Large Cell Neuroendocrine Carcinoma (LCNEC): A Comprehensive Disease Characteristics Report

Category: Neoplastic | **Primary MONDO ID:** MONDO:0005057 (site-agnostic) / MONDO:0003960 (pulmonary) | **ICD-O:** 8013/3 | **NCIT:** C4118

Summary

Large cell neuroendocrine carcinoma (LCNEC) is a rare, high-grade, poorly differentiated neuroendocrine carcinoma that accounts for approximately 0.3–3% of all lung cancers and also arises at extrapulmonary sites (thymus/mediastinum, gastrointestinal tract, uterus/cervix, breast, gallbladder, ovary). It is a tobacco-driven somatic malignancy of predominantly elderly male smokers. Diagnosis rests on non-small-cell neuroendocrine morphology — large cells, high mitotic rate (>10 mitoses/2 mm², typically ~70–75 mean), extensive necrosis, and organoid/palisading architecture — combined with **mandatory immunohistochemical confirmation** of neuroendocrine differentiation (chromogranin A, synaptophysin, CD56, with INSM1 and Ki-67 as adjuncts). Central pathology review reveals substantial interobserver variability, with LCNEC confirmed in only ~67% of submitted cases in one national registry, underscoring that this remains a diagnostically challenging entity.

Molecularly, LCNEC occupies a biological space that bridges small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Near-universal *TP53* alteration coexists with two dominant genomic subtypes: an **SCLC-like** subtype (*RB1* + *TP53* co-alteration) and an **NSCLC-like** subtype (*KEAP1*, *KRAS*, *STK11*, *SMARCA4*, *CDKN2A/B*). A third **carcinoid-like** group (*MEN1* mutation without *TP53*) is recognized in large comprehensive genomic profiling cohorts. Orthogonal transcription-factor and YAP1-based classifications further subdivide the disease into therapeutically distinct subsets (ASCL1/NEUROD1-driven, DLL3-high, immune-cold vs. YAP1-high, mesenchymal, inflamed). Tumor mutational burden is high (~12.7 mut/Mb), and homologous-recombination pathway defects, NOTCH-pathway alterations, and epigenetic dysregulation (DNMT1/DNMT3A upregulation, promoter hypermethylation, ASCL1 super-

enhancers) contribute to pathogenesis. LCNEC can also arise via neuroendocrine transformation of *EGFR*-mutant lung adenocarcinoma as an acquired resistance mechanism, driven by MYC amplification atop shared clonal *TP53*/*STK11* mutations.

Prognosis is poor overall — stage IV median overall survival (OS) is approximately 7.4 months — although early-stage resected disease reaches 53–86% 5-year survival. Treatment is largely extrapolated from SCLC and NSCLC: platinum-etoposide chemotherapy remains the first-line backbone, chemoimmunotherapy improves outcomes in advanced disease (pooled ORR 49%, first-line OS HR 0.72), surgery is central to localized disease, and DLL3-directed bispecific T-cell engager therapy (tarlatamab) is an emerging targeted option supported by early clinical activity in LCNEC and DLL3-high pulmonary carcinoid.

---

1. Disease Information

Overview. LCNEC is a poorly differentiated, high-grade neuroendocrine carcinoma composed of large cells with neuroendocrine morphology (organoid nesting, palisading, rosette-like structures, trabeculae) and confirmed neuroendocrine differentiation. In the WHO framework, lung neuroendocrine neoplasms are divided into well-differentiated typical/atypical carcinoids and poorly differentiated high-grade carcinomas comprising LCNEC and SCLC (PMID: 39756451; PMID: 28871510).

Key identifiers.

Resource	Identifier
MONDO (site-agnostic)	MONDO:0005057 — large cell neuroendocrine carcinoma
MONDO (pulmonary)	MONDO:0003960 — pulmonary large cell neuroendocrine carcinoma
MONDO (lung combined LCNEC)	MONDO:0004142
MONDO (parent NEC)	MONDO:0002120 — neuroendocrine carcinoma
MONDO (lung NE neoplasm)	MONDO:0005454
MONDO (thymic)	MONDO:0003047
MONDO (ovarian)	MONDO:0003049
MONDO (breast)	MONDO:0003959
MONDO (pancreatic)	MONDO:0006347
MONDO (cervical)	MONDO:0006138
ICD-O morphology	8013/3
NCIT	C4118 (Lung Large Cell Neuroendocrine Carcinoma)
MeSH	D018278 (Carcinoma, Neuroendocrine)
OMIM	None — somatic malignancy, no Mendelian entry

These identifiers were verified via EBI OLS4 MONDO lookup (2026-08) and are documented in **F014/F015** (PMID: 42526975; PMID: 39756451).

Synonyms / alternative names. Pulmonary large cell neuroendocrine carcinoma (PLCNEC); large-cell neuroendocrine carcinoma of the lung; high-grade neuroendocrine carcinoma, large cell type; combined LCNEC (when admixed with adenocarcinoma, squamous cell carcinoma, or other NSCLC components).

Source of information. Content is derived from aggregated disease-level resources — WHO Classification of Tumours, national registries (SEER, Netherlands Cancer Registry, French EPITHOR), comprehensive genomic profiling cohorts, and the primary literature — rather than individual EHR records.

2. Etiology

Causal factors. LCNEC is a **somatic, tobacco-driven malignancy**. There is no Mendelian/germline cause; disease arises through accumulation of somatic mutations, near-universally including *TP53* alteration, in the setting of heavy tobacco exposure (PMID: 36304941; **F002**, **F006**).

Environmental / lifestyle risk factors. - **Tobacco smoking** is the dominant risk factor: "Most of the LCNEC patients are elderly smoking male" (PMID: 36304941). Tobacco consumption is independently associated with OS in resected disease (PMID: 42341696). - **Age and male sex** — patients are typically elderly (mean age at surgery ~63.8 years) and male (~68.8%) (PMID: 42341696). - **Cannabis smoking** — associated with earlier age at lung cancer diagnosis and a higher relative frequency of LCNEC and adenocarcinoma histology among cannabis vs. tobacco-only smokers, though not an independent prognostic factor (PMID: 40393352).

Genetic risk factors. No established germline susceptibility loci. The relevant genetic events are somatic drivers (see Section 4). Homologous-recombination pathway alterations are present in a subset and are prognostically relevant (PMID: 35641209).

Protective factors. No validated genetic or environmental protective factors are established for LCNEC specifically. By analogy to lung cancer generally, smoking cessation is the principal modifiable protective behavior.

Gene–environment interactions. Tobacco carcinogen exposure drives the high mutational burden (TMB ~12.7 mut/Mb) and the *TP53*/*RB1* and NSCLC-driver mutation spectrum that defines LCNEC subtypes (PMID: 35641209; PMID: 40830141).

---

3. Phenotypes

Clinical manifestations are non-specific. LCNEC is often peripheral and in the upper lobes (PMID: 36304941).

Phenotype	Type	HPO suggestion	Characteristics
Cough	Symptom	HP:0012735	Adult/geriatric onset; non-specific
Dyspnea	Symptom	HP:0002094	Progressive with tumor burden
Hemoptysis	Sign	HP:0002105	Variable
Chest pain	Symptom	HP:0100749	Variable
Weight loss / cachexia	Constitutional	HP:0001824	Advanced disease
Pulmonary neoplasm	Physical	HP:0100526	Frequently peripheral, upper lobe
Bone metastasis	Complication	HP:0000766 (abnormal bone)	~23% synchronous at diagnosis in high-grade lung NEC (PMID: 40634407)
Brain metastasis	Complication	HP:0002060 (CNS neoplasm)	Independent adverse prognostic factor (PMID: 39268117)
Liver metastasis	Complication	HP:0006554	Independent adverse prognostic factor (PMID: 39268117)

Onset / severity / progression. Adult-to-geriatric onset; severe and rapidly progressive. "The clinical manifestations are not specific," which contributes to late-stage presentation (PMID: 36304941). Nearly half of patients present at advanced stage (PMID: 39287289). Unlike well-differentiated carcinoids, functional hormonal (carcinoid) syndromes are uncommon.

Quality-of-life impact. Direct EQ-5D/SF-36 LCNEC data were not identified; by extrapolation from high-grade lung cancer, symptom burden (dyspnea, pain from metastases, fatigue) and treatment toxicity substantially impair daily functioning. This is a knowledge gap.

4. Genetic / Molecular Information

Causal / driver genes and subtypes (F001, F004, F006). LCNEC has two dominant genomic subtypes plus a carcinoid-like minority:

Subtype	Defining alterations	Frequency / evidence
SCLC-like	*RB1* + *TP53* co-alteration	n=557 in CGP cohort (PMID: 38159439); ~80% align with SCLC transcriptional profile (PMID: 40830141)
NSCLC-like	*KEAP1*, *KRAS*, *STK11*, *SMARCA4*, *CDKN2A/B*, *MTAP*, *CCND1*, *FGF3/4/19*	(PMID: 40830141; PMID: 38159439)
Carcinoid-like	*MEN1* mutation without *TP53* GA	n=25 (PMID: 38159439)

> "Genomic analysis identifies distinct non-small cell lung cancer-like (NSCLC-like, KEAP1, KRAS, STK11 mutations) and SCLC-like (RB1, TP53 mutations) LCNEC subtypes, with 80% aligning with SCLC transcriptional profiles." (PMID: 40830141)

Additional recurrently altered genes. *NOTCH1*, *NOTCH2*, *PRKDC*, *SPTA1*, *PTPRD* are mutated at higher rates in LCNEC/SCLC than in carcinoids (PMID: 35641209). 26.3% of LCNECs harbor classical NSCLC driver-gene alterations. The NSCLC-like program also involves PI3K/AKT and RAS/MAPK genes (*PIK3CA*, *KRAS*, *STK11*, *KEAP1*).

Variant classification, type, and origin. Alterations are **somatic** (not germline). Types include truncating/nonsense and missense mutations (*TP53*, *STK11*), loss-of-function deletions (*RB1*, *CDKN2A/B*, *SMARCA4*), and copy-number events (MYC amplification during transformation; *FGF3/4/19*, *CCND1* amplification). *TP53* and *RB1* loss are loss-of-function tumor-suppressor events; *KRAS* is gain-of-function. Somatic origin is confirmed by COSMIC/TCGA-type profiling; there are no ClinVar germline pathogenic entries defining this disease.

Tumor mutational burden. High: "Large cell neuroendocrine carcinoma (12.7 mutations/Mb) and SCLC (11.9 mutations/Mb) showed higher tumor mutational burdens than TC (2.4 mutations/Mb) and AC (7.1 mutations/Mb)" (PMID: 35641209).

Transcription-factor / YAP1 axes (F004). YAP1 status defines two intrinsic subtypes (PMID: 39150543): - **YAP1-high:** mesenchymal, inflamed; co-alterations in *CDKN2A/B* and *SMARCA4* alongside *TP53*; vulnerable to MEK- and AXL-targeting. - **YAP1-low:** epithelial, immune-cold; *TP53*+*RB1* co-mutation; expresses SCLC transcription factors ASCL1 and NEUROD1; DLL3/CD56 targeting vulnerability.

Modifier genes. Homologous-recombination pathway alterations act as therapeutic-response modifiers, predicting longer PFS on systemic therapy (P=.005) (PMID: 35641209).

Epigenetic information (F011). First study of DNMT expression in LCNEC (18 cases) found "upregulation of both DNMT1 and DNMT3A compared to control normal lung tissue" (PMID: 41854102). Promoter hypermethylation of tumor suppressors (e.g., *RASSF1*, *CDKN2A*, *APC*, *BRCA1*, *CDH1*, *MGMT*, *RARβ*, *RUNX3*, *TIMP3*) links LCNEC to both NSCLC and SCLC — "LCNEC may serve as a biological bridge between non-small cell and small-cell lung carcinoma" (PMID: 39832203). ASCL1 acts as a master transcriptional regulator associated with super-enhancers (PMID: 30121393).

Chromosomal abnormalities. Chromosomal instability, MYC amplification (especially during neuroendocrine transformation), and copy-number alterations at *FGF*/*CCND1* loci. MSI occurs in ~10% of gastric/colorectal NEC but is uncommon in pulmonary LCNEC.

---

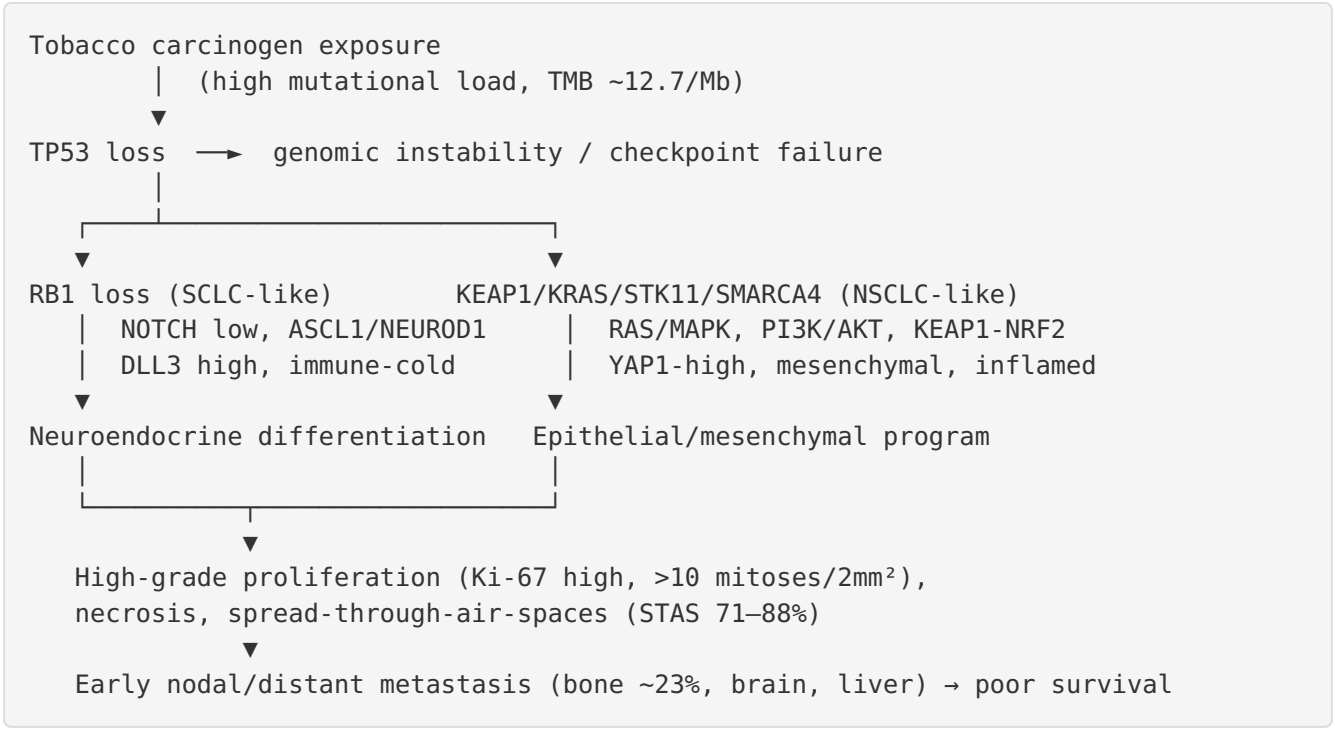
5. Environmental Information

- **Environmental factors:** Tobacco smoke carcinogens are the principal environmental driver; ionizing radiation and other inhaled carcinogens are plausible by analogy to high-grade lung cancers.
- **Lifestyle factors:** Cigarette smoking (dominant) and cannabis smoking (associated with earlier onset and higher relative LCNEC frequency; PMID: 40393352).
- **Infectious agents:** Not applicable for **pulmonary** LCNEC. However, HPV (particularly **HPV18**) is causally associated with **cervical** large cell neuroendocrine carcinoma (PMID: 42521492; PMID: 42351440). Merkel cell polyomavirus causes cutaneous Merkel cell carcinoma, a related high-grade NEC used as a comparator in the literature.

---

6. Mechanism / Pathophysiology

Causal chain (upstream → downstream).



Molecular pathways. RAS/MAPK, PI3K/AKT/mTOR, NOTCH signaling, KEAP1–NRF2 (via *KEAP1* mutation), Hippo/YAP1, and cell-cycle control (RB1–cyclin D1/CDKN2A) (PMID: 35641209; PMID: 39150543; PMID: 40830141). Suggested GO terms: GO:0007219 (Notch signaling pathway), GO:0007265 (Ras protein signal transduction), GO:0035329 (Hippo signaling), GO:0007049 (cell cycle).

Cellular processes. Cell-cycle dysregulation (RB1/CDKN2A loss), impaired apoptosis (TP53 loss), neuroendocrine lineage plasticity, and chromosomal instability. Suggested GO terms: GO:0006915 (apoptotic process), GO:0051301 (cell division), GO:0030154 (cell differentiation).

Protein dysfunction. Loss-of-function of p53 and RB1 tumor suppressors; SMARCA4 (BRG1) inactivation destabilizes the SWI/SNF chromatin-remodeling complex; gain-of-function KRAS. UniProt: TP53 (P04637), RB1 (P06400), SMARCA4 (P51532), KRAS (P01116), ASCL1 (P50553), DLL3 (Q9NYJ7).

Metabolic changes. L-type amino-acid transporter 1 (LAT1/SLC7A5) is overexpressed in 52.4% of LCNEC and correlates with Ki-67, nodal metastasis, and poor outcome (PMID: 18440724) — reflecting elevated amino-acid demand of proliferating tumor cells.

Immune involvement (F010). Modestly immunogenic relative to SCLC. PD-L1 on tumor cells ~15.1%; immune-cell infiltration and PD-L1-on-immune-cells more strongly correlate with LCNEC than SCLC (57.6% vs 23.3%; 45.8% vs 22.5%; both $p<0.01$), correlating with high nonsynonymous mutation burden (PMID: 29378266). PTEN loss occurs in ~9.5%. However,

ASCL1-high/YAP1-low tumors are immune-cold, and some extrapulmonary variants (HPV18+ cervical LCNEC) are poorly immunogenic (TMB 1.21/Mb, minimal PD-L1) with ICI resistance (PMID: 42521492).

Tissue damage mechanisms. Extensive tumor necrosis, spread-through-air-spaces (STAS identified in 71–88% of high-grade large-/small-cell NE carcinomas; PMID: 31201506), and destructive local/metastatic growth.

Cell types. Pulmonary neuroendocrine cells / their precursors are the presumed cell of origin; adenocarcinoma cells can transdifferentiate into LCNEC (see transformation, below). Suggested CL terms: CL:0000165 (neuroendocrine cell), CL:0002333 (pulmonary neuroendocrine cell), CL:0001063 (neoplastic cell).

Multi-omics / transformation (F013). Combined LCNEC-adenocarcinoma cases show shared clonal *TP53* and *STK11* mutations across components with **MYC amplification acquired during neuroendocrine transformation** (PMID: 39868963). Histologic transformation to LCNEC is an acquired *EGFR*-TKI resistance mechanism in *EGFR*-mutant adenocarcinoma (PMID: 28768973).

---

7. Anatomical Structures Affected

Organ level. Primary organ is most commonly the **lung** (~85% of LCNEC; UBERON:0002048), typically peripheral and upper-lobe. Extrapulmonary primaries (F007): **thymus/mediastinum** (UBERON:0002370), **gastrointestinal tract** — large-cell NEC was 42% of GI-NECs in a 143-case cohort (PMID: 36264285), **uterus/cervix** (UBERON:0000995/UBERON:0000002; PMID: 42111278), **breast** (UBERON:0000310; PMID: 39585672), **gallbladder** (UBERON:0002110; PMID: 40789532), and **ovary** (UBERON:0000992).

Secondary organ involvement. Bone (~23% synchronous), brain, liver, and regional lymph nodes are common metastatic sites and independent adverse prognostic factors (PMID: 39268117; PMID: 40634407).

Body systems. Respiratory (primary), plus skeletal, nervous (CNS), hepatic, and lymphatic systems (metastatic).

Tissue and cell level. Epithelial-derived neuroendocrine tumor; targeted/derived cell type is the neuroendocrine cell (CL:0000165) and pulmonary neuroendocrine cell (CL:0002333).

Subcellular level. Dense-core neurosecretory granules (basis of chromogranin A/synaptophysin positivity). Suggested GO cellular-component terms: GO:0030141 (secretory granule), GO:0005739 (mitochondrion), GO:0005634 (nucleus).

Localization / lateralization. Pulmonary LCNEC is typically a solitary peripheral mass, often upper lobe; laterality is variable (unilateral primary with potential bilateral/distant metastases).

---

8. Temporal Development

Onset. Adult/geriatric (mean age at surgery ~63.8 years; PMID: 42341696). Onset is insidious with non-specific symptoms, frequently leading to advanced-stage presentation (PMID: 36304941; PMID: 39287289).

Progression / staging. Staged by AJCC TNM (lung). Progression is rapid, with early nodal and distant metastasis; ~half present at advanced stage and ~23% of high-grade lung NEC have synchronous bone metastasis at diagnosis (PMID: 40634407). Disease course is aggressive and progressive rather than relapsing-remitting.

Duration / patterns. Chronic in the sense of a lethal, progressive course; median OS in stage IV is ~7.4 months (PMID: 41240593). Remissions are treatment-induced, generally not durable. The critical intervention window is at the localized/resectable stage, where surgery offers the best survival.

---

9. Inheritance and Population

Epidemiology. Incidence ~0.3–3% of lung cancers (PMID: 36304941); ~3% is a commonly cited figure (PMID: 41510101). Incidence appears to be rising, partly due to improved diagnostics (PMID: 40114491).

Inheritance. Not heritable — somatic, tobacco-driven malignancy with **no Mendelian OMIM entry** (F014). Concepts of penetrance, expressivity, anticipation, founder effects, consanguinity, and carrier frequency are **not applicable**.

Demographics. Male predominance (~68.8% men; PMID: 42341696); elderly smokers. Sex is an independent prognostic factor (DSS HR ~1.17 for the higher-risk sex; PMID: 39268117). Geographic distribution parallels tobacco-use patterns; no established ethnic predisposition beyond smoking prevalence.

---

10. Diagnostics

Histopathology + IHC (mandatory). Diagnosis requires non-small-cell neuroendocrine **morphology** (large cells, organoid/palisading architecture, extensive necrosis, severe atypia, >10 mitoses/2 mm² [typically mean ~70–75]) **plus IHC confirmation** of neuroendocrine differentiation. "The confirmation of the neuroendocrine signature by immunohistochemistry is mandatory for the diagnosis; a minimum panel comprising chromogranin A and synaptophysin is recommended" (PMID: 28871510). CD56 is diffusely positive; INSM1 and high Ki-67 aid diagnosis (PMID: 36304941; PMID: 40805240).

Ki-67 / grading. Grading in lung NE neoplasms uses mitotic count ±necrosis; Ki-67 is a helpful adjunct (and its formal inclusion is debated; PMID: 38728050). LCNEC shows a high Ki-67 index.

Diagnostic reliability. Substantial interobserver variability; central pathology review confirmed LCNEC in only 67% of submitted cases in the Netherlands Cancer Registry (others reclassified as SCLC 34%, NSCLC-NOS 34%) (PMID: 41240593). A systematic review found central pathology review is applied in <one-third of studies with marked methodological heterogeneity (PMID: 42556470).

Molecular / genomic testing. Comprehensive genomic profiling (NGS panels, WES) is useful for subtyping (SCLC-like vs NSCLC-like vs carcinoid-like) and for identifying actionable alterations (PMID: 38159439; PMID: 41653583). RB1 IHC (pRb status) is used for stratification in registry studies (PMID: 41240593). Emerging epigenomic cfDNA/liquid-biopsy approaches can detect neuroendocrine transformation noninvasively (PMID: 38912901).

Imaging. CT and PET for staging; brain MRI given CNS metastasis risk; pro-gastrin-releasing peptide (pro-GRP) can serve as a circulating tumor marker in NE tumors and tracks response (e.g., 1610 → 49.7 ng/mL on tarlatamab; PMID: 42491047).

Differential diagnosis. SCLC (smaller cells, finer chromatin, higher N:C ratio), basaloid squamous carcinoma, atypical carcinoid (lower mitoses, no necrosis), and metastatic NEC from other sites. IHC (INSM1, chromogranin, synaptophysin, TTF-1, Ki-67) and molecular context resolve most cases.

11. Outcome / Prognosis

Survival. Poor overall; stage-dependent.

Setting	Outcome	Source
Stage IV, panel-reviewed	Median OS ~7.4 months	PMID: 41240593
Resected (EPITHOR, n=1,229)	5-year OS 52.9% (vs SCLC 45.5%)	PMID: 42341696
Resected, stage-selected series	5-year survival ~86%	PMID: 41376913

Independent prognostic factors (SEER, n=2,897; F008). Surgery (HR 0.481, protective), chemotherapy (HR 0.450, protective), bone metastasis (HR 1.284), brain metastasis (HR 1.167), liver metastasis (HR 1.223), plus AJCC N-stage, tumor stage, sex, and age (PMID: 39268117). Tobacco, sex, TNM stage, and histologic type were independently associated with OS in EPITHOR (PMID: 42341696).

Molecular prognostic markers. Homologous-recombination pathway alterations predict longer PFS with systemic therapy (P=.005; PMID: 35641209); LAT1 overexpression predicts poor outcome (PMID: 18440724); immune-cell infiltration associates with better PFS (PMID: 29378266).

Complications. Bone, brain, and liver metastases; early death is common in stage IV (predictive nomograms achieve AUC ~0.85; PMID: 39287289).

12. Treatment

Treatment is extrapolated from SCLC and NSCLC. Suggested NCIT terms in parentheses.

Pharmacotherapy — first line. Platinum (cisplatin/carboplatin) + etoposide chemotherapy is the backbone: "In metastatic disease, etoposide-platinum chemotherapy remains the first-line treatment, while targeted therapy can be considered if tumors harbor actionable genomic alterations" (PMID: 41653583). NCIT: C63419 (etoposide), C376 (cisplatin), C1282 (carboplatin).

Chemoimmunotherapy (F003). Adding immune checkpoint inhibitors improves outcomes: pooled ORR 49% (95% CI 43–55); vs chemo alone ORR OR 2.52; first-line chemo+ICI improved OS (HR 0.72, 95% CI 0.58–0.89) without increasing grade ≥3 AEs (PMID: 42208366). Real-world registry data show a survival benefit of immunotherapy (median OS 10.7 vs 6.7 months; HR 0.53) although panel-reviewed cohorts show a smaller, non-significant effect (PMID: 41240593). The phase II FIRST-NEC trial (durvalumab + platinum-etoposide, NCT06393816) is prospectively evaluating first-line immunochemotherapy (PMID: 42526918). NCIT: C1649 (pembrolizumab), checkpoint inhibitors (durvalumab).

Targeted / emerging — DLL3-directed therapy (F009). DLL3 is highly expressed in SCLC-like/ASCL1-associated LCNEC. **Tarlatamab** (DLL3×CD3 bispecific T-cell engager) received FDA accelerated approval (2024) and full approval (2025) for SCLC (PMID: 42449715). In a relapsed/refractory LCNEC case (6th-line), tarlatamab produced a partial response (130→78 mm, 40% reduction) with pro-GRP falling 1610→49.7 ng/mL and only grade 1 CRS (PMID: 42491047). In DLL3-high pulmonary carcinoid (n=11), response rate was 73% with 100% disease control (PMID: 42562260). Additional emerging modalities: TROP2- and B7-H3-directed agents and antibody-drug conjugates (PMID: 42592685; PMID: 42582332). NCIT: C171398 (tarlatamab).

Surgery. Central to localized disease and independently protective (HR 0.481; PMID: 39268117). Anatomic resection is performed in ~97% of operable cases (90-day mortality ~8.3%; PMID: 42341696). In stage I, sublobectomy was an effective option in one SEER analysis (PMID: 40950692).

Radiotherapy. Chemoradiotherapy improves OS/CSS in stage III; its role in stage IV is context-dependent (PMID: 42231825).

Adjuvant therapy. SCLC-type adjuvant regimens are associated with better outcomes in resected disease, though in T1-2N0M0 SEER analyses adjuvant chemotherapy did not show a significant OS/CSS benefit over surgery alone in the overall cohort (PMID: 41510101; PMID: 41153253).

Neuroendocrine-transformed disease. In *EGFR*-mutant NSCLC with NE transformation, durvalumab + etoposide-platinum gave ORR 43%, median OS 10.2 months (ORCHARD; PMID: 42361644).

Personalized medicine. Genomic subtyping guides therapy: YAP1-high → MEK/AXL strategies; YAP1-low/DLL3-high → DLL3/CD56 targeting (PMID: 39150543); actionable NSCLC drivers → targeted agents (PMID: 41653583).

13. Prevention

- **Primary prevention:** Tobacco control and smoking cessation are the principal strategies, given the dominant smoking etiology (PMID: 36304941).
- **Secondary prevention:** Low-dose CT lung cancer screening in high-risk (heavy-smoking, elderly) populations may detect early-stage disease, where surgery is most effective — though LCNEC-specific screening data are lacking.
- **Tertiary prevention:** Surveillance for and management of bone/brain/liver metastases; multimodal therapy to prevent complications.
- **Immunization:** For **cervical** LCNEC, HPV vaccination is a plausible primary preventive measure given HPV18 causation (PMID: 42521492); not applicable to pulmonary LCNEC.
- **Genetic counseling / carrier screening:** Not applicable (somatic disease).

---

14. Other Species / Natural Disease

Species-specific data for LCNEC are limited. NCBI Taxonomy: *Homo sapiens* (9606). Orthologous driver genes are highly conserved across mammals (*Tp53*, *Rb1*, *Kras*, *Stk11*, *Ascl1*, *Dll3*), supporting cross-species relevance of the pathways involved. Naturally occurring high-grade neuroendocrine carcinomas are reported in companion animals (e.g., pulmonary and gastrointestinal NECs in dogs and cats via OMIA/veterinary literature), but LCNEC-specific comparative pathology was not systematically retrieved in this investigation and remains a knowledge gap. There is no zoonotic transmission (non-communicable neoplasm).

---

15. Model Organisms

Direct LCNEC-specific models were not the focus of the retrieved literature, but the field draws heavily on **SCLC genetically engineered mouse models (GEMMs)**, given the SCLC-like biology of most LCNEC. GEMMs based on conditional *Tp53/Rb1* inactivation (and *Trp53/Rb1/Myc* combinations) recapitulate high-grade neuroendocrine lung carcinoma and are used to validate driver mutations and targeted therapies (PMID: 31134494). Patient-derived xenografts (including circulating-tumor-cell–derived xenografts, CDX) and patient-derived organoids are

used for high-grade NE tumors and for mixed carcinomas (e.g., an endometrial mixed LCNEC organoid/xenograft revealing PI3K/VEGF vulnerabilities; PMID: 41886729). Cell lines expressing ASCL1 and NE markers model the ASCL1 super-enhancer program (PMID: 30121393).

Model resources: MGI (mouse), Cellosaurus/ATCC (cell lines), and PDX/organoid biobanks. **Limitations:** Few models are LCNEC-specific (as opposed to SCLC); the NSCLC-like and YAP1-high subtypes are underrepresented; models incompletely capture the human tumor immune microenvironment and the interobserver diagnostic ambiguity.

Mechanistic Model / Interpretation

LCNEC is best understood as a **lineage-plastic, tobacco-driven high-grade neuroendocrine carcinoma that molecularly bridges SCLC and NSCLC**. A unifying model:

Axis	SCLC-like pole	NSCLC-like pole
Drivers	*RB1* + *TP53*	*KEAP1/KRAS/STK11/SMARCA4/CDKN2A*
Transcription factors	ASCL1, NEUROD1 high	—
YAP1	Low	High
Surface target	DLL3 high, CD56	—
Immune phenotype	Immune-cold	Mesenchymal, inflamed
Therapeutic vulnerability	DLL3 (tarlatamab), platinum-etoposide	MEK/AXL, NSCLC-driver–targeted agents

Upstream, tobacco carcinogens generate a high mutational burden and near-universal *TP53* loss. The bifurcation into SCLC-like vs NSCLC-like programs — reinforced by epigenetic machinery (DNMT1/DNMT3A, ASCL1 super-enhancers, promoter hypermethylation) — determines transcription-factor identity, surface-antigen expression (notably DLL3), immune phenotype, and druggable vulnerabilities. Downstream, high-grade proliferation, necrosis, and spread-through-air-spaces produce early metastasis and poor survival. A distinct **transformation route** exists whereby *EGFR*-mutant adenocarcinoma converts to LCNEC under TKI pressure, acquiring MYC amplification atop shared clonal *TP53*/*STK11*. This model

directly rationalizes emerging precision approaches: DLL3-directed T-cell engagers for the SCLC-like/ASCL1/DLL3-high pole and MEK/AXL or driver-targeted agents for the YAP1-high/NSCLC-like pole.

Evidence Base

PMID	Contribution
40830141	Defines SCLC-like vs NSCLC-like genomic subtypes; DLL3-high in SCLC-like LCNEC
38159439	Large CGP cohort; SCLC-like (n=557), carcinoid-like (n=25) definitions
35641209	TMB (12.7/Mb); NOTCH/TP53 mutations; HR-pathway predicts PFS
39150543	YAP1-high vs YAP1-low subtypes and vulnerabilities
36304941	Incidence, demographics, IHC markers
28871510	Mandatory IHC (chromogranin A + synaptophysin); histologic features
31201506	STAS in 71–88% of high-grade NE carcinomas
42208366	Chemoimmunotherapy meta-analysis (ORR 49%, OS HR 0.72)
41653583	Platinum-etoposide first-line standard
39268117	SEER independent prognostic factors with HRs
42341696	EPITHOR resected 5-year OS 52.9%; demographics
41376913	Stage-selected resected 5-year survival ~86%
42491047	Tarlatamab clinical activity in LCNEC
42449715	Tarlatamab FDA approval status
42562260	Tarlatamab in DLL3-high pulmonary carcinoid (73% RR)
29378266	PD-L1/immune infiltration in high-grade lung NEC
41854102	DNMT1/DNMT3A upregulation in LCNEC
39832203	LCNEC as methylation bridge between NSCLC/SCLC
30121393	ASCL1 as master super-enhancer regulator
39868963	MYC-amplified NE transformation; clonal TP53/STK11
28768973	LCNEC transformation as EGFR-TKI resistance
41240593	Stage IV median OS 7.4 mo; 67% diagnostic confirmation
42556470	Central pathology review heterogeneity
18440724	LAT1 overexpression (52.4%) and poor outcome

PMID	Contribution
42521492	Immune-cold HPV18+ cervical LCNEC, ICI resistance

Limitations and Knowledge Gaps

1. **Diagnostic reproducibility.** LCNEC is confirmed in only ~67% of cases on central review, with substantial interobserver variability (PMID: 41240593; PMID: 42556470). This introduces classification bias into all registry-based epidemiology and outcomes data.
2. **Evidence quality.** Much survival/treatment evidence derives from retrospective SEER/registry analyses and single-arm/case reports; prospective randomized data specific to LCNEC are scarce (FIRST-NEC is ongoing).
3. **Rarity and subtype under-sampling.** NSCLC-like and YAP1-high subtypes, and extrapulmonary LCNEC, are underrepresented; treatment is largely extrapolated from SCLC/NSCLC.
4. **Quality-of-life data.** No LCNEC-specific EQ-5D/SF-36/PROMIS data were identified.
5. **Model organisms.** Few LCNEC-specific in vivo models exist; the field relies on SCLC GEMMs and PDX/organoids.
6. **Predictive biomarkers.** Reliable biomarkers for ICI benefit and hyperprogression risk are not established.
7. **Comparative/veterinary biology.** Naturally occurring LCNEC in other species is poorly characterized.

Proposed Follow-up Experiments / Actions

1. **Prospective subtype-stratified trials.** Complete and expand trials like FIRST-NEC (NCT06393816) and add DLL3-directed arms (tarlatamab) for SCLC-like/DLL3-high LCNEC, and MEK/AXL inhibitor arms for YAP1-high tumors.
2. **Standardize diagnosis.** Adopt the structured central-pathology-review reporting form and combine IHC + molecular subtyping (RB1 IHC, targeted NGS) to reduce misclassification (PMID: 42556470).

3. **Biomarker development.** Validate DLL3, ASCL1/NEUROD1/YAP1, TMB, PD-L1, and HR-deficiency as predictive biomarkers; develop cfDNA/epigenomic liquid biopsies for transformation detection and monitoring (PMID: 38912901).
4. **Model building.** Generate LCNEC-specific GEMMs and organoids representing NSCLC-like and YAP1-high subtypes for preclinical drug testing.
5. **Epigenetic therapy.** Test DNMT inhibitors (given DNMT1/DNMT3A upregulation) and ASCL1/super-enhancer-directed strategies (PMID: 41854102; PMID: 30121393).
6. **Extrapulmonary registries.** Establish site-specific registries (thymic, GI, gynecologic) to define subtype-specific biology and optimal therapy.
7. **Patient-reported outcomes.** Collect LCNEC-specific QoL data prospectively.

Report compiled from 15 confirmed findings across 67 reviewed papers. Evidence sources span human clinical (registries, cohorts, case reports), in vitro/genomic profiling, and computational/ontology lookups.
