Oncology Learning Network

DLL3-Positive vs DLL-High

What Pathologists Need to Know

Delta-like ligand 3 (DLL3) expression is commonly assessed using immunohistochemistry (IHC), including the VENTANA DLL3 (SP347) assay.[1,2,3]

- **Specimen type:** Formalin-fixed paraffin-embedded tumor tissue[4]
- **Detection system:** BenchMark IHC/ISH instruments with OptiView DAB IHC Detection Kit[4]
- **Readout:** Estimate the percentage of viable tumor cells demonstrating DLL3 staining at any intensity using the validated assay protocol; staining may be membranous and/or cytoplasmic.[4,5]

How to Report DLL3 Expression[6,7]

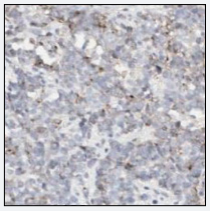
% DLL3-positive tumor cells

Percentage of viable tumor cells with any DLL3 staining

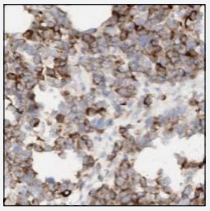
Staining intensity

Qualitative measure using intensity categories: null/low, moderate, or high

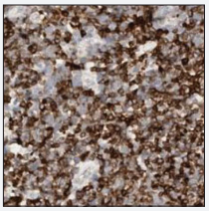
Intensity definitions vary by study and protocol



NULL/LOW INTENSITY



MODERATE INTENSITY



HIGH INTENSITY

Reporting both the percentage of positive tumor cells and staining intensity provides the information needed to support interpretation using study- or therapy-specific definitions.[1,2,6,8]

DLL3-positive ≠ DLL3-high[9]

DLL3-positive	DLL3-high
Indicates tumor cells express detectable DLL3 above a specified threshold	Indicates higher levels of expression defined by a study or therapy
Does not imply DLL3-high threshold is met	Incorporates both % DLL3-positive cells and staining intensity

There is currently no single universal definition of DLL3-high. Thresholds differ across assays, clinical trials, and investigational therapies.[7,10]

DLL3 Testing in Clinical Practice

Currently approved: Tarlatamab, a DLL3-directed therapy for extensive stage small cell lung cancer (ES-SCLC).[11]

Trials evaluating DLL3-targeted agents are now enriching for patients with specific levels of DLL3 expression or stratifying patients according to DLL3 expression level.

A DLL3-positive test result is not required prior to tarlatamab treatment initiation.[12]

Emerging DLL3-Targeted Trials: Expression Thresholds Vary by Study[1,2,8,13,14]

Therapy	Clinical trial	Tumor type	DLL3 eligibility criteria
Obrixtamig	DAREON-5	SCLC, LCNEC, epNEC	≥50% evaluable tumor cells exhibit moderate-strong DLL3 staining
Obrixtamig + carboplatin and etoposide	DAREON-NEC-1	epNEC	≥1% DLL3+
Tarlatamab	Tarlatamab basket trial	LCNEC, epNEC	Stage 1: ≥25% DLL3+; Stage 2: ≥1% DLL3+
Tarlatamab	DeLLight	epNEC	No DLL3 cutoff

DLL3, delta-like ligand 3; epNEC, extrapulmonary neuroendocrine carcinoma; LCNEC, large cell neuroendocrine carcinoma; SCLC, small cell lung cancer.

Current practice note: DLL3 IHC assays, 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 Takeaway for Pathologists

DLL3 is an emerging clinically relevant biomarker in neuroendocrine carcinomas. As DLL3-targeted therapies move into routine practice, pathologists will be critical in supporting treatment access by assessing DLL3 expression and determining whether expression meets specific trial- or therapy-defined thresholds.

References

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