Oncology Learning Network

DLL3 Across Neuroendocrine Carcinomas

Biology – Expression – Testing – Emerging Clinical Relevance

Understanding High-Grade Neuroendocrine Carcinomas[1,2]

Neuroendocrine neoplasms (NENs)

Neuroendocrine tumors (NETs)
Well-differentiated

Neuroendocrine carcinomas (NECs)
Poorly-differentiated

Small Cell Lung Cancer (SCLC)

- Most commonly diagnosed NEC[4]
- Aggressive growth phenotype[3]
- Delta-like ligand 3 (DLL3) established biomarker[5]

Large Cell NEC (LCNEC)

- High-grade[3]
- Pulmonary origin site[3]
- Reduced sensitivity to standard-of-care treatment[3]

Extrapulmonary NEC (epNEC)

- Various GI/GU sites of origin[6]
- Small and large cell morphology[6]
- High unmet need[6]

DID YOU KNOW?

High-grade does not necessarily indicate NEC. Well-differentiated Grade 3 NETs are biologically distinct from poorly differentiated NECs.[3]

One family of aggressive NECs with distinct clinical contexts.

Although they arise in different anatomic sites, all 3 NEC subtypes are poorly differentiated, high-grade NECs characterized by high proliferative activity (typically Ki-67 ≥20%, often substantially higher), early metastatic spread, and reliance on platinum-based chemotherapy. DLL3 is a neuroendocrine lineage-associated protein that is aberrantly expressed across all 3 subtypes, supporting ongoing investigation of its biologic and potential therapeutic relevance.[1,3,4]

DLL3 Is an Emerging Therapeutic Biomarker Across NEC Subtypes

DID YOU KNOW?

DLL3 is an atypical inhibitory Notch ligand. Unlike canonical activating ligands, it suppresses Notch signaling. Most normal adult tissues exhibit minimal DLL3 expression, but aberrant overexpression is observed in many poorly differentiated NECs.[3]

DLL3 Expression by Subtype[8]

Normal Tissue
epNEC
NET
SCLC
LCNEC

Expression varies by tumor subtype, primary site, and scoring methodology, and may differ between primary and metastatic lesions and within individual tumors.[3,8]

SCLC
a) DLL3 protein expression in a representative SCLC specimen with 98% positive staining.[3]

Rudin et al. 2023. Fig 1. CC BY-NC-ND 4.0

LCNEC
b) DLL3 protein expression in LCNEC of the lung.[3]

epNEC
c, d) DLL3 protein expression in LCNEC from the uterine cervix (c) and small cell NEC from the bladder (d).[3]

Serrano et al. 2024. Fig 3. CC BY-NC-ND 4.0

Key Features of DLL3

- Minimal expression in normal adult tissue creates a favorable therapeutic window.[3]
- Expression is predominantly cytoplasmic, with variable membranous localization supporting therapeutic targeting.[3,6]
- DLL3 is an emerging therapeutic biomarker rather than a diagnostic marker—it complements, but does not replace synaptophysin, chromogranin A (CgA), INSM1, or Ki-67.[3,4]
- Negative next-generation sequencing result does not imply IHC negativity—detection of protein expression requires IHC staining.[3,10]

Current Clinical Landscape in epNEC

Why outcomes remain poor

- Aggressive biology[4]
- Frequent presentation at advanced stage[4]
- Initial platinum-based chemotherapy response often followed by rapid relapse[4]
- No validated predictive biomarkers for epNEC[6]
- epNEC-specific trial data remain limited compared with SCLC[6]

Why DLL3 emerged as a target

- Low expression in normal tissue[3]
- High prevalence in aggressive NECs[6]
- Cell surface expression enables antibody based therapies[6]
- Multiple treatment modalities feasible: BiTE, ADC, CAR-T, and bi-specific antibodies[6]

epNEC Treatment Pathway[1,11,12]

STEP 1
Biopsy/tissue acquisition

STEP 2
Histopathologic evaluation
H&E, morphology

STEP 3
Diagnostic IHC
Synaptophysin, Chromogranin A, INSM1, Ki-67, Site-of-origin markers

STEP 4
Integrated NEC diagnosis
SCLC, LCNEC, epNEC

STEP 5
Treatment

STEP 6
Relapsed/recurrent disease

STEP 7
DLL3 IHC assessment
when clinically appropriate

STEP 8
Treatment planning/ clinical trial eligibility

Evolution of DLL3 as a Biomarker

2009 — DLL3 first implicated in SCLC biology[13]

2014 — DLL3 established as part of the achaete-scute family bHLH transcription factor 1 (ASCL1) neuroendocrine program[14]

2015 — DLL3 recognized as a potential therapeutic biomarker[15]

2016–2020 — Initial DLL3-directed ADC development

2024 — Tarlatamab receives initial approval in SCLC[16]

2026 — No approved DLL3-directed therapy for epNEC[6]
Multiple epNEC trials currently enrolling[3]

Current and Emerging DLL3-Targeted Therapeutic Landscape[16-22]

Agent		Study	Tumor type	Phase	Patient selection
BiTEs	Tarlatamab	DeLLphi-304	SCLC (approved)	Approved	Relapsed/refractory (R/R) late-stage SCLC; no DLL3 expression required
	Obrixtamig	DeLLight	epNEC	Phase 2	R/R epNEC; no DLL3 threshold specified
	Obrixtamig + carboplatin/etoposide	DAREON-5	epNEC	Phase 2	R/R epNEC; DLL3-high ≥50% expression
	Obrixtamig + carboplatin/etoposide	DAREON-NEC-1	epNEC	Phase 3	Unresectable advanced/ metastatic epNEC; DLL3-positive per protocol
Bispecific antibodies	Peluntamig	SKYBRIDGE	epNEC	Phase 1-2	Advanced/metastatic epNEC; DLL3-positive
CAR-T	AMG 119	NCT03392064	SCLC	Phase 1	R/R SCLC

DLL3 IHC assays, scoring algorithms, and positivity thresholds continue to evolve. "DLL3-positive" and "DLL3-high" are not interchangeable. Interpret results using the validated assay, reporting framework, and intended clinical context.[3]

Where Pathologists Fit

- ✓ Accurate diagnosis and classification
- ✓ Tissue stewardship to preserve material for current and future biomarker testing
- ✓ DLL3 test result interpretation and reporting
- ✓ Support for clinical trial identification

Key Takeaways

DLL3 expression extends beyond SCLC into multiple high-grade NECs.[6]

DLL3 assessment complements—but does not replace—accurate pathologic classification.[3]

IHC remains the preferred method for DLL3 assessment; reliable interpretation depends on appropriate fixation and specimen quality.[3]

DLL3 assays are not currently standardized. Antibody clones, scoring algorithms, and positivity thresholds vary across studies.[3,23]

Pathologists play a central role in tissue stewardship, biomarker assessment, and clinical trial readiness.

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