In Reply

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We appreciate the comments of Dr. Steven M. Sorscher regarding our recent publication and the use of targeted agents in neuroendocrine tumors. Neuroendocrine tumors (NETs) exhibit diverse clinical outcomes [1–4]. Several recent studies have demonstrated that tumor histology, which incorporates assessments of tumor differentiation, tumor grade, mitotic rate, and proliferative index, can be associated with clinical outcomes and overall survival [2, 5–7].

The majority of clinical trials to date have been performed in low- or intermediate-grade, well differentiated tumors. High grade, poorly differentiated tumors are widely perceived as being associated with aggressive behavior and a poor prognosis. Patients with such tumors are often treated with platinum-based chemotherapy regimens. The World Health Organization criteria currently define any neuroendocrine tumor with a proliferative index (Ki-67) of >20% as high grade (Table 1).

Recently, however, this criterion for defining high-grade tumors has been called into question. In some cases, for example, tumors with a Ki-67 between 20% and 50% may have well differentiated architecture; such tumors will not behave as aggressively as poorly differentiated neuroendocrine carcinomas (NECs). In contrast, tumors with Ki-67 indices of 80%–100% almost universally demonstrated poor differentiation and behave in a manner that parallels pulmonary small cell

carcinoma [8]. Such poorly differentiated neuroendocrine carcinomas may in fact possess a non-neuroendocrine cell lineage and be more closely related to a de novo carcinoma [9].

The concept that high-grade tumors (as currently defined) may in fact demonstrate variable clinical behavior has been further supported in a recent study by Sorbye et al., who reviewed data from 305 patients with gastrointestinal poorly differentiated NETs [10]. This study found that response rate to platinum-based chemotherapy was lower in patients with Ki-67 20%–55% than in those with a Ki67 >55% (14% vs. 44%, $p < .001$), although patients with the lower Ki-67 index had longer median survival (15 months) than those with Ki-67 >55% (10 months) ($p < .001$) [10].

Whether targeted agents should be used in some patients with Ki-67 indices of >20% is uncertain. Future prospective randomized studies are needed to evaluate whether patients with this group of tumors benefit more from targeted therapy or from a particular cytotoxic regimen.

DISCLOSURES

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Table 1. Grading system for neuroendocrine tumors

Differentiation	Grade	Mitotic Count	Ki-67 index (%)	Traditional Classification	ENETS, WHO Classification
Well-differentiated	Low (G1)	<2 per 10 HPF	≤2	Carcinoid, islet cell, pancreatic neuroendocrine tumor	Neuroendocrine tumor, grade 1
	Intermediate (G2)	2–20 per 10 HPF	3–20	Carcinoid, atypical carcinoid, islet cell, pancreatic neuroendocrine tumor	Neuroendocrine tumor, grade 2
Poorly differentiated	High (G3)	>20 per 10 HPF	>20	Small cell carcinoma	Neuroendocrine carcinoma, grade 3, small cell
				Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma, grade 3, large cell

Abbreviations: ENETS, European Neuroendocrine Tumor Society; HPF, high power field; WHO, World Health Organization.

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