Oncology Learning Network

The epNEC Biomarker Journey: Where Could DLL3 Fit?

A practical roadmap for pathologists navigating biomarker assessment in extrapulmonary neuroendocrine carcinoma

Diagnosis

Suspected high-grade neuroendocrine carcinoma (NEC)[1-3]

- Establish diagnosis using morphology (hematoxylin and eosin [H&E] staining)
- Confirm neuroendocrine differentiation
- Assess proliferation (Ki-67/mitotic activity)
- Obtain sufficient tissue for ancillary studies[4,5]
- Consider cell block approach when feasible[6]

Routine diagnostic markers:[3]

- Synaptophysin
- Chromogranin A
- Insulinoma-associated protein 1 (INSM1)
- Ki-67

Diagnosis precedes biomarker testing. Delta-like ligand 3 (DLL3) expression should not be used to establish a diagnosis of NEC.[3]

NEC Classification

Classify the Tumor[7]

- Confirm poorly differentiated NEC
- Determine site of origin when possible
- Distinguish from:
  - » Mixed neuroendocrine/ non-neuroendocrine neoplasm
  - » Metastatic small cell lung cancer
  - » Non-neuroendocrine mimics

Biomarker interpretation should follow—not replace—rigorous tumor classification.

Tissue Stewardship

Preserve tissue for current and future biomarker assessment[4]

- Maximize limited biopsy material while accounting for small biopsy limitations
- Prioritize clinically essential testing
- Ensure appropriate fixation and specimen quality
- Document specimen source

Thoughtful tissue stewardship supports both current diagnosis and future biomarker evaluation.

Biomarker Assessment

Emerging DLL3 Biomarker Evaluation[5]

- Assess DLL3 protein expression by immunohistochemistry (IHC).
- Interpret DLL3 expression using assay-specific scoring.
- Recognize potential heterogeneity in DLL3 expression.

Biomarker testing may be appropriate depending on:

✓ Clinical context[8] ✓ Disease stage[9] ✓ Available tissue[8] ✓ Clinical trial opportunities

DLL3 is an emerging biomarker of interest in high-grade NEC. Assessment is generally considered after diagnosis has been established and when clinically appropriate.

DLL3 ≠ Diagnostic marker | DLL3 = Complementary biomarker

Treatment Planning

Multidisciplinary Decision-Making

- Platinum-based chemotherapy remains the standard of care[10]
- Consider biomarker results in clinical context[11]
- Integrate pathology, biomarker, and clinical findings[10]
- Consider clinical trial eligibility when appropriate[10]

Pathology findings help inform multidisciplinary treatment planning.

Clinical Trial Evaluation

Patient Identification

Trial eligibility may depend on:[12]

- DLL3 biomarker expression threshold
- Assay used
- Previous lines of therapy

DLL3 expression requirements may vary across investigational studies.[12-15]

Clinical trial	Tumor type	DLL3 eligibility criteria
DAREON-5	R/R epNEC	DLL3-high (≥50%)
DAREON-NEC-1	Unresectable advanced/ metastatic epNEC	DLL3-positive
DeLLight	R/R epNEC	No threshold specified
SKYBRIDGE	Advanced/metastatic epNEC	DLL3-positive

DLL3, delta-like ligand 3; epNEC, extrapulmonary neuroendocrine carcinoma; R/R, relapsed or refractory.

Recurrence/Progression

Re-Evaluate Tissue and Biomarkers

Potential considerations:

- Consider repeat biopsy when feasible[16]
- Assess tissue adequacy[4]
- Biomarker landscape may evolve[11]
- Clinical trial eligibility may change[17]

Reassessment may be appropriate as new evidence and clinical trial opportunities emerge.

DLL3 IHC assays, antibody clones, scoring algorithms, and positivity thresholds continue to evolve. Interpretation should follow the validated assay, reporting framework, and intended clinical context, including clinical trial eligibility where applicable.

Key Principles for Pathologists

Accurate NEC classification remains foundational.[11]

Biomarker interpretation should follow assay-specific methods.[5,9]

Tissue stewardship supports current and future biomarker assessment.[4,16]

Multidisciplinary communication supports optimal patient care.[18]

DLL3 is an emerging biomarker—not a diagnostic marker.[11]

Pathologists remain central to biomarker implementation.[10]

References

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