P$ value = 0.78) (Fig. 1A). DCR was very heterogeneous across the examined studies with a pooled DCR of 52.74% (95% CI 44.12–61.20, $I^2 = 72.3\%$, $P$ value = 0.006) (Fig. 1B).

A waterfall plot was reported in four trials, comprising a total of 460 placebo-treated patients (Raymond et al. 2011, Yao et al. 2011, 2016, Caplin et al. 2014). The pooled rate of tumor shrinkage for any reduction in size of target lesions from baseline was 25.24% (95% CI 20.84–30.22%, $I^2 = 25.6\%$, $P$ value = 0.26) (Fig. 1C). The pooled rate of tumor shrinkage considering a decrease in the size of target lesions in the range between 10% and 30% was 5.83% (95% CI 3.47–9.64%, $F = 39.9\%$, $P$ value = 0.17) (Fig. 1D).

This meta-analysis showed that approximately one-quarter of NET patients enrolled in phase III trials had a tumor regression of variable extent upon placebo. This finding is relevant as it derives from prospective randomized studies where disease progression within the previous 6–12 months was a prerequisite for patient inclusion and tumor size changes were prospectively collected according to study protocol. However, although the tumor response assessment was centrally performed in each of the four examined trials, the baseline tumor progression status was not centrally assessed, except for the CLARINET trial (Caplin et al. 2014), which was also the only one with a pre-defined time frame for the baseline tumor status assessment.

Although four prospective randomized trials reported waterfall plots to describe the percent change from baseline in size of target lesions, the trial investigators

### Table 1 Characteristics of the eligible trials.

<table>
<thead>
<tr>
<th>Authors</th>
<th>(year)</th>
<th>Primary tumor origin</th>
<th>No. of patients enrolled</th>
<th>Treatment</th>
<th>Trial required disease progression</th>
<th>No. of evaluable patients in placebo arm</th>
<th>ORR in placebo arm (%)</th>
<th>Response criteria used</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rinke et al. (2009)</td>
<td>Midgut</td>
<td>85</td>
<td>Octreotide vs placebo</td>
<td>Not specified</td>
<td>43</td>
<td>2.30</td>
<td>WHO</td>
<td></td>
</tr>
<tr>
<td>Caplin et al. (2014)</td>
<td>Pancreas, midgut and hindgut</td>
<td>204</td>
<td>Lanreotide vs placebo</td>
<td>Not specified</td>
<td>103</td>
<td>2.30</td>
<td>WHO</td>
<td></td>
</tr>
<tr>
<td>Yao et al. (2011)</td>
<td>Pancreas</td>
<td>410</td>
<td>Everolimus vs placebo</td>
<td>Yes</td>
<td>203</td>
<td>2.30</td>
<td>RECIST 1.0</td>
<td></td>
</tr>
<tr>
<td>Raymond et al. (2011)</td>
<td>Pancreas</td>
<td>171</td>
<td>Sunitinib vs placebo</td>
<td>Yes</td>
<td>85</td>
<td>2.30</td>
<td>RECIST 1.0</td>
<td></td>
</tr>
<tr>
<td>Yao et al. (2016)</td>
<td>Lung and GI</td>
<td>302</td>
<td>Everolimus vs placebo</td>
<td>Yes</td>
<td>97</td>
<td>2.30</td>
<td>RECIST 1.0</td>
<td></td>
</tr>
</tbody>
</table>

Gi, gastrointestinal; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors; WHO, World Health Organization.

Figure 1

Forest plot of overall response rate (A), disease control rate (B), the rate of tumor shrinkage of target lesions (C) and the rate of tumor shrinkage of target lesions between 10% and 30% from baseline in the placebo arm of eligible studies. Horizontal lines represent 95% confidence interval. The area of each square represents the weight of the trial in the meta-analysis. Response evaluation according to WHO criteria; *data extracted from waterfall plots.
never discussed the phenomenon of tumor shrinkage in the placebo arm.

The clinical behavior of NETs is rather heterogeneous, and this may be the reason why the DCR showed a non-homogeneous distribution across the examined studies. Interestingly, the homogeneous distribution of tumor shrinkage across studies suggests that a reproducible proportion of patients with metastatic well-differentiated or moderately differentiated NET are destined to obtain a spontaneous tumor regression irrespective of NET origin and biology.

Spontaneous regressions were described in many histologic types, including NETs (Ghatalia et al. 2016), and host immune response against neoantigens expressed by the tumor is the most plausible explanation. Well-differentiated or moderately differentiated NETs are considered low immunogenic tumors due to their limited mutational load and consequently limited neoantigen expression. However, the available data show that the immune system interacts with the neuroendocrine system and may influence the prognosis of NET patients. CD3+ cell infiltration in intermediate-grade NETs was in fact associated with a better recurrence-free survival (Katz et al. 2010) whereas circulating T regulatory cells, which are known to counteract the antitumor immune response, were found in elevated numbers among midgut carcinoid patients (Vikman et al. 2009).

The expression of the programmed death-ligand 1 (PD-L1) with a cut-off of 1% by immunohistochemistry was reported to be associated with worse prognosis in a small series of patients with metastatic GEP-NETs (Kim et al. 2016). However, PD-L1 expression, a potential predictive biomarker of efficacy of immune-checkpoint inhibitors, was restricted to grade 3 tumors.

Admittedly, NET metastases have often poorly demarcated margins due to coalescence phenomena that may reflect tumor necrosis, especially in liver parenchyma; this could limit the response assessment of target lesions with either RECIST or WHO criteria. As a matter of fact, a modest reduction of tumor size might be due to the absorption of necrotic material and might not indicate a true reduction of viable tumor mass. Nevertheless, in the present meta-analysis of placebo arms of randomized trials, the pooled ORR according to RECIST or WHO criteria was approximately 1.5% and the reduction of target lesions between 10% and 30% from baseline, the so-called minor response, was homogeneously reported in the non-negligible proportion of nearly 6%.

In conclusion, the biological and clinical characteristics of patients with NET undergoing spontaneous regression need to be defined. These patients might benefit from active surveillance, thus avoiding the toxic effects of antitumor therapies. They could also be potential candidates for the new immunotherapies, and this is an interesting hypothesis for future research.

Vito Amoroso1,* Giorgio Maria Agazzi2,* Elisa Roca1 Nicola Fazio3 Alessandra Mosca4 Marco Ravanelli2 Francesca Spada3 Roberto Maroldi2 Alfredo Berruti1

1Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Medical Oncology Unit, University of Brescia at ASST Spedali Civili, Brescia, Italy
2Department of Medical and Surgical Specialties, Radiological Sciences, and Public Health, Radiology Unit, University of Brescia at ASST Spedali Civili, Brescia, Italy
3Unit of Gastrointestinal Medical Oncology and Neuroendocrine Tumors, European Institute of Oncology, Milan, Italy
4Medical Oncology Unit, Maggiore della Carità University Hospital, University of Eastern Piedmont, Novara, Italy
*(V Amoroso and G M Agazzi contributed equally to this work)

(Correspondence should be addressed to V Amoroso; email: vitoamoroso@alice.it)

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