The Oncologist, 2022, **27**, 940–951
https://doi.org/10.1093/oncolo/oyac161
Advance access publication 19 August 2022
Review Article

DLL3 as an Emerging Target for the Treatment of Neuroendocrine Neoplasms

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Abstract

Introduction: Neuroendocrine neoplasms (NEN) are heterogeneous malignancies that can arise at almost any anatomical site and are classified as biologically distinct well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC). Current systemic therapies for advanced disease, including targeted therapies, chemotherapy, and immunotherapy, are associated with limited duration of response. New therapeutic targets are needed. One promising target is delta-like ligand 3 (DLL3), an inhibitory ligand of the Notch receptor whose overexpression on the surface of NEN is associated with tumorigenesis.

Methods: This article is a narrative review that highlights the role of DLL3 in NEN progression and prognosis, the potential for therapeutic targeting of DLL3, and ongoing studies of DLL3-targeting therapies. Classification, incidence, pathogenesis, and current management of NEN are reviewed to provide biological context and illustrate the unmet clinical needs.

Discussion: DLL3 is overexpressed in many NENs, implicated in tumor progression, and is typically associated with poor clinical outcomes, particularly in patients with NEC. Targeted therapies using DLL3 as a homing beacon for cytotoxic activity mediated via several different mechanisms (eg, antibody-drug conjugates, T-cell engager molecules, CAR-Ts) have shown promising clinical activity in small-cell lung cancer (SCLC). DLL3 may be a clinically actionable target across NEN.

Conclusions: Current treatment options for NEN do not provide sustained responses. DLL3 is expressed on the cell surface of many NEN types and is associated with poor clinical outcomes. Initial clinical studies targeting DLL3 therapeutically in SCLC have been promising, and additional studies are expanding this approach to the broader group of NEN.

Key words: neuroendocrine tumors; neuroendocrine carcinoma; DLL3 protein, human; molecular targeted therapy.

Implications for Practice

Neuroendocrine neoplasms (NEN) are a heterogeneous group of tumors, most commonly located in the gastrointestinal tract, lung, bronchi, thymus, and pancreas. NENs are classified as well-differentiated neuroendocrine tumors (NET) or poorly differentiated neuroendocrine carcinomas (NEC). Targeted therapies, chemotherapy, and immune therapies have demonstrated clinical activity in NEN, but further improvements in response duration and survival are needed. Delta-like ligand 3 (DLL3) is overexpressed in many NENs, implicated in tumor progression, and associated with poor clinical outcomes, especially in patients with NEC. DLL3-targeting therapies are currently under clinical investigation, with promising antitumor activity demonstrated to date.

Received: 30 March 2022; Accepted: 1 July 2022.

Introduction

Neuroendocrine neoplasms (NEN) are a heterogeneous group of tumors defined by National Comprehensive Cancer Network criteria as having traits of both endocrine and nervous system tissues, and World Health Organization criteria as being of epithelial or neuronal/neuroectodermal origin.[1,2] NEN can form in almost every organ, but most commonly arise in the gastrointestinal tract, lung, bronchi, thymus, and pancreas.[3-5] They are typically characterized by neurosecretory granules as well as histology and immunoprofiles/protein expression profiles, depending on differentiation.[2,5] NEN are classified as well-differentiated neuroendocrine tumors (NET) and poorly differentiated neuroendocrine carcinomas (NEC).[2,6] This review describes NEN classification, incidence, pathogenesis, and current management, focusing on delta-like ligand 3 (DLL3) in NEN progression and prognosis. Therapeutic targeting of DLL3 is addressed, and ongoing studies of DLL3-targeting therapies are summarized.

Small-cell lung cancer (SCLC) is a poorly differentiated NEC, which is often discussed separately from other NEN because of differences in epidemiology, genetics, treatment, and prognosis.[1] The disease state section of this review focuses on NEN other than SCLC, providing some discussion of SCLC when included in a given analysis. The sections on DLL3 prevalence and DLL3-targeting therapies specifically include SCLC, as much of the understanding of DLL3 as a therapeutic target originated in SCLC, thus providing context for targeting DLL3 in NEN.

Methods

The authors performed a narrative review of relevant academic English language literature. Levels of evidence were not assessed. The review is limited to published data and data presented at scientific congresses.

Overview of NEN

Classification

NET and NEC are biologically distinct, with different morphological characteristics, risk factors, genetics, and clinical aggressiveness.[2,5] Essential features discriminating NET and NEC are histological tumor differentiation and grade, assessed by mitotic count and Ki-67 proliferation index (Table 1).[1,2,6-15] NET are well differentiated and can range from low- to high-grade tumors. Grade 1 (G1) NET are defined as well-differentiated low-grade tumors; G2 NET are well-differentiated intermediate-grade tumors; G3 NET, most frequently occurring in the pancreas, are well-differentiated high-grade tumors with >20% proliferative activity or high mitotic rate.[1] NEC are poorly differentiated and high-grade by definition. NEC are either large-cell (LCNEC) or small-cell NEC.

Mixed neuroendocrine–non-neuroendocrine neoplasms (MiNEN) also occur, having an aggressive course, with the non-neuroendocrine component frequently displaying as an adenocarcinoma or squamous cell carcinoma.[7,9] In most MiNEN, the neuroendocrine and non-neuroendocrine components are poorly differentiated; the neuroendocrine component proliferates at rates similar to other NEC.[1,6]

Treatment-emergent NEN describes those non-neuroendocrine cancers, such as prostate and lung cancers, that develop neuroendocrine features following treatment.[2] NEN are rarely present at initial diagnosis, but targeted therapy may be associated with neuroendocrine transformation.[16-18] Treatment-emergent neuroendocrine prostate cancers (NEPC) are most similar morphologically and genomically to poorly differentiated NEC and are typically characterized by small cells with prominent nuclei and rapid proliferation (small-cell carcinoma).[17,19,20] The limited cytoplasm contains eosinophilic granules, hyperchromatic nucleus, and salt-and-pepper chromatin.[17,21] Mixed histologies also can be observed.

Incidence

The 2012 US incidence of neuroendocrine tumors was estimated at 6.98 cases/100 000 people based on an analysis of data from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) registry.[3] Common sites of NET vary according to race or ethnic group.[4,22] Based on SEER data, Asian/Pacific Island and American Indian/Alaskan Native patients had a lower incidence of NET than White patients; African American patients had a higher incidence across all sites.[4] Similarly, age-adjusted incidence rates of NET, particularly small intestinal and rectal, were significantly higher in the SEER African American population than in the SEER/Norwegian Registry of Cancer White population.[22] Based on SEER data, Asian/Pacific Island and American Indian/Alaskan Native patients had a lower incidence of NEC than White and African American patients.

NEN most commonly arises from gastroenteropancreatic (GEP) structures. A SEER study of GEP NECs found that 38% were in the colon, rectum, or anus, while 23% started in the pancreas. A SEER study of GEP NETs found the rectum to be the most common primary site followed by the small intestine and pancreas, while studies from Asia and Europe found different rank orders.[23]

NEN are experienced by men and women at similar rates.[24] However, primary NEN locations vary significantly by sex, with females more likely to have primary tumors in the lung, stomach, appendix, or cecum and males in the thymus, duodenum, pancreas, jejunum/ileum, or rectum.[4]

Pathogenesis

Most NEN arise sporadically, typically as unifocal tumors, but 5-30% have an inherited component and are typically multifocal.[1,25,26] NET and NEC can be distinguished by the genomic landscape in addition to histological features. Mutations associated with >7% of pancreatic NET include *MEN1*, *DAXX*, *ATRX*, *PTEN*, and genes in the mTOR signaling pathway.[2,27] Clinically sporadic pancreatic NET have also been shown to be associated with germline mutations in DNA repair genes *MUTYH*, *CHEK2*, and *BRCA2*.[11,12,14] Recurrent mutations for well-differentiated NETs of other sites have not been well defined, although significant enrichments in *APC*, *TP53*, *KRAS*, or *BRAF* in NEC compared to G3 NET have been suggested as potential classifiers.[28] Large-scale chromosomal instability is common, with chromatin-remodeling genes and subunits of the SWI/SNF complex mutated in 40% and >20% of pulmonary NETs, respectively.[29] Specific patterns of chromosomal gain and loss appear to have independent prognostic values in NET subtypes.[30] Mutations associated with NEC include *TP53* or *RB1* mutations, with *KRAS* and *SMAD4* mutations also identified.[2,6,11] *BRAF* mutations have been identified in colorectal NEN.[15] In gastroenteropancreatic NEC

Table 1. Characteristics, classification, and grading criteria for NEN.[1,2,6-15] Adapted from Nagtegaal et al.[6]

	NET, G1	NET, G2	NET, G3[a]	NEC, SCNEC	NEC, LCNEC	MiNEN
Grade	Low	Intermediate	High	High[b]	High[b]	Variable[c]
Mitotic rate,[d] mitoses/2 mm^2	<2	2-20	>20	>20	>20	Variable[c]
Ki-67 index,[e] %	<3	3-20	>20	>20	>20	Variable[c]
Differentiation	Well differentiated	Well differentiated	Well differentiated	Poorly differentiated	Poorly differentiated	Well or poorly differentiated[c]
Additional characteristics	Produce secretory granules with high levels of neuroendocrine markers, and are characterized by well-developed "organoid" arrangements or neuroendocrine shape with nesting, trabecular, or gyriform/serpentine growth pattern			Characterized by a sheetlike proliferation pattern, with cells that have irregular nuclei, high mitotic features, fewer cytoplasmic secretory granules, and low levels of neuroendocrine markers		Mixed neuroendocrine and non-neuroendocrine histology
Commonly associated mutations	*MEN1*, *DAXX, PTEN*, and *ATRX*, and mTOR family member signaling pathway mutations are observed in pancreatic NETs; NOTCH1 is absent or poorly expressed Some sporadic pancreatic NETs have been shown to harbor germline mutations in the DNA repair genes *MUTYH*, *CHEK2*, and *BRCA2*			*TP53* or *RB1* mutations May also have *KRAS* and *SMAD4* mutations *BRAF* mutations in colorectal NEC		NOTCH1 and Hes1 expression is reduced or absent in the neuroendocrine cells, but both expressed in the adenomatous component The most frequent alterations occurred in *TP53*, *RB1, PTEN, APC, PIK3CA, KRAS, BRAF,* and MYC

[a]Only includes gastrointestinal and pancreatic NETs.
[b]Poorly differentiated NEC are not formally graded, but are considered high-grade by definition.
[c]In most MiNENs, both the neuroendocrine and non-neuroendocrine components are poorly differentiated, and the neuroendocrine component has proliferation indices in the same range as other NECs; this MiNEN category allows for one or both components to be well differentiated; when feasible, each component should therefore be graded separately.
[d]Mitotic rates are to be expressed as the number of mitoses/2 mm^2 as determined by counting in 50 fields of 0.2 mm^2 (i.e., in a total area of 10 mm^2).
[e]The Ki-67 proliferation index value is determined by counting at least 500 cells in the regions of highest labelling (hot-spots), which are identified at scanning magnification; the final grade is based on whichever of the 2 proliferation indexes places the neoplasm in the higher-grade category.
Abbreviations: DLL3, delta-like ligand 3; LCNEC, large-cell neuroendocrine carcinoma; MiNEN, mixed neuroendocrine–non-neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; SCNEC, small-cell neuroendocrine carcinoma.

and SCLC, molecular subtypes based on differential expression of A*SCL1, NEUROD1, POU2F3*, and other genes have been described.[31-33] De novo neuroendocrine bladder cancers are strongly associated with mutations characteristic of neuroendocrine or small-cell cancers, such as SOX2, EZH2, and RB/p53 pathway mutations.[34]

In addition to the expression of NEN-associated markers, treatment-emergent NEPC is associated with decreased androgen receptor and/or prostate-specific antigen (PSA) expression.[16,17,21,35] Transformed NEPC shares genomic features with prostate adenocarcinoma. *RB1* and *TP53* mutations are associated with the risk of transformation in prostate cancers and in a unique subset of *EGFR*-mutant lung cancers, with attenuated androgen receptor signaling through a reduction in androgen receptor splice variant 7 in castration-resistant NEPC.[36,37] Preliminary evidence suggests lower rates of *TMPRES-ERG* gene fusions in NEPC than prostate adenocarcinoma.[37] Mutations and/or copy number loss in DNA repair pathway genes were almost exclusive to treatment-emergent NEPC versus non–treatment-emergent tumors.[16] Transformation of metastatic castration-resistant prostate cancer (CRPC) to treatment-emergent small-cell NEPC was associated with *RB1* inactivation.[38]

Evolution and Prognosis

NET can evolve from G1 to G3 and eventually toward poorly differentiated NEC.[39-41] Prognosis in patients with NEN varies by tumor type, stage and grade, and age at diagnosis. Generally, a worse prognosis is associated with tumors originating in the lung; those with liver, brain, or bone metastasis; higher grade/stage of tumor; and older age at diagnosis.[3,42-44] Gastroenteropancreatic NET and NEC have differences in terms of prognosis; patients with gastroenteropancreatic NEC commonly develop distant metastasis, are characterized by rapid tumor growth, and have lower survival than patients with gastroenteropancreatic NET.[45]

Treatment-emergent NEC is associated with shorter survival and limited response to therapies.[16,18] Treatment-emergent NEPC was associated with shorter median overall survival (OS) and progression-free survival (PFS) than mixed histology disease[35] or metastatic CRPC.[21]

Current Management

Recommended treatments for NEN vary by subtype, stage/differentiation, and biologic characteristics.[1,42,46] Herein, systemic therapies for advanced disease are described.

Somatostatin analogues have been used for symptomatic management of NETs[47,48] and their antiproliferative effects.[46,49,50] Octreotide and lanreotide, targeting somatostatin receptors (SSTR) 2 and 5, prolonged time to tumor progression or PFS in patients with well-differentiated midgut, hindgut, pancreatic, and G1/2 enteropancreatic NETs[49,50]; however, OS was not improved in long-term trials.[50,51] In addition, lanreotide prolonged PFS and objective response rate (ORR) in patients with advanced bronchopulmonary NET.[52] The radiolabeled somatostatin analog, lutetium ^{177}Lu dotatate (LUTATHERA), is approved for SSTR-positive gastroenteropancreatic NETs.[53] ^{177}Lu dotatate plus standard-dose octreotide improved ORR (18%) and PFS compared to high-dose long-acting octreotide in patients with advanced midgut

NETs after progression on somatostatin analogues, but not OS.[54,55] Low or weak SSTR expression in many NEC[56] and transient responses in SSTR-positive tumors could present challenges for ^{177}Lu dotatate. The multi-tyrosine kinase inhibitor (TKI) sunitinib targets VEGFR 1-3 and is approved in patients with advanced, well-differentiated pancreatic NETs, providing improved PFS and an ORR of 9%.[57,58] A more recent TKI, surufatinib, was associated with improved PFS in extrapancreatic and pancreatic NETs.[57,59-62]

The PI3K/Akt/mTOR pathway plays a critical role in NEN pathogenesis, and clinical trials of inhibitors that target this signaling axis support the promise of this approach.[63] Everolimus is an approved therapy in adults with progressive gastrointestinal, pancreatic, and lung NETs, based on RADIANT-3 and -4 trials demonstrating PFS prolongation.[64-66] In RADIANT-2, everolimus plus octreotide improved median PFS, narrowly missing statistical significance versus placebo plus octreotide.[67,68] Currently, temozolomide-based chemotherapy and streptozotocin/5-FU are among the most well-established therapies for pancreatic well-differentiated NET and are associated with higher ORR than targeted agents.[69,70] Platinum-based chemotherapy is standard-of-care for poorly differentiated NEC, but second- and third-line treatment options are limited and generally associated with short duration of response.[51,71] Second-line options typically include the reintroduction of platinum chemotherapy and etoposide, irinotecan-based treatment (FOLFIRI),[72] and oxaliplatin-based treatments (FOLFOX).[73] The efficacy of second-line regimens is variable in G3 NET,[40,74] although functional imaging and timing of G3 NET diagnosis may aid in treatment selection.[41] FOLFOX has shown activity in poorly differentiated G3 NEC after cisplatinum-based chemotherapy.[73] Platinum-based therapy provided a better response in patients with NEC than in those with G3 NET; however, the duration of PFS (~5 months) and OS (~9 months) in NEC remained poor.[71,75]

Nivolumab in combination with ipilimumab may be considered in patients with progressive G3 NET and NEC,[1] with response rates up to 31-44% among patients with high-grade NEN,[76,77] and 33% in patients with atypical bronchial carcinoid.[76] In contrast, objective response was 0% in low-/intermediate-grade non-pancreatic NEN tumors.[77] In high-grade NEC independent of the primary organ site, objective response was reported in 5/19 (26%) patients, with a clinical benefit rate of 32%.[78] More recently, lower response rates were observed in a larger study in gastroenteropancreatic NEC and lung LCNEC (8 weeks: 14.9%).[79] It remains unclear which patients benefit from immunotherapy.

Despite some improvement in outcomes, an unmet need exists for novel therapies with increased response durability and survival, particularly in highly proliferating G3 NEN with poor prognosis.

DLL3 Signaling in NEN Tumorigenesis

Tumorigenesis of Notch1, DLL3 in NEN

The Notch pathway is a highly conserved cell signaling pathway that is implicated in malignant transformation, cell proliferation, cycle arrest, and apoptosis, epithelial to mesenchymal transition, and suppression of neuroendocrine differentiation.[80] The Notch signaling pathway is initiated by the binding of one of five ligands (Jagged 1 [Jag 1], Jag 2, DLL1, DLL3, DLL4) with one of four receptors (Notch 1-4).[80-82] The DLL family of proteins interact with EGF repeats on Notch receptors on cell membranes, triggering Notch signaling.[11,83] In canonical Notch signaling, ligand binding results in the intracellular cleavage of the receptor by metalloproteases, and the Notch intracellular domain then translocates into the nucleus and modulates transcription of Notch-responsive genes.[82] Notch signaling can be oncogenic or tumor suppressive depending on the cellular context. DLL1 has a tumor-suppressive role in lung cancer and is poorly expressed in the bone marrow of patients with lung cancer. In contrast, DLL1 has an oncogenic role in breast cancer, and its overexpression is associated with a poorer prognosis. DLL4 has an oncogenic role in a range of cancers.[11,83] DLL3 is a noncanonical inhibitory ligand of the Notch receptor that is involved in NEC/NET tumorigenesis.[80] DLL3 is thought to inhibit Notch signaling in cis; it does not bind or activate Notch receptors when presented in trans.[84] In normal tissues, DLL3 is generally expressed at low levels (if at all) and confined to the cytoplasm.[85-88] It regulates Notch signaling by preventing the localization of Notch receptors to the cell surface and redirecting them to the endosomes for degradation.[85]

DLL3 and Notch in Development of NEN

DLL3 expression is regulated by achaete-scute complex homolog 1 (ASCL1),[83] a transcription factor that dictates neuroendocrine cell fate and whose expression correlates with tumor-initiating cell capacity.[89] Upregulation of ASCL1 in *RB1*-mutated high-grade pulmonary NEC (SCLC and LCNEC) was associated with DLL3 overexpression compared with normal tissues. ASCL1 expression in SCLC is associated with DLL3 but negatively associated with Notch expression.[90] DLL3 is expressed on the surface of tumor cells, in addition to having cytoplasmic localization.[86-88] By modulating Notch1, DLL3 promotes migration and invasion in SCLC.[91] Conversely, Notch pathway activation was associated with low neuroendocrine differentiation and increased intrinsic tumor immunity in SCLC cells.[92] Both ASCL1 and DLL3 are highly expressed in NEPC. These were among the most differentially expressed Notch signaling genes in NEPC cells compared with adenocarcinoma, localized prostate adenocarcinoma, or benign cells.[93] Additionally, upregulated DLL3 expression in patients with gastrointestinal or bladder/urinary tract NECs was strongly associated with ASCL1 expression.[94] Notch2 and DLL3 were upregulated in patients with invasive versus non-invasive growth hormone–producing pituitary adenoma ($P < .05$).[95]

DLL3 and Inflammatory Biomarkers in NEN

The relationship between DLL3 expression and tumor immune environment may be complex. In consecutive surgically resected lung NEN, neoplasms with high DLL3 expression were often high-grade and more often displayed a moderate-to-severe inflammatory infiltrate than their low-expressing counterparts (65.6% vs. 27.7%).[97] This inflamed state may suggest that T-cell-based therapies could have improved efficacy in these tumors. On the other hand, studies in SCLC found that DLL3 levels varied between transcriptional subtypes and were lowest in a subtype characterized by expression of numerous immune checkpoints and human leukocyte antigens, designated the SCLC-inflamed subtype (SCLC-I).[32,33] The authors found that this inflamed subtype was associated with better responses to immune checkpoint blockade (ICB), raising the question of whether the patient

populations benefiting from ICB and DLL3-targeted therapies will be non-overlapping. A gene expression analysis in neuroendocrine bladder cancer (NEBC) found DLL3 expression to correlate with neuronal differentiation genes and high response rates in patients treated with atezolizumab.[34] Surprisingly, immune pathway gene expression signatures normally enriched in tumors sensitive to immune checkpoint blockade were suppressed in these NEBCs. In total, these examples in differing neuroendocrine tumors highlight the need for further study of the immune system in DLL3-positive NEN. Future studies will be needed to determine if DLL3 expression correlates with expression of inflammatory biomarkers, if DLL3 has a role in immune infiltration into NENs, and whether DLL3 expression is prognostic for ICB response.

DLL3 Expression in NEN

Across nonneoplastic tissues, DLL3 expression is generally absent or low and confined to the cytoplasm.[86,96] Numerous studies have established DLL3 mRNA and protein expression as features of NEN across several anatomic sites. DLL3 is particularly highly expressed in high-grade NETs and NECs, including on the tumor cell surface (described below). Representative prevalence of DLL3 by immunohistochemical (IHC) analysis according to NEN type and site is shown in Fig. 1[89,93,97-109]; representative DLL3 staining with lung NEN and NEPC as examples is shown in Fig. 2.[97,104]

DLL3 protein expression by IHC analysis is most consistently defined as negative (<1% positive tumor cells), positive (>1%), low expressing (<50%), or high expressing (>50%).[97,98,101,102,110-112] H scores (range 0-300), combining the percentage of DLL3-expressing cells and signal intensity, quantify DLL3 expression.[93,101] However, variability in quantification between studies is likely partially due to the use of different assays or cutoffs. In addition to tissue-based detection methods, blood-based biomarkers are being developed, such as specific neuroendocrine-related transcripts or circulating tumor cells, which could enable earlier and easier identification of patients most likely to respond to targeted therapies.[93,113-115]

Prevalence in NET

High DLL3 expression is frequently observed in high-grade NEN and less frequently in low-grade, well-differentiated NET.[97] Of 155 patients with lung NET, high DLL3 was observed in 12.2% of typical and 24.4% of atypical carcinoids (ie, low-grade tumors).[97] In 47 patients with gastroenteropancreatic NENs, DLL3 was detected in 76.9% of NECs, whereas DLL3 was absent in the 5 patients with G3 NET.[102]

Prevalence in NEC

Pulmonary NEC and SCLC

DLL3 expression has been investigated extensively in SCLC. High DLL3 protein expression with localization to the cytoplasm and/or membrane was demonstrated by IHC analysis in patients with SCLC.[96] Others reported DLL3 staining primarily in the Golgi apparatus and plasma membrane.[111] High DLL3 expression was observed in the majority of patients with extensive-stage SCLC.[90,116] Chinese patients with SCLC also had significantly higher DLL3 expression in SCLC tissue compared with matched para-noncancerous tissues.[117] Analyses from clinical trial populations demonstrate that DLL3 is expressed in >75% of SCLC.[110,118,119]

LCNEC is associated with high DLL3 expression.[120] In patients with LCNEC, 26/70 (37.1%) were DLL3 positive. The disease was stage I in 15 and 26 DLL3-positive and negative patients, respectively; stage II in 4 and 11; and stage III in 7 and 7 patients.[109] By IHC analysis, DLL3 expression was observed in 82% of 45 patients with SCLC, LCNEC, or neuroendocrine carcinoma with mixed histology.[99] A high percentage (75%) of stage IV LCNEC shows DLL3 expression, with the majority being cytoplasmic.[98] Similarly, IHC analysis of 73 patients revealed high DLL3 expression in 54% of patients with LCNEC and 75% with SCLC.[97]

NEPC

DLL3 is expressed in NEPC.[93,104] DLL3 was expressed in most patients with castration-resistant NEPC (n = 36/47 [76.6%]), but only a subset of those with CRPC adenocarcinoma (n = 7/56 [12.5%]).[93] Another study using 21 NEPC tumor samples reported 16 (76%) were DLL3-positive.[104]

Other NEC

DLL3 expression was demonstrated in gastroenteropancreatic, bladder, and cervical NEN.[34,102,103] In a retrospective study of 47 patients, DLL3 was expressed on 76.9% of poorly differentiated gastroenteropancreatic NEC; DLL3 expression correlated with *RB1* loss (P < .001), a negative Ga-PET/CT scan (P = .001), and an unfavorable clinical outcome.[102]

In transcriptomic and protein analyses of 63 patients with small-cell bladder cancer, 79% had increased small-cell component (>50%), and DLL3 and CD56 protein expression (>1% of tumor cells) was 68% and 81%, respectively, in 53 patients with available samples.[103] Similarly, samples from patients with neuroendocrine bladder cancer showed strong enrichment with biomarkers characteristic of neuroendocrine or small-cell malignancies, including DLL3.[34] In patients with NEC of the cervix, DLL3 expression was found in 81% and was inversely correlated or mutually exclusive with other commonly observed mutations.[105] DLL3 expression was upregulated in 49% of patients with extra-pulmonary NEC (gastrointestinal tract, n = 4; bladder, n = 7).[94] Almost all patients with Merkel cell carcinoma (MCC; ~90%) had DLL3 expression, with over half having ≥50% tumor cells positive for DLL3 expression.[100,101]

DLL3 overexpression was also observed in patients with growth hormone–producing pituitary adenoma, with DLL3 more highly expressed in invasive versus non-invasive tumors.[95] Similarly, in medullary thyroid carcinoma, DLL3 expression correlated with stromal desmoplasia and lymph node metastases, and may indicate aggressive disease.[108] In DLL3-high tumors, protein distribution was primarily membranous; localization in DLL3-low tumors was primarily cytoplasmic.

Clinical Implications of DLL3 in NEN

High DLL3 expression is primarily associated with various NEC and extensive-/late-stage disease and is negatively correlated with survival in most studies.[102,111,112,116,120] Recent analysis of 155 samples of lung NENs found high DLL3 expression was more common in patients who smoked (current/former) and was associated with peripheral tumors.[97] High DLL3 expression was associated with lower OS

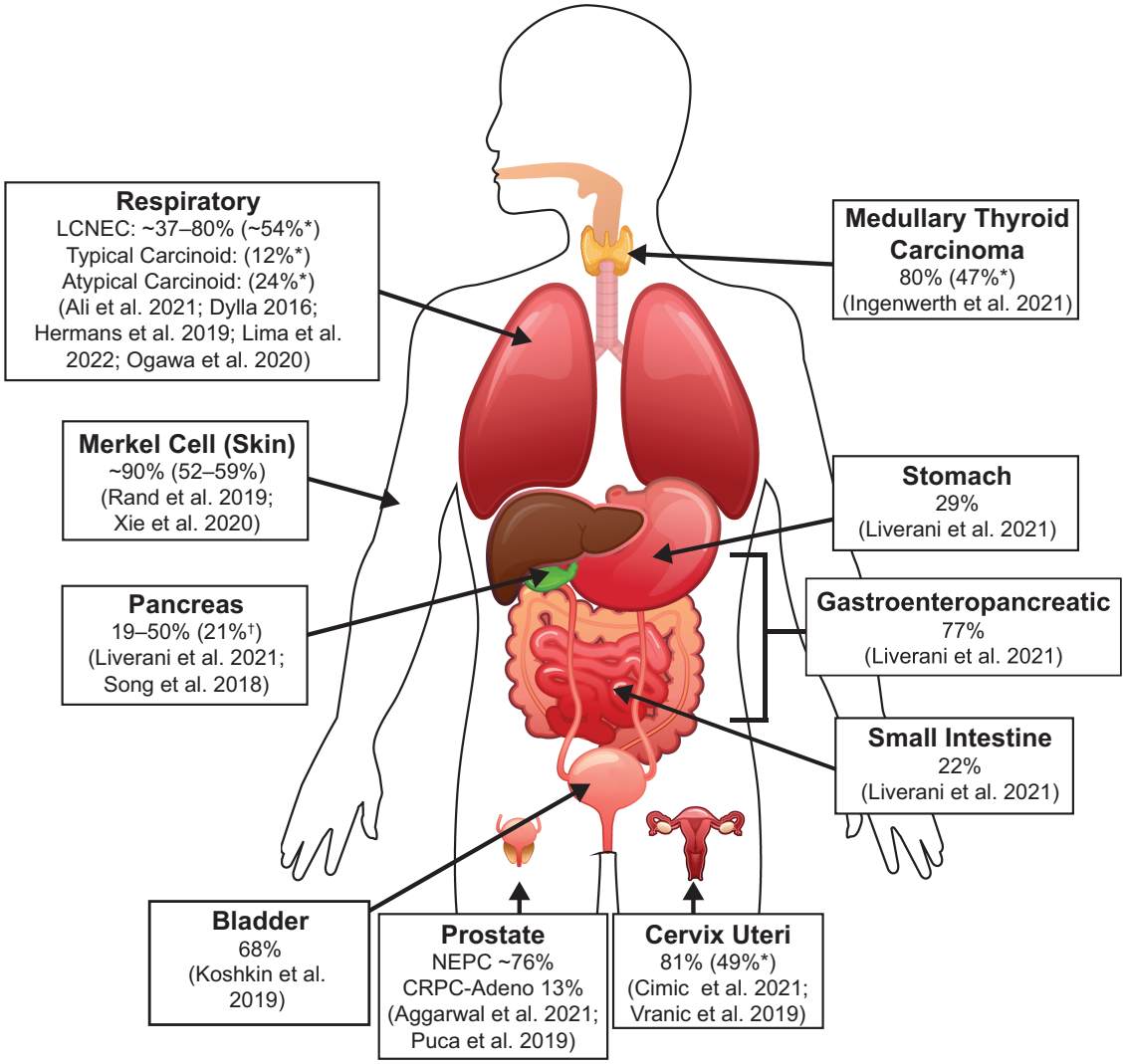

Figure 1. Representative DLL3 prevalence (ie, >1% DLL3-expressing cells) by immunohistochemistry in NEN tumors.[89,93,97-109]
*Prevalence of high DLL3 expression (ie, ≥50% of DLL3-expressing cells). †Strongly positive for DLL3.
Abbreviations: Adeno, adenocarcinoma; CRPC, castration-resistant prostate cancer; DLL3, delta-like ligand 3; LCNEC, large-cell neuroendocrine cancer; NEPC, neuroendocrine prostate cancer; NEN, neuroendocrine neoplasms.

(P = .001) and disease-free survival (DFS; P < .01). DLL3 expression correlated with other features associated with high-grade NEC (ie, high mitosis number, Ki-67 index, and necrosis). In 76 patients with growth hormone–producing pituitary adenoma, low DLL3 expression was associated with significantly longer DFS compared with high DLL3 expression (P = .027).[95] In patients with small-cell bladder cancer, low protein expression of both CD56 (≤30%) and DLL3 (≤10%) was associated with a longer median OS (103.4 vs. 18.4 months, P = .01) and PFS (92.2 vs. 11.4 months, P = .02) relative to patients with high expression of either biomarker.[103] In contrast, multivariate analysis in a preliminary study in archival lung NET (SCLC, n = 22; LCNEC, n = 6) found low ASCL1 and DLL3 expression presented high risk of death (OR=3.79; P = .05).[121]

However, DLL3 expression has not always been reported as a prognostic indicator.[111] In patients with SCLC, there was no difference in PFS (242.0 vs. 165.0 days, P = .900) or OS (160.0 vs. 250.0 days, P = .975) according to DLL3 expression.[116] Similarly, in a retrospective study of samples from 43 Chinese patients with SCLC, DLL3 expression was not associated with reduced DFS or OS.[117] In addition, analysis of 45 high-grade lung NET did not reveal any correlation between DLL3 expression and OS.[99]

Current therapies have a limited duration of response in G3 NET or NEC. Among patients with DLL3-positive surgically resected LCNEC, no difference was found in 5-year OS and relapse-free survival (RFS) between patients treated with versus without adjuvant chemotherapy (5-year OS, 58.3% vs. 35.7%, P = .36; 5-year RFS, 41.7% vs. 35.7%, P = .74). In contrast, in those with DLL3-negative tumors, a significantly greater 5-year OS and RFS was observed for patients treated with versus without adjuvant chemotherapy (5-year OS, 90.0% vs. 26.9%, P < .01; 5-year RFS, 80.0% vs. 21.7%, P < .01).[109]

DLL3-Targeting Therapies

Several different DLL3-targeting modalities are being pursued, including antibody-drug conjugates (ADC), T-cell engagers, and chimeric antigen receptor (CAR) T cells. Preclinical and clinical experience with some of these agents is summarized here.

Despite its development being terminated, Rova-T, an ADC consisting of a DLL3-targeting monoclonal antibody, cathepsin-cleavable linker, and pyrrolobenzodiazepine (PBD) warhead, demonstrated the potential of targeting DLL3.[86] Preclinical efficacy of Rova-T in combination with the mTOR inhibitor everolimus was demonstrated in pancreatic and bronchial NEN cell lines.[122] The first-in-human clinical trial of Rova-T in recurrent SCLC found an overall ORR of 18% in evaluable patients and 38% in patients with high DLL3 expression despite often severe side effects attributable to the PBD warhead.[110] However, in the phase II TRINITY study, Rova-T did not demonstrate differential benefits in DLL3-positive disease versus the overall population.[119]

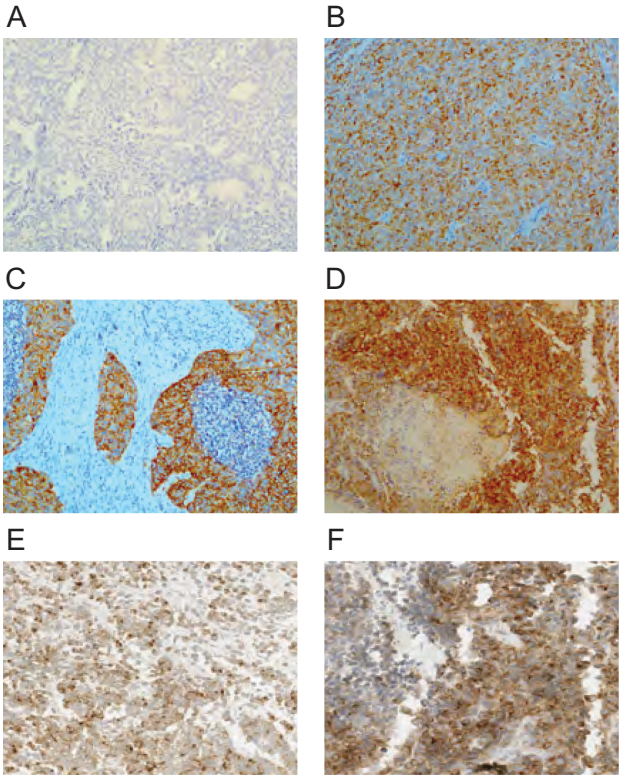

Figure 2. DLL3 immunohistochemical staining by the site of origin, including (**A-D**) Lung NET (reproduced with permission from Drs Ali, Di Stefano, Poma, Ricci, Proietti, Davini, Lucchi, Melfi, and Fontanini from their original publication in *Front Oncol*[97]), and (**E-F**) NEPC. Representative images showing variable percentages of DLL3 immunohistochemical staining in lung NET: (**A**) typical carcinoid DLL3 negative; (**B**) a case of atypical carcinoid showing combined cytoplasmic and membranous staining with moderate intensity; (**C**) Large-cell NEC with strong and diffuse DLL3 staining; (**D**) high (>50% positive tumor cells) immunohistochemical expression level of DLL3 in a small-cell lung carcinoma specimen (magnification, ×20) using rabbit anti-DLL3 antibody (clone SP347; Ventana Medical Systems, Inc. Tucson, AZ, USA); (**E**) adenocarcinoma with neuroendocrine component (H-score of 65, 80% positive cells) and (**F**) NEPC (H-score of 150, 90% positive cells) using rabbit anti-DLL3 antibody (clone SP347).[97,104]
Abbreviations: DLL3, delta-like ligand 3; NEC, neuroendocrine carcinoma; NEPC, neuroendocrine prostate cancer; NET, neuroendocrine tumor.

A phase I/II study of Rova-T was conducted in 101 patients with NEN (pulmonary and extrapulmonary LCNEC, *n* = 13; high-grade gastroenteropancreatic NEC, *n* = 36; NEPC, *n* = 21; pooled other NEC/NET, *n* = 31) and 99 patients with other solid tumors (melanoma, *n* = 20; medullary thyroid cancer, *n* = 13; glioblastoma, *n* = 23; other solid tumors, *n* = 43). Overall, confirmed responses were reported for 10% of patients treated at 0.3 mg/kg, including 13% with NEC/NET; the median PFS and OS were 4.1 (95% CI, 2.8-4.8) and 7.1 (95% CI, 5.6-9.7) months, respectively. Median PFS and OS were 4.3 (95% CI, 2.7-6.1) and 7.4 (95% CI, 5.6-13.1) months in patients with high DLL3 expression, and 3.3 (95% CI, 2.4-4.8) and 7.1 (95% CI, 4.3-9.9) months among patients with low DLL3 expression.[123] Similarly, treatment with Rova-T did not provide benefit compared with topotecan in the second-line setting for SCLC or as maintenance after induction etoposide/platinum in the first-line setting.[124,125]

Another DLL3-targeting ADC, SC-002, was designed to reduce the toxicity observed with Rova-T. In a phase Ia/Ib study in 35 patients with relapsed and/or refractory SCLC or LCNEC, 5 patients (14%) achieved a partial response as the best overall response; however, the toxicity profile of SC-002 prevented further development.[126]

The toxicities of Rova-T and SC-002 were primarily attributed to the cytotoxic warhead, suggesting that DLL3 remained a compelling target. Indeed, the DLL3-targeting bispecific T-cell engager (BiTE) molecule tarlatamab (AMG 757) has shown promising clinical activity, and the DLL3-targeting T-cell–engaging agents BI 764532 and HPN328 are under clinical investigation (Table 2).

Tarlatamab engages and redirects T cells to kill DLL3-expressing SCLC and other NET cells in vitro,[127] and induces antitumor activity in patient-derived xenograft and orthotopic NET mouse models in vivo.[88] In a phase I SCLC study, tarlatamab showed preliminary antitumor activity with confirmed partial responses in 20% of patients, with a median response duration of 8.7 months.[128] Additional ongoing studies of tarlatamab in SCLC include a phase II study in third-line and beyond patients (NCT05060016) and a phase I study in combination with a PD-1 inhibitor (NCT04885998). Tarlatamab is also being evaluated in a phase I study of NEPC patients.[104]

Table 2. Select ongoing clinical trials of DLL3-targeting therapies

Treatment	Study ID	Tumor type	Target enrollment, n	Phase (status)
Tarlatamab	NCT03319940	SCLC	382	Phase I (recruiting)
	NCT04702737	NEPC	60	Phase I (recruiting)
	NCT04885998	SCLC	50	Phase I (recruiting)
	NCT05060016	SCLC	160	Phase II (recruiting)
BI 764532	NCT04429087	SCLC and other NEN	110	Phase I (recruiting)
HPN328	NCT04471727	SCLC and other high-grade NET	57	Phase I/II (recruiting)

NET, neuroendocrine tumor; NEPC, neuroendocrine prostate cancer; SCLC, small-cell lung cancer.

BI 764532 is a DLL3-targeting T-cell–engaging bispecific antibody shown to selectively bind DLL3 on tumor cells and CD3 on T cells, resulting in T-cell activation and directed lysis of SCLC cells in vitro.[129] Treatment with BI 764532 resulted in infiltration of T cells into tumor tissue and tumor regression in xenograft models. BI 764532 is being studied in phase I in patients with DLL3-expressing SCLC, LCNEC, or other NEC or small-cell carcinoma of any other origin.[130] HPN328 is a tri-specific T-cell–activating construct that consists of 3 binding domains, namely, CD3 on T cells, DLL3 on tumor cells, and human serum albumin to extend half-life.[131] HPN328 mediated T-cell cytotoxicity against target cells in a dose- and DLL3-dependent manner. A phase I/II study in patients with DLL3-expressing SCLC or other high-grade NETs who have failed standard available therapy is currently recruiting patients.[132] CAR T cells targeting DLL3, including AMG 119 (NCT03392064), are also in clinical development.

Conclusions

NEN are a heterogeneous group of tumors most commonly located in the gastrointestinal tract, lung, bronchi, thymus, and pancreas. They are classified based on histology and grading as well-differentiated NET or poorly differentiated NEC. Though targeted therapies, chemotherapy, and, to a limited extent, immunotherapies confer some clinical benefit to patients with NEN, a need remains to identify new treatments associated with more sustained responses and improved survival particularly for high-grade (G3) NET and NEC. The recognition that DLL3 is enriched in high-grade NENs and associated with worse clinical outcomes opens these challenging tumors up to the promise of DLL3-targeting agents, some of which have already demonstrated clinical antitumor activity.

Acknowledgments

The authors thank Miranda Tradewell, Erin P. O'Keefe, Lisa Denny, Lee Hohaia (ICON, Blue Bell, PA), and Eugene Gillespie (Amgen Inc.), whose work was funded by Amgen Inc., for medical writing assistance in the preparation of this manuscript.

Funding

This study was sponsored and funded by Amgen Inc.

Conflict of Interest

James Yao: Hutchmed, Ipsen, Amgen, Chiasm (C/A); **Emily Bergsland:** Amgen, RayzeBio, Hutchmed, Advanced Accelerator Applications (C/A [unpaid]), Merck (RF [institutional]); **Rahul Aggarwal:** Clovis Oncology (H), Dendreon, Advanced Accelerator Applications, Clovis Oncology, Axiom Biotechnologies, AstraZeneca, Pfizer, Merck, Amgen, Jubliant Pharmaceuticals, Alessa Therapeutics (C/A), Zenith Epigenetics, Novartis, Xynomic Pharma, Cancer Targeted Technology, Janssen, Merck, AbbVie, Amgen, AstraZeneca, BioXCel Therapeutics (RF [institutional]); **Ana Aparicio:** Astellas, Janssen (C/A), American Cancer Society (education services); **Himisha Beltran:** Janssen, Astellas, AstraZeneca, Merck, Pfizer, Foundation Medicine, Blue Earth Diagnostics, Oncorus, Amgen (C/A), Janssen, AbbVie/Stemcentrx, Eli Lilly, Millennium Pharmaceuticals, Bristol Myers Squibb (RF), Amgen, Oncternal (SAB); **Judy S. Crabtree:** Amgen (SAB); **Christine L. Hann:** Janssen, AstraZeneca (C/A), Amgen, AbbVie, BMS, Genentech (RF [institutional]), Amgen (SAB); **Toni Ibrahim:** Amgen, Pharmamar (H, SAB); **Lauren A. Byers:** AstraZeneca, GenMab, Sierra Oncology, PharmaMar, AbbVie, Bristol Myers Squibb, Alethia, Merck, Pfizer, Jazz Pharmaceuticals, Genentech, Debiopharm Group (C/A), AstraZeneca, GenMab, Sierra Oncology, ToleroPharmaceuticals (RF); **Hironobu Sasano:** Novartis Oncology Japan, Teijin Pharm Co. Ltd., Nobel Pharma Co. Ltd. (RF, H); **John Umejiego:** Amgen (E, OI); **Marianne Pavel:** AAA, Ipsen, Novartis, Amgen, Lilly, Riemser (C/A), MSD, Boehringer Ingelheim, AAA, Ipsen, Novartis, Lilly (H), AAA, Crinetics (SAB).

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

Data analysis and interpretation, manuscript writing, and final approval of manuscript: All authors.

Data Availability

No data were generated for this article; published references are cited at the end of the article.

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