Is There a Place for Temozolomide plus Nivolumab among Neuroendocrine Neoplasms?

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SUMMARY

Immune checkpoint inhibitors have revolutionized the treatment of multiple solid malignancies, but their role in the treatment of neuroendocrine neoplasms (NEN) is unclear. The accompanying article reports on a study combining the programmed cell death (PD-1) inhibitor nivolumab with the alkylating agent temozolomide in patients with advanced NENs.

See related article by Owen et al., p. 731

In this issue of *Clinical Cancer Research*, Owen and colleagues evaluated the combination of the oral alkylating agent temozolomide with the immune checkpoint inhibitor nivolumab in a cohort of patients with advanced neuroendocrine neoplasms (NEN; ref. 1). Checkpoint inhibitors have revolutionized the treatment of multiple solid malignancies and are routinely used in the initial treatment of extensive-stage small cell lung cancer (2). However, their role in the treatment of other NENs is not well established, with conflicting data on antitumor activity in this group of malignancies (3). Temozolomide has been proven effective in G1 and G2 NENs, but not in neuroendocrine carcinomas (NEC; refs. 4, 5). To contextualize the findings of Owens and colleagues, it is important to consider the different entities within NENs.

NEN is an umbrella term that encompasses a heterogeneous group of malignancies that share histologic, structural, and neuroendocrine immune-phenotypic features (6). NENs represent a group of neoplasms with different biological features, behavior, genetic alterations, and prognosis (6). Classification of NENs is based on their morphologic features, anatomic site of origin, and proliferation rate, as these features have treatment and prognostic implications (7). Neuroendocrine tumor (NET) refers to NENs that are well differentiated, while NEC refers to poorly differentiated NENs (7).

On the basis of the relatively low incidence of NENs, these neoplasms are often grouped in clinical trials (7). However, while NENs are sometimes described as a spectrum of disease, there is no evidence that one NEN evolves into another, making it more appropriate to consider them distinct neoplasms, with shared features, along a continuum (8). Somatic genetic aberrations in NETs include alterations in *MEN1*, *DAXX*, *ATRX*, *PTEN*, *MUTYH*, *CHECK2*, mTOR, and *BRCA2*. NECs tend to have higher tumor mutational burden (TMB), commonly including mutations in *RB1* and *PT53* (9, 10). Studies have shown that higher-grade tumors are more likely to express PD-L1 and have T-cell infiltration (3, 11).

Because of the differences in biology, prognosis, and behavior of NENs, treatment can range from observation to cytotoxic chemotherapy (**Fig. 1**; ref. 12). Somatostatin analogs are the mainstay of therapy in metastatic well-differentiated G1 and G2 NETs, with a median progression-free survival (PFS) of 14.3 months with lanreotide compared with 6.0 months with placebo with an objective response rate (ORR) of 2% (13). ^{177}Lu-DOTATATE represents another treatment option for patients with somatostatin receptor-positive G1 or G2 midgut NETs, with a randomized study showing improvement in PFS but not in overall survival (OS; ref. 14). The mTOR inhibitor everolimus has been proven to be effective in patients with G1 and G2 NETs with studies showing a median PFS of 11.0 months with everolimus compared with 3.9 months with placebo but with low ORR of 2%. Sunitinib, a multitargeted tyrosine kinase inhibitor, was also shown to improve PFS in patients with G2 pancreatic NETs but not in pulmonary or midgut NETs (15). The combination of temozolomide with capecitabine yielded similar ORR compared with temozolomide monotherapy in pancreatic G1 and G2 NETs (ORR of 39.7% vs. 33.7%, respectively) but median PFS was significantly superior in the combination arm compared with monotherapy (22.7 vs. 14.4 months; ref. 5).

Treatment options for NECs are usually limited to cytotoxic chemotherapy (12). A platinum chemotherapeutic plus etoposide or irinotecan is frequently used in the first-line setting for advanced gastroenteropancreatic NECs with ORR of 40% to 50%, median PFS 6 to 8 months, and median OS 10 to 15 months (16). However, the ORR and median PFS with cisplatin and etoposide in lung NECs are lower (17). Temozolomide monotherapy has yielded discouraging results in patients with NECs with ORR around 15% and median PFS of 1.8 months (4). Other regimens, including 5-fluorouracil and oxaliplatin, are used in later lines of therapy, but the data to support their use are mostly retrospective (16).

Studies evaluating single-agent checkpoint inhibitors in NENs have yielded disappointing results, with ORRs around 10% or less and median PFS of less than 5 months (16). Results from a phase II study evaluating ipilimumab plus nivolumab in patients with NENs, showed an ORR of 44% in the G3 NEN cohort and 0% in the G1 and G2 NEN cohorts (18). As such, there is interest in developing strategies to increase response to checkpoint inhibitors in NENs with the use of other agents, such as temozolomide (19). In this issue of *Clinical Cancer Research*, Owen and colleagues evaluated the combination of nivolumab with temozolomide in a group of 28 patients with advanced NENs both in the first-line and subsequent line settings.

Temozolomide has been shown to be mutagenic and can lead to mutations that inactivate the mismatch repair pathway, which has been well described in patients with gliomas but not as extensively in

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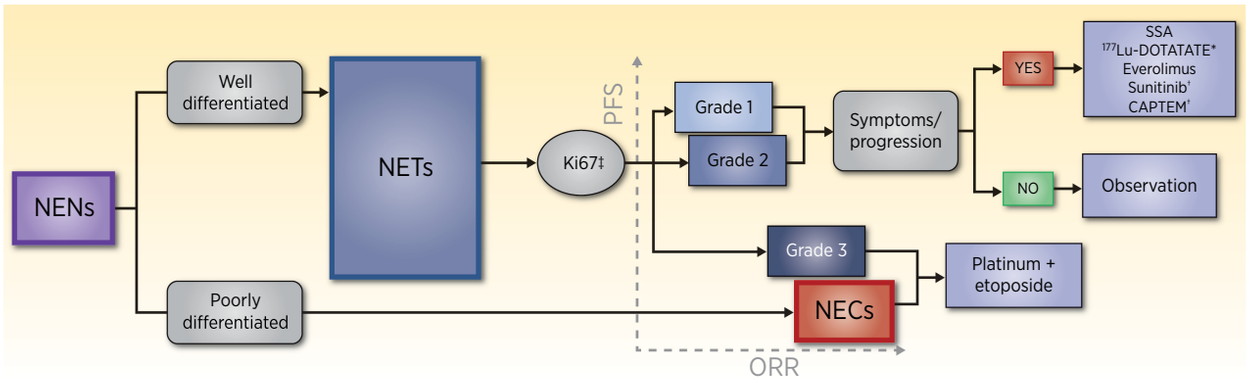

Figure 1.

Simplified definitions, schema of outcomes with chemotherapy, and checkpoint inhibition based on available data and treatment approach algorithm based on available evidence and recommendations for metastatic NENs. CAPTEM, capecitabine and temozolomide; NEC, neuroendocrine carcinoma; NEN, neuroendocrine neoplasia; NET, neuroendocrine tumor; ORR, objective response rate; PFS, progression-free survival; SSA, somatostatin analog. *^{177}Lu-DOTATATE is approved only for tumors that express the somatostatin receptor. †Data only for NETs of pancreatic origin. ‡Definition of grade based on a Ki67 cut-off varies based on tumor origin.

NENs (19). It has been hypothesized that this temozolomide-associated hypermutation phenomenon can lead to an increase in TMB, resulting in higher neoantigen load and potentially greater benefit from checkpoint inhibitors (19). Owen and colleagues should be congratulated on conducting a trial to evaluate efficacy in this rare population of patients. Results from the study showed that in the entire cohort, the ORR was 32.1% with a median PFS of 8.8 months. Outcomes in the lung and pancreatic groups were superior to the rest of the population. Only 1 of 13 patients in the group of NENs that originated outside the lung or pancreas experienced a response. The heterogeneity of the patients and the impact of that heterogeneity on the data obtained is probably most clearly demonstrated when assessing clinical outcome based on the proliferative rate cut-off point of 3%. There were no observed responses in patients with a Ki67 <3%, but this group had a median PFS that was superior to those with a Ki67 >3%. There is a risk that inappropriate enthusiasm could be based on a higher response rate than expected, driven entirely by patients with higher proliferative rate tumors, and longer PFS than expected on the basis of patients with indolent low proliferative rate disease. While the ORR and median PFS were similar between the patients who received this regimen in the first-line setting or as a later line, it is hard to determine whether patients with prior lines of therapy have more indolent tumors from those who received it in the first-line setting, allowing for similar results between the cohorts. Because there was no comparator arm that received either single-agent temozolomide or nivolumab, it is hard to determine whether the results observed are secondary to additive or synergistic activity between the two agents. Finally, the authors should be congratulated on obtaining correlative data evaluating the immune cell landscape in peripheral blood for potential predictors or response. These data will allow generation of hypotheses which could be further explored in larger studies with more homogeneous patient populations.

In summary, NENs are a heterogenous group that is challenging to study. Treatment strategies differ based on their proliferative rate, site of origin, and degree of differentiation (12). The article by Owen and colleagues provides important information on which NENs might be most likely to derive benefit from the combination of PD-1 inhibition plus temozolomide. However, results are difficult to interpret due to the heterogeneity of the groups and small sample size. Larger studies investigating more homogeneous groups will be needed to determine the true efficacy of this regimen.

Authors' Disclosures

E.B. Garon reports grants and personal fees from ABL-Bio, AstraZeneca, and Bristol Myers Squibb; personal fees from AbbVie, Boehringer Ingelheim, Eli Lilly, EMD Serono, Gilead, Merck, Novartis, Eisai, GlaxoSmithKline, Ipsen, Natera, Personalis, Sanofi, Shionogi, and Xilio; and grants from Dracen Pharmaceuticals, Genentech, Iovance, Mirati, and Neon outside the submitted work; in addition, E.B. Garon has a patent for motif neoepitopes for cancer immunotherapy issued. No disclosures were reported by the other author.

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