Review

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Narrative Review

Lung NETs and GEPNETs: One Cancer with Different Origins or Two Distinct Cancers?

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Simple Summary: This study examined the disparities between lung neuroendocrine tumors and gastroenteropancreatic neuroendocrine tumors, two types of neuroendocrine tumors that originate from different parts of the body and have historically been treated similarly. This research delves into the differences in genetic makeup, behavior, and response to treatments such as chemotherapy, immunotherapy, and targeted therapies between these two types of tumors. This study aimed to explore these distinctions to develop more personalized and effective treatment strategies for patients with lung and gastroenteropancreatic neuroendocrine tumors. Recognizing and treating these two types of cancer as distinct entities, rather than as a single disease, the medical community can significantly improve patient outcomes and highlight the importance of this research.

Abstract: Lung neuroendocrine tumors (LNETs) and gastroenteropancreatic neuroendocrine tumors (GEPNETs) are two distinct types of neuroendocrine tumors (NETs) that have traditionally been treated as a single entity despite originating from different sources. Although they share certain phenotypic characteristics and the expression of neuroendocrine markers, they exhibit differences in their microenvironment, molecular mutations, and responses to various therapeutic regimens. Recent research has explored the genetic alterations in these tumors, revealing dissimilarities in the frequently mutated genes, role of EGFR in carcinogenesis, presence of transcription factors, and immunogenicity of the tumor and its microenvironment. Spread Through Air Spaces (STAS), a phenomenon unique to lung carcinomas, appears to play a crucial role in LNET prognosis. These distinctions are also evident in the cascade response of lung and GI tract neuroendocrine tumors to somatostatin analogs, Peptide Receptor Radionuclide Therapy (PRRT), chemotherapy, and immunotherapy. Identifying similarities and differences between the two groups may improve our understanding of the underlying mechanisms and facilitate the development of more effective treatment strategies.

Keywords: Lung NETs; neuroendocrine tumors; typical carcinoid; atypical carcinoid; pulmonary NETs; EGFR; DLL3; immunotherapy

1. Introduction

The scarcity of occurrence and lack of research data over several decades has resulted in great uncertainty in the management of different scenarios in clinical practice for patients with lung NETs.

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In the majority of pharmaceutical trials in recent decades, lung NETs have not been included in the patient population sample or are represented in very small proportions compared to gastroenteropancreatic NETs (GEPNETs); hence, the efficacy of various treatments in this group remains uncertain **[1–3]**. The first guidelines from the European Society of Medical Oncology (ESMO) for the management of carcinoid lung tumors were only published in 2021, filling a gap that had existed for many years, unlike the guidelines for GEPNETs in which both ENETs and NANETs had been published several years before **[4–6]**. The past decade has seen significant research efforts aimed at elucidating various aspects of carcinogenesis and the biological behavior of both lung carcinoids and GEPNETs, with a focus on similarities and important differences that often result in divergent treatment pathways.

Well-differentiated NETs are classified as low- or intermediate-grade tumors (G1 and G2) according to the criteria established by the World Health Organization (WHO) **[7]**. The G1 and G2 nomenclature is mainly used for NETs of the gastrointestinal tract, mainly characterized by ki67% positivity, which must be less than 20%. For lung NETs, the terms typical and atypical carcinoids were used for G1 and G2, respectively. However, the differentiation of lung carcinoids is not based on ki67% positivity but on mitotic count per 2 mm2, and 10 mitoses are considered the maximum threshold. These tumors exhibit certain common phenotypic characteristics, including rosette formation, solid nesting architecture, and trabeculae, as well as the expression of neuroendocrine markers, such as chromogranin A, synaptophysin, and CD56/NCAM. However, they also possess distinct features such as the microenvironment in which they grow, the molecular mutations they harbor, their response to various therapeutic regimens, and their biological behavior. Recognizing the similarities and differences between these tumors is crucial for developing more effective treatment strategies and identifying novel therapeutic options tailored to the specific characteristics of each group.

Methods

For this narrative review, a comprehensive literature search was performed to gather evidence on the treatment and characteristics of LNETs and GEPNETs. The databases searched included MEDLINE/PubMed, with the search concluded on October 30, 2023. Our search strategy was designed to encompass a broad range of terms relevant to our study objectives, including "lung neuroendocrine tumors," "carcinoid," "gastroenteropancreatic neuroendocrine tumors," "EGFR," "immunotherapy," "chemotherapy," "targeted therapy," and "clinical trials." We excluded articles not written in English to maintain consistency in the data analysis. The scope of our review deliberately omitted studies that focused on local therapeutic approaches for both LNETs and GEPNETs, aiming to concentrate on systemic treatment. The selection of articles for inclusion was meticulously performed by the authors, prioritizing the most pertinent and recent publications that provided insights into the distinctions and similarities between LNETs and GEPNETs, with particular emphasis on therapeutic outcomes and molecular characteristics.

2. Delineating the Diversity: Dissecting the Multifaceted Differences Between Lung NETs and GEPNETs

2.1. Genetic Alterations

Two studies have yielded essential insights into the molecular changes that occur in lung neuroendocrine tumors. Fernandez-Cuesta et al. conducted a study to investigate genetic mutations in 69 carcinoids through RNA sequencing (RNAseq) and 44 tumor-normal pairs through whole-genome sequencing or whole-exome sequencing (WES) in typical and atypical carcinoids. The results revealed that mutations in TP53 and RB1 occurred infrequently, and mutations in chromatin-remodeling genes were identified in approximately 51.1% of the analyzed samples. Alterations have been found in 40% of histone modifier genes, such as MEN1, PSIP1, and ARID1A, with no genetic segregation observed between typical and atypical carcinoids [8].

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Asiedu et al. used gene expression and high-density single-nucleotide polymorphism (SNP) arrays to evaluate the classification of LNETs based on differential gene expression and copy number variation (CNV). Clustering of differentially expressed genes failed to differentiate between typical and atypical carcinoids, and no correlations were observed between clinical outcomes and gene expression in carcinoid tumors. However, the analysis of chromatin remodeling genes that were significantly mutated revealed different genes, DPF1, RNF212, and TAPBPL, compared to those found in the study by Fernandez-Cuesta et al. The most frequently mutated genes were ATP1A2, CNNM1, MACF1, RAB38, NF1, RAD51C, TAF1L, EPHB2, POLR3B, and AGFG1. Pathway analysis of differentially expressed genes with CNV changes identified the involvement of the NF-kB and MAPK/ERK signaling pathways [9].

In contrast, in a study of 724 GEP-NENs, including 335 low-grade cases, Puccini et al. discovered significant variations in the genes that were most frequently mutated in pancreatic and low-grade GI NETs. Specifically, MEN1, ATRX, FOXO3, and PTEN were identified as the most frequently mutated genes in pancreatic NETs, while APC was found to be the most frequently mutated gene in GI NETs [10]. In terms of mutated genes, there was a substantial disparity between GEPNETs and lung NETs, with the exception of MEN1, which was found in both groups. The pathways commonly implicated in the pathogenesis of GEPNETs are PI3K/Akt/mTOR and INK4a/ARF and RB1, which are distinct from the pathways of LNETs [11–13].

Table 2. Comparison of Molecular Characteristics between Lung Neuroendocrine Tumors (LNET) and Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET): This table delineates key genetic alterations, signaling pathways involved, and potential therapeutic targets identified in LNET versus GEP-NET, highlighting the distinct molecular profiles and implications for targeted treatment strategies.

Characteristic	LNETs	GEPNETs
Frequent mutated genes	ATP1A2, CNNM1, and MACF1	ATRX, ARID1A, and MEN1
Pathway involved	MAPK/ERK and NF-kB	PI3K/Akt/mTOR INK4a/ARF and RB1
EGFR	Detected in cell membrane Overexpressed in 48% of LNETs	Detected in cytoplasm focally
Tumor immune microenvironment (TIME)	heterogeneous	PanNENs express higher TILs, PD-1 compared to other GEPNETs
Spread Through Air Spaces (STAS)	Described	
DLL3	Overexpressed in Carcinoids A	Absent in low-grade GEPNETs

2.2. The Role of Epidermal Growth Factor Receptor

The epidermal growth factor receptor (EGFR) is a critical regulator of epithelial tissue development and maintenance, and its activation has been implicated in cancer progression. EGFR

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is a key driver of tumor growth in certain types of cancers, such as lung cancer and glioblastoma, and is also present in neuroendocrine tumors, exhibiting distinct expression patterns in GEPNETs and lung NETs [14].

Papouchado et al. found that 91% of small intestine neuroendocrine tumors displayed positive immunohistochemical results for EGFR compared to only 25% of pancreatic neuroendocrine tumors. In these instances, EGFR was predominantly located in the cytoplasm, with only a minimal presence at the cell membrane. Additionally, immunohistochemical detection of EGFR is confined to focal localization rather than diffuse distribution [15,16]. In contrast, in pulmonary neuroendocrine tumors, EGFR is prominently displayed on the cell membrane in approximately 48% of cases, and is typically expressed at high levels [17]. Elevated EGFR expression was more prominent in lung carcinoid tumors than in carcinomas, and upregulated EGFR expression was significantly associated with a lower IASLC-Grade ($p=0.0005$). Interestingly, when primary tumors and metastatic foci were analyzed by FISH for elevated mean EGFR copy number, there was heterogeneity in test positivity, with 30% of cases having elevated mean EGFR copy number in the primary focus but not in the metastatic lesion [18].

Despite the absence of detectable targeted mutations in the EGFR kinase domain in both GEPNETs and lung carcinoids, preclinical data from a cancer cell series of lung NETs suggested that the combination of Erlotinib and Everolimus may have synergistic effects on the inhibition of the EGFR/AKT/mTOR axis. Further in vivo and clinical investigations of the combined inhibition are warranted [19,20].

2.3. ASCL1 and DLL3

The transcription factor ASCL1 (Achaete-scute homologue 1) is a critical factor for neuroendocrine differentiation, as evidenced by the findings of a study that showed that mice deficient in ASCL1 did not exhibit pulmonary neuroendocrine cells [21]. Furthermore, ASCL1 regulates the expression of DDL3, a Notch ligand that is highly expressed in SCLC and other neuroendocrine tumors but is minimally expressed in normal tissues [22].

ASCL1 is highly frequent in Small Cell Lung Cancer (SCLC), occurring in approximately 70% of cases and can be detected immunohistochemically [23]. Its presence is associated with the upregulation of several genes and expression of DLL3 receptors [24,25]. A subtype with high ASCL1 and DLL3 expression has been identified in type I LCNEC, and similar findings were reported by Alcala et al. for Carcinoid A1 [26,27]. Targeting DLL3 receptors is a promising area of research for many targeted therapies being tested in clinical trials for neuroendocrine tumors [28–30]. However, DLL3 expression is significantly more frequent in aggressive neuroendocrine neoplasms than in typical and atypical carcinoids [31,32].

Notch has been suggested to function as a tumor suppressor in ileal NETs/carcinoids because its expression is low or absent in these tumors. Notch signaling in non-tumorigenic cells triggers a series of events that ultimately lead to ASCL1 protein inhibition. ASCL1 is overexpressed in ileal NETs and in vitro experiments have shown that transient overexpression of Notch1 in carcinoid cell lines can reverse ASCL1 overexpression, indicating that Notch1 activation may be a potential therapeutic strategy [33]. In a study of 47 patients with GEPNENs, including both NETs and NECs, immunohistochemical detection of DLL3 in formalin-fixed, paraffin-embedded (FFPE) samples was absent in all well-differentiated GEPNETs and high-grade features (G3 NET) and present in 76.9% of poorly differentiated NECs (G3 NEC) [34].

2.4. PDL1 and Immune Response

In a recent study, formalin-fixed paraffin-embedded (FFPE) samples from 168 patients with pulmonary neuroendocrine tumors were analyzed. A 1% cut-off value was employed, and 5% of typical carcinoids were deemed positive for programmed death ligand 1 (PD-L1) expression. Atypical carcinoids were negative for PD-L1 expression. The expression of PD-L1 was observed to be significantly associated with mediastinal lymph node metastasis at the time of diagnosis as well as the overall metastatic potential of the tumor. Notably, typical carcinoids showed a slightly lower

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CD8+ T cell density than atypical carcinoids did. However, the difference was not statistical significance [35].

In GEPNETs, the expression of PDL1 is infrequent. In the archival tissue of 64 well-differentiated small intestine NETs and 31 pancreatic neuroendocrine tumors (pNETs), no cases of small intestine NETs exhibited tumoral PD-L1 expression, whereas only 7.4% of pancreatic NETs showed such expression. Additionally, high CD8 intratumoral detection was observed in 3% of pancreatic NETs, whereas no such detection was found in small intestine NETs [36].

The microenvironments of typical and atypical carcinoids do not exhibit an immunologically sterile profile. According to Alcala et al., dendritic cells were detected in the majority of carcinoids (60%), whereas the presence of alveolar macrophages in large or small numbers did not seem to be associated with patient prognosis [27]. Single-cell analysis revealed significant intratumoral heterogeneity in these tumors, with a variety of immune cells, including conventional T cells, CD8+ T cells, NK cells, B cells, and plasma cells, present in the microenvironment. The detection rate of lymphoid cell types was similar to that of healthy tissues, and exhaustion signature scores were low. In contrast, populations of monocytes, macrophages, and mast cells were found at different concentrations compared to normal tissues, with prominent washout of monocytes [37]. It has been observed that the expression of IFNγ-associated genes and intratumoral T-cell infiltration are low in both NET G1/G2 and NET G3/NEC. While neuroendocrine carcinomas (NECs) exhibit hot immune microenvironments with an abundance of tumor-infiltrating lymphocytes (TILs), neuroendocrine tumors (NETs) possess a cold immune microenvironment with fewer TILs [38]. Among the comparatively well-differentiated GEPNETs, pancreatic NETs exhibit higher TILs, PD-1, and PD-L1 expression levels than non-pancreatic NENs. Among SINENs, duodenal NENs demonstrate higher immune infiltration than jejunal or ileal NENs [39].

2.5. Spread Through Air Spaces (STAS)

STAS is defined as the presence of micropapillary (MP) clusters, solid nests, or single cells extending beyond the primary tumor into air spaces. Currently, STAS is widely acknowledged as an invasive adenocarcinoma pattern. There is a debate on whether STAS is a real phenomenon or an artifact. Although some evidence suggests that it is an artifact created during tissue processing, many studies have shown that it is a significant risk factor for recurrence. Standardization in diagnosing STAS is lacking and more studies are required to reach a consensus.

In a study by Altinay et al., STAS was present in 48% of patients with atypical carcinoids as opposed to 20.5% of patients with typical carcinoids. This finding was later corroborated by the research of Chae, who discovered STAS in 22% of typical carcinoids patients and 50% of atypical carcinoid patients [40,41].

In a study conducted by Aly et al., 487 patients with typical carcinoids, atypical carcinoids, large-cell neuroendocrine carcinomas, and small-cell lung carcinomas were evaluated for the presence of STAS. The findings of the multivariate analysis stratified by stage indicated that STAS was significantly associated with a higher risk of recurrence and death in the overall cohort and in the AC, LCNEC, and SCLC subgroups. However, owing to the limited number of recurrences and deaths in the typical carcinoid cohort, prognostic analysis could not be performed [42].

3. Navigating Therapeutic Strategies: Efficacy in Treating Lung NETs and GEPNETs

3.1. Somatostatin Analogues in Lung NETs

The available data on the effectiveness of somatostatin analogs in the treatment of GEPNETs are more abundant than those for lung carcinomas. Although there has been no direct comparison between the two groups, certain inferences can be drawn from the combined data that currently exist. In the Clarinet study, lanreotide demonstrated a statistically significant improvement in progression-free survival (PFS) for both G1 and G2 GEPNETs. It is worth noting that up to 10% of G2 patients were included in the study, and the hazard ratio (HR) for G2 was 0.45 (0.22 - 0.91), similar to the HR of 0.43 (0.25 - 0.74) in G1. The median PFS for all GEPNETs was also statistically significant, with an

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HR of 0.47 (95% CI, 0.30 to 0.73). In contrast, the SPINET trial, which assessed Lanreotide in typical and atypical lung carcinomas, did not show a statistically significant improvement in PFS for all carcinomas (typical and atypical) with a value of 0.90 (95% CI, 0.46, 1.88), p = 0.769. Furthermore, there was a notable difference in treatment benefits between typical and atypical carcinomas, with the latter demonstrating no statistically significant PFS benefits [43].

In light of these dissimilarities and considering data from retrospective studies, a recent publication by specialists in the field of neuroendocrine tumors recommended the use of somatostatin analogs only in low-grade metastatic lung carcinomas. Although guidelines recommend SSAs as a potential therapeutic option for advanced lung NETs, they have not been formally approved for pulmonary NETs [44].

3.2. Peptide Receptor Radionuclide Therapy (PRRT) in Lung NETs

The NETTER 1 study demonstrated significant benefits of PRRT in GEPNET carcinoids and has also introduced the potential for therapeutic effects in neuroendocrine tumors. The ability to target lesions due to somatostatin receptor expression offers the potential for targeted treatment of multiple foci, whereas the effect of treatment on adjacent clones within the lesion via the cross-fire effect may help treat heterogeneous metastatic foci [45]. However, it should be noted that this study did not include lung carcinomas and its efficacy in these tumors has not been confirmed. While metastatic lung carcinoids often do not express somatostatin receptors homogeneously or at the same level as GEPNETs, retrospective studies suggest that PRRT may be an effective treatment for a limited number of patients with metastatic lung NETs with high and homogeneous SSR expression [46–48]. It is important to note that immunohistochemical detection of somatostatin receptors in pulmonary NETs may not always match the detection by 68Ga-DOTANOC-positron emission tomography, suggesting that negative immunohistochemistry for SSR should not discourage clinicians from requesting 68Ga-DOTANOC-positron emission tomography for staging lung NETs [49].

3.3. Everolimus

Mammalian target of rapamycin (mTOR) plays a pivotal integrative function in numerous cellular processes and serves as a receptor for extracellular stimuli derived from energy levels, nutrient availability, growth factors, oxygen supply, and stress. Its prominent role in the development and progression of NETs has been extensively documented in both preclinical research and late-stage clinical trials [50].

The mTOR kinase inhibitor everolimus, which is currently the only approved targeted therapy for pulmonary neuroendocrine tumors, exhibited comparable benefits in both GEPNETs and pulmonary NETs, as demonstrated in the RADIANT 4 study. Furthermore, the significance of these benefits persisted regardless of the prior treatments received by the patients, and real-world data have confirmed the similar efficacy of the drug for both types of NETs [51–53]. Conversely, the results demonstrated notable disparities in efficacy between typical and atypical carcinomas, with atypical carcinomas benefiting significantly less. Although the incidence of grade ≥ 3 toxicity increases significantly in patients pretreated with chemotherapy or PRRT, administering the drug early in the treatment line series has been shown to significantly reduce the incidence of adverse side effects. Additionally, a reduction in dosage did not appear to have a statistically significant effect on efficacy, although a numerical difference was observed [54].

3.4. Chemotherapy

3.4.1. 5-FU or Capecitabine-Based Regimens

The use of 5-FU in gastrointestinal neuroendocrine tumors is based on its long-standing use as the backbone of chemotherapy in gastrointestinal adenocarcinomas, as both tumor types share a common microenvironment despite differences in genetic mutations and pathological pathways. However, 5-FU has not been proven effective in the treatment of non-small cell lung cancer and small cell neuroendocrine carcinoma (SCLC); thus, it is not used in clinical practice [55,56]. Nevertheless,

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some studies have suggested that its use for lung NETs may be beneficial in certain cases. For instance, retrospective data showed that 20% of patients with pulmonary NETs responded to treatment with either FOFLOX or GEMOX, and the combination of FOLFOX with bevacizumab has been demonstrated to be effective for both GEPNETs and Lung NETs, although the number of patients with lung NETs was small in this study, and maintenance bevacizumab treatment appeared to provide a significant survival benefit for these patients [57–59].

XELOX levels were evaluated in a retrospective study of patients with pulmonary GEPNETs. The study comprised five individuals with lung NETs, three of whom demonstrated a response to treatment according to the I.T.M.O. criteria, which assess tumor growth, symptom presence/severity, and marker behavior separately rather than the RECIST criteria [60]. Owing to the limited number of patients with pulmonary carcinoids in the aforementioned studies, it is essential to conduct large prospective multicenter trials to determine the efficacy of 5-FU therapies in the treatment of pulmonary neuroendocrine tumors. FOLFIRI, a commonly used regimen for adenocarcinomas of the gastrointestinal tract, has also been administered to patients with neuroendocrine neoplasms, particularly to those with neuroendocrine carcinomas [61]. Currently, limited data are available on the efficacy of this treatment for pulmonary neuroendocrine tumors, and its value in clinical practice is yet to be validated.

3.4.2. Streptozocin -Based Regimens

Streptozocin is an approved drug for the treatment of metastatic pancreatic neuroendocrine tumors. Although it is commonly used off-label for the treatment of gastrointestinal neuroendocrine tumors, its efficacy in lung neoplasms has not been demonstrated. However, it has also been tested for pulmonary carcinoids. In a clinical trial, patients with both GEPNETs and Lung NETs were tested with a combination of STZ and either cyclophosphamide or 5-fluorouracil, revealing a difference in response between the two groups. The combination of STZ with cyclophosphamide showed an objective response (ORR) of 0% in patients with pulmonary NETs and 37% in patients with GEPNETs, whereas the combination of STZ with 5-FU resulted in a significantly higher ORR in pulmonary NETs, although it was still lower than that of GEPNETs (29% vs. 44%) [62].

3.4.3. Temozolomide Plus Capecitabine

Combination therapy with capecitabine and temozolomide, commonly known as CAPTEM, has shown significant efficacy in patients with pancreatic neuroendocrine tumors. Reports indicate that the objective response rates for this treatment approach vary between 33% and 70%, while the median progression-free survival spans 18 to 22.7 months [63–65]. A retrospective study assessed the efficacy of temozolomide monotherapy in 31 patients with metastatic lung neuroendocrine tumors, achieving a response rate (RR) of 14% and median progression-free survival (PFS) of 5.3 to 13 months [66]. Another study evaluated the effectiveness of a combination therapy of temozolomide and capecitabine in 20 patients with lung NETs, demonstrating an RR of 30% and a median PFS of 13 months [67]. These findings suggest reduced efficacy of TEMCAP in lung carcinoids compared with GEPNETs, contrary to the results of other studies. A recent multicenter trial indicated that the origin of the primary tumor did not exhibit a statistically significant influence on the efficacy of combination therapy; however, the line of treatment in which it was employed displayed a notable impact [68].

3.5. Immunotherapy in LNETs and GEPNETs

Immunotherapy has greatly enhanced the therapeutic landscape of lung cancer, but its efficacy in treating gastrointestinal carcinomas is limited. Specific patient populations, such as those with MSS-deficient tumors, may derive greater benefits from immunotherapy for gastrointestinal carcinomas. Studies have investigated the effectiveness of immunotherapy in LNETs and GEPNETs with varying results (Table 2).

Table 2. Overview of Immune Checkpoint Inhibitor Trials in Neuroendocrine Tumors Across Different Organs.

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Drug	Line	ORR LNETs	ORR GI NETs	ORR panNETs
Pembrolizumab	≥ 2	NR	2%	7.5%
Pembrolizumab	≥ 2	12.0%	NI	6.3%
Durvalumab plus tremelimumab	≥ 2	11.1%	0.0%	6.3%
Spartalizumab	≥ 2	16.7%	3.1%	3.0%
Avelumab	≥ 1	No objective responses in NETs		
Toripalimab	≥ 2	NR	13.0%	22.2%
Ipilimumab plus nivolumab	≥ 1	No objective responses in NETs		
Nivolumab plus Temozolomide	≥ 1	64%	NR	67%
Atezolizumab plus Bevacizumab	≥ 3	NR	NR	20%

Table 2 ORR: Overall Response Rate, LNETs: Lung neuroendocrine tumors, GI NETs: gastrointestinal neuroendocrine tumors, panNETs: pancreatic neuroendocrine tumors, NR: not reported, NI: not included.

The Dune study was conducted in a multicenter setting to evaluate the efficacy of durvalumab in combination with tremelimumab for various types of neuroendocrine tumours, including lung neuroendocrine tumours. Patients with typical and atypical carcinoids (Lung NETs) demonstrated the highest overall response rate (ORR), with no statistically significant difference in progression-free survival (PFS) between Lung NETs and other groups, such as gastrointestinal and pancreatic NETs. However, in terms of overall survival, patients with Lung NETs experienced a greater benefit than those in other study groups [69].

Pembrolizumab has been investigated in neuroendocrine neoplasms in the KEYNOTE-028 and KEYNOTE-158 clinical trials using varying dosing schedules [70,71]. Despite this, both studies enrolled patients with neuroendocrine neoplasms of lung and gastrointestinal origins. In both trials, pembrolizumab was administered as solitary therapy and not in combination with any other medication. In both studies, the overall response rate (ORR) was markedly superior for lung neuroendocrine compared to gastrointestinal or pancreatic NETs, with nearly twice the proportion of patients responding favorably to immunotherapy. The treatment also had a good toxicity profile, with rates similar to those reported in clinical studies on other neoplasms.

Spartalizumab has been evaluated as a monotherapy for the treatment of neuroendocrine tumors, demonstrating varying levels of efficacy depending on the origin of the tumor. Specifically, the overall response rate for lung carcinoids was 16.7%, whereas that for GEPNET was 3%. These findings indicate that immune responses differed markedly between the two groups [72].

Toripalimab is another immune checkpoint inhibitor that has demonstrated objective response rates (ORR) in individuals with neuroendocrine tumors. In accordance with the tissue origin, the ORR for pancreatic GI-derived, pancreatic NENs, and non-digestive NENs were 13.0%, 22.2%, and 37.5%, respectively. Furthermore, the response rates for poorly and well-differentiated NETs are 18.7% and 25%, respectively [73].

In the NET-001 and NET-002 trials, 21 patients with GEPNET and six patients with neuroendocrine lung carcinomas were administered avelumab monotherapy, although patients with typical carcinoids were excluded from the study. No objective responses were observed in either of the groups. Nevertheless, stable disease was achieved in 33% of patients, and the disease control rate at six months was 21% [74]. In the DART SWOG 1609 study, which examined the combination of Nivolumab with Ipilimumab in both well-differentiated NETs and NECs, no objective responses were observed in NETs regardless of their origin [75].

In the study NCT03728361, the efficacy of Nivolumab in combination with Temozolomide was evaluated in NETs as well as neuroendocrine carcinomas originating from various organsThe study

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confirmed that patients with LNETs showed a greater benefit compared to those with NETs from other organs (lung vs. others, p = 0.020). An overall response rate of 32% was observed, including a 64% response rate in patients with lung neuroendocrine neoplasms. Responses were observed in patients with both NET and NEC, but confirmed responses were observed only in patients with lung and pancreatic tumors. Exploratory immune cell profiling revealed an increase in circulating CD8+ T cells and decrease in CD4+ T cells during treatment [76].

The clinical trial NCT03074513 was conducted to evaluate the efficacy of atezolizumab in combination with bevacizumab in patients with advanced, progressive grade 1–2 neuroendocrine tumors. A total of 40 patients were enrolled, including 20 with pancreatic neuroendocrine tumors and 20 with extrapancreatic neuroendocrine tumors (epNETs), and five of them had LNETs. The results showed that 20% of the patients with pNETs and 20% of those with epNETs achieved an objective response. Additionally, this study found that PD-L1 expression in greater than 1% of tumor cells by immunohistochemistry may be associated with efficacy [77].

4. Discussion

The growing recognition of the specific genetic and molecular that distinguishes LNETs from GEPNETs highlights the need for a precision medicine approach tailored to the individual characteristics of each tumor type. This tailored approach is essential for improving diagnostic accuracy and therapeutic effectiveness. The variation in their responses to treatments such as somatostatin analogs, peptide receptor radionuclide therapy (PRRT), chemotherapy, and immunotherapy also underscores the biological differences between the two tumor types and argues against a universal treatment approach.

Additionally, the tumor microenvironment of LNETs and GEPNETs varies significantly, with significant differences in immune system cell concentration and composition. These discrepancies are particularly important in the context of immunotherapy, where LNETs generally display higher response rates than GEPNETs, except for pancreatic NETs. Moreover, the presence of spread through air spaces (STAS) in LNETs distinguishes them from GEPNETs and highlights the need for specific translational approaches to understand the unique pathophysiological mechanisms that contribute to the carcinogenesis of these diseases.

Future Directions and Conclusions

In the future, it is essential to recognize that neuroendocrine tumors exhibit distinct characteristics based on their origin, necessitating a departure from conventional classification and treatment strategies. This nuanced understanding can inform the design of more effective clinical trials and therapeutic strategies, particularly as we explore the potential of targeting specific molecular pathways such as EGFR and DLL3, which present promising avenues for innovative treatments. The differential expression of EGFR in pulmonary NETs, despite the absence of detectable targetable mutations, and the emerging role of DLL3 as a therapeutic target in advanced and metastatic neuroendocrine tumors, highlights the evolving landscape of treatment options. Furthermore, incorporating STAS into patient assessment for lung NETs could enhance both risk evaluation and therapeutic decision making.

To achieve more successful outcomes with combination therapies, it is crucial to design trials that recognize the disparities between LNETs and GEPNETs. By classifying NETs based on their origin and distinct molecular characteristics, it may be possible to develop more effective combination treatment options that maximize therapeutic benefits and minimize toxicity. Adopting a paradigm shift towards individualized treatment strategies, grounded in a comprehensive understanding of the unique aspects of LNETs and GEPNETs, is essential for advancing the field of neuroendocrine tumor research and care.

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