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

Table 1 Characteristics of the eligible trials.

Authors (year)	Primary tumor origin	No. of patients enrolled	Treatment	Trial required disease progression	No. of evaluable patients in placebo arm	ORR in placebo arm (%)	Response criteria used
Rinke <i>et al.</i> (2009)	Midgut	85	Octreotide vs placebo	Not specified	43	2.30	WHO
Caplin <i>et al.</i> (2014)	Pancreas, midgut and hindgut	204	Lanreotide vs placebo	Not specified	103	0	RECIST 1.0
Yao <i>et al.</i> (2011)	Pancreas	410	Everolimus vs placebo	Yes	203	2	RECIST 1.0
Raymond <i>et al.</i> (2011)	Pancreas	171	Sunitinib vs placebo	Yes	85	0	RECIST 1.0
Yao <i>et al.</i> (2016)	Lung and GI	302	Everolimus vs placebo	Yes	97	1	RECIST 1.0

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

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%, I^2 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

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 (D) 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.

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this article.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

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Received in final form 6 December 2016

Accepted 13 December 2016

Accepted Preprint published online 13 December 2016