Introduction

The incidence of neuroendocrine tumors (NETs) is increasing and is estimated to be around 1.01–5.25 cases per 100,000 population based on data from the United States, Japan, and European registries [1–3]. Several forms of locoregional and systemic medical and surgical therapies have been used with varying efficacies. Immunootherapy, particularly with immune checkpoint inhibitors (ICIs) has only recently emerged as one of the options for systemic therapy for NETs. To date, the role of ICI therapy and other forms of immunotherapy in the management of NETs is not well established.

Review

Immune Checkpoint Inhibitor Therapy in Neuroendocrine Tumors

Authors

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Key words

neuroendocrine tumor, neuroendocrine, immunotherapy, immunity, somatostatin analogues, medullary thyroid carcinoma; MTC, thyroid, pheochromocytoma, paraganglioma

ABSTRACT

Neuroendocrine tumors (NETs) occur in various regions of the body and present with complex clinical and biochemical phenotypes. The molecular underpinnings that give rise to such varied manifestations have not been completely deciphered. The management of neuroendocrine tumors (NETs) involves surgery, locoregional therapy, and/or systemic therapy. Several forms of systemic therapy, including platinum-based chemotherapy, temozolomide/capecitabine, tyrosine kinase inhibitors, mTOR inhibitors, and peptide receptor radionuclide therapy have been extensively studied and implemented in the treatment of NETs. However, the potential of immune checkpoint inhibitor (ICI) therapy as an option in the management of NETs has only recently garnered attention. Till date, it is not clear whether ICI therapy holds any distinctive advantage in terms of efficacy or safety when compared to other available systemic therapies for NETs. Identifying the characteristics of NETs that would make them (better) respond to ICIs has been challenging. This review provides a summary of the current evidence on the value of ICI therapy in the management of ICIs and discusses the potential areas for future research.
The various molecular and cellular mechanisms as well as the tumor microenvironmental factors that may regulate the response of NETs to ICI therapy are yet to be completely understood. In this review, we discuss the current knowledge on the efficacy of ICI therapy in the treatment of NETs and discuss the potential areas for future research.

Neuroendocrine tumor biology and current standard of care

NETs are benign or malignant tumors that demonstrate variable rates of growth and have the ability to secrete biologically active peptides and amine compounds [4]. These tumors arise from the so-called diffuse neuroendocrine system of the body, the embryologic origins of which thought to be either from the neural crest or from the gut endoderm [5]. NETs arise from the various neuroendocrine cell types, including the ganglionic cells of the nervous system, paraganglionic chromaffin cells, pancreatic islets, adrenal medulla, and thyroid C-cells [5]. These tumors also demonstrate immunohistochemical reactivity to neuronal markers such as chromogranin A, synaptophysin, or neuron-specific enolase [4]. NETs can occur in various regions of the body, including but not limited to the gastrointestinal tract, pancreas, lungs, bronchus, thymus, skin, cervix, prostate, and the thyroid [6–10]. While most of these tumors are slow growing, some tumors such as high-grade NETs, neuroendocrine carcinomas (NECs), medullary thyroid cancer (MTC), Merkel cell carcinoma (MCC), and certain forms of pheochromocytomas and paragangliomas (PPGLs) tend to be more aggressive and can metastasize to distant sites [6, 11, 12].

As per the 2019 World Health Organization guidelines, NETs are classified into different grades depending on the mitotic rate or Ki-67 proliferative index: G1 (< 2 mitoses/10 high power field (HPF), < 3 % Ki-67 index), G2 (2–20 mitoses/10 HPF, 3–20 % Ki-67 index), and G3 (> 20 mitoses/10 HPF, > 20 % Ki-67 index) [13]. NECs are now a distinct subtype from NETs and are further classified into small-cell NECs (SCNECs) and large-cell NECs (LCNECs). While both G3 NETs and NECs have a high mitotic rate/Ki-67 index, the main difference lies in their differentiation and clinical response to treatment: NECs tend to be poorly differentiated and respond to platinum-based chemotherapy while G3 NETs are well-differentiated and relatively resistant to platinum-based chemotherapy but can be less aggressive than NECs [13, 14]. Apart from these, mixed NET-non-NET neoplasms are also a part of this classification where the differentiation and histopathology can be variable. The course of management of NETs is determined by the anatomical location of the primary tumor, biochemical phenotype, histological grade of the tumor, and staging of the disease [12, 15–17]. Surgery is the preferred modality of treatment for localized non-metastatic NETs, and a cytoreductive surgical approach could be utilized for the treatment of metastatic disease [18]. Locoregional therapies such as radiofrequency ablation, transarterial embolization, stereotactic radiotherapy, and chemoembolization are also feasible options for liver metastases, as well as palliative radiation to bone metastases [18–20].

Such a multimodality approach is displayed in the illustrative history of a 48-year-old man who was found to have an elevated serum calcium up to 14 mg/dl (normal, 8.6–10.0), alkaline phosphatase and gamma glutamyl transferase during routine blood work in 2018. Computed tomography (CT) of the abdomen revealed a pancreatic mass and liver tumors. Biopsy of the pancreatic mass showed a low-grade neuroendocrine tumor. Hypercalcemia was mediated by parathyroid hormone-related peptide. He received monthly long-acting octreotide (Sandostatin LAR) 30 mg and was started on denosumab and switched to zoledronic acid with slight decline but without normalization of serum calcium. In 3/2020, he underwent transarterial chemoembolization of multiple metastases within the right and left hepatic lobe. Hypercalcemia continued. He then had a gallium-68 (68Ga)-DOTATATE positron emission tomography computed tomography (PET/CT) imaging (▶ Fig. 1a, ▶ 2a) and underwent therapy with 4 cycles of lutetium-177 (177Lu)-DOTATATE therapy in 09/2020, 11/2020, 1/2021, 3/2021. The lesions were stable on 02/2022. 68Ga-DOTATATE PET/CT imaging (▶ Fig. 1b, ▶ 2b). Several months later his serum Ca has dropped but remains above normal range and in 06/2022 was measured at 10.6 mg/dl (8.6–10.0) while continuing monthly Sandostatin LAR 30 mg. Zoledronic acid was stopped in June 2021.

In patients with metastatic disease but with low tumor burden, frequent follow-up with or without treatment with somatostatin analogs (SSAs) such as octreotide [21, 22], and lanreotide [23, 24], especially in patients with somatostatin receptor-positive (SSTR +) NETs and/or hormonally active NETs such as carcinoids, insulinomas, glucagonomas, and others [20] is needed. Several systemic therapy options are available for the treatment of advanced, metastatic NETs [6, 12, 17, 20, 25]. Some of the systemic therapy options include mechanistic target of rapamycin (mTOR) inhibitor everolimus [26, 27], tyrosine kinas inhibitor (TKI) sunitinib [28, 29], vascular endothelial growth factor (VEGF) inhibitor bevacizumab [30], interferon α [30, 31], and for the treatment of SSTR + NETs,
peptide receptor radionuclide therapy (PRRT) with radiolabeled SSAs such as lutetium-177 (177 Lu)-DOTA-Tyr3-octreotate (DOTATATE) [32]. A combination of these therapies is also utilized for the treatment of NETs [27, 30, 32]. Chemotherapeutic regimens are also utilized in the treatment of more aggressive forms of NETs/neuroendocrine carcinomas (NECs), some of which include cisplatin/etoposide [33], carboplatin/etoposide [20], oxaliplatin-based therapy (FOLFOX, CAPEOX) [20], irinotecan-based therapy (cisplatin/etoposide, FOLFIRI, FOLFIRINOX) [20], and temozolomide, either as a single agent or with capecitabine [34, 35].

Such a treatment approach including immunotherapy is shown in the history of a 43-year-old man who presented with abdominal pain due to small bowel obstruction in 2015. He was previously worked up for irritable bowel syndrome in 2013 and had ongoing diarrhea before 2013. After small bowel resection and ongoing abdominal discomfort and diarrhea, he presented to a NET center in 2016 and underwent an indium-111 (111In)-octreoscan showing evidence of mesenteric lymphadenopathy Fig. 3a, b). Bulky mesenteric lymph nodes, small bowel containing the primary G3 NET (Ki-67 index 25 %), and the gallbladder were resected, and monthly octreotide LAR was started in an adjuvant setting. Four months later, imaging studies suggested tumor recurrence in the liver and peritoneum and the patient started systemic therapy with capecitabine and temozolomide, however, developed progressive disease Fig. 4a). Therapy was changed to carboplatin/etoposide for 8 months which was ineffective, and then the patient received 3 cycles of pembrolizumab, unfortunately with disease progression Fig. 4b).

A meta-iodobenzylguanidine (MIBG) scan in 6/2016 was not avid for liver lesions that were seen on magnetic resonance imaging (MRI). Molecular profiling did not find disease associated mutations or variants of uncertain significance. Microsatellite instability (MSI) testing with immunohistochemical stains for MLH1, MSH2, PMS2, and MSH6 showed continued nuclear expression of all four proteins in the poorly differentiated NEC, implying low probability of a MSI high tumor. PD-L1 expression was negative.

The National Comprehensive Cancer Network (NCCN) 2021 guidelines endorses the use of all of these locoregional and systemic therapy for the management of NETs as category 2 A (low-level evidence and uniform NCCN consensus that a therapy is appropriate) recommendations [20]. The North American Neuroendocrine Tumor Society (NANETS) released its compendium guidelines in 2021 in partnership with the Commonwealth Neuroendocrine Tumor Research Collaboration (CommNETs) comprising Canada, Australia, and New Zealand, along with endorsements and updating of the 2015 European Neuroendocrine Society (ENETS) guidelines [36]. In the NANETS guidelines, most of these systemic therapies were endorsed as grade B or C recommendations as per the Oxford Centre for Evidence-Based Medicine [36].

Role of immune checkpoint inhibitor therapy in neuroendocrine tumors

ICIs are monoclonal antibodies that target the immune co-inhibitory receptors as well as their respective ligands, including programmed cell death protein-1 (PD-1), PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte antigen 4 (CTLA-4) [37, 38]. The efficacy of ICIs has been well-demonstrated in the management of various cancers [39–43]. In addition to these proteins, the T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), lymphocyte activation gene-3 (LAG-3), and T-cell immunoglobulin and ITIM domain (TIGIT) are additional co-inhibitory proteins that could serve as potential targets for the next generation of ICIs [44, 45].

Several phase Ib and phase II studies as well as retrospective studies have evaluated the efficacy of ICIs for the treatment of a variety of NETs [46–62]. A summary of data published on ICI therapy in NETs is provided in Table 1. As evident in this table, full-length articles related to ICI therapy in NETs, except for MCC, have been published only since as recently as 2020. However, the objective response rates (ORR) have been low to modest, with most trial
studies demonstrating ORRs of < 10%. In the phase II KEYNOTE-158 study which investigated the safety and efficacy of pembrolizumab across multiple malignancies, the drug’s utility in 107 patients with advanced, well-differentiated NETs was also evaluated [50]. After a median follow-up of 24.2 months, ORR was seen in 3.7% (4/107) patients, with partial response (PR) noted in all four and with none achieving complete response (CR). Moreover, all four patients had no PD-L1 expression in the NETs while 17 patients from the remainder of the study population demonstrated positive PD-L1 expression, therefore suggesting poor correlation between PD-L1 tumor expression and likelihood of response to ICI [63]. Similarly, in another study evaluating pembrolizumab therapy in 29 patients with G3 extrapulmonary NETs, ORR was seen in one (3.4%) patient with esophageal NEC [51]. Moreover, there were no differences in the disease control rate, overall survival (OS), or progression-free survival (PFS) between patients with PD-L1-positive and PD-L1-negative NETs. While there are individual reports of combination of PD-1 therapy and chemotherapy being effective in tum-
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<tr>
<th>Study</th>
<th>Year</th>
<th>Phase</th>
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<th>Type of ICI (target protein)</th>
<th>Duration of follow-up in months</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehnert et al. (KEYNOTE-028) [46]</td>
<td>2020</td>
<td>I</td>
<td>41</td>
<td>25 carcinoid</td>
<td>pembrolizumab (PD1) 16 pNETs</td>
<td></td>
<td>carcinoid: ORR: 12% (95% CI: 2.5–31.2%) PR: 12% (3/25 patients) SD at ≥6 months: 32% (8/25 patients) PD: 28% (7/25 patients) Median PFS in months: 5.6 (range: 3.5–10.7) Median OS in months: 21.1 (95% CI: 9.1–2.4) AEs: 17 (68%) patients SAEs: 8 (32%) patients pNET: ORR: 6.3% (0.2–30.2%) PR: 6.3% (1/16 patients) SD at ≥6 months: 31.3 (5/16 patients) PD: 6.3% (1/16 patients) Median PFS in months: 4.5 (95% CI: 3.6–8.3) Median OS in months: 21 (95% CI: 20.2–not reached) AEs: 11 (68.8%) patients SAEs: 1 (6.3%) patient</td>
</tr>
<tr>
<td>Patel et al. (DART SWOG 1609) [48]</td>
<td>2020</td>
<td>II</td>
<td>32</td>
<td>Non-pancreatic NETs: 15 GI NETs</td>
<td>ipilimumab (CTLA4) + nivolumab (PD1)</td>
<td>Up to 15</td>
<td>ORR: 25% (95% CI: 13–42%) CR: 3% (1/32 patients) PR: 22% (7/32 patients) PD: 34% (11/32 patients) Median PFS in months: 4 Median OS in months: 11 AEs: 27 (84.4%) patients SAEs: 16 (50%) patients</td>
</tr>
<tr>
<td>Lu et al. [49]</td>
<td>2020</td>
<td>Ib</td>
<td>40</td>
<td>32 GEP-NETs</td>
<td>toripalimab (PD1)</td>
<td>Up to 24</td>
<td>ORR: 20% (95% CI: 9.1–35.7%) PR: 20% (8/40 patients) SD: 15% (6/40 patients) PD: 80% (24/40 patients) Median PFS in months: 2.5 (95% CI: 1.9–3.1) Median OS in months: 7.8 (95% CI: 5.0–10.8) AEs: 38 (95%) patients SAEs: 11 (27.5%) patients</td>
</tr>
</tbody>
</table>
### Table 1  List of studies evaluating the efficacy of ICI in NETs.

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<th>Study</th>
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<tbody>
<tr>
<td>Klein et al. (CA209-538) [58]</td>
<td>2020</td>
<td>II</td>
<td>29</td>
<td>10 bronchial carcinoids 1 lung LCNEC 7 GEP-NETs 3 GEP-NECs 5 thymic NETs 1 prostate NET 1 cervical NET</td>
<td>ipilimumab (CTLA4) + nivolumab (PD1)</td>
<td>26+</td>
<td>ORR: 24%  SD: 48.3 % (14/29 patients)  PD: 10% (3/29 patients)  Median PFS in months: 4.82 (95 % CI: 2.71–10.53)  Median OS in months: 4.78 (95 % CI: 4.07–21.25)  AEs: 19 (66%) patients  SAEs: 10 (34%) patients</td>
</tr>
<tr>
<td>Strosberg et al. (KEYNOTE-158) [50]</td>
<td>2020</td>
<td>II</td>
<td>107</td>
<td>83 GEP-NETs 14 lung NETs 10 NETs at other sites</td>
<td>pembrolizumab (PD1)</td>
<td>Median: 24.2 (range: 0.6–33.4)</td>
<td>ORR: 3.7 % (95 % CI: 1.0–9.3)  CR: 0/107 patients  PR: 4/107 patients  Median PFS in months: 4.1 (95 % CI: 3.5–5.4)  Median OS in months: 24.2 (95 % CI: 15.8–32.5)  AEs: 81 (75.7 %) patients  SAEs: 23 (21.5 %) patients</td>
</tr>
<tr>
<td>Vijayvergia et al. [51]</td>
<td>2020</td>
<td>II</td>
<td>29</td>
<td>24 GEP-NETs 5 non-GEP-NETs</td>
<td>pembrolizumab (PD1)</td>
<td>Up to 36</td>
<td>ORR: 3.4 % (1/29 patients)  CR: 0/107 patients  SD: 20.7 % (6/29 patients)  DCR: 24.1 % (7/29 patients)  PD: 58.6 % (17/29 patients)  Median PFS in months: 2 (95 % CI: 6–9.43)  Median OS in months: 4.7 (95 % CI: 12.86–not estimated)  AEs: 36 events  SAEs: 9 events</td>
</tr>
<tr>
<td>Frumovitz et al. [56]</td>
<td>2020</td>
<td>II</td>
<td>7</td>
<td>6 cervical SCNEC 1 vulvar SCNEC</td>
<td>pembrolizumab (PD1)</td>
<td>Up to 27</td>
<td>ORR: 0 %  CR: 0 % (0/27 patients) at 27 weeks  SD: 100 % (7/7 patients)  DCR: 40 % (3/7 patients)  PD: 60 % (4/6 patients)</td>
</tr>
<tr>
<td>Özdik et al. [66]</td>
<td>2020</td>
<td>Retrospective study</td>
<td>8</td>
<td>1 larynx NET 1 kidney NET 6 GEP-NETs, including a mixed NET</td>
<td>Monotherapy: pembrolizumab (PD1)  avelumab (PD-L1) Combination therapy: ipilimumab (CTLA4) + pembrolizumab (PD1)</td>
<td>3–32</td>
<td>PR: 37.5 % (3/8 patients)  SD: 12.5 % (1/8 patients)  PD: 50 % (4/8 patients)</td>
</tr>
<tr>
<td>Sherman et al. [62]</td>
<td>2020</td>
<td>Retrospective study</td>
<td>23</td>
<td>Lung LCNEC</td>
<td>Monotherapy: pembrolizumab (PD1) nivolumab (PD1), atezolizumab (PD-L1) ipilimumab (CTLA4) + pembrolizumab (PD1)</td>
<td>Median: 6.2 (IQR 2.2–12.1)</td>
<td>ORR: 33 %  CR: 11 % (2/23 patients)  PR: 22 % (4/23 patients)  SD: 6 % (1/23 patients)  PD: 61 % (11/23 patients)  Median PFS in months: 4.2 (95 % CI: 2.4–8.1)  Median OS in months: 11.8 (95 % CI: 3.7–not reached)</td>
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<th>Type of ICI (target protein)</th>
<th>Duration of follow-up in months</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Shirasawa et al. [61] | 2020 | Retrospective study | 13 | Lung LCNEC | nivolumab (PD1) or pembrolizumab (PD1) | NA | PR: 39 % (5/13 patients)  
SD: 16 % (2/13 patients)  
PD: 45 % (6/13 patients)  
Median PFS in months: 4.2 (95 % CI: 2.7–5.7)  
Median OS in months: 25.2 (95 % CI: 21.3–29.1) |
| Yao et al. [47] | 2021 | II | 116 | 95 thoracic NETs and GEP-NETs  
21 GEP-NECs | spartalizumab (PD1) | Median: 13.4 (range 11–17) | NETs: ORR: 7.4 % (95 % CI: 3.3–14.6 %)  
PR: 7.4 % (7/95 patients)  
SD: 55.8 % (55/95 patients)  
PD: 30.5 % (29/95 patients)  
Median PFS in months: 3.8  
Median OS in months: not estimated  
AEs: 91 (95.8 %) patients  
SAEs: 46 (48.4 %) patients  
NECs: ORR: 4.8 % (95 % CI: 0.1 %–23.8 %)  
PR: 4.8 % (1/21 patients)  
SD: 14.3 % (3/21 patients)  
PD: 66.7 % (14/21 patients)  
Median PFS in months: 1.8  
Median OS in months: 6.8  
AEs: 19 (90.5 %) patients  
SAEs: 12 (57.1 %) patients |
| Gile et al. [63] | 2021 | Retrospective study | 57 | 11 NETs: 8 GEP-NETs  
3 NETs at other sites (6 G1 + G2 NETs, and 5 G3 NETs)  
46 NECs: 18 GEP-NECs  
28 NECs at other sites | Monotherapy: pembrolizumab (PD1)  
nivolumab (PD1), atezolizumab (PD-L1)  
Combination therapy: ipilimumab (CTLA4) + pembrolizumab (PD1)  
ICIs + platinum-based chemotherapy | NETs (all received monotherapy):  
Median: 79.8 (95 % CI: 7.9–251)  
NECs: Median: 10.7 (95 % CI: 1.7–97.9) | G1 + G2 NETs: ORR: 25 %  
CR: 0 %  
PR: 17 % (1/6 patients)  
SD: 17 % (1/6 patients)  
PD: 33 % (2/6 patients)  
Median PFS in months: not reached (95 % CI: 1.5–not reached)  
Median OS in months: 25.2 (95 % CI: 2.1–not reached)  
G3 NETs: ORR: 0 %  
CR: 0 %  
PR: 0 %  
SD: 20 % (1/5 patients)  
PD: 40 % (2/5 patients)  
Median PFS in months: 2.9 (95 % CI: 1.4–4.2)  
Median OS in months: 15.4 (95 % CI: 13.7–17.2)  
NECs: ORR: 19 %  
CR: 2 % (1/46 patients)  
PR: 11 % (5/46 patients)  
SD: 17 % (8/46 patients)  
PD: 39 % (18/46 patients)  
Median PFS in months: NA  
Median OS in months: 7.2 (95 % CI: 3.9–10.8) |
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<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al.* [53]</td>
<td>2018</td>
<td>Ib</td>
<td>23</td>
<td>5 NETs 15 NECs 3 mixed adenoNECs Sites: GEP and non-GEP</td>
<td>toripalimab (PD1)</td>
<td>NA</td>
<td>ORR: overall: 28.6% NETs: 40% NECs: 25% Median PFS in months: 2.8 (95% CI: 1.6–4) SAEs 2 (9%) patients PR: 7% (2/29 patients)</td>
</tr>
<tr>
<td>Fottner et al.* (AVENEC) [54]</td>
<td>2019</td>
<td>II</td>
<td>29</td>
<td>11 G3 NET 16 G3 NEC Sites: both GEP and non-GEP</td>
<td>avelumab (PD-L1)</td>
<td>NA</td>
<td>SD: 14% (4/29 patients) Median OS in months: 4.2 (1 - &gt;12) AEs: 11 (38%) patients</td>
</tr>
<tr>
<td>Mulvey et al.* [55]</td>
<td>2019</td>
<td>II</td>
<td>14</td>
<td>extra-pulmonary NECs 11 SCNECs 1 LCNECs 2 not specified</td>
<td>pembrolizumab (PD1)</td>
<td>NA</td>
<td>ORR: 7% CR: 7% (1/14 patients) PR: 0% (0/14 patients) SD: 14% (2/14 patients) PD: 71% (10/14 patients) Median PFS in months: 2</td>
</tr>
<tr>
<td>Halperin et al.* [52]</td>
<td>2020</td>
<td>II</td>
<td>40</td>
<td>20 pNETs 20 epNETs</td>
<td>atezolizumab (PD-L1)+ bevacizumab (VEGF)</td>
<td>NA</td>
<td>pNETs: ORR: 20% (95% CI: 6–44%) Median PFS in months: 19.6 (95% CI: 10.6–not reached) epNETs: ORR: 15% (95% CI: 3–38%) Median PFS in months: 14.9 (95% CI: 6.1–not reached)</td>
</tr>
<tr>
<td>Rodriguez-Freixinos et al.* [57]</td>
<td>2020</td>
<td>IIb</td>
<td>9</td>
<td>epNECs</td>
<td>avelumab (PD-L1)</td>
<td>NA</td>
<td>ORR: 0% Median PFS in months: 3 (1–10) Median OS in months: 5 (2–15)</td>
</tr>
<tr>
<td>Capdevila et al.* [59]</td>
<td>2020</td>
<td>II</td>
<td>123</td>
<td>cohort (C)1 lung carcinoids C2. G1/G2 G1-NETs C3. G1/G2 pNETs C4. G3 GEP-NETs</td>
<td>durvalumab (PD-L1) + tremelimumab (CTLA4)</td>
<td>10.8</td>
<td>ORR: C1/2/3/4: 7.4%/6.3%/9.1% respectively. CBR: C1/2/3: 7.4%/32.3%/25% respectively. OS rate for C4 at 9 months: 36.1%</td>
</tr>
<tr>
<td>Chan et al.* [60]</td>
<td>2021</td>
<td>II</td>
<td>22</td>
<td>extra-pulmonary NECs 8 SCNECs 6 LCNECs 8 not specified</td>
<td>pembrolizumab + irinotecan or paclitaxel</td>
<td>NA</td>
<td>ORR: 9% PR 9% (2/22 patients) SD 14% (3/22 patients) PD 60% (13/22 patients) Median PFS in months: 2 Median OS in months: 4 SAEs: 7 (32%) patients</td>
</tr>
<tr>
<td>Jimenez et al. [87]</td>
<td>2020</td>
<td>II</td>
<td>11</td>
<td>metastatic PPGL</td>
<td>pembrolizumab (PD1)</td>
<td>Median: 17.9 (IQR: 9.3–20.2)</td>
<td>PR: 9% (1/11 patients) SD: 64% (7/11 patients) PD: 27% (3/11 patients) Median PFS in months: 5.7 (95% CI: 4.3–not reached) Median OS in months: 19 (95% CI: 9.9–not reached) AEs: 26 events SAEs: 4 events</td>
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<td>Kaufman et al. [102]</td>
<td>2016</td>
<td>II</td>
<td>88</td>
<td>MCC</td>
<td>avelumab (PD-L1)</td>
<td>Median: 10.4 (IQR 8.6–13.1)</td>
<td>ORR: 31.8% (95% CI: 42.3%–79.3%) CR: 9% (8/88 patients) PR: 23% (20/88 patients) SD: 10% (9/88 patients) PD: 36% (32/88 patients) Median PFS: 2.7 months (95% CI 1.4–6.9) Median OS: 11.3 months (7.5–14.0) AEs: 62 (70%) patients SAEs: 4 (5%) patients</td>
</tr>
<tr>
<td>D'Angelo et al. [103]</td>
<td>2018</td>
<td>II</td>
<td>29</td>
<td>MCC</td>
<td>avelumab (PD-L1)</td>
<td>Median: 5.1 (range: 0.3–11.3)</td>
<td>3-month ORR 62.1% (95.9% CI: 21.9%–43.1%) CR: 13.8% (4/29 patients) PR: 48.3% (14/29 patients) SD: 10.3% (3/29 patients) PD: 24.1% (7/29 patients) AEs: 28 (71.8%) patients SAEs: 8 (20.5%) patients</td>
</tr>
<tr>
<td>Nghiem et al. [101]</td>
<td>2019</td>
<td>II</td>
<td>50</td>
<td>MCC</td>
<td>pembrolizumab (PD-1)</td>
<td>Median: 14.9 (range: 0.4–36.4+)</td>
<td>ORR: 56% (95% CI: 41.3%–70%) CR: 24% (12/50 patients) PR: 32% (16/50 patients) SD: 10% (5/50 patients) PD: 32% (16/50 patients) Median PFS: 16.8 months (95% CI: 4.6 months–not estimable) Median OS: not reached AEs: 50 (100%) patients SAEs: 14 (28%) patients</td>
</tr>
<tr>
<td>Topalian et al. (CheckMate 358) [100]</td>
<td>2020</td>
<td>I/II</td>
<td>36</td>
<td>MCC</td>
<td>neoadjuvant nivolumab (PD1) 4 weeks prior to surgery</td>
<td>Median: 20.3 (range: 0.5–39.7)</td>
<td>CR: 47.2% (17/36 patients) PR: 54.5% (18/33 patients) AEs: 18 (46.2%) patients SAEs: 3 (7.7%) patients</td>
</tr>
</tbody>
</table>

NET: Neuroendocrine tumor; GEP: Gastroenteropancreatic; p: Pancreatic; ep: Extrapancreatic; GI: Gastrointestinal; NEC: Neuroendocrine carcinoma; SCNEC: Small cell NEC; LCNEC: Large cell NEC; PPGL: Pheochromocytoma and paraganglioma; MCC: Merkel cell carcinoma; PD-1: Programmed cell death protein-1; PD-L1: PD-ligand 1; CTLA-4: Cytotoxic T-lymphocyte antigen 4; VEGF: Vascular endothelial growth factor; ORR: Objective response rate; PR: Partial response; SD: Stable disease; PD: progressive disease; TTP: Time-to-progression; OS: Overall survival; PFS: Progression-free survival; DCR: Disease control rate; CBR: Clinical benefit rate; CI: Confidence interval; IQR: Interquartile range; AE: Adverse event; SAE: Severe adverse event; NA: Not available; * These data are currently only published in the form of abstracts.
ors with high tumor mutational burden (TMB) such as pancreatic NECs, a strong correlation between TMB and efficacy of ICI therapy in cancers in general has not been identified to date [64]. In a retrospective study on LCNEC patients, those on anti-PD1 therapy with dense tumoral CD8 + T lymphocyte infiltration (> 38 cells/mm²) had a significantly better PFS and OS than patients with lower infiltration density [60]. In this study, 90 % of the 13 patients who received anti-PD1 therapy had PD-L1-negative tumors, yet they responded to anti-PD1 therapy. Moreover, three patients with a pathogenic TP53 variant along with other co-occurring variants such as PIK3CA and RB1 responded well to anti-PD1 therapy, suggesting a probable correlation between presence of certain pathogenic gene variants and response to ICI therapy.

The PD1 inhibitor spartalizumab was utilized to treat 95 patients with thoracic and GEP-NETs as well as 21 GEP-NECs in a phase II study [47]. After a median follow-up of 13.4 months, the ORR in the NET group was 7.4 % in the NET patients and 4.8 % in the NEC patients, while the median PFS was 3.8 months and 1.8 months in the NET and NEC groups, respectively, with the 12-month Kaplan-Meier estimated median PFS rate of 19.5 % in the NET group and 0 % in the NEC group. The therapy was also associated with SAEs in close to half the patients in both NET and NEC cohorts, and a quality-of-life assessment did not reveal any meaningful improvement from the PD1 therapy in the global health status or functional scales in these patients. Forty patients with recurrent/metastatic GEP and non-GEP-NETs were treated with the PD1 inhibitor toripalimab in a phase Ib study [49]. The ORR was 20 % and the disease control rate (DCR) was 35 %, with a median duration of response of 15.2 months. Patients with high PD-L1 expression (> 10 %) and a high TMB had better ORRs compared to patients with low PD-L1 expression and a low TMB. One patient who responded to therapy had multiple genomic rearrangement with high prediction score for neoantigens, but interestingly had low TMB, negative PD-L1 expression and a low TMB. One patient who responded to therapy had high TMB had better ORRs compared to patients with low PD-L1 expression. An other meta-analysis by Park et al. compared 10 studies comprised of 464 patients with advanced/metastatic NETs [68]. The pooled ORR was 15.5 % (95 % CI: 9.5–24.3 %; I² = 72 %). The ORR was better with thoracic NETs (24.7 %) compared to GEP-NETs (9.5 %). Interestingly, poorly-differentiated NET group had better ORR (22.7 %) compared to the well-differentiated NET group (10.4 %), with the probable explanation being that the poorly-differentiated NETs may have a higher PD-L1 expression and a higher TMB [69]. The median PFS was 3.8 months (95 % CI: 3.5–4.1), and the median OS was 22.7 months (95 % CI: 20.1–25.9), with the shortest median OS noted with poorly-differentiated GEP-NETs and longest OS with well-differentiated thoracic NETs. Similar to the first meta-analysis, combination therapy resulted in better ORRs compared to monotherapy. The differences noted with ORRs between this meta-analysis and the meta-analysis by Bongiovanni et al. was due to different set of studies included: the Park et al. study included only full-length studies (phase I/II studies and retrospective studies), while the Bongiovanni et al. study included phase I/II full-length studies and abstracts but did not include retrospective studies. In comparison, the ORRs and survival outcomes, and AE profiles have been somewhat better with some of the other established systemic therapies for NETs as summarized in Table 2. However, it must be noted that these are not head-to-head comparisons, and the type of study is not the same across the articles described in Table 2.

**Medullary thyroid cancer**

While surgery and systemic chemotherapy were the main treatment options available for MTC for several years [11], the management of advanced/metastatic MTC has dramatically changed over the past decade, mainly due to the advent of the tyrosine kinase inhibitors (TKIs) such as vandetanib and cabozantinib [70, 71], and of selective rearranged during transfection (RET) inhibitors, including selpercatinib and pralsetinib [72, 73]. As with other NETs, several studies have utilized PRRT to treat MTC with reasonable success [74–79]. As with other NETs, the utility of ICI in MTC is yet to be thoroughly investigated.

The immune landscape of MTC has been described in a few studies, although the implications of the findings in the clinical management of these tumors needs to be established. PD1/PD-L1 expression has been identified in certain MTC post-surgical specimens, and PD-L1 expression in the tumor cells and the associated immune cells has been shown to be associated with distant metastases at the time of surgery and co-expression of PD1/PD-L1 has shown significant association with advanced stages (III/IV), worse OS, but not with worse PFS [80]. Other immune checkpoint-relat-
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study type</th>
<th>Number of patients</th>
<th>Types of NET</th>
<th>Type of treatment</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Bongiovanni et al. [67] | 2021 | Meta-analysis | 636 | Multiple | Various ICIs (monotherapy and combination) | **ORR:** 10% (95% CI: 6–15%)  
**DCR:** 42% (95% CI: 28–56%)  
Median **PFS** in months: 4.1 (95% CI: 2.6–5.4)  
Median **OS** in months: 11 (95% CI: 4.8–21.1)  
**trSAEs:** 22% (95% CI: 13–32%) |
| Park et al. [68] | 2022 | Meta-analysis | 464 | Multiple | Various ICIs (monotherapy and combination) | **ORR:** 15.5% (95% CI: 9.5–24.3%)  
Median **PFS** in months: 3.8 (95% CI: 3.5–4.1)  
Median **OS** in months: 22.7 (95% CI: 20.1–25.9)  
**SAEs:** NA |
| Strosberg et al. (NETTER-1) [32] | 2017 | Phase III RCT, LAR octreotide alone as control group | 116 in treatment group | Midgut NETs | \( ^{125} \text{I}-\text{DOTA-TATE (with LAR octreotide)} \) | **ORR:** 18%  
**Estimated PFS:** 65%  
**trSAEs:** 9% |
| Yao et al. (RADIANT-4) [26] | 2015 | Phase III, placebo-controlled RCT | 203 in treatment group | WD lung and GEP-NETs | everolimus | Median **PFS** in months: 11 (95% CI: 9.2–13.3)  
**trSAEs:** <1–9% |
| Raymond et al. [28] | 2011 | Phase III, placebo-controlled RCT | 86 in treatment group | WD pNETs | sunitinib | **ORR:** 9.3%  
Median **PFS:** 11.4 months  
**SAEs:** 1–12% |
| Caplin et al. [23] | 2014 | Phase III, placebo-controlled RCT | 101 in treatment group | EP-NETs | lanreotide | Median **PFS:** not reached  
**SAE:** 26% |
| Rinke et al. (PROMID) [21] | 2009 | Phase IIb, placebo-controlled RCT | 42 in treatment group | midgut NETs | octreotide LAR | Median **TTP:** 14.3 months  
**SD:** 66.7% at 6 months  
serious **AEs:** 11 patients |
| Al-Toubah et al. [35] | 2021 | Retrospective analysis | 462 | WD and PD NETs from multiple sites | capecitabine + temozolomide | **ORR:** 46%  
**DCR:** 81%  
Median **PFS** in months: 18 (95% CI: 14.0–21.9)  
Median **OS** in months: 51 (95% CI: 42.8–59.2)  
**trSAEs:** 0.2–8.4% |

**NETs:** Neuroendocrine tumors; **ICI:** Immune checkpoint inhibitor; **RCT:** Randomized controlled trial; **GEP:** Gastroenteropancreatic; **EP:** Enteropancreatic; **p:** Pancreatic; **ORR:** Objective response rate; **DCR:** Disease control rate; **PFS:** Progression-free survival; **AE:** Adverse events; **SAEs:** Severe adverse events; **tr:** Treatment-related; **WD:** Well-differentiated; **PD:** Poorly-differentiated; **LAR:** Long-acting repeatable; **NA:** Not available.
ed candidate antigens such as CD276 have been also identified to be overexpressed in MTC cells as compared to normal thyroid tissue [81]. In a study evaluating tissue microarray expression of immune inhibitory receptors expression comprised of CTLA-4, PD1, TIM-3, LAG-3, and TIGIT in MTC surgical specimens from 200 patients, positive expression was identified at variable levels, ranging from 48% of patients for TIM-3 positivity to 3% for LAG-3 and TIGIT [82]. In this study, CTLA-expression, PD-1/PD-L1 co-expression, and TIM-3 expression were associated with worse recurrence-free survival, and moderate to strong CTLA-4, PD-1, or PD-L1 expression along with consistent TIM-3 expression was noted in MTC of patients who developed advanced disease. Currently, data on ICI therapy in thyroid cancer, including MTC, is extremely sparse [83, 84]. In one report, a patient with advanced, metastatic MTC demonstrated substantial improvement in calcitonin doubling time and tumor burden following yeast-CEA vaccine, followed by surgery and then ICI therapy with avelumab under a phase I trial [85]. Further studies are needed to establish the role of ICI therapy in MTC. For instance, a phase 2 clinical trial (NCT03246958) is evaluating the safety and efficacy of the combination of nivolumab and ipilimumab in the treatment of aggressive thyroid cancer, including cohorts of MTC.

**Pheochromocytomas and paragangliomas**

Current standard of care of PPGL includes surgery, locoregional interventions such as radiofrequency or cryosablation and chemoembolization, temozolomide, TKIs, and PRRT [17, 86]. PPGLs with germline pathogenic variants can have varying biochemical and phenotypic presentations (clusters 1, 2, and 3), and the current management of PPGL has been steering towards personalized/targeted therapy, for instance, hypoxia pathway-targeting agents for treating cluster 1 tumors and TKIs for treating cluster 2 tumors [86]. Similar to MTC and other NETs, the utility of ICI therapy has been understudied in PPGL. In a phase II study, pembrolizumab was utilized in 11 patients with progressive, metastatic PPGL, eight of whom at least had prior surgery with or without other systemic therapy (Table 1) [87]. The primary endpoint of non-progression at 27 weeks was observed in four patients, while the ORR was 9%, and a clinical benefit rate of 73%. Grade 3 adverse events were noted in four patients while none had Grade 4 or 5 adverse events. However, the favorable treatment responses did not correlate with primary tumor PD-L1 positivity, hormonal status, hereditary syndrome status, or infiltrating mononuclear cells in the primary tumor. A combination therapy with ipilimumab and nivolumab used off-label in a 60-year-old patient with sporadic, metastatic, inoperable pheochromocytoma resulted in substantial reduction in tumor burden after close to 20 months of therapy [88].

**Pituitary tumors**

Pituitary tumors are considered as a subtype of NETs and the potential for the utility of ICI in the treatment of these tumors has recently gained some interest [89–91]. While most pituitary tumors are adenomas and can be cured with surgery, the gross tumor resection rate is about 66.4–74% [92]. Also, the so-called refractory adenomas which tend to be more invasive with a high Ki-67 index as well as pituitary carcinomas can cause substantial morbidity and mortality and are challenging to treat [93]. Temozolomide has been used to treat aggressive forms of pituitary tumors but only about 60% of the tumors respond to this treatment [91]. The immune cell population seems to be different between normal pituitary gland and pituitary adenomas, and among different pituitary adenomas, 3 distinct immunophenotypic clusters of pituitary adenomas have been identified with each cluster comprising a different set of immune checkpoint molecular expression [94]. Later studies have also identified increased PD-L1 expression in pituitary tumors invading the cavernous sinus and in functional and more aggressive adenomas [89, 95]. Anti-PD-L1 therapy has demonstrated reduction in tumor growth and in ACTH levels, and improved survival in murine models of Cushings’s disease [96]. In a recent case report, ipilimumab and nivolumab combination therapy followed by maintenance therapy with nivolumab in a 41-year-old patient with recurrent, invasive adrenocorticotropic hormone (ACTH)-producing pituitary adenoma (refractory to bilateral adrenalectomy and temozolomide therapy) led to biochemical response with reduction in ACTH and cortisol levels, and radiographically stable disease 12 months into ICI therapy [97]. In another report, immunotherapy with autoantigens along with a T helper 1 adjuvant for 24 consecutive weeks resulted in substantial biochemical, radiographic, and clinical response in a 31-year-old lady with refractory macroadenoma [98]. Further studies on a larger cohort are needed to establish the role of ICIs and other immunotherapies in the management of aggressive pituitary adenomas and pituitary carcinomas.

**Merkel cell carcinoma**

MCC is a rare, aggressive form of non-melanoma skin cancer predominantly occurring in the sun-exposed areas in older, fair-skinned individuals [99]. Due to its immunogenic nature, these tumors can be targeted with ICIs. While CTLA-4 inhibitors are not well-studied in this condition, the PD-L1 inhibitor, avelumab and PD-1 inhibitors pembrolizumab and nivolumab have been studied in advanced MCCs in various trials, including KEYNOTE-017, CheckMate 358, and JAVELIN Merkel 200-part A and part B trials [100–103]. ICI therapy in MCC is associated with higher ORRs (31.8–62.1%) compared to conventional NETs [101–103], and a neoadjuvant approach has also been utilized with tumor regression in close to 50% of the patients [100]. Further optimization of ICI-based treatment is being evaluated in early phase trials targeting other immune checkpoint markers such as TIM-3, LAG-3, TIGIT in advanced cancers [99].

**Summary of the current knowledge**

In general, the role of ICI in the treatment of NETs has not been well-established, and the currently available data demonstrate only modest efficacy. Combination ICI therapy is superior to monotherapy. Some of the factors that determine favorable response to ICI therapy include aggressive tumor biology, high TMB, higher T lymphocyte and other inflammatory cell infiltration into the tumor microenvironment, and presence of certain additional pathogenic gene variants. On the other hand, the extent of PD-L1 expression has not shown clear correlation with response to ICI therapy. The NCCN 2021 guidelines recommend the use of pembrolizumab as a monotherapy as a category 2B recommendation (low-level evi-
In general, NETs are described as having a ‘cold’ tumor microenvironment which is thought to be the reason for the modest efficacy of ICI therapy. One of the main areas of further research lies in exploring the mechanisms that can turn these immunologically ‘cold’ tumors into ‘hot’ (more immunogenic) tumors. The three major immunologically ‘cold’ cancer phenotypes described include: 1) the immune desert phenotype which comprises tumors that lack T lymphocyte priming, suboptimal antigen processing and presentation, and lack of antigen-presenting cell – T lymphocyte interaction, 2) the immune included phenotype in which the T lymphocytes do not effectively infiltrate the tumor, and 3) the immune inflamed phenotype in which the T lymphocytes infiltrate the tumor but these cells are rendered ineffective either due to T cell exhaustion or due to checkpoint activation [109]. Several mechanisms underline the ‘cold’ tumor phenotype, including low multiple histocompatibility complex I (MHC I) expression, low TMB, activation of certain oncogenic pathways, epigenetic modifications, altered tumor vasculature, tumor hypoxia, tumor microbiome, immunosuppressive tumor microenvironment, among others [109]. The molecular landscape of both sporadic and familial NETs demonstrates involvement of protooncogenes as well as tumor suppressor genes, several of which are involved in the development of one or more of the above-described immune evasion phenotypes of tumors [109, 110]. Certain molecular phenotypes such as metastasis-like primary-1 (MLP-1) subtype of pancreatic NETs are associated with worse prognosis, increased levels of immune-related genes expression including T cell-inflamed-related genes, immune checkpoint antigens, and other immune evasion mechanisms, and such enhanced immune-related gene expressions are associated with hypoxia and necrosis in pancreatic NETs [111]. Several approaches have been attempted to convert the immunologically ‘cold’ tumors into ‘hot’ tumors. Some of these mechanisms include promoting T cell priming (immunodervants, oncolytic viruses, chemotherapy/radiation mediating an ‘abscopal effect’, local ablative therapies), antigen-specific T cell expansion (adoptive cellular therapy such as CAR-T cells, anticancer vaccines), and improving T cell trafficking and infiltration (oncogenic pathway inhibitors, epigenetic modifier inhibitors, antiangiogenic therapies, TGFβ inhibitors, CXCR4 inhibitors) [112–121]. Some of these mechanisms may hold the key to enhancing the response of NETs to ICI or other forms of immunotherapy (Fig. 5). Further details on the mechanisms on converting immunologically ‘cold’ into ‘hot’ tumors are described elsewhere [109].

Apart from the canonical targets of CTLA-4, PD-1, or PD-L1, targeting other components related to immunoregulation may serve as alternative therapy or augment the clinical efficacy of ICIs. For instance, targeting indoleamine 2,3-dioxygenase, an enzyme that plays a role in immune evasion in cancers may potentiate the effects of ICIs [122]. Other proteins involved in immune checkpoint cascade, including TIM-3, LAG-3, and TIGIL also serve as potential targets for novel therapy in the management of NETs [82, 99]. Other strategies such as targeted arterial injection of recombinant viruses or vaccination against anti-apoptotic molecules such as surviving combined with immunogenic adjuvants are being evaluated for the treatment of NETs [122]. It is possible that those NETs that are deemed unlikely to respond to PRRT due to lack of avidity on diagnostic SSA-based imaging, may in fact be candidates for ICI therapy. The reason for this ‘flip-flop’ phenomenon could be because the less-avid NET lesions tend to be dedifferentiated, which may in turn translate to increased TMB and immunogenicity leading to increased susceptibility towards ICI therapy. This mechanism is probably analogous to the flip-flop phenomenon observed with differentiated thyroid cancers, in which tumors that are radiodine non-avid tend to be avid on fluorodeoxyglucose (FDG)-PET/CT scan [123]. In this context, it is important to be aware of the distribution of SSTRs 1–5 in normal human tissue and a normative database [124]. The expression profile of neuropeptide receptors can vary across different types of immune cells [125]. Human monocytes express SSTR2A and SSTR1 when induced to differentiate into macrophages or dendritic cells. NETs can be infiltrated by lymphocytes,
Heavy tumor infiltration by T regulatory cells is associated with weaker anti-tumor immunity [126–128]. A high-density SSTR expression occurs not only on tumor cells but also on peritumoral vessels, activated lymphocytes and monocytes. Somatostatin can inhibit inflammation both locally and distant from the site of release [129]. Certain drugs, for instance, valproic acid which can inhibit the histone deacetylase, can elicit an upregulation of SSTR2 mRNA and protein expression in human NET cells [130, 131]. Glucocorticoids are anti-inflammatory and in patients with ectopic ACTH secretion and cortisol excess the use of selective non-steroidal glucocorticoid receptor antagonist/modulator mifepristone and relacorilant can lead to an upregulation of SSTR2 expression in ACTH-secreting neuroendocrine tumors [132]. Inhibition of proprotein convertase subtilisin/kexin type 9 (PCSK9) can lead to increased MHC I expression on tumor cells leading to augmented intratumoral CD8+ lymphocyte infiltration [133]. Whether these mechanisms would turn “cold” NETs into “hot” tumors with regards to improving T-cell infiltration and thereby making such NET more responsive to ICI therapy needs to be shown.

Studies in mouse models have revealed that the effects of ICIs are potentially modulated by the gut microbiome, which is in part mediated through certain microbiome-derived metabolites such as inositol [134]. Studies of the human microbiome and its impact on the efficacy of immunotherapy on NETs needs further investigation. Although ICI therapy is technically effective in treating tumors with high-TMB [68], particularly with NECs [135], the cut-offs associated with TMBs have thus far been inconsistent with the predictability of response to ICI therapy, and on some other cancers, ICI therapy has not resulted in improved ORR among patients with high-TMB as compared to patients with low-TMB [64]. The current FDA-approved indication for the use of pembrolizumab on the basis of high-TMB may be too broad and further tailoring of indications based on other factors such as environmental carcinogen exposure are being suggested for consideration [136].

Several clinical trials are ongoing to investigate the role of ICI therapy (clinicaltrials.gov), particularly in conjunction with other therapies such as VEGF-inhibitors (NCT05000294), TKIs (NCT04197310), platinum-based chemotherapy (NCT03980925), stereotactic radiation (NCT03110978), and 177Lu-DOTATATE (NCT04525638), for the treatment of NETs and NECs. Deciphering the molecular mechanisms and extraneous factors that modulate the immunogenicity of NETs, and further research on systemic therapies or other agents that could potentially enhance the effects of ICIs hold the key to progressing the field of immunotherapy in the management of NETs.

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Conflict of Interest
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References


