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. Immunotherapy, 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.
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 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) 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. The lesions were stable on 02/2022. 68Ga-DOTATATE PET/CT imaging (Fig. 1b). 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 kinase 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 (177Lu)-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, either as a single agent or with capecitabine [34, 35].

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-

Fig. 3  a: 111In-Octreoscan in whole body display. Scan was on 06/2016 without significant focal lesions (cold tumors). b: 111In-Octreoscan in transaxial fused image focusing on liver. Scan was on same day of whole-body scan with small liver lesions but no activity above liver background (cold tumors).

Fig. 4  a: CT of abdomen in trans axial display. Scan was on 12/2016 with more small liver lesions. Same patient as Fig. 3 and therapy changed from temozolomide/capecitabine to carboplatin/etoposide. b: CT of abdomen in trans axial display. Scan was on 11/2017. There are more liver lesions (in large circle in center, also posteriorly) and new peritoneal metastases (in smaller circle to right). The overall findings were suggestive of disease progression.
Table 1 List of studies evaluating the efficacy of ICI in NETs.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Phase</th>
<th>Number of patients</th>
<th>Types of NET</th>
<th>Type of ICI (target protein)</th>
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</table>
| Mehnert et al. (KEYNOTE-028) [46] | 2020 | I     | 41                 | 25 carcinoid | pembrolizumab (PD1)         | 16 pNETs                       | 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 |
| Patel et al. (DART SWOG 1609) [48] | 2020 | II    | 32                 | Non-pancreatic NETs: 15 GI NETs | ipilimumab (CTLA4) + nivolumab (PD1) | Up to 15 | 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 |
| Lu et al. [49] | 2020 | Ib    | 40                 | 32 GEP-NETs | toripalimab (PD1)           | Up to 24 | 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 |
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<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)  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%  PD: 100% (7/7 patients) at 27 weeks  Median PFS in months: 2.1 (range: 0.8–3.3)  AEs: 7 events  SAEs: 2 events</td>
</tr>
<tr>
<td>Özdirik 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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## Table 1 List of studies evaluating the efficacy of ICI in NETs.

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<th>Study</th>
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<th>Outcomes</th>
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</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>Type of ICI (target protein)</th>
<th>Duration of follow-up in months</th>
<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</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</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</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%/0%/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% (2/11 patients) PD: 27% (3/11 patients) Median PFS in months: 5.7 (95% CI: 4.37–not reached) Median OS in months: 19 (95% CI: 9.9–not reached) AEs: 26 events SAEs: 4 events</td>
</tr>
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| Kaufman et al. [102] | 2016 | II    | 88                 | MCC          | avelumab (PD-L1)             | Median: 10.4 (IQR 8.6–13.1)   | 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)  
|                      |      |       |                    |              |                              |                                | AE: 62 (70%) patients  
|                      |      |       |                    |              |                              |                                | SAE: 4 (5%) patients  
| D'Angelo et al. [103] | 2018 | II    | 29                 | MCC          | avelumab (PD-L1)             | Median: 5.1 (range: 0.3–11.3)  | 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)  
|                      |      |       |                    |              |                              |                                | AE: 28 (71.8%) patients  
|                      |      |       |                    |              |                              |                                | SAE: 6 (20.5%) patients  
| Nghiem et al. [101]  | 2019 | II    | 50                 | MCC          | pembrolizumab (PD1)          | Median: 14.9 (range: 0.4–36.4+) | 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  
|                      |      |       |                    |              |                              |                                | AE: 50 (100%) patients  
|                      |      |       |                    |              |                              |                                | SAE: 14 (28%) patients  
| Topalian et al.      | 2020 | I/II  | 36                 | MCC          | neoantibody (PD1)            | Median: 20.3 (range: 0.5–39.7)  | CR: 47.2% (17/36 patients)  
| (CheckMate 358) [100]|      |       |                    |              |                              |                                | PR: 54.5% (18/33 patients)  
|                      |      |       |                    |              |                              |                                | AE: 18 (46.2%) patients  
|                      |      |       |                    |              |                              |                                | SAE: 3 (7.7%) patients  

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 without microsatellite instability. SAEs were noted in <30% of the patients.

PD-L1 inhibitor monotherapy has also been evaluated with ave-lumab, and atezolizumab [53, 56, 61, 62, 65], although most data are from retrospective studies in which other ICIs including PD1 inhibitors or combination ICI therapies were utilized (►Table 1). In a phase II study, combination therapy with the PD-L1 inhibitor atezolizumab + bevacizumab in 40 pancreatic and extrapancreatic NETs led to an ORR of 20 and 15%, and a median PFS of 19.6 months and 14.9 months, respectively [66]. A combination of PD1 or PD-L1 + CTLA4 inhibitors have also been utilized in various studies, including the combinations of nivolumab and ipilimumab [48, 57], pembrolizumab and ipilimumab [61, 62, 65], and durvalumab and tremelimumab [58]. The ORRs with combination therapies have been better compared to monotherapy with PD1 inhibitors, ranging from 24% to 33%, with a comparable AE profile (►Table 1).

A meta-analysis on 14 phase I/II studies was performed by Bongiovanni et al. to evaluate the safety and efficacy of ICI therapy in NETs [67]. The efficacy data were available from 636 patients. The pooled ORR was 10% (95% CI: 6–15%; I² = 67%), with a DCR of 42% (95% CI: 28–56%, I² = 93%). The highest ORR was noted with toripalimab, and combination regimens of PD1 + CTLA4 inhibitors (nivolumab + ipilimumab) or PD-L1 + VEGF inhibitors (atezolizumab + bevacizumab) were superior compared to PD1 inhibitor monotherapy. The DCR was better for G1/G2 NETs as compared to G3 NETs and NECs, but the DCR was not significantly different based on the site of origin of the tumors. Most common AEs noted were dermatologic conditions (rash, pruritis, dermatitis), fatigue, gastrointestinal symptoms, transaminase elevation, hypothyroidism, and loss of appetite. SAEs were noted at a rate of 22% for treatment-related AEs and 18% for immune-related AEs. The median OS was 4.1 months (95% CI: 2.6–5.4; I² = 96%), and the median OS was 11 months (95% CI: 4.8–21.1; I² = 98%). A sub-analysis of studies in which PD-L1 expression available [49, 50, 52, 58] revealed that patients with tumors positive for PD-L1 expression had a better ORR compared to patients without PD-L1 tumor expression. Another 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 is negative, and OS, but not with worse PFS [80]. Other immune checkpoint-relat-
### Table 2: A comparison of outcomes of ICI therapy and other systemic therapies in NETs.

<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>
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</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 | 177Lu-DOTATATE (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: 11 months (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 IIIb, 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 tis-
tue [81]. In a study evaluating tissue microarray expression of im-
mune inhibitory receptors expression comprised of CTLA-4, PD1,
TIM-3, LAG-3, and TIGIT in MTC surgical specimens from 200 pa-
tients, 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 expres-
sion 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 sur-
gery 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 evalu-
ating the safety and efficacy of the combination of nivolumab and
ipilimumab in the treatment of aggressive thyroid cancer, includ-
ing cohorts of MTC.

Pheochromocytomas and paragangliomas
Current standard of care of PPGL includes surgery, locoregional in-
terventions such as radiofrequency or cryosablation and chemoem-
bolization, 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/tar-
geted 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 util-
ized 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 syn-
drome 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 po-
tential for the utility of ICI in the treatment of these tumors has re-
cently gained some interest [89–91]. While most pituitary tumors
are adenomas and can be cured with surgery, the gross tumor re-
section 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 im-
mune checkpoint molecular expression [94]. Later studies have also
identified increased PD-L1 expression in pituitary tumors in-
vading the cavernous sinus and in functional and more aggressive
adenomas [89, 95]. Anti-PD-L1 therapy has demonstrated reduc-
tion in tumor growth and in ACTH levels, and improved survival in
murine models of Cushing’s disease [96]. In a recent case report,
ipilimumab and nivolumab combination therapy followed by main-
tenance therapy with nivolumab in a 41-year-old patient with re-
current, invasive adrenocorticotrophic hormone (ACTH)-producing
pituitary adenoma (refractory to bilateral adrenalectomy and te-
mozolomide 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 consec-
tutive weeks resulted in substantial biochemical, radiographic, and
clinical response in a 31-year-old lady with refractory macropro-
lingtona [98]. Further studies on a larger cohort are needed to estab-
lish the role of ICIs and other immunotherapies in the manage-
ment of aggressive pituitary adenomas and pituitary carcinomas.

Merkel cell carcinoma
MCC is a rare, aggressive form of non-melanoma skin cancer pre-
dominantly occurring in the sun-exposed areas in older, fair-
skinned individuals [99]. Due to its immunogenic nature, these tu-
mors 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, Check-
Mate 358, and JAVELIN Merkel 200-part A and part B trials [100–
103] (Table 1). 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 monother-
apy. Some of the factors that determine favorable response to ICI
therapy include aggressive tumor biology, high TMB, higher T lym-
phocyte and other inflammatory cell infiltration into the tumor mi-
croenvironment, 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-
dence and NCCN consensus that a therapy is appropriate) in patients with NETs harboring high-TMB (> 10 mutations/Megabase) as confirmed by an FDA-approved test, that have progressed on prior therapies and there are no alternative satisfactory therapies available [20]. The combination of ipilimumab and nivolumab is also recommended (category 2B) by the NCCN guidelines for patients with locally advanced or metastatic NETs with unfavorable tumor biology as an alternative to clinical trials [20]. The NANETS 2021 guidelines comment on ICI therapy particularly for pancreatic NETs and endorse the minimal treatment benefit noted in NET patients with single agent PD-1/PD-L1 therapy and recommend the use of immunotherapy for pancreatic NECs in a clinical trial setting [36, 104]. Similarly, NANETS guidelines on PPGl also acknowledge the lack of knowledge on the mechanisms that determine favorable outcomes with ICI therapy in PPGl and suggest the use of ICI to be limited to clinical trials [17, 36].

**Future directions**

In addition to ICI therapy per se, targeting additional immunotherapeutic mechanisms may enhance the anti-tumor activity of ICIs, especially in NETs which are particularly indolent and relatively less sensitive to ICI therapy compared to other tumors. Some of these targets include alteration of the tumor microenvironment and tumor vascularity, T cell homing, prevention of T cell exhaustion, enhancement of metabolic pathways or cytokines that sustain a robust CD8+ lymphocyte response, and vaccination of a given patient with the antigens derived from their tumor cells [105]. These strategies may hold potential as combination therapies along with ICIs. The intratumoral heterogeneity exhibited at cellular and genomic levels also contributes towards variable immune response towards these tumors and the relative resistance towards several targeted therapies and may partly explain the biology of treatment-refractory NETs [105, 106]. Understanding the immune-microenvironmental mechanisms driving the intratumoral heterogeneity and identifying potential treatment targets may allow for further optimization of immunotherapy in NETs. Some progress has been made in the description of the NET immune-microenvironment. The immune-microenvironment seems to be higher in pancreatic NETs compared to midgut NETs but without any clear association with expression of immune checkpoint markers or mutational profile [107], and a higher density of T cell infiltration in pancreatic NET primary tumors has been associated with a higher recurrence-free survival meanwhile a high regulatory T cell infiltration has been associated with a lower OS among patients with liver NET metastases [108].

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 presentation and processing, and lack of antigen-presenting cell – T lymphocyte interaction, 2) the immune excluded 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 underlie 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 (immune adjuvants, 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, CXCRI4 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 radioiodine 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,
as shown by immunohistochemistry for CD3, CD4, and CD8. Heavier 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


