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**Katarzyna Stencel[1], Maciej Bryl[1], Renata Langfort[2]**

[1]Eugenia and Janusz Zeyland Wielkopolska Center of Pulmonology and Thoracic Surgery, Poznan, Poland
[2]Department of Pathology, National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland

# Pulmonary large cell neuroendocrine carcinoma — diagnostic and therapeutic clinical dilemmas

**Address for correspondence:**
Katarzyna Stencel, MD PhD
Eugenia and Janusz Zeyland
Wielkopolska Center of Pulmonology
and Thoracic Surgery
ul. Szamarzewskiego 62,
60–599 Poznan, Poland
e-mail: kstencel@wcpit.org

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## ABSTRACT

Pulmonary large cell neuroendocrine carcinoma (LCNEC) belongs to a heterogeneous group of lung cancers that show morphological, ultrastructural, and immunohistochemical similarities but differ in etiopathogenesis, molecular profile, clinical course, prognosis, and treatment.

The prognosis for pulmonary LCNEC is extremely poor, and median overall survival usually does not exceed one year. According to the 2015 classification of the World Health Organization, LCNECs belong to neuroendocrine tumors, along with typical and atypical carcinoid tumors and small cell lung cancer (SCLC). The optimal therapeutic approach in LCNEC patients has not yet been determined. Accurate LCNEC diagnosis is crucial, and management algorithms should be developed on the basis of multicenter prospective clinical trials.

This review presents the diagnosing criteria for large cell neuroendocrine carcinoma and reviews the effectiveness of available therapeutic options.

**Keywords**: large cell neuroendocrine carcinoma, chromogranin A, synaptophysin, NCAM/CD56

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## Introduction

Large cell neuroendocrine carcinomas (LNECs) belong to a diverse group of lung cancers. They demonstrate morphological, ultrastructural, and immunohistochemical similarities, but differ in etiopathogenesis, molecular profile, clinical course, prognosis, and treatment. Neuroendocrine carcinomas include tumors with good and intermediate differentiation and relatively low malignant potential, as well as forms with low histological maturity, high malignant potential, and aggressive course. According to the current 2021 World Health Organization (WHO) classification, the former group is called "neuroendocrine tumors" and includes typical carcinoids and atypical carcinoids, while the latter group, called "neuroendocrine carcinomas" includes large cell neuroendocrine carcinoma and small cell carcinoma [1].

## Classification of pulmonary neuroendocrine tumors

The classification of pulmonary neuroendocrine tumors has been evolving for many years, which is related to the development of new diagnostic methods, especially molecular biology (Tab. 1) [2]. The first classification of lung cancers presented by the WHO in 1967 included only two types of neuroendocrine tumors — carcinoid and small cell carcinoma with its morphological variants (polygonal/fusiform, lymphocyte-like) and forms containing a component of non-small cell carcinoma (squamous or adenocarcinoma) [3].

In 1982, three morphological subtypes of small cell carcinomas were distinguished (intermediate, oat cell, and combined) with essential prognostic significance [4]. In 1988, the classification of small cell carcinomas was modified again, introducing a monomorphic, mixed

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**Table 1. History of the pulmonary neuroendocrine carcinomas subclassification**

| WHO (1967) | WHO (1982) | WHO/IASLC (1988) | WHO/IASLC (1999/2004) | WHO/IASLC (2015) | WHO/IASLC (2021) |
|---|---|---|---|---|---|
| — **Carcinoid tumor**<br>— **SCLC**<br>types:<br>• polygonal/fusiform<br>• lymphocyte-like<br>• with NSCLC component | — **Carcinoid tumor**<br>— **SCLC**<br>types:<br>• intermediate<br>• oat cell<br>• combined (SCLC + NSCLC) | — **Carcinoid tumor**<br>— **SCLC**<br>types:<br>• monomorphic<br>• mixed (SCLC + LCC)<br>• combined (SCLC + NSCLC) | — **Carcinoid tumor**<br>types:<br>• TC<br>• AC<br>— **SCLC**<br>types:<br>• combined (SCLC + NSCLC)<br>— **LCC**<br>types:<br>• LCNEC<br>a) combined (LCNEC + NSCLC) | **NEUROENDOCRINE TUMORS**<br>— **Carcinoid tumor**<br>types:<br>• TC<br>• AC<br>— **SCLC**<br>types:<br>• combined (SCLC + NSCLC)<br>— **LCNEC**<br>types:<br>• combined (LCNEC + NSCLC) | **NEUROENDOCRINE TUMORS**<br>**Neuroendocrine tumors**<br>— **Carcinoid tumor**<br>types:<br>• TC<br>• AC<br>**NEUROENDOCRINE CARCINOMAS**<br>— **SCLC**<br>types:<br>• combined (SCLC + NSCLC)<br>— **LCNEC**<br>types:<br>• combined (LCNEC + NSCLC) |

AC — atypical carcinoid; DIPNECH — diffuse idiopathic pulmonary neuroendocrine-cell hyperplasia; IASLC — International Association for the Study of Lung Cancer; LCC — large cell carcinoma; LCNEC — large cell neuroendocrine carcinoma; NSCLC — non-small cell lung carcinoma; SCLC — small cell lung carcinoma; TC — typical carcinoid; WHO — World Health Organization

form, containing a component of small and non-small cell carcinoma, and a complex form, composed of an element of small cell carcinoma and another form of non-small cell lung cancer (NSCLC) [5, 6].

The large cell neuroendocrine carcinoma form was introduced in 1999 by Travis et al. [7] and was initially classified as a subtype of large cell carcinoma. At that time in 2004, the WHO also published a classification of pulmonary neuroendocrine tumors, which aimed to systematize and emphasize the distinctive features of neuroendocrine growths in relation to other lung tumors [7, 8].

The 2015 WHO classification of lung tumors was the only one that distinguished neuroendocrine tumors as a separate group, including typical and atypical lung carcinoids, corresponding to low- and intermediate-grade neuroendocrine tumors as well as high-grade neuroendocrine carcinomas [LCNEC and small cell lung cancer (SCLC)] [9]. This classification results from the clinical and pathological similarities of LCNECs and SCLCs, which are different from bronchopulmonary carcinoid tumors. Large cell neuroendocrine carcinomas and SCLCs are characterized by a similar aggressive course, poor prognosis, close relationship with exposure to tobacco smoke as well as a high proliferative and mitotic index.

In approximately 25% of resected SCLCs and LCNECs, microscopic examination reveals a component of another NSCLC (most often — adenocarcinoma or squamous cell carcinoma, less often — pleomorphic carcinoma or large cell carcinoma). These forms are called combined SCLC and combined LCNEC, respectively. Small cell carcinomas with histological components of large cell neuroendocrine carcinoma are classified as mixed SCLC [1, 2].

## Criteria for microscopic diagnosis of large cell neuroendocrine carcinoma

The main criterion for differentiating neuroendocrine tumors is histoformative ability, the number of cell division figures, and the presence of necrosis. The proliferative index (Ki-67) assessed by immunohistochemistry is also helpful [1, 2, 10].

Histoformative ability is characterized by the formation of the so-called organoid structures, visible under a microscope in the form of palisades, rosettes, trabeculae, coils, and small cell nests. As cancer grade increases, the tumor loses its organoid component, the number of mitotic figures and the proliferative index increases, and extensive necrosis appears [1, 10]. Microscopic examination reveals features of organoid differentiation, usually extensive areas of necrosis, sometimes with dystrophic calcification foci, numerous cell mitotic figures, most often > 70/2 mm$^2$, high proliferative index (usually 40–80%), and the expression of at least one or more neuroendocrine markers. The extent of expression in cancer cells is of no importance as long as the cancer has an organoid structure. This rule applies primarily to markers other than CD56, which is the least specific, and even in the case of an extensive reaction, it is advisable to add another

**Table 2. Criteria for microscopic diagnosis of large cell neuroendocrine carcinoma [according to the 2021 World Health Organization (WHO) classification]**

| |
|---|
| Organoid structure (trabeculae, rosettes, palisades, small coils, and solid cell nests) |
| Areas of necrosis, often extensive, sometimes with calcifications or in the central part of tumor nests |
| Usually larger cancer cells (> 3 lymphocytes), with a vesicular nucleus, thick nuclear membrane, coarse chromatin, visible nucleoli, distinct cytoplasm, often amphophilic |
| Numerous cell mitotic figures (> 10/2 mm$^2$, median 70/2 mm$^2$) |
| High proliferative index (Ki-67 > 30%, most often 40–80%) |
| Expression of at least one or more neuroendocrine markers (chromogranin A, synaptophysin, CD55/NCAM) |
| Immunohistochemical tests:<br>— cytokeratins (+), usually strong reaction, sometimes of the perinuclear type ("dot-like")<br>— TTF-1 (+) in approximately 50% of LCNECs<br>— napsin A (–)<br>— p40 (–)<br>— CK5/6 (–)<br>— 34βE12 (–) |

neuroendocrine marker. Large cell neuroendocrine carcinomas show a strong reaction with anti-cytokeratin antibodies. Sometimes the reaction may be of the perinuclear type (so-called "dot-like"), which is usually found in small cell carcinomas. Approximately 50% of LCNECs express TTF-1, but not Napsin A. Markers characteristic of squamous cell carcinomas may rarely be expressed (p40, CK5/6, 34βE12), but they usually occur focally and affect only a few cancer cells (Tab. 2) [1, 11].

## Morphological spectrum of large cell neuroendocrine carcinoma

Despite specific histological and cytological features, LCNEC is characterized by a variety of morphological forms, which may cause diagnostic difficulties and even discrepancies in establishing a microscopy diagnosis [11].

The classic form of LCNEC shows neuroendocrine and organoid (palisades, rosettes, trabeculae) structure and meets the cytological criteria for LCNEC; its neuroendocrine activity is confirmed by immunohistochemical tests.

The second group consists of LCNECs, which lose their organoid structure. The cancer cells are smaller, contain less cytoplasm, and the nuclei resemble those of SCLC. This form raises most problems and diagnostic discrepancies, even among experienced pathologists specializing in lung diseases.

The third group of LCNECs resembles the morphological and cytological structure of atypical carcinoid tumors. However, an increased number of cell division figures (> 10/2 mm$^2$) and an increased proliferative index (Ki-67 > 30%) meet the criteria for large cell neuroendocrine carcinoma diagnosis (Fig. 1) [11, 12].

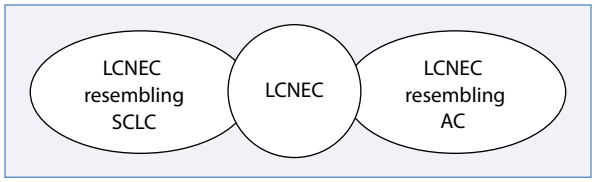


**Figure 1.** Morphological forms of large-cell neuroendocrine carcinoma (LCNEC); AC — atypical carcinoid; SCLC — small cell lung cancer

## Diagnosis of large-cell neuroendocrine carcinoma from biopsy material

Diagnosis of LCNEC from a small tissue sample or cytological material (cytoblock) may be difficult. According to the current WHO classification guidelines, LCNEC diagnosis in a small biopsy material requires determination of the neuroendocrine morphology of the tumor and the expression of at least one neuroendocrine marker [1].

Recently, a proposal for using histological criteria to differentiate LCNEC from NSCLC in biopsy was published. The system includes scoring for the presence of neuroendocrine differentiation, necrosis, Ki-67 ≥ 40%, and confirmation of neuroendocrine function by one or more markers. However, the system requires further validation [13].

## Large-cell neuroendocrine carcinoma differentiation

Large cell neuroendocrine carcinomas require differentiation both from other types of neuroendocrine carcinomas [SCLC, typical carcinoid (TC), atypical

carcinoid (AC)] and other forms of non-small cell lung cancers, most often adenocarcinomas, basaloid squamous cell carcinomas (BSCC), and large cell carcinomas [10, 11]. The main criterion for differentiation from other forms of neuroendocrine tumors is the number of cell division figures, the presence of necrosis, and its extent. The proliferation index is also helpful. In differentiating from other types of non-small cell lung cancers, additional tests are useful, mainly for the presence of intracytoplasmic mucus and immunohistochemistry, using markers indicating glandular (TTF-1, napsin A) and squamous cell differentiation (p40, CK5/6, 34βE12). It should be noted that approximately 10–20% of NSCLCs, especially adenocarcinomas, may express neuroendocrine markers. However, it usually occurs focally, affects some cells, and is limited to one of the markers.

Large cell neuroendocrine carcinoma requires differentiation from thoracic SMARCA4-deficient undifferentiated tumor (SMARCA4-DUT), which often shows synaptophysin expression. Determining the loss of BRG1 protein expression by immunohistochemistry is important to diagnose SMARCA4-DUT [10, 11].

### Large-cell neuroendocrine carcinoma epidemiology and clinical data

Large cell neuroendocrine carcinomas account for approximately 3% of all primary epithelial lung tumors. The results of epidemiological studies indicate an increase in the prevalence of LCNECs, which is probably related to the improvement in pathological diagnostics and the wider use of neuroendocrine immunohistochemical markers [14–16].

Large cell neuroendocrine carcinomas are characterized by many features shared with small cell lung cancers including aggressive course, unfavorable prognosis, high Ki-67, and extensive tumor necrosis. In approximately 40–50% of cases, distant metastases occur already at diagnosis. These tumors are more commonly diagnosed in men, and older people and are strongly related to tobacco smoking. However, unlike small cell lung cancers, in over 75% of cases, large cell neuroendocrine carcinomas are located in the peripheral parts of the lungs [17], more often in the upper lobes [18]. Large-cell neuroendocrine carcinoma cells usually do not produce vasoactive amines, which is associated with the rare occurrence of paraneoplastic syndromes.

The main etiological factor of LCNEC is smoking. However, cases of transformation of adenocarcinoma with mutations in the epidermal growth factor receptor (*EGFR*) gene into LCNEC as a result of treatment with small molecule EGFR tyrosine kinase inhibitors (TKIs) have also been reported.

The prognosis for patients diagnosed with LCNEC is unfavorable and comparable to SCLC. The median overall survival (OS) rate in the advanced stage of the disease is from 8 to 12 months, and the 5-year survival rate does not exceed 8% [19, 20]. The 5-year survival rates in all stages range from 13 to 57%, and patients after radical surgery experience recurrences more often than in the case of non-neuroendocrine NSCLC [21–24].

## Molecular diagnostics and its clinical importance

Next-generation sequencing (NGS) allowed the identification of the main molecular subtypes of LCNECs, which are large cell neuroendocrine carcinomas with molecular features similar to SCLC (SCLC-like LCNEC) with molecular features similar to NSCLC (NSCLC-like LCNECs). The distinction between the above-mentioned subtypes is important in the context of selecting a therapeutic approach. The most common genetic abnormalities revealed by NGS testing performed in 45 patients with LCNEC, concerned the *TP53* (78%), *RB1* (38%), *STK11* (33%), *KEAP1* (31%), and *KRAS* (22%) genes. The genomic profile of patients classified as SCLC-like LCNEC subtype (n = 18, 40%) was characterized by the presence of *RB1*/*TP53* mutations or inactivation of these genes resulting in the lack of RB1 protein expression and the presence of other disorders characteristic for SCLC (including *MYCL* amplification). Additionally, no mutations in the *STK11* or *KRAS* genes were found in this subtype. In turn, in the NSCLC-like LCNEC subtype (n = 25, 60%), no *RB1*/*TP53* mutation was detected, and the expression of the RB1 protein was determined by the wild-type *RB1* gene. Loss of *RB1* gene activity occurs in 95% of SCLC, therefore, doubts regarding the expression of the RB1 protein may support the diagnosis of LCNEC rather than SCLC. In the NSCLC-like LCNEC subtype, additional genetic disorders were found (e.g. in *KRAS*, *STK11,* or *KEAP1* genes), which may co-occur with the *TP53* gene mutation [20] (Tab. 3). Disorders in the *RB1* gene or RB1 protein expression may be an important predictive factor in the selection of a chemotherapy regimen. It was shown that LCNEC patients with no *RB1* gene disorders or RB1 protein expression have benefited more in terms of OS from chemotherapy regimens used in NSCLCs [platinum-based doublets in combination with gemcitabine or taxoid (NSCLC-gem/tax)] than from regimens used in SCLCs [platinum-based doublet in combination with etoposide (SCLC-PE)]. In patients treated with the NSCLC-gem/tax regimen, median OS was 9.6 months, while in patients receiving SCLC-PE, median OS was 5.8 months (p = 0.026), and in patients receiving pemetrexed (NSCLC-pem), median OS was 6.5 months (p = 0.039) [25].

**Table 3. Large cell neuroendocrine carcinoma (LNEC) subtypes**

| NSCLC-like LCNEC | SCLC-like LCNEC |
|---|---|
| Wild-type *RB1* gene → RB1 protein expression<br>Without *RB1*/*TP53* co-mutation | *RB1* gene inactivation → without RB1 protein expression 1<br>*RB1*/*TP53* co-mutation |
| *KRAS*, *STK11*/*KEAP1* genes mutations ± *TP53* gene mutation | Without *STK11*, *KRAS* gene mutations |
| **Alterations occurring almost exclusively in the NSCLC-like LCNECs:** *MAP2K1, ERBB2, BRAF, CDKN2A* | **Alterations occurring almost exclusively in the SCLC-like LCNECs:** *PTEN, MYC* amplification |
| **Type I** | **Type II** |
| $DLL3^{high}/ASCL1^{high}/Notch^{low}$<br>Often coexists with *STK11*/*KEAP1* gene mutations | $DLL3^{low}/ASCL1^{low}/Notch^{high}$<br>Often coexists with *RB1*/*TP53* co-mutation |

NSCLC — non-small cell lung cancer; SCLC — small cell lung cancer

In another study including 54 patients, their classification into SCLC-like LCNEC and NSCLC-like LCNEC was made on the basis of the genomic profile determined using NGS from circulating cell-free DNA (cfDNA). The concordance between genomic profiling of tumor tissue and cfDNA for LCNEC subtype determination was 90%. Significantly higher Ki-67 expression was found in patients with the SCLC-like LCNEC subtype ($p < 0.05$). All patients had clinical stage III or IV, which made radical treatment impossible. All patients received first-line platinum-based chemotherapy. A higher overall response rate (ORR) was demonstrated in patients with the SCLC-like LCNEC subtype (46.7% *vs.* 25.6% in patients with the NSCLC-like LCNEC subtype), although median OS was lower (9.8 months *vs.* 14.4 months, respectively; $p = 0.18$). Additionally, patients with the SCLC-like LCNEC subtype treated with the SCLC-PE regimen showed 1) significantly higher disease control rates (DCRs) than patients receiving NSCLC-pem (100% *vs.* 20%, respectively; $p = 0.007$) and 2) significantly higher ORR (75% *vs.* 0%, respectively; $p = 0.02$). In patients with the SCLC-like LCNEC subtype who received the SCLC-PE regimen, a longer median progression-free survival (PFS) rate was also observed compared to patients receiving the NSCLC-pem or NSCLC-gem/tax regimen (median PFS 8.3 months *vs.* 2.4 months, respectively; $p = 0.002$) [26].

Other authors also highlighted a new molecular target, the delta-like ligand 3 (DLL3) protein. Delta-like ligand 3 protein expression has been demonstrated in many patients with SCLC and LCNEC. It may be a potential target for antibody-drug conjugates (ADCs) or bispecific T-cell engager (BITE) antibodies directed against both DLL3 and CD3, which are currently the subject of intensive research in SCLC patients. Based on transcriptome and quantitative gene expression analysis, 2 subtypes of LCNEC were distinguished. Type I (37%) showed high expression of neuroendocrine genes (*ASCL1* and *DLL3*) and suppression of Notch signaling pathway genes ($ASCL^{high}/DLL3^{high}/NOTCH^{low}$), which often correlates with the mutations in the *STK11*/*KEAP1* or *TP53* genes. Conversely, type II (42%) showed low expression of neuroendocrine markers, *ASCL1* and *DLL3*, and activation of the NOTCH signaling pathway genes ($ASCL^{low}/DLL3^{low}/NOTCH^{high}$). In type II, the occurrence of *RB1*/*TP53* mutations was often observed, as well as high expression of genes encoding proteins of immune-related pathways, which may have implications in the context of predicting response to immune checkpoint inhibitors [27].

The occurrence of molecular disorders characteristic of lung adenocarcinoma has also been reported in LCNEC patients (e.g. mutations in the *EGFR* gene — 1%, *ALK* gene rearrangements, mutations in the *KRAS* and *FGFR1* genes— 5% each, and ERBB2 — 4%), which may influence decisions regarding the use of molecularly targeted drugs [28–32].

## Treatment

### Adjuvant treatment

The unfavorable prognosis for LCNEC patients is illustrated by the 5-year survival rate in patients with stage I tumors undergoing surgery, which is 54.5% compared to 89.3% in other types of NSCLC [33]. Data regarding the efficacy of adjuvant chemotherapy in stage I are inconclusive, and some researchers point to its benefits, including increased median OS in patients receiving platinum-etoposide regimen compared to other regimens used in NSCLC (42 months *vs.* 11 months, respectively; $p < 0.001$) [34, 35].

### Chemotherapy

Due to the low prevalence of LCNEC (only 1–3% of NSCLC patients) and the lack of phase III clinical trials, the optimal strategy for systemic treatment of patients with advanced or generalized disease has not been established yet.

**Table 4. Prospective clinical trials assessing the efficacy of chemotherapy in large-cell neuroendocrine carcinoma (LCNEC)**

| Author | Study type | Sample size (n) | Intervention | Results |
|---|---|---|---|---|
| Niho, 2013 [40] | Single-arm, multicenter, phase II | n = 44<br>LCNEC n = 30<br>SCLC n = 10 | **IRI 60 mg/m$^2$**<br>day 1, 8, 15<br>**CDDP 60 mg/m$^2$**<br>day 1<br>cycle 4 weeks | RR 54%<br>mPFS 5.9 months, mOS 15.1 months<br>**LCNEC *vs.* SCLC:**<br>— RR 46.7% *vs.* 80%; p = 0.0823<br>— mPFS 5. 8 months *vs.* 6.2 months; p = 0.382<br>— mOS 12.6 months *vs.* 17.3 months; p = 0.047 |
| Le Treut, 2013 [41] | Single-arm, multicenter, phase II | n = 42<br>LCNEC n = 31<br>SCLC n = 9<br>NSCLC n = 1<br>AC n = 1 | **CDDP 80 mg/m$^2$**<br>day 1<br>**Etopozyd 100 mg/m$^2$**<br>days 1–3<br>cycle 21 days | mPFS 5.2 months<br>mOS 7.7 months<br>1-year PFS 14.3%<br>1-year OS 26.8%<br>**LCNEC vs. SCLC:**<br>— PFS 5.0 months *vs.* 3.1 months<br>— mOS 8.0 months *vs.* 7.0 months; p = 0.55 |
| Christopoulos, 2017 [42] | Single-arm, multicenter, phase II | n = 49 | **CBDCA AUC5**<br>**PACLI 175 mg/m$^2$**<br>day 1<br>cycle 21 days<br>**EVERO 5 mg/day**<br>**× 4 → EVERO 5 mg/day** | ORR 45%<br>DCR 74%<br>mPFS 4.4 months<br>mOS 9.9 months |

AC — atypical carcinoid tumor; AUC — area under the curve; CBDCA — carboplatin; CDDP — cisplatin; DCR — disease control rate; EVERO — everolimus; IRI — irinotecan; mOS — median overall survival; mPFS — median progression-free survival; NSCLC — non-small cell lung cancer; PACLI — paclitaxel; RR — response rate; SCLC — small cell lung cancer

The majority of data on the efficacy of different chemotherapy regimens come from retrospective analyses covering small groups of several to several dozen patients, receiving chemotherapy regimens used in SCLC (platinum derivatives-etoposide) or NSCLC (platinum-taxane, platinum-irinotecan, platinum-pemetrexed) patients [35–39].

Retrospective analysis of the data from the Netherlands Cancer Registry and the Netherlands Pathological Registry (PALGA) included 124 patients with stage IV LCNEC treated in 2003–2009. It was shown that patients receiving regimens for NSCLC (NSCLC-type; n = 60, 46%) had a better prognosis than patients receiving regimens containing pemetrexed (NSCLC-pt; n = 16, 20%) or regimens for SCLC (SCLC-type; n = 48, 38%). The median OS rate in these groups of patients was 8.5 months *vs.* 5.9 months [hazard ratio (HR) = 2.51; p = 0.002) and 6.7 months (HR = 1.66; p = 0.02), respectively. It should be emphasized that the choice of chemotherapy regimen did not depend on the LCNEC subtype (NSCLC-like LCNEC/SCLC-like LCNEC), and over the years, chemotherapy typical of NSCLC was less widely used (59% in 2003–2009 and 31% in 2010–2012), while the platinum-etoposide regimen was more common (31% and 53%, respectively) [36].

Retrospective analysis of 45 LCNEC patients treated at Samsung Medical Center in Seoul in 2001–2010 showed an improvement in the efficacy of chemotherapy regimens typical of SCLC; however, without statistical significance. In patients receiving platinum with etoposide in the first treatment line (n = 11), the benefits in terms of the treatment response rate (73% *vs.* 50%; p = 0.19), median PFS (6.1 months *vs.* 4.9 months; p = 0.41), and median OS by more than 7 months (16.5 months *vs.* 9.2 months; p = 0.10) were obtained. As in the previous analysis, the choice of chemotherapy regimen was at the investigator's discretion and did not depend on the LCNEC subtype [35]. The efficacy of various chemotherapy regimens was also assessed in prospective clinical trials (Tab. 4 [40–42]).

In the multicenter phase II clinical trial, the effectiveness of the combination of irinotecan and cisplatin was assessed in 44 patients. The treatment response rate was 54.5%, median PFS 5.9 months, and median OS 15.1 months. After central pathological verification, the diagnosis was changed from LCNEC to SCLC in 10 of 44 patients. Treatment response rates were higher in patients with SCLC than in LCNEC (80% *vs.* 46.7%; p = 0.0823), and the use of irinotecan in combination

with cisplatin was also associated with prolonged median OS in SCLC patients (6.2 months *vs.* 5.8 months and 17.3 months *vs.* 12.6 months) [40].

Similarly, lower efficacy of chemotherapy in LCNEC patients compared to SCLC patients was observed in a retrospective analysis of 45 patients. The ORR in patients receiving platinum-based doublet chemotherapy in combination with etoposide was only 37%, while patients receiving other chemotherapy regimens did not respond to treatment (0%) [43].

## Immunotherapy

Immunotherapy alone or in combination with chemotherapy is now the standard of care and first-line treatment of NSCLC patients; however, LCNEC patients were not included in pivotal trials. The addition of an immune checkpoint inhibitor (atezolizumab or durvalumab) to platinum-based standard chemotherapy with etoposide has led to survival improvement in SCLC patients. The efficacy data of immunotherapy in LCNEC patients are mainly from single case reports or case series. The incidence rate of the programmed cell death ligand 1 (PD-L1) positive expression is lower in LCNEC patients than in SCLC ones. In a retrospective analysis, 17 of 76 LCNEC patients who underwent radical resection between 1998 and 2010 showed positive PD-L1 expression on tumor cells [> 1%, tumor cell (TC)+ 22%]. In 12 of these patients, PD-L1 expression was not detected on tumor-infiltrating immune cells (IC–). In turn, in 16 of 28 IC+ patients, no PD-L1 expression was detected on tumor cells (TC–). The lowest percentage of patients with 5-year tumor-specific survival (TSS) was demonstrated in the TC+/IC– group (0% *vs.* 60% in TC–/IC+ patients; $p < 0.017$). A similar relationship was shown in patients with metastatic LCNEC. PD-L1 expression > 1% was found in 11% of 68 patients with LCNEC. Patients with PD-L1 expression > 1% had shorter overall survival compared to patients without PD-L1 expression (4 months *vs.* 11 months), however, without statistical significance. TC+/IC– patients had the worst prognosis, especially compared to TC–/IC+ patients (2 months *vs.* 8 months; $p = 0.004$), and most of them received platinum-etoposide chemotherapy [44]. However, data regarding the prognostic value of positive PD-L1 expression in patients with LCNEC are contradictory and some authors indicate a better prognosis in TC+ patients [45–47]. In a case series, response rates to immunotherapy ranged from 29% to 60%, with nivolumab or pembrolizumab administered in the second or subsequent treatment lines [48, 49].

In a retrospective study assessing the efficacy and safety of immunotherapy in 23 LCNEC patients, median OS was 11.8 months [48]. Another retrospective analysis showed that using immunotherapy in 37 patients was associated with improved OS both in univariate (HR for OS in patients receiving immunotherapy = 0.63; $p = 0.0112$) and in multivariate analysis (HR = 0.64; $p = 0.0164$) compared to patients who did not receive immunotherapy [49]. A 12-month OS rate in patients receiving and not receiving immunotherapy was 34% and 24.1%, respectively, and the 18-month OS rate was 29.1% and 15%, respectively [43]. Extremely valuable observations are provided by data from patients treated in routine clinical settings [real-world evidence (RWE)]. Of 41 patients who received immunotherapy in any treatment line, 10% received nivolumab in combination with ipilimumab, 7% received platinum derivatives with pemetrexed and pembrolizumab, 5% received platinum with etoposide and atezolizumab, and the remaining patients received immunotherapy alone. The median OS rate from LCNEC diagnosis was longer in patients receiving immunotherapy (12.4 months *vs.* 6 months in patients not receiving immunotherapy; HR = 0.59, $p = 0.02$) and the median OS rate from immunotherapy introduction was 11 months [95% confidence interval (CI) 6.1–19.4]. In the group of patients undergoing immunotherapy, there were fewer patients with the Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2–4 (25% *vs.* 56%), and they were relatively younger, with a median age of 63 years *vs.* 67.5 years. After adjusting for age and PS, median OS was 12.5 months *vs.* 8.4 months, respectively ($p = 0.046$). The 1- and 2-year survival rates in patients who received and did not receive immunotherapy were 55% *vs.* 25% and 32% *vs.* 18%, respectively. Despite the retrospective nature of this analysis, the data regarding the use of immune checkpoint inhibitors should be considered encouraging [50]. Another analysis including 17 LCNEC patients showed that in patients receiving nivolumab in the second or subsequent treatment lines, mOS was 12.1 months, median PFS was 3.9 months, and the ORR and DCR were 29.4% and 58.8%, respectively [51]. Several clinical trials assessing the efficacy and safety of immunotherapy in LCNEC are currently ongoing (Tab. 5), both in the first and subsequent treatment lines, and the results of some of them are expected in the near future [52].

## Targeted therapy

As mentioned above, molecular disorders characteristic of NSCLC are detected much less frequently in LCNEC patients. In the analysis of 467 LCNEC patients, potentially targetable genetic alterations included exon 19 deletions (19del) in the *EGFR* gene (0.48% of patients), *exon 21 L858R substitution* (*L858R*) in the *EGFR* gene (0.48%), *ALK* gene fusions (1.7%), and *KRAS* G12C mutations (2.9%). *EGFR* and *ALK* gene alterations affected only patients with the NSCLC-like LCNEC subtype. *BRAF*

**Table 5. Clinical trials with immunotherapy in large-cell neuroendocrine carcinoma (LCNEC) patients**

| Study | Phase/status | Indication | Treatment arms | Primary endpoints | Sample size (n) |
|---|---|---|---|---|---|
| NCT02834013 DART SWOG 1609 | Prospective, phase II, active, non-recruiting<br>End of study 31.10.2024 | — LCNEC<br>— progression after at least one line of CHT | NIVO + IPI<br>*vs.*<br>NIVO | ORR | 818 |
| NCT03591731 (NIPINEC) | Prospective, phase II, active, non-recruiting<br>End of study 09.2023 | — poorly differentiated neuroendocrine tumors, including LCNEC<br>— progression after one or two lines of CHT, including one platinum-based | NIVO<br>*vs.*<br>NIVO + IPI | ORR | 185 |
| NCT03728361 | Prospective, phase II, active, non-recruiting<br>End of study 31.12.2023 | — SCLC, neuroendocrine tumors regardless of differentiation and location, including LCNEC<br>— progression after one line of chemoimmunotherapy (cohort A) or any line of treatment (cohort B) | NIVO + temozolomid | ORR | 55 |
| NCT03976518 | Prospective, phase II, active, non-recruiting<br>End of study 31.10.2023 | — rare NSCLC subtypes, including LCNEC | ATEZO | DCR | 43 |
| NCT06049966 | Prospective, phase I, non-recruiting<br>End of study | — first line | ATEZO + CBDCA + ETOPOSID → ATEZO | PFS<br>OS | 22 |
| NCT05470595 | Prospective, phase II, single-arm, recruiting<br>End of study 31.01.2029 | — first line | ATEZO + CBDCA + ETOPOSID → ATEZO | OS | 67 |
| EUDRACT 2020-005942-41 (DUPLE) | Prospective, phase II, active, recruiting | — LCNEC<br>— first line | DURVA + CBDCA + ETOPOSID ×4 → DURVA | 1-year OS | 49 |

ATEZO — atezolizumab; CBDCA — carboplatin; CHT — chemotherapy; DCR — disease control rate; DURVA — durvalumab; IPI — ipilimumab; NIVO — nivolumab; NSCLC — non-small cell lung cancer; ORR — objective response rate; SCLC — small cell lung cancer

V600E mutation and *RET* or *NTRK* gene fusion were not detected in any patient [53]. However, case reports of patients successfully treated with ALK TKI with mOS lasting up to 36 months have been published [54–57].

## Conclusions

Large cell neuroendocrine carcinomas account for 3% of all diagnosed lung cancers. They are very similar to SCLC (including occurrence mainly in older people and a strong connection with smoking). The prognosis is extremely poor, and median OS usually does not exceed one year. According to the 2015 WHO classification, large cell neuroendocrine carcinomas are classified as neuroendocrine tumors, alongside TC and AC as well as SCLC. The diagnosis of LCNEC requires the presence of typical morphology (organoid structure, trabecular, palisade structures, rosettes) and at least one of the immunohistochemical neuroendocrine markers (chromogranin A, synaptophysin, or NCAM/CD56).

The optimal therapeutic approach in LCNEC patients has not yet been determined. Based on NGS results, two subtypes of large cell neuroendocrine carcinomas can be distinguished: SCLC-like LCNEC type with the presence of *TP53*/*RB1* co-mutation and NSCLC-like LCNEC type, usually without the *RB1* mutation but with the *KRAS* or *STK11*/*KEAP1* genes mutations. This distinction may be the basis for therapeutic decisions on chemotherapy regimens typical of SCLC (platinum–etoposide) or NSCLC (platinum–gemcitabine, platinum–taxoid), which has been shown to improve treatment outcomes. Data on the efficacy of immunotherapy in LCNEC patients are encouraging, but they are limited and most often come from case reports or case series and RWE analyses.

Accurate LCNEC diagnosis is crucial, and treatment algorithms should be developed based on multicenter prospective clinical trials.

## Article Information and Declarations

### Author contributions

K.S., R.L.: conception, writing, final approval; M.B.: writing, review.

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### Conflict of interest

Authors declare no conflict of interest

### Supplementary material

None.

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