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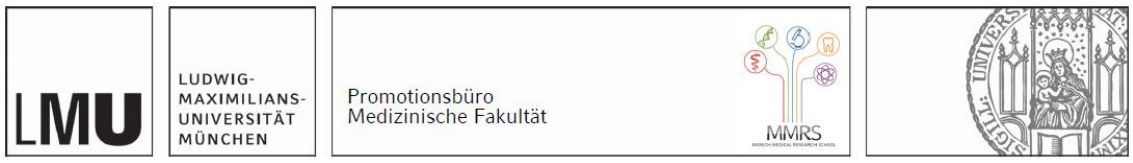

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List of abbreviations

A list of abbreviations can be helpful to the reader, especially if when you are using numerous and uncommon abbreviations.

AE – Adverse Events

ADA – Anti-Drug Antibody

ADC – Antibody Drug Conjugate

AJCC – American Joint Committee on Cancer

ASCL1 – Achaete-Scute Complex Homolog 1

CBR – Clinical Benefit Rate

ChT – Chemotherapy

CI – Confidence Interval

Cmax – Maximum Concentration

CNS – Central Nervous System

CR – Complete Response

cCRT – Concomitant Chemoradiotherapy

CT-computed tomography

DCvac – Dendritic Cell Vaccine

DCR – Disease Control Rate

DDR – DNA Damage Repair

DOR – Duration of Response

DLT – Dose Limiting Toxicity

ECOG – Eastern Cooperative Oncology Group

ESMO-European Society of Medical Oncology

ES-extensive stage

FACT-L – Functional Assessment of Cancer Therapy–Lung

FFPE- Formalin-Fixed, Paraffin-Embedded

FNA-fine needle aspiration

H&E-Hematoxylin & eosin

HIF-1α – Hypoxia-Inducible Factor 1-alpha

HR – Hazard Ratio

ICIs – Immune Checkpoint Inhibitors

irORR – Immune-Related Objective Response Rate

IASLC – International Association for the Study of Lung Cancer

I-DXd – Ifinatamab Deruxtecan

IASLC – International Association for the Study of Lung Cancer

IHC- Immunohistochemistry

LDRT – Low-Dose Radiotherapy

LD – Limited Disease

LDCT-Low dose CT

LCC-large cell carcinoma

LCNEC-large cell neuroendocrine carcinoma

LMU – Ludwig-Maximilians-Universität

LS-limited stage

mOS – Median Overall Survival

mPFS – Median Progression-Free Survival

M-Metastasis

MSI – Microsatellite Instability

MTD – Maximum Tolerated Dose

MVD-Microvessel density

N-node

NET-neuroendocrine tumour

NLST-National Lung Cancer Screening Trial

NSCLC- non-small cell lung cancer

ORR – Objective Response Rate

OS – Overall Survival

PCI- Prophylactic Cranial Irradiation

PD-1 – Programmed Cell Death Protein 1

PD-L1 – Programmed Death-Ligand 1

PFS – Progression-Free Survival

PFSR – Progression-Free Survival Rate

PK – Pharmacokinetics

PR – Partial Response

PARP – Poly (ADP-Ribose) Polymerase

18F-FDG PET/CT – Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

QoL – Quality of Life

RP2D – Recommended Phase 2 Dose

RT – Radiotherapy

SAE – Serious Adverse Events

SCLC – Small Cell Lung Cancer

SoC – Standard of Care

T-Tumor

TACs – Time Activity Curves

TBI – Total Body Irradiation

TEAEs – Treatment-Emergent Adverse Events

TMB – Tumor Mutational Burden

TTP – Time to Treatment Progression

TTCD – Time to Confirmed Deterioration

TTDD – Time to Definitive Deterioration

TTR – Time to Response

VEGF – Vascular Endothelial Growth Factor

WHO-World Health Organization

WBRT-whole brain radiotherapy

1. Epidemiology

1.1 Incidence

Lung cancer remains the deadliest form of cancer worldwide, contributing to nearly one in every five cancer-related fatalities. As the World Health Organization (WHO) notes, "lung cancer remains the leading cause of cancer death globally, accounting for nearly one in five deaths from cancer worldwide" [1]. Despite considerable progress in diagnostic tools and therapeutic strategies, the disease still presents a significant public health challenge (see [2]).

According to data from the Robert Koch Institute (RKI), "in Germany in 2020, approximately 57,500 new cases of lung cancer were diagnosed (37,000 in men and 20,500 in women)" [3]. In terms of frequency, lung cancer ranks as the second most common malignancy in men (after prostate cancer) and the third in women (following breast and colorectal cancers) [3]. The estimated lifetime risk of developing the disease in Germany is 1 in 9 for men and 1 in 20 for women [3].

Representing roughly 15% of all lung cancer diagnoses worldwide, small cell lung cancer (SCLC) is known for its aggressive nature, marked by swift disease progression and early metastatic spread. [4]. It is particularly aggressive and is characterized by rapid progression and early metastasis. As highlighted in global estimates, "more than 200,000 new cases of SCLC occur annually worldwide" [4]. The majority of cases occur in individuals over 60 and are strongly associated with smoking, with"over 90% of cases occur in current or former smokers, many of whom present with pre-existing cardiopulmonary or metabolic comorbidities" [5].

Significant regional differences in incidence rates are evident within Germany. The RKI states: "higher incidence rates are observed in eastern federal states, which reflect historical differences in smoking prevalence" [3]. The national age-standardized incidence is estimated at 67 per 100,000 men and 34 per 100,000 women [3]. Urban and industrialized areas report notably higher rates, likely due to occupational and environmental risk exposures.

Between 2008 and 2019, the incidence of lung cancer in women steadily increased by 2.8% annually [3]. This trend is largely attributed to delayed effects of increased smoking prevalence among women in previous decades.

These developments emphasize the persistent public health burden posed by lung cancer and the need for targeted prevention and early detection strategies adapted to changing demographic and behavioral patterns.

1.2 Mortality

As of 2020, lung cancer was the leading cause of cancer-related deaths among men in Germany and the second most common in women. The RKI reported that "27,751 men and 17,066 women died of lung cancer in 2020" [3]. Lung cancer thus accounted for 22.8% of all male cancer deaths and 15.8% of those in women [3].

The age-adjusted mortality rate in Germany in 2020 stood at 40.5 per 100,000 for men and 21.9 per 100,000 for women [3]. Between 2015 and 2020, mortality from lung cancer decreased by 9.2% in men but increased by 6.0% in women [3]. These shifts mirror historic smoking trends in Germany, where male smoking rates have steadily declined, while female smoking prevalence increased later in the 20th century.

This divergence highlights the urgency of preventive measures focusing on smoking cessation and health education—particularly among women—as critical tools in reducing the mortality burden of lung cancer.

1.3 Survival

Despite advances in treatment, survival rates for lung cancer remain low. According to the RKI, "the 5-year relative survival rate is approximately 19% for men and 25% for women" [3].

Outcomes vary significantly depending on the disease stage at diagnosis. Patients with limited-stage SCLC have a considerably better prognosis compared to those with extensive disease. According to SEER data, "the 5-year survival rate is about 26% for limited-stage SCLC, whereas extensive-stage patients have survival rates between 1% and 2%" [6].

1.4 Prevalence

In 2020, five-year prevalence estimates indicated that about 55,500 men and 41,300 women in Germany were living with a lung cancer diagnosis [3]. Extending the observation window to ten years, prevalence increases to 77,300 for men and 57,500 for women [3].

These statistics reflect the aggressive course of the disease and the frequency of late-stage diagnosis that contributes to the persistently low long-term survival rates observed.

Looking back, outcomes were even worse in earlier decades. As the RKI reported: "a study analyzing data from 2000–2002 found markedly low 10-year relative survival rates for lung cancer patients," underscoring the severity and lethality of the disease at that time [3].

2. Prevention

2.1 Risk Factors

Tobacco use continues to be the most significant contributor to SCLC, accounting for nearly all diagnosed cases. It has been reported that "approximately 95% of all cases of SCLC" are attributable to smoking, including cigarettes, cigars, and pipes [7].

Multiple indicators of smoking exposure, such as the length of time smoked, intensity, age at initiation, and pack-years, are closely tied to lung cancer risk (see [8, 9]). One comprehensive pooled analysis found that "the risk is much higher in current smokers (OR = 42.0, 95% CI: 21.7–81.2) than former smokers (OR = 17.1, 95% CI: 9.5–31.0)" [10]. Although the risk decreases after quitting, it "remained higher than the baseline risk among never smokers, even 35 years after quitting" [11].

While pack-years are commonly used in clinical and epidemiological assessments, some studies suggest that the temporal pattern of smoking matters more than the cumulative quantity. As reported by Lubin et al., "for an equal total exposure, smoking at a lower intensity over a longer time period leads to a higher risk of lung cancer compared with smoking at a higher intensity over a shorter time period" [9–12].

The type of cigarette, use of filters, and inhalation patterns can also influence the risk. Specifically, "use of filter and lower-tar cigarettes is associated with a higher risk of peripherally located lung cancer (e.g., adenocarcinoma and large cell cancer) whereas nonfilter cigarette consumption is linked to a higher incidence of centrally located lung cancer (e.g., squamous cell lung cancer and SCLC)" [13,15].

Although rare, SCLC can occur in never-smokers. "It is estimated that 2 to 3% of the SCLCs occur among never smokers"[16,17]. In these cases, environmental and occupational factors are believed to play a key role. Substances such as radon, diesel exhaust, asbestos, arsenic, and heavy metals (e.g., cadmium, chromium, nickel) have all been linked to elevated lung cancer risk [18].

In Germany, occupational exposures are believed to contribute to approximately 9–15% of all lung cancer cases. In particular, high radon exposure is a notable risk, especially in regions where naturally occurring radon gas accumulates indoors. According to national estimates, "around 2,800 lung cancer deaths per year in Germany are attributable to residential radon exposure" [19].

Radon gas (specifically isotopes ^{222}Rn and ^{220}Rn) can seep into enclosed spaces like basements and accumulate, exposing inhabitants to radioactive decay products such as polonium, bismuth, and lead. These particles can be inhaled and lodge in the lungs, causing mutations. Studies have shown that "radon exposure is associated with tumor suppressor TP53 gene somatic mutation, which is found in up to 90% of patients with SCLC compared with 23% to 65% in non-small cell lung cancer (NSCLC)" [22,23].

The occupational lung cancer burden differs by sex. "The attributable fraction for lung cancer from occupational exposures has been reported to be as high as 15% in males and 5% in females", with major culprits including asbestos, diesel exhaust, crystalline silica, and polycyclic aromatic hydrocarbons [24,25].

Air pollution—both indoor and outdoor—also plays a role in lung carcinogenesis. However, most studies do not differentiate between histological subtypes, limiting the available data specific to SCLC [26,27]. Hormonal and dietary influences may also contribute, although the evidence is limited by small sample sizes and inconsistent findings across studies [28–31].

Screening strategies targeting individuals at high risk, particularly long-term smokers, offer an opportunity to detect lung cancer earlier and improve survival outcomes [32].

2.2 Primary and Secondary Prevention

Efforts to prevent lung cancer fall into two main categories: primary prevention, which aims to eliminate or reduce exposure to known risk factors, and secondary prevention, which focuses on early detection. Primary prevention emphasizes measures such as smoking cessation programs, stricter regulation of occupational and environmental pollutants, public health campaigns, and improved indoor air quality [33]. Tobacco taxation, legislative bans on smoking in enclosed spaces, and workplace safety reforms are key components.

Secondary prevention involves screening individuals at elevated risk to catch the disease at a more treatable stage. Low-dose computed tomography (LDCT) is the most widely studied and validated method for this purpose. The National Lung Screening Trial demonstrated that LDCT could reduce lung cancer mortality by 20% when compared to chest X-ray screening." [34]. While the findings were largely positive, researchers have raised concerns about overdiagnosis. However, "a pathology review according to the recent classification made this unlikely, as it categorized 97% of the detected cancers as invasive" [35–38].

This finding was supported by the European NELSON trial, which showed that volume-based CT screening could “reduce ten-year lung cancer mortality by at least 25% in high-risk populations” [39].

It is important to note, however, that these screening benefits do not appear to extend to SCLC. Studies indicate that "LDCT did not reveal survival benefit for SCLC" [39–41]. In earlier screening trials, "the proportion of SCLC cases of all staged combined only ranged from 0.7% to 15% with absolute incidence ranging from 22 to 97 in 100,000 person-years" [41].

3. Diagnostic Framework, Staging, and TNM Classification

3.1 Histopathological Classification and Immunohistochemical Characterization

SCLC is classified based on the guidelines outlined in the 5th edition of the WHO Classification of Thoracic Tumours [42]. According to this source, *"the vast majority of lung carcinomas (>95%) are attributed to four primary histological subtypes: squamous cell carcinoma (SCC), adenocarcinoma, large cell neuroendocrin carcinoma (LNEC) and SCLC"* [42].

It is recognized as a unique clinicopathologic entity, requiring both morphological assessment and immunohistochemical analysis for accurate diagnosis—particularly when small biopsy samples are involved. Due to overlapping features with other poorly differentiated tumors, mmunohistochemistry (IHC) is essential in confirming neuroendocrine differentiation.

3.2 Morphological and Immunohistochemical Features

SCLC cells generally appear small, round to oval, with limited cytoplasm and granular chromatin. Hematoxylin and eosin (H&E) stains are typically used to evaluate these features. In ambiguous cases, IHC becomes crucial.

WHO recommends assessing markers such as chromogranin A, synaptophysin, and CD56 to support a neuroendocrine diagnosis. While these markers are not exclusive to SCLC, their expression helps distinguish it from other malignancies.

Interpretative challenges can arise when neuroendocrine markers are focally expressed in other NSCLC, such as large cell neuroendocrine carcinoma (LNEC), which may result in misclassification [43–45].

3.3 Cytological Specimens and Immunohistochemistry

Diagnosis of SCLC can be achieved using formalin-fixed paraffin-embedded (FFPE) tissue samples or cytological specimens, such as those obtained through transbronchial needle aspiration (TBNA), transthoracic fine needle aspiration (FNA), or pleural fluid sampling. Preparing cell blocks from cytologic material improves the ability to perform IHC, particularly in instances where biopsy tissue is sparse.

Cell block specimens enable IHC analysis of neuroendocrine differentiation and biomarkers such as PD-L1. Nevertheless, direct cytologic smears may offer superior preservation of nucleic acids and reduced fixation artifacts, making them more suitable for molecular testing in certain scenarios.

Given these technical strengths, a comprehensive diagnostic protocol that integrates cytological morphology, IHC, and molecular techniques is recommended to ensure precise classification and appropriate treatment planning.

3.4 Molecular Pathology

SCLC was once considered molecularly uniform, but newer research highlights its biological heterogeneity. Nearly all cases involve biallelic loss of tumor suppressors TP53 and RB1, pivotal regulators of the cell cycle [46-48].

These alterations are frequently due to mutations, deletions, or abnormal splicing. Additional genes—such as RBL1, RBL2, and TP73—also contribute to its aggressive phenotype [49-51].

Transcriptomic profiling has led to the identification of subtypes:

- **SCLC-A**: Characterized by ASCL1 expression, the most prelevant subtype (40-50%), sensitive to chemotherapy [52].
- **SCLC-N**: Marked by NEUROD1, expressed in 25-30% of the cases, potentially responsive to DNA repair-targeted agents [52].
- **SCLC-P**: accounts for 7-16% of the cases, features POU2F3, suggesting tuft cell lineage [52, 53].
- **SCLC-I**: represents ~15% of tumors, defined by YAP1, potentially susceptible to immune checkpoint blockade [52, 54].

This molecular subclassification reinforces the heterogeneity of SCLC and underlines the importance of biomarker-guided therapeutic approaches as molecular diagnostics become standard practice.

3.5 Staging and Classification

3.5.1 Clinical Evaluation and Imaging-Based Staging

SCLC staging has historically relied on a two-tiered system: limited-stage (confined to one hemithorax and treatable in a single radiotherapy field) and extensive-stage (disease spread beyond a single field or with distant metastases).

Advanced imaging plays a crucial role in defining disease extent. Per **ESMO guidelines**, when lung cancer is suspected on chest radiograph, the next step is *"a contrast-enhanced computed tomography (CT) scan of the chest and abdomen"* to assess tumor burden and possible metastatic spread [55].

To improve staging accuracy, **PET-CT with 18F-FDG** is used to detect otherwise occult metastases, especially in lymph nodes and bone. While more sensitive than standard CT, false positives due to inflammatory conditions must be considered [56].

Brain imaging—either cranial CT or MRI—is recommended due to SCLC's high risk of CNS spread. Though its necessity in asymptomatic patients is debated [57], neuroimaging is routinely used when staging does not clearly confirm early-stage disease.

3.5.2 Staging Systems

SCLC has traditionally been staged using a binary system proposed by the IASLC in 1989 [58]:

- **Limited-stage (LS-SCLC)** includes disease confined to one hemithorax, including mediastinal and supraclavicular lymph nodes, and treatable within a single radiotherapy field.
- **Extensive-stage (ES-SCLC)** denotes distant metastasis or spread beyond a single radiation portal.

While this two-stage approach remains relevant in clinical settings, it lacks granularity for personalized treatment. More recently, the TNM system, developed by the **AJCC and UICC,** has been adopted to provide better granularity. Tumor size (T), nodal involvement (N), and distant metastases (M) are scored independently. The latest TNM updates, including subdivisions of N2 and M1c, improve prognostic precision and may influence management in borderline cases [59]:

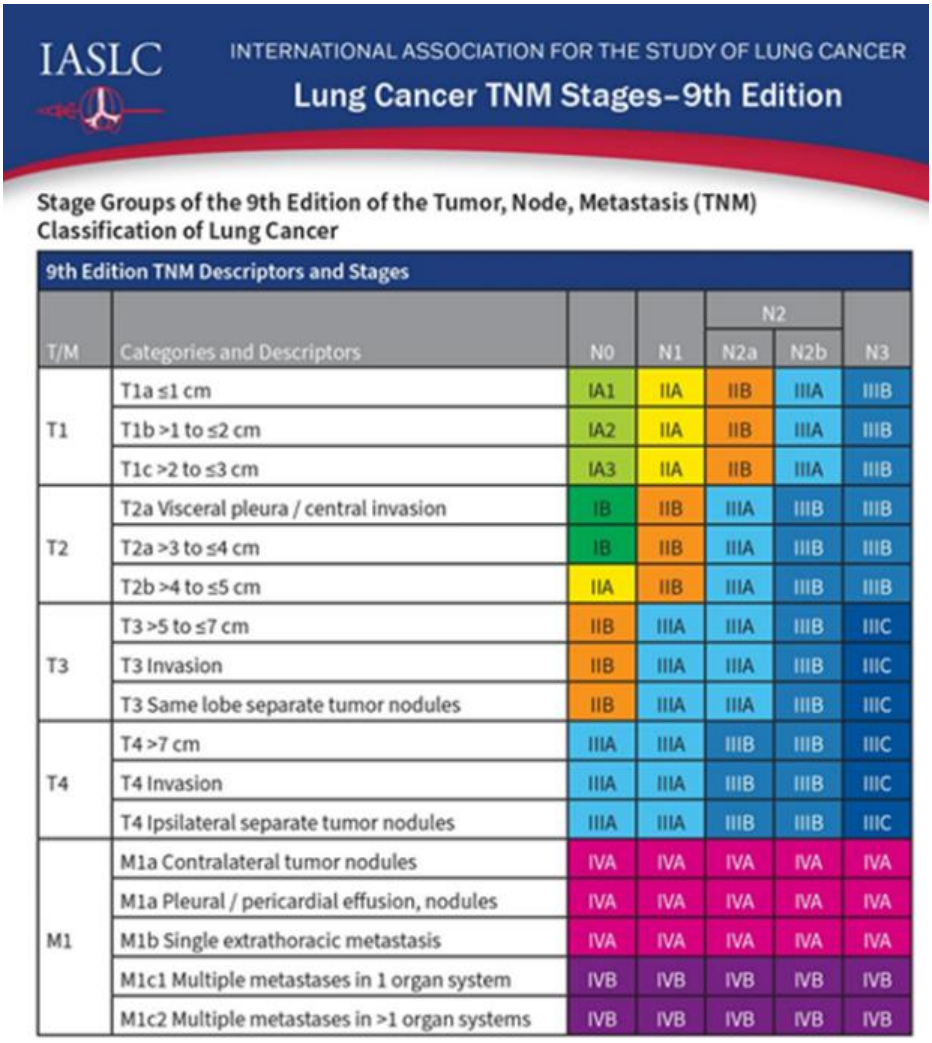
- **N2** is now subdivided into:
    - **N2a:** Single mediastinal node station.
    - **N2b:** Multiple mediastinal stations.
- **M1c** is subdivided into:
    - **M1c1:** Metastases in a single organ system.
    - **M1c2:** Metastases across multiple systems.

These changes improve prognostic stratification and may influence treatment decisions, especially for early or oligometastatic disease where aggressive therapy is under consideration.

Table 1. IASCL 1989 SCLC Classification

Stage	Definition
LS-SCLC	Tumor confined to one hemithorax, which may include: Involvement of contralateral mediastinal or supraclavicular lymph nodes. Ipsilateral pleural effusion, regardless of cytology.
ED-SCLC	Disease that extends beyond the definition of LD, including: Malignant pleural or pericardial effusions. Contralateral hilar or supraclavicular lymph nodes. Hematogenous metastases.

Figure 1. IASCL 9th TNM Edition



IASLC

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

Lung Cancer TNM Stages–9th Edition

Stage Groups of the 9th Edition of the Tumor, Node, Metastasis (TNM) Classification of Lung Cancer

9th Edition TNM Descriptors and Stages						
				N2		
T/M	Categories and Descriptors	N0	N1	N2a	N2b	N3
T1	T1a ≤1 cm	IA1	IIA	IIB	IIIA	IIIB
	T1b >1 to ≤2 cm	IA2	IIA	IIB	IIIA	IIIB
	T1c >2 to ≤3 cm	IA3	IIA	IIB	IIIA	IIIB
T2	T2a Visceral pleura / central invasion	IB	IIB	IIIA	IIIB	IIIB
	T2a >3 to ≤4 cm	IB	IIB	IIIA	IIIB	IIIB
	T2b >4 to ≤5 cm	IIA	IIB	IIIA	IIIB	IIIB
T3	T3 >5 to ≤7 cm	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Invasion	IIB	IIIA	IIIA	IIIB	IIIC
	T3 Same lobe separate tumor nodules	IIB	IIIA	IIIA	IIIB	IIIC
T4	T4 >7 cm	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Invasion	IIIA	IIIA	IIIB	IIIB	IIIC
	T4 Ipsilateral separate tumor nodules	IIIA	IIIA	IIIB	IIIB	IIIC
M1	M1a Contralateral tumor nodules	IVA	IVA	IVA	IVA	IVA
	M1a Pleural / pericardial effusion, nodules	IVA	IVA	IVA	IVA	IVA
	M1b Single extrathoracic metastasis	IVA	IVA	IVA	IVA	IVA
	M1c1 Multiple metastases in 1 organ system	IVB	IVB	IVB	IVB	IVB
	M1c2 Multiple metastases in >1 organ systems	IVB	IVB	IVB	IVB	IVB

4. Treatment of Early-Stage Small Cell Lung Cancer

4.1 Role of Surgery

Surgery plays a limited role in managing early-stage SCLC, which represents a small fraction of cases—typically those with T1-T2 tumors without lymph node involvement (N0) [55]. While historically underutilized, surgery may offer benefit for select patients when carefully staged and evaluated [55, 66].

A 2017 Cochrane review concluded that “currently available randomized controlled trials do not support a role for surgery in the management of stage I–III SCLC” [60]. However, retrospective data suggest that select patients may benefit. In a large cohort study from the National Cancer Database, patients with stage I/II SCLC who underwent lobectomy followed by adjuvant chemotherapy had a median overall survival (OS) of 48.6 months, compared to 28.7 months for those treated with concurrent chemoradiotherapy (cCRT) ($p < 0.0001$) [61].

When surgery is considered, comprehensive mediastinal staging is essential to exclude nodal disease [62, 63]. Postoperative chemotherapy is indicated to address micrometastatic spread [64], and in cases of confirmed nodal involvement, additional thoracic radiotherapy is typically recommended to improve local disease control [63]. Multidisciplinary team decision-making is emphasized to ensure optimal treatment planning [65].

4.2 Chemoradiotherapy

cCRT is the mainstay treatment for patients with limited-stage SCLC who are not eligible for surgery. Combining systemic and local therapies provides a better chance of long-term control compared to chemotherapy alone [55, 66].

As shown by Pignon et al. in a meta-analysis, “the addition of thoracic radiotherapy to chemotherapy reduced the risk of death by 14% and improved 3-year survival by 5.4%” [67]. This benefit was particularly notable in patients younger than 55 years.

Fractionation schedules vary; the CONVERT trial compared hyperfractionated and conventional schedules (45 Gy in 1.5 Gy twice daily vs. 66 Gy in 2 Gy) but found no significant difference in overall survival, “30 months vs. 25 months (HR 1.18; 95% CI 0.95–1.45; $p = 0.14$)” [68]. However, side effect profiles differed, particularly with respect to hematologic toxicity, “with grade 4 neutropenia more frequent in the hyperfractionated group” (49% vs. 38%; $p = 0.05$) [68].

Recent studies have introduced immunotherapy into the treatment landscape for limited-stage disease. The ADRIATIC trial—a phase III, placebo-controlled study—evaluated durvalumab ± tremelimumab as consolidation after cCRT. Durvalumab significantly improved both OS and progression-free survival (PFS), with “median OS of 55.9 vs. 33.4 months” (HR 0.73, $p = 0.01$) and “median PFS of 16.6 vs. 9.2 months” (HR 0.76, $p = 0.02$) [69]. Toxicities were manageable, with grade 3–4 adverse events in 24.4% (durvalumab) vs. 24.2% (placebo) [69].

These results underscore the need to tailor treatment according to the individual’s clinical status, comorbidities, and tolerance of potential toxicities.

4.3 Prophylactic Cranial Irradiation (PCI)

Due to the high likelihood of brain metastases in SCLC—both at diagnosis and over the disease course—prophylactic cranial irradiation (PCI) is commonly used in patients who respond to initial therapy. PCI aims to prevent the emergence of symptomatic or radiographically evident brain metastases [55, 66].

A 2019 meta-analysis involving 2,114 patients demonstrated that “PCI was associated with a significant survival benefit (HR 0.82; 95% CI: 0.71–0.94)” [70]. The benefit was most evident in patients who had not undergone prior brain imaging, likely due to reduced incidence of symptomatic brain metastases.

The standard dose of PCI was established by comparing 25 Gy in 10 fractions with a higher dose of 36 Gy. Results showed no added benefit with the higher dose, solidifying the 25 Gy regimen as standard [71].

However, neurocognitive toxicity remains a concern. The NRG-CC003 study assessed PCI with and without hippocampal avoidance, finding that “the addition of hippocampal avoidance led to a 23% reduction in the risk of first failure in any cognitive domain” (HR 0.77; 95% CI: 0.61–0.98; p = .033) [72]. These findings mirrored those of NRG-CC001, where hippocampal avoidance combined with WBRT and memantine produced a “26% reduction in the risk of cognitive failure” (adjusted HR 0.74; 95% CI: 0.58–0.95; p = 0.02) [73].

MRI surveillance is now being explored as an alternative to PCI. A retrospective study of 1,068 LS-SCLC patients found that while PCI reduced brain metastases, it did not significantly improve overall survival compared to MRI monitoring alone [74].

Two ongoing trials—MAVERICK (SWOG S1827) and PRIMALung (EORTC-1901) —are evaluating whether MRI surveillance can replace PCI in terms of OS, cognitive function, and quality of life [75, 76]. Their outcomes may shift future guidelines by helping balance efficacy with neuroprotection.

4.4 Emerging Therapies

A range of new strategies are under investigation to enhance treatment efficacy for patients with limited-stage SCLC. Immunotherapy combinations and targeted agents are the focus of several ongoing and recently completed trials.

The phase II STIMULI trial explored consolidation therapy using nivolumab and ipilimumab following cCRT. While this dual checkpoint blockade approach showed promise in other cancers, it did not significantly extend progression-free survival in this setting [77].

Likewise, the NRG-LU005 trial assessed the addition of atezolizumab during cCRT but found no improvement in overall survival in its interim results [78]. Trials like KEYLYNK-013 are investigating the benefit of maintenance pembrolizumab, alone or combined with the PARP inhibitor olaparib, following standard chemoradiation [79].

Other innovative therapies include bispecific T-cell engagers such as tarlatamab, which targets DLL3—a protein highly expressed in SCLC. The DeLLphi-306 trial is currently evaluating this agent post-cCRT [80]. These trials reflect a continued effort to bring precision medicine to SCLC by exploiting novel molecular targets and immunologic mechanisms. An overview of these ongoing trials is provided in Table 2 [64, 77–93].

Table 2. Clinical trial in LS-SCLC

ClinicalTrials.gov Identifier	Phase	Intervention	Objective	Status
NCT03703297 [69]	III	Durvalumab + Tremelimumab or Durvalumab+ placebo after cCRT	PFS, OS, ORR, PFS18, PFS24, OS24, OS36, PFS2, QoL, safety	Active, not recruting
STIMULI [77]	II	Nivolumab + Ipilimumab after cCRT	Assess efficacy of immunotherapy consolidation	No significant PFS benefit observed
NCT03811002 [78]	II/III	Atezolizumab + cCRT	Evaluate OS benefit of adding Atezolizumab to cCRT	Active, not recruiting
NCT04624204 [79]	III	Pembrolizumab + cCRT, followed by Pembrolizumab ± Olaparib	Investigate PFS and OS with immune and targeted therapy	Ongoing
NCT06117774 [80]	III	Tarlatamab after cCRT	Assess efficacy and safety of Tarlatamab post-cCRT	Ongoing
NCT06295926 [81]	II	Serprulimab +cCRT	Access efficacy of Serprulimab +cCRT	Ongoing
NCT06095583 [82]	III	Toriplimab alone or in combination with Tifcemalimab (JS004/TAB004) as consolidation after cCRT	Safety and efficacy of Toriplimab alone or in combination with Tifcemalimab (JS004/TAB004)	Ongoing
NCT06719700 [83]	II	cCRT+ Toripalimab+ Surufatinib	Safety and efficacy or cCRT + Toriplimab+ Surufatinib	Ongoing
NCT06773910 [84]	II	BMS-986489 (Atigotatug + Nivolumab) vs Durvalumab after cCRT	Evaluate the efficacy of BMS-986489 vs durvalumab Evaluate the safety profile of BMS-986489	Ongoing
NCT05623267 [85]	II-III	Sugemalimab consolidation therapy versus placebo after cCRT	Evaluate efficacy of sugemalimab consolidation therapy	Ongoing
NCT05904015 [86]	II	Envafolimab+ cCRT	Efficacy and safety of envafolimab+ cCRT	Not yet recruiting
NCT04647357 [87]	II	SHR-1316 after cCRT	PFS	Unknown status
NCT06773156 [88]	II	Adebrelimab Plus Apatinib after cCRT	PFS, OS, Safety, QoL	Enrolling by invitation
NCT03811002 [89]	III	cCRT vs cCRT+ Atezolizumab	OS, PFS, ORR, QoL; safety, PRO-CTCAE	Active, not recruiting
NCT05443646 [90]	II	Serprulimab after Hypofractionated cCRT	PFS, OS, ORR, TTF, DpR, DCR	Ongoing
NCT05483543 [91]	II	Pamiparib after cCRT	1-year PFS, efficaccy and toxicity of Pamiparib after cCRT	Unknown status
NCT02738723 [92]	II	BVRT vs IMRT with cCRT	PFS, OS, Safety and tolerability, tumor response rate	Active, not recruiting
NCT04691063 [93]	III	SHR-1316 or placebo + cCRT	OS and safety of SHR-1316 or placebo + cCRT	Enrolling by invitation

cCRT: concomitant chemoradiotherapy; CTCAE: Common Terminology Criteria for Adverse Events; DCR: Disease control rate; DOR: duration of response; PFS: Progression-Free Survival; PFSR: Progression-Free Survival Rate; ORR: objective response rate; OS: overall survival; PD-1: programmed cell death -1; PD-L1: programmed death ligand-1; QoL: quality of life; RT: radiotherapy; SAE: serious adverse events;

5. Extensive disease

5.1 First-Line Treatment

ES-SCLC is known for its rapid progression and early spread. At the time of diagnosis, over 60% of patients already present with widespread disease [55, 66].

Platinum-based chemotherapy combined with etoposide has long served as the primary treatment approach for patients with extensive-stage SCLC. This regimen, typically involving either cisplatin or carboplatin, leads to high initial response rates but often with short-lived benefit due to rapid development of resistance, with a “median OS of 9–10 months and PFS of 5–6 months, with approximately 35% of patients surviving beyond one year” [94].

Recent advances have introduced immunotherapy into the first-line setting.Two pivotal randomized phase III trials—IMpower133 and CASPIAN—have established chemoimmunotherapy as the new standard for ES-SCLC [95, 96].

In the IMpower133 study, the addition of atezolizumab to carboplatin and etoposide led to “a median OS of 12.3 months versus 10.3 months in the placebo group (HR 0.70, 95% CI: 0.54–0.91; p=0.007)” [95]. PFS was also significantly longer (5.2 vs. 4.3 months; HR 0.77, 95% CI: 0.62–0.96; p = 0.02) [95]. The treatment was generally well tolerated. Long-term follow-up from the IMbrella A extension study showed that “the addition of atezolizumab resulted in a 5-year OS rate of 12% (95% CI, 7%–17%)” [96].

Similarly, the CASPIAN trial demonstrated a meaningful survival advantage with the addition of durvalumab to chemotherapy, showing “a median OS of 13.0 compared to 10.3 months with ChT alone (HR 0.73; 95% CI: 0.59–0.91; p = 0.0047)” [97]. The benefits were consistent across patient subgroups, and toxicity remained manageable. However, the inclusion of tremelimumab did not enhance efficacy compared to chemotherapy alone [97].

In contrast, other immune checkpoint inhibitors have shown limited benefits. The KEYNOTE-604 trial tested pembrolizumab in combination with chemotherapy but did not reach statistical significance for OS despite an HR of 0.80 (95% CI, 0.64–0.98; p = 0.0164) [98]. Additionally, CheckMate 451, which evaluated maintenance nivolumab plus ipilimumab following induction chemotherapy, failed to improve survival, with median OS of 9.2 months vs. 9.6 months for placebo (HR 0.92; 95% CI: 0.75–1.12; p = 0.37) [99].

Thoracic radiotherapy has also been explored in ES-SCLC. In the Jeremic trial, patients with complete response to chemotherapy at distant sites were randomized to receive either thoracic radiotherapy plus chemotherapy or chemotherapy alone. The trial demonstrated that “median OS was 17 months in the thoracic RT group versus 11 months in the control group; 5-year OS rates were 9.1% vs. 3.7%, respectively (p = 0.041)” [100].

The CREST trial investigated the use of thoracic RT after chemotherapy in patients who had responded systemically. While the 1-year OS did not differ significantly (33% vs. 28%), a secondary analysis showed “2-year OS of 13% versus 3% in favor of the thoracic RT arm (p = 0.004)” [101]. Importantly, treatment-related toxicity was similar between groups.

5.2 Second-Line Treatment and Beyond

Treatment options following progression on first-line chemo-immunotherapy are limited. Topotecan remains an approved second-line agent, especially for platinum-resistant patients, though its efficacy is modest and associated with significant hematologic toxicity [102–104].

For those with a chemotherapy-free interval (CTFI) ≥90 days, rechallenging with platinum-etoposide is a viable option. A recent study showed that, in platinum-sensitive relapse, platinum rechallenge led to "superior PFS (4.7 months vs. 2.7 months; HR = 0.57; p = .0041), but similar OS (7.5 vs. 7.4 months)" compared to topotecan [105, 106].

Another option is lurbinectedin, a synthetic alkaloid that has demonstrated activity in relapsed SCLC. In a phase II basket trial (NCT02454972), lurbinectedin achieved "an objective response rate (ORR) of 35.2% (95% CI: 26.2–45.2), with a median OS of 9.3 months and median PFS of 3.5 months" [107]. Higher responses were observed in patients with a CTFI ≥90 days.

Tarlatamab, a bispecific T-cell engager targeting DLL3 and CD3, is a promising novel therapy. In the DeLLphi-301trial, it yielded "an ORR of 40% (95% CI: 31%–51%) and a median OS of 14.3 months," with durable responses and manageable toxicity [108]. In May 2024, the FDA granted accelerated approval for tarlatamab for use in adults with ES-SCLC after progression on platinum-based therapy.

Other targeted therapies under investigation include antibody-drug conjugates (ADCs). Ifinatamab deruxtecan, which targets B7-H3, showed encouraging efficacy in the IDeate-Lung01 study, with "an ORR of 54.8% (95% CI: 38.7–70.2), median PFS of 5.5 months, and median OS of 11.8 months" in previously treated ES-SCLC patients [109].

Sacituzumab govitecan, which targets the Trop-2 antigen, has also shown early promise. In the TROPiCS-03 phase II trial, it achieved an ORR of 41.9% (95% CI: 27.0%–57.9%) with "median DoR, PFS, and OS of 4.73, 4.40, and 13.60 months," respectively [110].

These emerging therapies—including T-cell engagers and ADCs—offer hope for improved outcomes in relapsed SCLC. Continued investigation through clinical trials (see Table 3 [109, 111–166]) is essential to define the optimal use of these agents and refine their safety profiles.

Table 3. Clinical trial in ES-SCLC

ClinicalTrials.gov Identifier	Status	Study overview	Phase	Treatment cohort	Setting
NCT05595460 [111]	Active, recruiting	Safety, Antitumor activity, PK	I	RYZ101+Carboplatin/Etoposide /Atezolizumab in SSTR	1st line
NCT05844150 [112]	Active, recruiting	ORR, OS, PFS, DCR, DOR, TTR; ADA, PK; TRAEs	II-III	PM8002(Anti-PD-L1/VEGF) + Platinum-etoposide	1st line
NCT05544149 [113]	Active, recruiting		II	Thoracic RT after first line ICIs	1st line
NCT04221529 [114]	Active, not recruiting	OS, ORR, PFS, QoL, TRAEs, SAE	II	Atezolizumab+Carboplatin+Etoposide in ECOG ≥2	1st line

NCT06672133 [115]	Active, not yet recruiting	PFS, OS, ORR, DCR, DOR, TRAEs,6m and 1-year PFS, 1–2-year OS,	III	Thoracic RT+ adebrelimab vs. adebrelimab alone as maintenance after debrelimab plus chemotherapy	1st line
NCT06812260 [116]	Active, not yet recruiting	Response (CR or PR), OS, PFS, ORR, DOR, safety	II	HLX10 (Recombinant Humanized Anti-PD-1 Monoclonal Antibody Injection) + Carboboplatin/Etoposid	1st line
NCT06838208 [117]	Active, not yet recruiting	PFS, ORR, DCR, DOR, 6m and 1-year PFS, 1-year OS, TRAEs	II	Tislelizumab +ChT+ thoracic RT	1st line
NCT06530797 [118]	Active, not yet recruiting	Safety, OS, PFS, DOR, ORR, DCR	Observational	Cohort 1: Adebrelimab in first-line Cohort 2: Adebrelimab in second-line and beyond	1st line 2 st line
NCT05623319 [119]	Active, recruiting	PFS, ORR, irORR; OS, 6m and 12m-24m- PFS; AEs, PD-L1 analysis, DDR, TMB, MSI	II	Pembrolizumab/Olaparib as maintenance after first-line ChT+ICIs	1st line
NCT05703971 [120]	Active, recruiting	MTD and/or RP2D, PFSR, safety, PFS phase 1 and 2, OS phase 1 and 2, PK	I/II	quaratusugene ozeplasmid+ Atezolizumab as maintenance	1st line
NCT05116007 [121]	Completed	AEs, ORR, DCR, PFS, OS	I	AK112 (anti PD-1/VEGF)+ Cht	1st line
NCT06477523 [122]	Active, recruiting	TRAEs, PFS, 6m-12m-PFS; DCR, OS, 12m-24m-OS, ORR	I/II	LDRT+AK112+ChT	1st line
NCT06536868 [123]	Active, recruiting	PFS, ORR, DCR, OS, AEs	II	Tilelizumab+Cht+ thoracic RT	1st line
NCT06441344 [124]	Active, not yet recruiting	OS, DOR, DCR, ORR, 6m-12m-PFS, 12m-18m-OS, FACT-L	III	platinum+etoposide → toripalimab plus anlotinib) vs platinum+etoposide+ toripalimab → toripalimab	1st line
NCT06739928 [125]	Active, recruiting	1-year OS, OS, PFS, ORR, DOR, DCR, AEs rate	II	Irinotecan liposome (II) combined with adebrelimab and carboplatin vs. etoposide combined with adebrelimab and carboplatin	1st line
NCT04562337 [126]	Active, not yet recruiting	OS, PFS, ORR, DCR, DOR, AEs, 6m-12m-PFS, 1y-2y-OS	II	SHR1316+ ChT and sequential thoracic RT	1st line
NCT04745689 [127]	Active, not yet recruiting	OS, OFS, PK AZD2811, AEs, QoL	II	AZD2811+Durvalumab after Durvalumab +ChT	1st line
NCT06110572 [128]	Active, recruiting	AEs rate; OS, PFS, ORR, DCR, DOR, intracranial control	I/II	Atezolizumab+ChT+TBI	1st line

		rate, thoracic control rate			
NCT06350162 [129]	Active, recruiting	1y-PFS, PFS, OS, DCR, ORR, AEs	II	Serprulimab+ thoracic RT vs. Serprulimab alone after Serprulimab+ ChT	1st line
NCT06732258 [130]	Active, not yet recruiting	DLTs, ORR, DCR, DOR, PFS, OS	I	LDRT+ChT+ Toripalimab+ Tifcemalimab	1st line
NCT06223711 [131]	Active, recruiting	OS, PFS	II	Durvalumab +cCRT-followed by durvalumab maintenance therapy in combination with stereotactic radiotherapy	1st line
NCT05142696 [132]	Active, recruiting	DLTs, AEs, SAEs, OS, ORR, DOR, PFS, TACs, Absorbed radiation doses of [177Lu]Lu-DOTA-TATE, concentration of [177Lu]Lu-DOTA-TATE in blood, and urine, [plasma Cmax of [177Lu]Lu-DOTA-TATE	I/II	[177Lu]Lu-DOTA-TATE in Combination With Carboplatin, Etoposide and Atezolizumab	1st line
NCT04170946 [133]	Active, recruiting	Safety, MTD, locoregional recurrence, PFS, OS, acute and chronic toxicity	I	Talazoparib+ LDRT	1st line
NCT04402788 [134]	Active, recruiting	PFS, OS, AEs, Tumor burden	II/III	Thoracic Rt after Atezolizumab+ChT	1st line
NCT05361395 [135]	Active, not recruiting	Dose exploration/Dose expantion, DLT, TAEs, Number of Participants with Clinically Significant Changes in Vital Signs, ECG, clinical laboratory tests, 6m-PFS, ORR, DCR, DOR, OS, serum concentration of Tarlatamab	I	Tarlatamab+Atezolizumab +Carboplatin+Etoposide	1st line
NCT06497530 [136]	Active, not yet recruiting	PFS, OS, ORR, DOR, AEs	II	Lurbinectidin+ Serprulimab as maintenance after Serprulimab+ChT	1st line
NCT06125041 [137]	Active, recruiting	PFS, OS, ORR, DCR, DOR,	II	Adebelizumab Combined With Chemotherapy and Sequential Adebelizumab Combined With Radiotherapy	1st line
NCT06211036 [138]	Active, recruiting	OS, PFS, ORR, DCR, DOR, 6m-1y-2y-PFS, 6m-1y-2y-	III	Tarlatamab +Durvalumab vs Durvalumab Alone after Durvalumab+ChT	1st line

		3y-OS, TTP, TEAEs, fatal TEAEs, AEs, Serum Concentrations of Tarlatamab, TTD, QoL			
NCT05668767 [139]	Active, not yet recruiting	PFS, OS, ORR, DCR, AEs, QoL	II	Surufatinib in Combination of Durvalumab and Etoposide and Carboplatin/Cisplatin	1st line
NCT06030258 [140]	Active, recruiting	DLTs, RP2D, PFS, ORR, DOR, DCR, OS, AEs, PK,	I/II	IN10018+ Tislelizumab+ ChT	1st line
NCT05745350 [141]	Active, recruiting	12m-PFS, ORR; DOR, PFS, OS, AEs	II	Pembrolizumab, Plinabulin Plus Etoposide and Platinum	1st line
NCT06362252 [142]	Active, recruiting	DLTs, TEAEs, PFS, ORR, DOR, DCR, CBR, TTR, OS, PK, Cmax, ADA	I/II	I-DXd+ Atezolizumab with or without carboplatin	1st line
NCT05384015 [143]	Active, recruiting	AEs, PFS, DOR, OS, ORR,	II	Pembrolizumab+Lenvatinib+ChT	1st line
NCT06769971 [144]	Active, recruiting	ORR, safety, DCR, DOR, TTR, OS, PFS,	II	Ivonescimab (PD1/VEGF Bispecific) and Cadonilimab（PDL1/CTLA4 Bispecific) + Carboplatin/Etoposide	1st line
NCT06217757 [145]	Active, recruiting	Safety, PFS, OS, ORR	I/II	LDRT + sugemalimab, olaparib, ChTy in the first-line treatment of SLFN-11 positive	1st line
NCT06712355 [146]	Active, recruiting	OS, PFS, ORR, TEAEs, QoL,	III	BNT327 (PD1/VEGF Bispecific) + ChT vs. atezolizumab+ChT	1st line
NCT05896059 [147]	Active, recruiting	1y-PFS, PFS, OS, ORR, DCR, DOR, TEAEs	II	Tislelizumab+ Anlotinib as maintanance after Tislelizumab+ ChT	1st line
NCT05228496 [148]	Active, not yet recruiting	1y-PFS, PFS, OS, ORR, DCR, DOR, AEs	II	Tislelizumab+ sitrvatinib as maintanance after Tislelizumab+ ChT	1st line
NCT04487756 [149]	Active, not recruiting	6m-PFS, safety (AEs, SAEs), DCB, ORR, OS	I/II	Atezolizumab +DCvac	1st line
NCT04699838 [150]	Active, recruiting	PFS, TTP, Time to CNS progression, Time to systemic progression; ORR, DCR, DOR; OS, AEs	II	ChT+ICIs Followed by Durvalumab and Ceralasertib	1st line
NCT05091567 [151]	Active, not recruiting	PFS, OS, ORR, ADA TTCD	III	Lurbinectidin+Atezolizumab vs. Atezolizumab as maintanance after Atezolizumab+ ChT	1st line
NCT04728230 [152]	Active, recruiting	Incidence of DLT, ORR, PFS, OS, In-	I/II	olaparib + durvalumab+ carboplatin, etoposide with or without RT	1st line

		tra- and extra-thoracic recurrence rates			
NCT06429696 [153]	Active, not recruiting	6m-PFS, PFS, OS,	II	PD-L1 inhibitor combined with apatinib maintanance after ChT+ICIs	1st line
NCT06646276 [154]	Active, recruiting	OS, TTDD, AEs, SAEs, DOR, OS, ORR	III	BMS-986489 (Anti-fucosyl-GM1+ Nivolumab) + Carboplatin + Etoposide vs. Atezolizumab/Carboplatin/ Etoposide	1st line
NCT04924101 [155]	Active, not yet recruiting	ORR; PFS, DOR, OS, AEs, Tumor size change, QoL	II	Investigational agents (MK-4830, boserolimab (MK-5890) and lenvatinib (MK-7902)) in combination with pembrolizumab + etoposide/platinum	1st line
NCT06478043 [156]	Active, not yet recruiting	ORR, AEs, DCR, DOR, OS, PFS,	II	Ivonescimab+ Irinotecan Liposome	2 st line
NCT05874401 [157]	Active, recruiting	OS, PFS, ORR, DCR, AEs	IV	Trilaciclib+Topotecan vs placebo+ Topotecan	2 st line
NCT04698941 [158]	Unknown	DCR, ORR, PFS, OS, AEs	II	Simvastatin+ albumin paclitaxel	2 st line
NCT05731518 [159]	Active, recruiting	MDT, RP2D, safety and tolerability, ORR, DCR, PFS, OS, AEs, Maximum blood concentration	I/II	SC0245+ Irinotecan	2 st line
NCT06801834 [160]	Active, not yet recruiting	ORR, OS, PFS, DOR, TRAEs	III	Sacituzumab govitecan vs. SoC	2 st line
NCT06663098 [161]	Active, not yet recruiting	OS, PFS, ORR, frequency of AEs	II	Rechallenge atezolitumab + ChT	2 st line
NCT06332950 [162]	Active, not yet recruiting	Safety, 6m-PFS, ORR, PFS, OS, DCR, DOR	I/II	Adebrelimab Plus Irinotecan Liposome (II) With or Without Famitinib	2 st line
NCT05280470 [109]	Active, not yet recruiting	ORR; TEAEs, PFS, OS, DOR, TTR, DCR, plasma Cmax, Terminal Half-Life, ADA	II	Ifinatamab Deruxtecan	2 st line
NCT06749691 [163]	Active, recruiting	6m-PFS, PFS, OS, ORR	II	Liposomal Irinotecan and Apatinib	2 st line
NCT05901584 [164]	Active, recruiting	PFS, OS, DCR, ORR	II	Cadunilumab (Anti-PD-1/CTLA-4) in Combination With or Without Chemotherapy	2 st line
NCT06227546 [165]	Active, recruiting	ORR, AEs, PFS, DOR, OS, 6m-PFS	II	MGC018(B7-H3 ADC)	2 st line

NCT04938817 [166]	Active, recruiting	DLTs, AEs, ORR; PFS, DOR	I/II	Coformulation Pembrolizumab/Quavonlimab alone or in combination with lenvatinib or +MK-4830; Coformulation Favezelimab/Pembrolizumab	2 st line

ADA: Anti-drug antibody; ADC: antibody drug conjugate; AE: adverse events; ChT: chemotherapy; CR: complete response; cCRT: concomitant chemoradiotherapy; Cmax: maximum concentration; CBR: clinical benefit rate; CNS: central nervous system; DCvac: dentritic cell vaccine; DCR: Disease control rate; DDR: DNA damage repair; DOR: duration of response; DLT: dose limiting toxicity; ECG: Electrocardiogram; FACT-L:health-related quality of life; ICIs: Immune checkpoint inhibitors; I-DXd: Ifinatamab deruxtecan; LDRT: low-dose radiotherapy; MTD: maximum tolerated dose; MSI: MicroSatellite Instability; PFS: Progression-Free Survival; PFSR: Progression-Free Survival Rate; ORR: objective response rate; irORR: Immune-related Objective response rate; OS: overall survival; PD-1: programmed cell death -1; PD-L1: programmed death ligand-1; PK: Pharmacokinetic parameters; PR: partial response; QoL: quality of life; RP2D: Recommended Phase 2 Dose; RT: radiotherapy; SAE: serious adverse events; SoC: standard of care; TRAEs: Treatment related adverse events; TBI: total body irradiation; TTR: Time to response; TMB: tumor mutational burden; TACs: Time activity curves; TEAEs: Treatment-Emergent Adverse Events; TTP: time to treatment progression; TTCD: ,Time to Confirmed Deterioration; TTDD: Time to definitive deterioration; VEGF: Vascular endothelial growth factor.

6. The role of laterality in cancers

The human body exhibits inherent asymmetry in the structure and function of paired organs like the lungs, breasts, and kidneys. These differences, extending to organ positioning, vascular anatomy, and lymphatic drainage, are well recognized in anatomical literature. However, their impact on cancer development, progression, and patient outcomes—collectively termed "laterality"—has not been extensively studied in oncology.

Recent evidence, however, suggests that the side on which a cancer develops may affect its incidence, stage at diagnosis, and even survival. One of the most extensive investigations into this topic was conducted by Roychoudhuri et al., who analyzed over 260,000 unilateral tumors using data from the Thames Cancer Registry. Their findings highlight that “asymmetries in organ structure and function are mirrored in cancer incidence and, to a lesser extent, clinical outcomes” [167].

In their analysis, paired organs such as the lungs, breasts, kidneys, ovaries, and testes were evaluated for side-specific differences. Testicular cancer, for instance, showed a marginal but statistically significant survival advantage for left-sided tumors (five-year survival: 98.2% vs. 96.9% for right-sided; $p < 0.01$). This may relate to physiological differences such as “the higher and warmer position of the right testis” [167].

A similar trend was observed in ovarian cancer, where left-sided non-germ cell tumors had a slight survival benefit (52.3% vs. 49.5%), although the underlying mechanisms remain uncertain. Possible explanations include differences in pelvic anatomy or surgical accessibility.

In contrast, no substantial survival differences were observed in kidney and breast cancers between left- and right-sided tumors, suggesting that laterality may not always be prognostically relevant.

Lung cancer presents a more nuanced picture. Among women, right-sided tumors have been associated with “modestly better five-year survival rates (4.6% vs. 3.8%, $p < 0.01$)” [167] . This trend persisted even in surgical subgroups, with right-sided resections showing slightly improved outcomes. These disparities may reflect differences in lymphatic drainage pathways or mediastinal anatomy, which could influence treatment response or recurrence patterns.

Right-sided lung tumors also occur more frequently than left-sided ones. This may relate to tracheobronchial structure: the right main bronchus is shorter, wider, and more vertically oriented, facilitating easier entry of inhaled substances. In contrast, the left bronchus is longer and deflected by the aortic arch, potentially limiting exposure. This structural variation results in “preferential airflow and particle deposition into the right lung, especially the right lower lobe” [168–170].

This hypothesis is supported by imaging and autopsy studies, which consistently show more severe emphysematous and bronchitic changes in the right lung of smokers [171]. Autopsy reports also document more aspiration-related damage and foreign material in the right lung, corroborating this anatomical vulnerability. Autopsy studies further corroborate this by documenting a higher prevalence of “aspiration-related pathology and foreign material in the right lung” [172]. These findings are not limited to anatomical observation; aerosol studies in both humans and animals have demonstrated that “the right lung receives a disproportionately higher share of inhaled particulate matter” under conditions of normal (tidal) breathing [173].

These patterns are especially relevant when considering the inhalation of carcinogens, such as polycyclic aromatic hydrocarbons and nitrosamines in tobacco smoke. Chronic exposure in the right lung may contribute to the observed higher incidence of right-sided lung cancers. Roychoudhuri et al. reported that the “incidence-rate ratio of left-to-right lung cancers was 0.88 in males and 0.86 in females”, which

closely corresponds to the differences in lung mass, strengthening the argument for a combined volume–exposure model of carcinogenesis [167].

One of the most clinically important examples of cancer laterality is found in colorectal cancer. Right-sided (proximal) and left-sided (distal) colon tumors differ not only anatomically but also in their biology, symptomatology, and response to treatment.

Right-sided lesions more frequently exhibit microsatellite instability (MSI), BRAF mutations, and a CIMP-high phenotype, while left-sided tumors are more commonly associated with chromosomal instability, TP53 mutations, and KRAS alterations. [174–176]. These molecular variations influence symptomatology—right-sided tumors often present with anemia, while left-sided lesions more commonly lead to bowel obstruction—and affect treatment response.

Prognostically, patients with left-sided tumors tend to have better survival, especially when treated with chemotherapy and targeted agents. For instance, patients with RAS wild-type, left-sided tumors are more likely to benefit from anti-EGFR agents like cetuximab or panitumumab. In contrast, right-sided tumors derive less benefit from these therapies and may respond better to alternatives like bevacizumab [177].

Treatment decisions in metastatic colorectal cancer now routinely consider tumor laterality. Several studies have shown that patients with RAS wild-type, left-sided tumors derive substantial benefit from anti-EGFR therapies such as cetuximab or panitumumab. Conversely, “patients with right-sided tumors derive limited benefit from these agents and may be better suited to other biologics like bevacizumab” [178].

In summary, laterality in cancer reflects a complex interplay between anatomical, molecular, and environmental factors. While not universally predictive or prognostic, it provides an additional dimension for understanding tumor behavior and optimizing patient management. From both a clinical and research perspective, incorporating laterality into cancer analyses could uncover subtle patterns that enhance personalized treatment strategies and improve outcomes.

7. Aim of the study

SCLC continues to pose a major clinical challenge due to its highly aggressive nature, rapid progression, and early dissemination. Unlike many solid tumors where systemic therapies have notably improved outcomes, advancements in the management of SCLC have lagged behind the pace of its clinical deterioration. Most patients present with a high symptom burden, including severe respiratory symptoms, weight loss, and paraneoplastic syndromes, which often result in a swift decline in performance status and overall health.

The introduction of immune checkpoint inhibitors has reshaped the first-line therapeutic landscape for extensive-stage SCLC, offering modest survival improvements when combined with chemotherapy. Nevertheless, once disease progresses beyond the first line, outcomes remain dismal. This reality underscores the necessity to optimize initial treatment duration and efficacy, as therapeutic options in later lines are generally limited in benefit.

Unlike NSCLC, where treatment is increasingly guided by biomarkers such as PD-L1 expression, tumor mutational burden (TMB), and oncogenic drivers, SCLC lacks validated predictive biomarkers to guide immunotherapy selection [179,180]. The reasons for this are multifaceted:

1. **Low Tumor Cellularity**: Most SCLC biopsies provide limited cellular material, which hampers accurate PD-L1 testing.
2. **Necrosis and Sample Size**: The predominance of necrotic zones and the typically small biopsy size limit reliable molecular profiling, including TMB evaluation.
3. **Absence of Reliable Predictors**: Although PD-L1 and TMB are used in other settings, they have not proven predictive in SCLC. As noted in recent reviews, *"PD-L1 expression and TMB do not reliably stratify SCLC patients for ICI therapy. Consequently, these factors have been largely abandoned as criteria for patient selection in clinical trials and routine practice"* [179].

Historically, SCLC was seen as a molecularly uniform disease, largely due to its consistent loss of TP53 and RB1 and strong neuroendocrine features. However, recent molecular analyses have challenged this view, revealing the existence of biologically distinct subtypes. These subtypes, defined through transcriptional profiling, appear to differ in their response to chemotherapy, immunotherapy, and emerging targeted agents.

This molecular heterogeneity opens the door to a more individualized approach to treatment. Initial studies suggest that these subtypes may exhibit unique therapeutic vulnerabilities, although prospective validation is still required. As one group of researchers put it, *"these findings require prospective validation in well-designed clinical trials to establish their predictive value and inform personalized treatment strategies"* [179].

Recognizing the unmet need for better patient stratification and treatment personalization in SCLC, our study was designed to explore prognostic and potentially predictive factors that could guide clinical decision-making.

We conducted a retrospective analysis involving patients with stage III and IV SCLC treated at institutions in Italy and Germany. This investigation sought to determine whether specific clinical features or molecular subtypes were associated with differences in survival or treatment response.

Our objectives were as follows:

- **To identify clinical and molecular prognostic indicators** that could help distinguish patients with more favorable versus poorer survival outcomes.

- **To evaluate the influence of molecular subtypes** on therapeutic efficacy and disease trajectory, aiming to define subgroups that may benefit from particular treatment strategies.
- **To propose refined risk stratification methods**, with the goal of optimizing treatment allocation, personalizing therapeutic decisions, and tailoring follow-up plans to individual patient risk.

By drawing on real-world data from a multinational cohort, our study aims to bridge the gap between daily clinical practice and evolving concepts in precision oncology. We hope that our findings will contribute to the effort of moving SCLC management toward a more nuanced, biomarker-driven framework, particularly in a disease long considered resistant to personalization.

8. Materials and Methods

This retrospective, multicenter observational study included **222 patients diagnosed with SCLC** who received first-line treatment at institutions in Italy and at the **Lungenklinik of Ludwig-Maximilians-Universität München (LMU)**. The study was conducted in compliance with the ethical standards outlined in the **Declaration of Helsinki** and was approved by the **Institutional Ethics Committee of the University Hospital of Munich** (LMU) (Approval Code: 476-16 UE, approval date: 5 August 2016).

8.1 Patient Population

Eligible patients were adults with a confirmed diagnosis of SCLC, based on histological or cytological criteria, in accordance with the **2015 WHO classification of lung tumors**.

Included patients had either **locally advanced (unresectable stage III)** or **metastatic (stage IV)** disease at the time of diagnosis. Treatment strategies varied depending on disease extent and clinical fitness. Patients with stage III disease typically received **concurrent or sequential chemoradiotherapy**, while patients with stage IV disease were treated with either **platinum-based chemotherapy alone** or **first-line chemoimmunotherapy**, according to institutional protocols and clinical eligibility.

Patients were excluded if their diagnosis did not meet SCLC histological criteria (e.g., adenocarcinoma, squamous cell carcinoma, large cell carcinoma), if they had undergone **curative-intent surgery**, or if their disease was classified as **early-stage** at diagnosis.

After application of these criteria, a total of **222 patients** were included in the final analysis. A diagram illustrating the patient inclusion and exclusion process is shown in **Figure 2**.

All procedures involving human participants were conducted in line with the Declaration of Helsinki, which emphasizes that *"research involving human subjects must be conducted only if the importance of the objective outweighs the risks and burdens to the research subjects"* (World Medical Association, 2013).

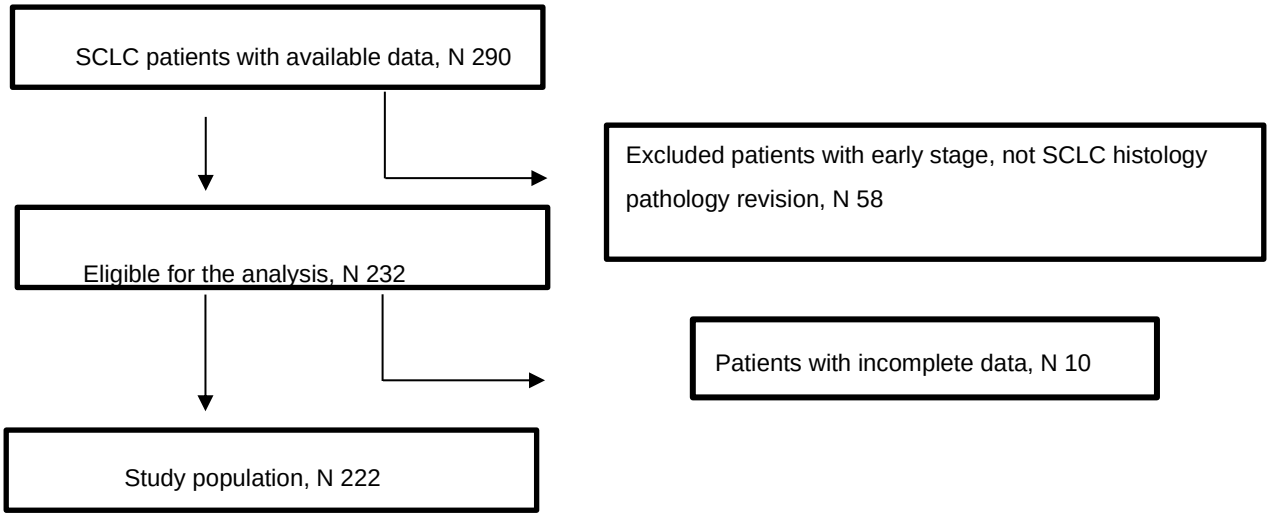


Figure 2. Patients' selection flow chart

8.2 Clinical and Pathological Characteristics of Patients

For all patients included in the study, detailed clinical data were systematically collected. This included demographic factors such as age, sex, and smoking status. Tumor characteristics were recorded, including tumor laterality (i.e., localization in the right or left lung), TNM staging as per the 8th edition of the AJCC, and the individual T, N, and M components. Specific information was gathered on tumor size, the extent of lymph node involvement, and presence and sites of distant metastases, including common locations such as the brain, liver, bone, lungs, pleura, adrenal glands, soft tissues, and other affected organs.

Further clinical variables included the date of diagnosis and the initiation of systemic treatment. From a pathological standpoint, tumor grading, the Ki-67 proliferation index, and expression of neuroendocrine markers such as synaptophysin and chromogranin A were assessed, in line with standard SCLC diagnostic criteria.

Outcomes analyzed in this study included PFS and OS. These were used to assess clinical prognosis and therapeutic response across the study population.

8.3 Statistical Analysis

Descriptive statistics were applied to summarize baseline characteristics. Categorical variables are reported as absolute numbers and percentages, while continuous variables are described using medians and ranges.

Survival outcomes (PFS and OS) were estimated using the Kaplan–Meier method. PFS was defined as the interval from the start of first-line treatment to either radiological disease progression (as determined by RECIST v1.1) or death from disease-related causes. OS was calculated from the date of treatment initiation to death from any cause or the date of last follow-up.

To explore potential associations between clinical/pathological variables and survival outcomes, we first used the Chi-square test to evaluate relationships between categorical variables. Statistical significance was set at $p < 0.05$.

Univariate analyses were performed using Cox proportional hazards regression to estimate the effect of each variable on PFS and OS. For continuous variables, cut-off thresholds were based on the median value of the study population. Variables with statistically significant results in univariate testing were subsequently entered into a multivariate Cox regression model to determine independent prognostic factors.

Survival data are presented as hazard ratios (HR) along with corresponding 95% confidence intervals (95% CI). As recommended for clinical oncology studies, this approach provides an estimate of relative risk over time.

All statistical procedures were conducted using R software (version 4.0) in RStudio. Microsoft Excel and RStudio were used to create tables and visual representations of the data.

In line with best practice, the study followed established statistical conventions for survival analysis, including the use of Kaplan–Meier curves and proportional hazards modeling, acknowledging that *“a p-value of <0.05 was considered statistically significant”* for all analyses conducted.

9. Results

9.1 Patient Characteristics

A total of 222 patients diagnosed with SCLC were included in the analysis, with 107 patients (48.2%) treated at the LMU Clinic and 115 patients (51.8%) treated at Italian center between January 2020 and December 2022. The median age at diagnosis was 69 years, ranging from 46 to 87 years. The majority of patients were male, accounting for 60.4% (n = 134), while 39.6% (n = 88) were female. Smoking history was prevalent in the cohort, with 91% of patients being either current or former smokers.

At the time of diagnosis, most patients had a good performance status. Specifically, 58.6% (n = 130) had an ECOG performance status of 0, and 38.2% (n = 85) had a status of 1. Only a small number of patients presented with a more compromised performance status, with six patients (2.7%) having an ECOG-PS of 2 and one patient (0.5%) presenting with a score of 3.

Regarding disease staging, the majority of patients—167 individuals, or 75.2%—had stage IV disease, while the remaining 55 patients (24.8%) were classified as stage III according to the 8th edition of the TNM classification by the AJCC. The tumor was located in the right lung in 110 patients (49.5%) and in the left lung in 111 patients (50%). In one case, the central location of the tumor made it difficult to assign it to either side definitively.

Lymph node involvement was frequent at diagnosis. Locoregional lymph node metastases were detected in 95.5% of patients, and distant lymph node metastases were found in 26.6%. Bone metastases were present in 69 patients (31.1%), and liver metastases were observed in 65 patients (29.3%). Metastatic spread to the contralateral lung occurred in 29.3% of cases, while brain metastases were reported in 21.6% of patients at diagnosis. Pleural involvement was identified in 17.1% of the population, and soft tissue metastases in 7.7%. Adrenal gland metastases were present in 13.1% (n = 29), with additional, less frequent metastatic sites including the pancreas (3.6%), pericardium (0.5%), peritoneum (1%), and kidney (1%).

As for systemic therapy, 116 patients (52.3%) received a first-line regimen consisting of carboplatin, etoposide, and the immune checkpoint inhibitor atezolizumab. This subgroup included 114 patients with stage IV disease and two patients with stage III disease who were not considered suitable candidates for locoregional treatment. Additionally, eight patients with stage IV disease were treated with a first-line combination of carboplatin or cisplatin, etoposide, and durvalumab. A platinum-based chemotherapy doublet—carboplatin or cisplatin plus etoposide—without immunotherapy was administered to 53 patients with stage III disease and to 45 patients with stage IV disease.

Thoracic radiotherapy was integrated into the treatment strategy for several patients. Specifically, 28 patients (12.6%) underwent sequential chemoradiotherapy, whereas 25 patients (11.3%) received concurrent chemoradiotherapy. In both settings, radiotherapy was combined with platinum–etoposide chemotherapy.

A full overview of baseline patient characteristics and treatment patterns is provided in Table 4.

Table 4. Patient charachteristics

9.2 Prognostic Impact on Progression-Free and Overall Survival

After a median follow-up period of 11 months (range: 3 to 28 months), our analysis revealed a statistically significant association between tumor laterality and patient outcomes in small-cell lung cancer. Specifically, patients with tumors originating in the **left lung** had markedly worse OS compared to those with right-sided tumors. The median OS was 8 months for left-sided tumors versus 12 months for right-sided tumors, with a **HR of 2.020** and a **p-value of 0.001**, indicating a substantial negative prognostic effect.

When examining PFS, tumor laterality also demonstrated a significant impact. Patients with right-sided tumors had a median PFS of 7.7 months, compared to 6.7 months for those with left-sided tumors (**HR 1.293**, **p = 0.009**), suggesting that laterality may play a role not only in survival but also in disease progression dynamics.

Smoking status was another variable that showed a strong association with clinical outcomes. In univariate analysis, active or prior smoking was significantly correlated with poorer overall survival (**p < 0.001**). However, in multivariate Cox regression analysis, smoking retained its significance as an independent prognostic factor only for OS (**p = 0.064**) but not for PFS, suggesting its influence may be more pronounced in long-term mortality rather than short-term disease control.

Performance status at diagnosis, measured by the ECOG scale, emerged as a critical predictor of outcome. Patients with worse ECOG scores experienced significantly shorter survival durations. This was confirmed in the multivariate analysis, where ECOG-PS was identified as an independent negative prognostic factor for both OS (**p = 0.025**) and PFS (**p < 0.001**), supporting its utility in baseline risk stratification.

As anticipated, **advanced stage at diagnosis (stage IV)** was strongly associated with unfavorable outcomes. In the multivariate model, stage IV disease was found to be an independent negative prognostic variable for both overall survival and progression-free survival (**p < 0.001** for both endpoints).

The number and distribution of metastatic sites also influenced prognosis. Patients presenting with **two or more distant metastatic lesions** at the time of diagnosis had significantly poorer survival outcomes,

affecting both OS and PFS (**p < 0.001**). Among specific metastatic sites, **distant lymph node involvement** and **liver metastases** were strongly correlated with reduced overall survival (**p < 0.001** for both). Additionally, **bone metastases** at diagnosis were associated with worse outcomes in patients with stage IV disease, negatively impacting both PFS (**p = 0.035**) and OS (**p = 0.021**).

Conversely, our analysis did not show statistically significant associations between survival outcomes and other variables, including **patient sex**, **locoregional lymph node involvement**, or the presence of metastases in the **brain**, **lungs**, **soft tissue**, **pleura**, or **adrenal glands**.

The multivariate model identified several factors independently associated with survival, all of which are summarized in **Tables 5 and 6**. Corresponding **Kaplan–Meier survival curves** illustrating the prognostic impact of key clinical and pathological variables are displayed in **Figure 3**.

Figure 3. Overall survival all study population (N=222); B) Progression free survival all study population

10. Discussion

SCLC remains one of the most aggressive and lethal forms of thoracic malignancy, largely due to its rapid progression, early dissemination, and the absence of effective targeted therapies. Despite significant advancements in the molecular characterization of SCLC over the past decade, these insights have yet to translate into substantial clinical benefit. Recent genomic studies have unveiled a complex mutational profile, involving alterations in transcription factors, receptor tyrosine kinases, and epigenetic regulators such as chromatin-modifying enzymes [182–186]. However, as summarized in current reviews, *"clinical trials evaluating targeted therapies have not yet demonstrated a significant survival benefit"* in SCLC [187].

Although several clinical and pathological factors—such as age, sex, Ki-67 index, tumor differentiation, and neuroendocrine marker expression—have been investigated for their prognostic relevance, results have been inconsistent and inconclusive [189]. Given the dismal survival associated with this malignancy, there is an ongoing need to identify biomarkers that can support both risk stratification and therapeutic decision-making.

Among emerging variables, tumor laterality has gained attention due to anatomical and physiological differences between the lungs. For instance, in colorectal cancer, sidedness has proven to be a meaningful factor, reflecting disparities in embryological origin, vascular supply, and genomic alterations, all of which influence treatment response and prognosis [190]. Similarly, population-based data in renal cell carcinoma from the SEER database indicated that left-sided tumors were linked with inferior outcomes, potentially due to their higher grade and stage at diagnosis [191].

However, the relevance of laterality in lung cancer, particularly in SCLC, remains unclear. Some studies in non-small cell lung cancer (NSCLC) have observed procedural risks associated with right-sided resections. For example, one investigation of 1,465 NSCLC patients undergoing pneumonectomy reported higher perioperative mortality for right-sided procedures following neoadjuvant therapy, although no long-term survival difference was observed [192].

More recently, a study by La Salvia et al. examined 300 cases of lung neuroendocrine tumors (NETs) and found a significant prognostic role for laterality. The authors observed that **left-sided typical and atypical carcinoids** were associated with worse survival outcomes. As they noted, *"left-sided NETs displayed a significantly higher prevalence of tumor necrosis,"* suggesting a possible biological mechanism underpinning these findings [193].

To the best of our knowledge, the present study is the first to demonstrate a significant impact of tumor laterality on prognosis in patients with SCLC. Our results indicate that tumors originating in the **left lung parenchyma** are associated with significantly worse overall and progression-free survival compared to right-sided tumors. These findings suggest potential anatomical or biological differences that could influence tumor behavior and disease progression.

The relevance of these findings is further supported by molecular observations in NETs. In the same study by La Salvia et al., tumors in the right lung showed higher microvessel density (MVD), whereas those in the left lung exhibited increased expression of **hypoxia-inducible factor-1 alpha (HIF-1α)**.

According to the authors, *"higher HIF-1α expression was significantly associated with poor differentiation, increased necrosis, and reduced MVD"* [194]. These characteristics, when applied to SCLC—which is itself a high-grade neuroendocrine carcinoma—raise the hypothesis that similar hypoxia- and angiogenesis-related mechanisms may also drive the observed prognostic differences in laterality.

If validated, these biological differences may hold translational relevance. Specifically, biomarkers associated with hypoxia and vascularization could support the development of prognostic tools or therapeutic targets in SCLC, potentially guiding more personalized treatment strategies. However, the biological mechanisms behind laterality remain speculative and require prospective validation, especially within the broader context of lung neuroendocrine tumors.

In addition to tumor laterality, our study confirmed several well-established clinical factors associated with poor outcomes in SCLC, including **worse ECOG performance status**, **advanced stage at diagnosis**, and the presence of **liver metastases**. These findings are consistent with previous literature and support the robustness of our data. Importantly, the impact of **tumor laterality** remained significant even after adjusting for these variables, suggesting its potential role as an **independent prognostic marker**.

Despite the novelty and relevance of our findings, some limitations must be acknowledged. First, the **retrospective nature** of the study may introduce selection and information bias. Second, the **modest sample size** could limit the power of subgroup analyses, particularly in multivariable models. Moreover, **incomplete clinical data**, such as missing values for smoking status or neuroendocrine marker expression, may restrict the generalizability of our conclusions. To overcome these limitations, prospective studies involving **larger, well-characterized patient cohorts** and comprehensive **molecular profiling** are needed.

In summary, our results suggest that **tumor laterality may represent a novel prognostic factor in SCLC**. This observation warrants further investigation, as it could have implications for both clinical trial design and individualized treatment strategies. Understanding the underlying biology of laterality-related differences—especially those related to angiogenesis and hypoxia—may also open new avenues in the management of this challenging disease.

11. Conclusions

This study presents novel clinical evidence indicating that the side of origin of the primary tumor—tumor laterality—may serve as an independent prognostic factor in patients with SCLC. The significant differences in survival outcomes observed between left- and right-sided tumors suggest that laterality may not simply reflect anatomical variation but instead may be indicative of underlying biological heterogeneity.

If confirmed in prospective datasets, tumor laterality could be integrated into prognostic assessment tools and contribute to more individualized treatment planning in SCLC. As noted in earlier oncological studies, *"anatomical differences may reflect deeper biological mechanisms influencing tumor behavior"* [La Salvia et al., 2021].

To explore this hypothesis further, we propose to conduct in-depth biological characterization of tumor samples from our patient population. Planned analyses include immunohistochemistry, targeted gene profiling, and transcriptomic studies, focusing particularly on pathways involved in neuroendocrine regulation and hypoxia. Special attention will be given to markers such as **ASCL1**, **HIF-1α**, and other regulators known to influence angiogenesis and tumor proliferation. As La Salvia et al. observed in lung NETs, *"HIF-1α expression was significantly associated with necrosis, poor differentiation, and lower vascular density"*, suggesting that similar mechanisms may be operative in SCLC [194].

12. Summary

Importance: SCLC remains among the most therapeutically challenging thoracic malignancies, marked by rapid progression, high metastatic potential, and limited long-term survival. Established prognostic factors—such as performance status, tumor stage, and liver metastases—are important but insufficient for accurate patient stratification. This gap highlights the need for new, clinically meaningful markers that could guide individualized treatment decisions.

Objective: Recent studies in well-differentiated pulmonary neuroendocrine tumors have shown that the side of tumor origin (laterality) can influence prognosis, with worse outcomes reported for left-sided carcinoids. Given the neuroendocrine lineage of SCLC, albeit poorly differentiated, we hypothesized that tumor laterality might similarly affect survival in SCLC. Our study aimed to assess whether the side of the lung in which the primary tumor develops serves as a prognostic indicator, potentially reflecting underlying biological variation.

Design, Setting, and Participants: This was a multicenter, retrospective, observational study involving three institutions—two in Italy and one in Germany. The cohort included consecutive patients diagnosed with histologically or cytologically confirmed SCLC, treated between January 2020 and December 2022, and followed for a minimum of three months. Treatment approaches varied according to disease stage and institutional standards.

Main Outcomes and Measures: We collected comprehensive clinical and pathological data, including patient demographics, tumor characteristics (location, histology, stage), metastatic spread, and treatment details. The key outcome measures were PFS and OS. We evaluated the prognostic impact of tumor laterality in the context of other clinical variables such as age, sex, ECOG performance status, metastatic sites, and therapy received.

Results: A total of 222 patients were included in the analysis. The cohort was predominantly male (60.4%) and comprised a high proportion of individuals with a smoking history (90.1%). Most patients were diagnosed with advanced disease, with 75.2% at stage IV. Tumors were almost equally distributed between the lungs: 49.5% in the right and 50.5% in the left.

Consistent with existing literature, poorer survival was observed in patients with advanced stage, poor ECOG status, and liver metastases at diagnosis. Notably, our study found that tumor laterality independently influenced prognosis. Patients with right-sided tumors had significantly better median OS than those with left-sided tumors (12 vs. 8 months, $p = 0.001$; HR = 2.020). A similar pattern was observed for PFS: right-sided tumors had a median PFS of 7.8 months, compared to 6.7 months for left-sided tumors ($p = 0.009$; HR = 1.293).

Additional prognostic factors identified included smoking status, ECOG performance score, and the presence of distant lymph node or bone metastases. In contrast, no significant association was found between OS or PFS and patient sex, or metastases to the brain, lung, adrenal glands, or pleura.

Conclusions and Relevance: Our findings suggest, for the first time in the context of SCLC, that the location of the primary tumor may hold prognostic value. This observation is in line with previous work

on lung carcinoids, and may reflect biological differences between the left and right pulmonary environments. As La Salvia et al. noted in lung NETs, *“tumor laterality was associated with necrosis, angiogenesis, and microenvironmental differences, contributing to survival disparities”* [La Salvia et al., 2021].

We hypothesize that differential exposure to inhaled carcinogens, asymmetric lymphatic drainage, or variations in local hypoxia may contribute to this effect. These findings support the need for further research into how anatomical and molecular tumor characteristics interact, and whether tumor laterality could be integrated into prognostic models or used as a stratification factor in clinical trials.

13. Zusammenfassung

Hintergrund: Das kleinzellige Lungenkarzinom (SCLC) zählt zu den aggressivsten Tumorentitäten der Lunge und ist durch eine äußerst ungünstige Prognose gekennzeichnet. Auch wenn klinische Parameter wie der Allgemeinzustand (ECOG Performance Status), das Krankheitsstadium und das Vorhandensein von Lebermetastasen etablierte prognostische Faktoren darstellen, reichen sie alleine nicht aus, um eine differenzierte Risikobewertung bei SCLC-Patienten vorzunehmen.

Zielsetzung: In früheren Arbeiten zu gut differenzierten neuroendokrinen Lungentumoren wurde gezeigt, dass die Seitenlokalisation des Primärtumors – also ob dieser in der rechten oder linken Lunge entsteht – einen unabhängigen Einfluss auf das Überleben nehmen kann. Insbesondere zeigten sich linksseitige Karzinoide mit schlechteren klinischen Verläufen. Da SCLC ebenfalls eine neuroendokrine Tumorform darstellt, wenn auch schlecht differenziert, untersuchten wir in dieser Studie, ob sich ein ähnlicher Einfluss der Tumorlokalisation auch bei SCLC feststellen lässt.

Studiendesign, Setting und Teilnehmer: Unsere retrospektive multizentrische Beobachtungsstudie umfasste Patienten mit histologisch oder zytologisch gesichertem SCLC, die zwischen Januar 2020 und Dezember 2022 in drei Kliniken in Italien und Deutschland behandelt wurden. Die Behandlungsstrategie richtete sich dabei jeweils nach dem initialen Tumorstadium. Voraussetzung für die Studienteilnahme war eine Mindestnachbeobachtungszeit von drei Monaten.

Hauptergebnisse und Messgrößen: Neben soziodemografischen Merkmalen und klinischen Basisdaten wurden unter anderem Tumorstadium, histopathologische Charakteristika, Metastasenmuster sowie die eingesetzten Therapien systematisch erfasst. Zielgrößen der Analyse waren das Gesamtüberleben (OS) und das progressionsfreie Überleben (PFS). Es erfolgte eine multivariate Auswertung, um den unabhängigen Einfluss der Tumorseite im Vergleich zu weiteren prognostischen Faktoren wie Alter, Geschlecht, ECOG, Therapieschema und Metastasierungsmuster zu bestimmen.

Ergebnisse: Insgesamt wurden 222 Patienten in die Analyse eingeschlossen. Der Großteil war männlich (60,4 %) und über 90 % der Patienten hatten eine aktuelle oder frühere Rauchhistorie. Bei 75,2 % wurde ein Stadium IV diagnostiziert. Der Primärtumor war nahezu gleich verteilt zwischen der rechten (49,5 %) und linken Lunge (50,5 %).

Wie erwartet, zeigten sich ein schlechter ECOG-Status, ein fortgeschrittenes Tumorstadium und das Vorliegen von Lebermetastasen als signifikant negative Einflussfaktoren auf das Überleben. Darüber hinaus ergab unsere Analyse, dass auch die Seite des Primärtumors eine unabhängige Rolle spielt: Patienten mit rechtsseitigem Tumor wiesen ein signifikant längeres medianes OS auf als Patienten mit linksseitigem Tumor (12 Monate vs. 8 Monate, $p = 0{,}001$; $HR = 2{,}020$). Auch im Hinblick auf das PFS ergab sich ein Unterschied zugunsten der rechtsseitigen Tumoren (7,8 Monate vs. 6,7 Monate; $HR = 1{,}293$, $p = 0{,}009$).

Weitere negative Einflussfaktoren waren ein schlechter Allgemeinzustand (ECOG ≥1), aktives oder früheres Rauchen sowie das Vorliegen von Fernmetastasen in Lymphknoten und Knochen. Dagegen zeigten sich kein signifikanter Einfluss von Geschlecht oder Metastasen in Gehirn, Lunge, Pleura oder Nebenniere auf das Überleben.

Schlussfolgerung und Relevanz: Unsere Ergebnisse deuten erstmalig darauf hin, dass die Lokalisation des Primärtumors bei SCLC – analog zu gut differenzierten neuroendokrinen Tumoren – einen prognostischen Einfluss haben könnte. Dies legt nahe, dass Unterschiede in der Tumormikroumgebung oder Tumorbiologie je nach Lungenhälfte existieren. In einer früheren Arbeit zu neuroendokrinen Lungentumoren wurde berichtet, dass „rechtsseitige Tumoren eine höhere mikrovaskuläre Dichte (MVD) und damit ein besseres Überleben aufwiesen, während linksseitige Tumoren häufiger Nekrosen zeigten und mehr HIF-1α exprimierten“ [La Salvia et al., 2021].

Wir vermuten daher, dass auch bei SCLC Unterschiede in Hypoxie, Angiogenese und Mikromilieu – etwa durch asymmetrische lymphatische Drainage oder Aspiration – eine Rolle spielen könnten. Diese Hypothese sollte in zukünftigen prospektiven Studien weiter validiert werden, um die klinische Relevanz der Tumorlateralisierung in der Therapieplanung und Risikostratifizierung von SCLC-Patienten zu prüfen.

References

1. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA: A Cancer Journal for Clinicians 69 (1): 7-30. https:// doi: 10.3322/caac.21442. Epub 2018 Jan 4.
2. 2. Travis WD, Brambilla E, Nicholson AG et al (2015) The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J Thorac Oncol 10: 1243-1260.
3. 3. Koch Institut Robert. Krebs in Deutschland für 2017/2018 [Robert Koch Institute. Cancer in Germany (2019/2020)]. https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2023/kid_2023_c33_c34_lunge.pdf?__blob=publicationFile. Accessed February 2, 2025.
4. Rudin CM, Brambilla E, Faivre-Finn C, et al. Small-cell lung cancer. *Nat Rev Dis Primers*. 2021; 7:3.
5. Islami F, Torre LA, Jemal A. Global trends of lung cancer mortality and smoking prevalence. *Transl Lung Cancer Res*. 2015; 4:327–338.
6. Eberle A, Jansen L, Castro F, et al. Lung cancer survival in Germany: A population-based analysis of 132,612 lung cancer patients. Lung Cancer. 2015 Dec;90(3):528-33. doi: 10.1016/j.lungcan.2015.10.007. Epub 2015 Oct 20. PMID: 26480866.
7. Melikian AA, Djordjevic MV, Hosey J, et al. Gender differences relative to smoking behavior and emissions of toxins from mainstream cigarette smoke. Nicotine Tob Res 2007; 9:377–87. 10.1080/14622200701188836.
8. Hegmann KT, Fraser AM, Keaney RP, et al. The effect of age at smoking initiation on lung cancer risk. *Epidemiol (Camb Mass)*. 1993; 4:444–448.
9. Lubin JH, Caporaso NE. Cigarette smoking and lung cancer: modeling total exposure and intensity. *Cancer Epidemiol Biomarkers Prev*. 2006; 15:517–523.
10. Khuder SA. Effect of cigarette smoking on major his- tological types of lung cancer: a meta-analysis. *Lung Cancer*. 2001; 31:139–148.
11. Pesch B, Kendzia B, Gustavsson P, et al. Cigarette smoking and lung cancer–relative risk estimates for the major histological types from a pooled analysis of case- control studies. *Int J Cancer*. 2012; 131:1210–1219.
12. Pleasants RA, Rivera MP, Tilley SL, et al. Both duration and pack-years of tobacco smoking should be used for clinical practice and research. *Ann Am Thorac Soc*. 2020; 17:804–806.
13. Brooks DR, Austin JH, Heelan RT, et al. Influence of type of cigarette on peripheral versus central lung cancer. *Cancer Epidemiol Biomarkers Prev*. 2005;14:576–581.
14. Ito H, Matsuo K, Tanaka H, et al. Nonfilter and filter cigarette consumption and the incidence of lung cancer by histological type in Japan and the United States: analysis of 30-year data from population-based cancer registries. *Int J Cancer*. 2011; 128:1918–1928.
15. Ettinger DS, Aisner J. Changing face of small-cell lung cancer: real and artifact. *J Clin Oncol*. 2006; 24:4526– 4527.
16. Ou SH, Ziogas A, Zell JA. Prognostic factors for survival in extensive stage small cell lung cancer (ED-SCLC): the importance of smoking history. *J Thorac Oncol*. 2009;4:37–43.

17. Varghese AM, Zakowski MF, Yu HA, et al. Small-cell lung cancers in patients who never smoked cigarettes. *J Thorac Oncol*. 2014; 9:892–896.

18. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans Arsenic, Metals, Fibres, and Dusts. *IARC Monogr. Eval. Carcinog. Risks Hum.* 2012; 100:11–465.

19. WHO *Handbook on Indoor Radon: A Public Health Perspective.* World Health Organization; Geneva, Switzerland: 2009.

20. Lorenzo-González M, Torres-Durán M, Barbosa-Lorenzo R, et al. Radon exposure: a major cause of lung cancer. Expert Rev Respir Med 2019; 13:839–50.

21. Leiter A, Veluswamy RR, Wisnivesky JP. The global burden of lung cancer: current status and future trends. *Nat Rev Clin Oncol*. 2023;20(9):624-639.

22. Ruano-Ravina A, Faraldo-Valles MJ, Barros-Dios JM. Is there a specific mutation of p53 gene due to radon exposure? A systematic review. *Int J Radiat Biol*. 2009;85:614–621.

23. Mogi A, Kuwano H. TP53 mutations in nonsmall cell lung cancer. *J Biomed Biotechnol*. 2011;2011:583929.

24. Field RW, Withers BL. Occupational and environmental causes of lung cancer. *Clin Chest Med*. 2012;33:681– 703.

25. Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. *Am J Ind Med*. 2005; 48:419–431.

26. Kim CH, Lee YC, Hung RJ, et al. Exposure to second- hand tobacco smoke and lung cancer by histological type: a pooled analysis of the International Lung Cancer Consortium (ILCCO). *Int J Cancer*. 2014; 135:1918–1930.

27. Du Y, Cui X, Sidorenkov G, et al. Lung cancer occur- rence attributable to passive smoking among never smokers in China: a systematic review and meta-anal- ysis. *Transl Lung Cancer Res*. 2020; 9:204–217.

28. Baik CS, Strauss GM, Speizer FE, Feskanich D. Repro- ductive factors, hormone use, and risk for lung cancer in postmenopausal women, the Nurses' Health Study. *Cancer Epidemiol Biomarkers Prev*. 2010;19:2525–2533.

29. Pesatori AC, Carugno M, Consonni D, et al. Hormone use and risk for lung cancer: a pooled analysis from the International Lung Cancer Consortium (ILCCO). *Br J Cancer*. 2013; 109:1954–1964.

30. Wang Q, Ru M, Zhang Y, et al. Dietary phytoestrogen intake and lung cancer risk: an analysis of the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial. *Carcinogenesis*. 2021; 42:1250– 1259.

31. Wang Q, Hashemian M, Sepanlou SG, et al. Dietary quality using four dietary indices and lung cancer risk: the Golestan Cohort Study (GCS). *Cancer Causes Con- trol CCC*. 2021; 32:493–503.

32. Lam S, Bai C, Baldwin DR, et al. Current and future perspectives on computed tomography screening for lung cancer: a roadmap from 2023 to 2027 from the International Association for the Study of Lung Cancer. J Thorac Oncol. 2024;19(1):36–51. doi: 10.1016/j.jtho.2023.07.019.

33. Ebbert JO, Yang P, Vachon CM, et al. Lung cancer risk reduction after smoking cessation: observations from a prospective cohort of women. J Clin Oncol. 2003 Mar 1;21(5):921-6. doi: 10.1200/JCO.2003.05.085. PMID: 12610194.

34. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011; 365:395-409.

35. Patz Jr EF, Pinsky P, Gatsonis C, et al. Overdiagnosis in low-dose computed tomography screening for lung cancer. JAMA Intern Med. 2014; 174:269-274.

36. Travis WD, Brambilla E, Noguchi M, et al. International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011; 6:244-285.

37. Franklin WA, Merrick DT, et al. Reclassification of lung cancers detected by CT imaging in the American College of Radiology Imaging Network National Lung Screening Trial. J Thor Oncol. 2015; 10: S220.

38. van Iersel CA, de Koning HJ, Draisma G, et al. Risk-based selection from the general population in a screening trial: selection criteria, recruitment and power for the Dutch-Belgian randomized lung cancer multi-slice CT screening trial (NELSON) Int J Cancer. 2006; 120:868–74. doi: 10.1002/ijc.22134.

39. Thomas A, Pattanayak P, Szabo E, et al. Characteristics and outcomes of small cell lung cancer detected by CT screening. *Chest*. 2018; 154:1284–1290.

40. Silva M, Galeone C, Sverzellati N, et al. Screening with low-dose computed tomography does not improve sur- vival of small cell lung cancer. *J Thorac Oncol*. 2016;11:187–193.

41. Cuffe S, Moua T, Summerfield R, et al. Characteristics and outcomes of small cell lung cancer patients diagnosed during two lung cancer patients diagnosed during two lung cancer computed tomographic screening programs in heavy smokers. *J Thorac Oncol*. 2011; 6:818–822.

42. WHO Classification of Tumours Editorial Board. *Thoracic Tumours*. 5th ed. Lyon: International Agency for Research on Cancer; 2021. Available from: https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/Thoracic-Tumours-202.

43. Wang, Z., et al. "Molecular characterization of lung cancers with neuroendocrine features: A comparison of small cell lung carcinoma and large cell neuroendocrine carcinoma." *Journal of Thoracic Oncology*. 2017: 12(2), 316-324.

44. Skov, B. G., et al. "Molecular profile of neuroendocrine differentiation in non-small cell lung cancer." *Oncology Letters*. 2020: 19(6), 4137-4145.

45. Fujita, Y., et al. "Molecular and clinicopathological features of high-grade neuroendocrine carcinoma of the lung." *Histopathology*. 2021: 79(4), 485-492.

46. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. *Nature*. 2015; 524:47–53.

47. Wistuba II, Gazdar AF, Minna JD. Molecular genetics of small cell lung carcinoma. *Semin Oncol*. 2001;28(suppl 4):3–13.

48. Peifer M, Fernandez-Cuesta L, Sos ML, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. *Nat Genet*. 2012; 44:1104– 1110.

49. Yang F, Gao Y, Geng J, et al. Elevated expression of SOX2 and FGFR1 in correlation with poor prognosis in patients with small cell lung cancer. *Int J Clin Exp Pathol*. 2013; 6:2846–2854.

50. Hainaut P, Pfeifer GP. Patterns of p53 G–>T trans- versions in lung cancers reflect the primary mutagenic signature of DNA-damage by tobacco smoke. *Carcino- genesis*. 2001; 22:367–374.

51. Dick FA, Rubin SM. Molecular mechanisms underlying RB protein function. *Nat Rev Mol Cell Biol*. 2013; 14:297– 306.

52. Rudin CM, Poirier JT, Byers LA, et al. Molecular sub- types of small cell lung cancer: a synthesis of human and mouse model data. *Nat Rev Cancer*. 2019; 19:289– 297.

53. Huang YH, Klingbeil O, He XY, et al. POU2F3 is a master regulator of a tuft cell-like variant of small cell lung cancer. *Genes Dev*. 2018; 32:915–928.

54. Gay CM, Stewart CA, Park EM, et al. Patterns of tran-scription factor programs and immune pathway acti- vation define four major subtypes of SCLC with distinct therapeutic vulnerabilities. *Cancer Cell*. 2021; 39:346– 360.e7.

55. Dingemans, A.-M.C, Früh A, Ardizzoni A, et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology, Volume 32, Issue 7, 839 - 853

56. Bustos García de Castro A, Ferreirós Domínguez J, Delgado Bolton R, et al. PET-CT in presurgical lymph node staging in non-small cell lung cancer: the importance of false-negative and false-positive findings. Radiologia. 2017 Mar-Apr;59(2):147-158. English, Spanish. doi: 10.1016/j.rx.2016.12.001. Epub 2017 Feb 24. PMID: 28238444.

57. Kalemkerian GP. Staging and imaging of small cell lung cancer. Cancer Imaging. 2012 Jan 12;11(1):253-8. doi: 10.1102/1470-7330.2011.0036. PMID: 22245990; PMCID: PMC3266593.

58. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer – what limits limited disease? Lung Cancer. 2002; 37:271–6. doi: 10.1016/S0169-5002(02)00072-7.

59. Rami-Porta R, Nishimura K.K, Girouth D et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groups in the Forthcoming (Ninth) Edition of the TNM Classification for Lung Cancer. JTO Vol. 19 No. 7: 1007–1027 27 February 2024.

60. Barnes H; See K, Barnett S, et al. Surgical for limited-stage small cell lung cancer. Cochrane Database Syst ev. 2017; 4 (4): Cd011917.

61. Wakeam E, Acuna SA, Leigh NB, et al. Suergery versus chemotherapy and radiotherapy for early and locally advanced small cell lung cancer: a propensity-matched analysis of survival. Lung Cancer. 2017; 109:78-88.

62. Ernani V, Ganti AK. Surgery for limited-stage small cell lung cancer: ready for prime-time? J Thorac Dis. 2017; 9(10): 3576-3578.

63. Stinchcombe TE. Current treatments for surgically resectable, limited-stage, and extensive-stage small cell lung cancer. Oncologist 2017; 22 (12):1510-1517.

64. Yang CF, Chan DY, Speicher PJ, et al. Role of the adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol. 2016; 34 (10):1057-1064.

65. Walter J, Moeller C, Resuli B, et al. Guideline adherence of tumor board recommendations in lung cancer and transfer into clinical practice. J Cancer Res Clin Oncol. 2023 Oct;149(13):11679-11688. doi: 10.1007/s00432-023-05025-1. Epub 2023 Jul 5.

66. Ramon J, Soria JC, Peters S. Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. Annals of Oncology, Volume 32, Issue 12, 1637 – 1642. Soria JC.

67. Pignon JP, Arriagada R, Daniel C, et al. A Meta-Analysis of Thoracic Radiotherapy for Small-Cell Lung Cancer. N Engl J Med 1992;327:1618-1624.

68. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol. 2017 Aug;18(8):1116-1125. doi: 10.1016/S1470-2045(17)30318-2. Epub 2017 Jun 20. PMID: 28642008; PMCID: PMC5555437.

69. Cheng Y, Spigel DR, Byoung Ch, et al. Durvalumab after Chemoradiotherapy in Limited-Stage Small-Cell Lung Cancer. N Engl J Med 2024; 391:1313-132.

70. Yin X, Yan D, Qiu M, Huang L, Yan SX. Prophylactic cranial irradiation in small cell lung cancer: a systematic review and meta-analysis. BMC Cancer. 2019 Jan 21;19(1):95. doi: 10.1186/s12885-018-5251-3. PMID: 30665432; PMCID: PMC6341615.

71. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2011 Sep 1;81(1):77-84. doi: 10.1016/j.ijrobp.2010.05.013. Epub 2010 Aug 26. PMID: 20800380; PMCID: PMC3024447.

72. Gondi V, Pugh S, Mehta MP, et al. Primary Endpoint Results of NRG CC003: Phase IIR/III Trial of Prophylactic Cranial Irradiation (PCI) with or without Hippocampal Avoidance (HA) for Small Cell Lung Cancer (SCLC). International Journal of Radiation Oncology, Biology, Physics, Volume 117, Issue 4, e3.

73. Brown PD, Gondi V, Pugh S, et al. Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001. J Clin Oncol. 2020 Apr 1;38(10):1019-1029. doi: 10.1200/JCO.19.02767. Epub 2020 Feb 14. PMID: 32058845; PMCID: PMC7106984.

74. Chen Y, Wang Y, Ren F, et al. Prophylactic cranial irradiation (PCI) versus active surveillance in patients with limited-stage small cell lung cancer: a retrospective, multicentre study. Respir Res. 2022 Oct 2;23(1):274. doi: 10.1186/s12931-022-02196-2. PMID: 36184624; PMCID: PMC9526908.

75. S1827 (MAVERICK) Testing Whether the Use of Brain Scans Alone Instead of Brain Scans Plus Preventive Brain Radiation Affects Lifespan in Patients With Small Cell Lung Cancer. https://clinicaltrials.gov/study/NCT04155034, Accessed February 2025.

76. Lew, A. Berghmans T, Andratscgke N, et al. 174TiP PRIMALung (EORTC-1901): Prophylactic cerebral irradiation or active brain magnetic resonance imaging surveillance in small cell lung cancer patients. Journal of Thoracic Oncology, Volume 18, Issue 4, S136.

77. Peters S, Pujol JL, Dafni U, Dómine M, Popat S, Reck M, Andrade J, Becker A, Moro-Sibilot D, Curioni-Fontecedro A, Molinier O, Nackaerts K, Insa Mollá A, Gervais R, López Vivanco G, Madelaine J, Mazieres J, Faehling M, Griesinger F, Majem M, González Larriba JL, Provencio Pulla M, Vervita K, Roschitzki-Voser H, Ruepp B, Mitchell P, Stahel RA, Le Pechoux C, De Ruysscher D; ETOP/IFCT 4-12 STIMULI Collaborators. Consolidation nivolumab and ipilimumab versus observation in limited-disease small-cell lung cancer after chemo-radiotherapy - results from the randomised phase II ETOP/IFCT 4-12 STIMULI trial. Ann Oncol. 2022 Jan;33(1):67-79. doi: 10.1016/j.annonc.2021.09.011. Epub 2021 Sep 23. PMID: 34562610.

78. Ross JH, Hu Ch, Higgings AK, et al. NRG Oncology/Alliance LU005: A phase II/III randomized clinical trial of chemoradiation versus chemoradiation plus atezolizumab in limited stage small cell lung cancer. JCO May 2020, Volume 38, Number 15_suppl. TPS9082.

79. Rimner A, Lai WV, Califano R, et al. Rationale and Design of the Phase 3 KEYLYNK-013 Study of Pembrolizumab With Concurrent Chemoradiotherapy Followed by Pembrolizumab With or Without Olaparib for Limited-Stage Small-Cell Lung Cancer. Clin Lung Cancer. 2022 Jul;23(5): e325-e329. doi: 10.1016/j.cllc.2022.04.005. Epub 2022 Apr 29. PMID: 35613997; PMCID: PMC10905605.

80. Hummel H, Paz-Ares L, Blackhall F, et al. Annals of Oncology (2024) 9 (suppl_3): 1-11. 10.1016/esmoop/esmoop102577.

81. Serplulimab Combined With CCRT for LS-SCLC. Full Text: https://clinicaltrials.gov/study/NCT06295926?cond=LS-SCLC&rank=2. Accessed on 28 February 2025.

82. Cheng Y, Zhang W, Wu L, et al. Toripalimab Plus Chemotherapy as a First-Line Therapy for Extensive-Stage Small Cell Lung Cancer: The Phase 3 EXTENTORCH Randomized Clinical Trial. JAMA Oncol. 2025 Jan 1;11(1):16-25. doi: 10.1001/jamaoncol.2024.5019. PMID: 39541202; PMCID: PMC11565370.

83. Concurrent Chemoradiotherapy Combined With Toripalimab and Surufatinib in the Treatment of Limited-Stage Small Cell Lung Cancer. Full Text: https://clinicaltrials.gov/study/NCT06719700?cond=LS-SCLC&rank=5. Accessed on 28 February 2025.

84. BMS-986489 (Atigotatug + Nivolumab) vs Durvalumab in Limited-stage Small-cell Lung Cancer (TIGOS-LS) (TIGOS-LS). Full Text: Study Details | BMS-986489 (Atigotatug + Nivolumab) vs Durvalumab in Limited-stage Small-cell Lung Cancer (TIGOS-LS) | ClinicalTrials.gov. Accessed on 28 February 2025.

85. Zhao S, Chen K, Shi X, et al. Design and Rationale for a Phase II/III, Randomized, Double-Blind, Placebo-Controlled Study of Sugemalimab as Consolidation Therapy in Patients With Limited-Stage Small-Cell Lung Cancer Who Have Not Progressed Following Concurrent or Sequential Chemoradiotherapy: The SURPASS Study. Clin Lung Cancer. 2023 Nov;24(7):e254-e258. doi: 10.1016/j.cllc.2023.06.009. Epub 2023 Jun 15. PMID: 37442748.

86. The Study of Envafolimab Combined With Concurrent Chemoradiotherapy In LS-SCLC. Full Text: Study Details | The Study of Envafolimab Combined With Concurrent Chemoradiotherapy In LS-SCLC | ClinicalTrials.gov. Accessed on 28 February 2025.

87. A Trial of SHR-1316 Maintenance Therapy for Limited Stage Small Cell Lung Cancer. Full Text: https://clinicaltrials.gov/study/NCT04647357?cond=LS-SCLC&rank=9. Accessed on 28 February 2025.

88. Adjuvant Adebrelimab Plus Apatinib After Chemoradiation in Limited-Stage Small Cell Lung Cancer. Full text: Study Details | Adjuvant Adebrelimab Plus Apatinib After Chemoradiation in Limited-Stage Small Cell Lung Cancer | ClinicalTrials.gov. Accessed on 28 February 2025.

89. Testing the Addition of a New Immunotherapy Drug, Atezolizumab (MPDL3280A), to the Usual Chemoradiation (CRT) Therapy Treatment for Limited Stage Small Cell Lung Cancer (LS-SCLC). Full text: Study Details | Testing the Addition of a New Immunotherapy Drug, Atezolizumab (MPDL3280A), to the Usual Chemoradiation (CRT) Therapy Treatment for Limited Stage Small Cell Lung Cancer (LS-SCLC) | ClinicalTrials.gov. Accessed on 28 February 2025.

90. Wu, Y, Den L, Wang J, et al. 1795P Consolidation serplulimab following concurrent hypofractionated chemoradiotherapy for limited-stage SCLC: Preliminary analysis of phase II ASTRUM-LC01 study. Annals of Oncology, Volume 35, S1067.

91. Pamiparib for Consolidation Treatment of Unprogressed LS-SCLC After Concurrent Chemoradiotherapy. Full text: Study Details | Pamiparib for Consolidation Treatment of Unprogressed LS-SCLC After Concurrent Chemoradiotherapy | ClinicalTrials.gov. Accessed on 28 February 2025.

92. SBRT Compared With IMRT Concurrently With Chemotherapy in Treating Patients With LS-SCLC. Full Text: https://clinicaltrials.gov/study/NCT02738723?cond=LS-SCLC&page=2&rank=16. Accessed on 28 February 2025.

93. The Study is Being Conducted to Evaluate the Efficacy and Safety of SHR-1316 in Combination With Chemo-radiotherapy in Patients With LS-SCLC. Full Text: https://clinicaltrials.gov/study/NCT04691063?cond=LS-SCLC&page=2&rank=18. Accessed on 28 February 2025.

94. Mascaux C, Paesmans M, Berghmans T, et al. A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis. Lung Cancer. 2000; 30 (1):51-54.

95. Horn L, Mansfield SA, Szczesna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. N Engl J Med 2018; 379:2220-2229. DOI: 10.1056/NEJMoa1809064.

96. Reck M, Dziadziuszko R, Sugawara Sh, et al. Five-year survival in patients with extensive-stage small cell lung cancer treated with atezolizumab in the Phase III IMpower133 study and the Phase III IMbrella A extension study. Lung Cancer, Volume 196, 107924.

97. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019 Nov 23;394(10212):1929-1939. doi: 10.1016/S0140-6736(19)32222-6. Epub 2019 Oct 4. PMID: 31590988.

98. Rudin CM, Awad MM, Navarro A, et al. Pembrolizumab or Placebo Plus Etoposide and Platinum as First-Line Therapy for Extensive-Stage Small-Cell Lung Cancer: Randomized, Double-Blind, Phase III KEYNOTE-604 Study. J Clin Oncol. 2020 Jul 20;38(21):2369-2379. doi: 10.1200/JCO.20.00793. Epub 2020 May 29. PMID: 32468956; PMCID: PMC7474472.

99. Taofeek K. Owonikoko et al., Nivolumab and Ipilimumab as Maintenance Therapy in Extensive-Disease Small-Cell Lung Cancer: CheckMate 451. JCO 39, 1349-1359(2021). DOI:10.1200/JCO.20.02212.

100. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: a randomized study. *J Clin Oncol.* 1999; 17:2092-2099.

101. Slotman B.J, van Tinteren H, Praag J.O, et al. Radiotherapy for extensive stage small-cell lung cancer—authors' reply. Lancet 2015; 385:1292-1293.

102. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol. 2006 Dec 1;24(34):5441-7. doi: 10.1200/JCO.2006.06.5821. PMID: 17135646.

103. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol. 2007 May 20;25(15):2086-92. doi: 10.1200/JCO.2006.08.3998. Erratum in: J Clin Oncol. 2007 Aug 1;25(22):3387. PMID: 17513814.

104. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol. 1999 Feb;17(2):658-67. doi: 10.1200/JCO.1999.17.2.658. PMID: 10080612.

105. Baize N, Monnet I, Greillier L, et al. Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2020 Sep;21(9):1224-1233. doi: 10.1016/S1470-2045(20)30461-7. PMID: 32888454.

106. Ardizzoni A, Tiseo M, Boni L. Validation of standard definition of sensitive versus refractory relapsed small cell lung cancer: a pooled analysis of topotecan second-line trials. Eur J Cancer. 2014 Sep;50(13):2211-8. doi: 10.1016/j.ejca.2014.06.002. Epub 2014 Jun 26. PMID: 24981975.

107. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol. 2020 May;21(5):645-654. doi: 10.1016/S1470-2045(20)30068-1. Epub 2020 Mar 27. Erratum in: Lancet Oncol. 2020 Dec;21(12):e553. doi: 10.1016/S1470-2045(20)30676-8. PMID: 32224306.

108. Ahn MJ, Cho BC, Felip E, et al. Tarlatamab for Patients with Previously Treated Small-Cell Lung Cancer. N Engl J Med. 2023 Nov 30;389(22):2063-2075. doi: 10.1056/NEJMoa2307980. Epub 2023 Oct 20. PMID: 37861218.

109. Rudin C, Ahn, M, Johnson, M, et al. Ifinatamab deruxtecan (I-DXd) in extensive-stage small cell lung cancer (ES-SCLC): interim analysis of IDeate-Lung01. Presented at: 2024 IASLC World Conference on Lung Cancer; September 7-10, 2024; San Diego, CA. Abstract OA04.03.

110. Dowlati A, Chiang AC, Cervantes A, et al. Phase 2 Open-Label Study of Sacituzumab Govitecan as Second-Line Therapy in Patients With Extensive-Stage SCLC: Results From TROPiCS-03. J Thorac Oncol. 2025 Jan 2:S1556-0864(24)02549-8. doi: 10.1016/j.jtho.2024.12.028. Epub ahead of print. PMID: 39755168.

111. Study of RYZ101 in Combination With SoC in Subjects With SSTR+ ES-SCLC. Full Text: Study Details | Study of RYZ101 in Combination With SoC in Subjects With SSTR+ ES-SCLC | ClinicalTrials.gov. Accessed on 4 March 2025.

112. A Study of PM8002 (Anti-PD-L1/VEGF) in Combination With Chemotherapy in Patients With ES-SCLC. Full Text: Study Details | A Study of PM8002 (Anti-PD-L1/VEGF) in Combination With Chemotherapy in Patients With ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

113. TRT for ES-SCLC After First Line Treatment With Immune Checkpoint Inhibitors. Full Text: Study Details | TRT for ES-SCLC After First Line Treatment With Immune Checkpoint Inhibitors | ClinicalTrials.gov. Accessed on 04 March 2025.

114. Patients With ES-SCLC and ECOG PS=2 Receiving Atezolizumab-Carboplatin-Etoposide (SPACE). Full Text: Study Details | Patients With ES-SCLC and ECOG PS=2 Receiving Atezolizumab-Carboplatin-Etoposide | ClinicalTrials.gov. Accessed on 04 March 2025.

115. Adebrelimab Combined with Chemotherapy and Thoracic Radiotherapy for First-line Treatment of ES-SCLC (RALLY). Full Text: Study Details | Adebrelimab Combined with Chemotherapy and Thoracic Radiotherapy for First-line Treatment of ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

116. A Single-arm, Open-label, Phase II Study to Evaluate Efficacy, Safety and Pharmacokinetics of HLX10 + Chemotherapy in Patients with ES-SCLC. Full Text: Study Details | A Single-arm, Open-label, Phase II Study to Evaluate Efficacy, Safety and Pharmacokinetics of HLX10 + Chemotherapy in Patients with ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

117. Tislelizumab Combined with Chemotherapy and Relayed Radiotherapy in First-line Treatment of ES-SCLC. Full text: Study Details | Tislelizumab Combined with Chemotherapy and Relayed Radiotherapy in First-line Treatment of ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

118. A Multicenter Real-World Cohort Study of Adebrelimab Injection in the Treatment of Extensive-Stage Small Cell Lung Cancer. Full Text: Study Details | A Multicenter Real-World Cohort Study of Adebrelimab Injection in the Treatment of Extensive-Stage Small Cell Lung Cancer | ClinicalTrials.gov. Accessed on 04 March 2025.

119. Pembrolizumab and Olaparib Treatment of Extensive Small Cell Lung Cancer (ES-SCLC) (THOR). Full Text: Study Details | Pembrolizumab and Olaparib Treatment of Extensive Small Cell Lung Cancer (ES-SCLC) | ClinicalTrials.gov. Accessed on 04 March 2025.

120. Quaratusugene Ozeplasmid (Reqorsa) and Atezolizumab Maintenance Therapy in ES-SCLC Patients (Acclaim-3). Full text: Study Details | Quaratusugene Ozeplasmid (Reqorsa) and Atezolizumab Maintenance Therapy in ES-SCLC Patients | ClinicalTrials.gov. Accessed on 04 March 2025.

121. Anti-PD-1 and VEGF Bispecific Antibody AK112 in Combination With Chemotherapy in Patients With ES-SCLC. Full Text: Study Details | Anti-PD-1 and VEGF Bispecific Antibody AK112 in Combination With Chemotherapy in Patients With ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

122. Phase 1b/2 Study of LDRT in Combination With AK104 Plus Chemotherapy as First-line Treatment for ES-SCLC. Full Text: Study Details | Phase 1b/2 Study of LDRT in Combination With AK104 Plus Chemotherapy as First-line Treatment for ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

123. Tislelizumab Combined With Chemotherapy and Thoracic Radiotherapy in ES-SCLC. Full Text: Study Details | Tislelizumab Combined With Chemotherapy and Thoracic Radiotherapy in ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

124. Toripalimab Plus Anlotinib for the Maintenance of Extensive Stage Small Cell (SCLC). Full Text: Study Details | Toripalimab Plus Anlotinib for the Maintenance of Extensive Stage Small Cell | ClinicalTrials.gov. Accessed on 04 March 2025.

125. Irinotecan Liposome (II) or Etoposide Combined With Adebrelimab and Carboplatin in the Treatment of ES-SCLC. Full Text: Study Details | Irinotecan Liposome (II) or Etoposide Combined With Adebrelimab and Carboplatin in the Treatment of ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

126. SHR-1316 Combined With Chemotherapy and Chest Radiotherapy in ES-SCLC. Full Text: Study Details | SHR-1316 Combined With Chemotherapy and Chest Radiotherapy in ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

127. Study of AZD2811 + Durvalumab in ES-SCLC (TAZMAN). Full Text: Study Details | Study of AZD2811 + Durvalumab in ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

128. Phase I/II Trial in ES-SCLC to Enhance Response to Atezolizumab Plus Chemotherapy With Total Body Irradiation (TESSERACT). Full Text: Study Details | Phase I/II Trial in ES-SCLC to Enhance Response to Atezolizumab Plus Chemotherapy With Total Body Irradiation | ClinicalTrials.gov. Accessed on 04 March 2025.

129. Testing the Addition of Radiation Therapy to the Immune Therapy Treatment for ES-SCLC. Full Text: Study Details | Testing the Addition of Radiation Therapy to the Immune Therapy Treatment for ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

130. Low-dose Radiotherapy Combined with Concurrent Chemotherapy, Toripalimab and Tifcemalimab in the Treatment of ES-SCLC. Full text: Study Details | Low-dose Radiotherapy Combined with Concurrent Chemotherapy, Toripalimab and Tifcemalimab in the Treatment of ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

131. Durvalumab With Consolidative Radiochemotherapy and Ablative Stereotactic Radiotherapy in Oligometastatic ES-SCLC. Full Text: Study Details | Durvalumab With Consolidative Radiochemotherapy and Ablative Stereotactic Radiotherapy in Oligometastatic ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

132. A Study of [177Lu]Lu-DOTA-TATE in Newly Diagnosed ES-SCLC Patients in Combination With Carboplatin, Etoposide and Atezolizumab. Full Text: Study Details | A Study of [177Lu]Lu-DOTA-TATE in Newly Diagnosed ES-SCLC Patients in Combination With Carboplatin, Etoposide and Atezolizumab | ClinicalTrials.gov. Accessed on 04 March 2025.

133. Talazoparib and Thoracic RT for ES-SCLC. Full Text: Study Details | Talazoparib and Thoracic RT for ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

134. Testing the Addition of Radiation Therapy to the Usual Immune Therapy Treatment (Atezolizumab) for Extensive Stage Small Cell Lung Cancer, The RAPTOR Trial. Full Text: Study Details | Testing the Addition of Radiation Therapy to the Usual Immune Therapy Treatment (Atezolizumab) for Extensive Stage Small Cell Lung Cancer, The RAPTOR Trial | ClinicalTrials.gov. Accessed on 04 March 2025.

135. First-Line Tarlatamab in Combination With Carboplatin, Etoposide, and PD-L1 Inhibitor in Subjects With Extensive Stage Small Cell Lung Cancer (ES-SCLC). Full Text: Study Details | First-Line Tarlatamab in Combination With Carboplatin, Etoposide, and PD-L1 Inhibitor in Subjects With Extensive Stage Small Cell Lung Cancer (ES-SCLC) | ClinicalTrials.gov. Accessed on 04 March 2025.

136. Maintenance Lurbinectedin in Combination With Serplulimab for Patients With ES-SCLC. Full Text: Study Details | Maintenance Lurbinectedin in Combination With Serplulimab for Patients With ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

137. Adebelizumab Combined With Chemotherapy and Radiotherapy Treat ES-SCLC. Full Text: Study Details | Adebelizumab Combined With Chemotherapy and Radiotherapy Treat ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

138. Perol M, Ahn MJ, Cheng Y, et al. P1.13A.02 Tarlatamab Plus Durvalumab as First-Line Maintenance in Extensive-Stage Small Cell Lung Cancer: DeLLphi-305 Phase 3 Trial. JTO, 2024. Volume 19, Issue 10, Supplement, October 2024, Pages S206-S207.

139. Surufatinib in Combination of Durvalumab and EP/EC in the Firstly-line Treatment of ES-SCLC. Full Text: Study Details | Surufatinib in Combination of Durvalumab and EP/EC in the Firstly-line Treatment of ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

140. IN10018 Combination Therapy in Treatment-naïve ES-SCLC. Full Text: Study Details | IN10018 Combination Therapy in Treatment-naïve ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

141. First Line Pembrolizumab, Plinabulin Plus Etoposide and Platinum (EP) for ES-SCLC. Full Text: Study Details | First Line Pembrolizumab, Plinabulin Plus Etoposide and Platinum (EP) for ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

142. Study of Pembrolizumab, Lenvatinib and Chemotherapy Combination in First Line Extensive-stage Small Cell Lung Cancer (PEERS). Full Text: Study Details | Study of Pembrolizumab, Lenvatinib and Chemotherapy Combination in First Line Extensive-stage Small Cell Lung Cancer | ClinicalTrials.gov. Accessed on 04 March 2025.

143. Study of Pembrolizumab, Lenvatinib and Chemotherapy Combination in First Line Extensive-stage Small Cell Lung Cancer (PEERS). Full Text: Study of Pembrolizumab, Lenvatinib and Chemotherapy Combination in First Line Extensive-stage Small Cell Lung Cancer (PEERS). Accessed on 04 March 2025.

144. Phase II Study of Ivonescimab and Cadonilimab in Combination with Chemotherapy in Patients with ES-SCLC. Full text: Study Details | Phase II Study of Ivonescimab and Cadonilimab in Combination with Chemotherapy in Patients with ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

145. Safety and Tolerability of LDRT+Sugemalimab+Chemotherapy+Olaparib for First-Line Treatment of SLFN-11 Positive ES-SCLC. Study Details | Safety and Tolerability of LDRT+Sugemalimab+Chemotherapy+Olaparib for First-Line Treatment of SLFN-11 Positive ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

146. Safety and Effectiveness of BNT327, an Investigational Therapy in Combination With Chemotherapy for Patients With Untreated Small-cell Lung Cancer. Full Text: Study Details | Safety and Effectiveness of BNT327, an Investigational Therapy in Combination With Chemotherapy for Patients With Untreated Small-cell Lung Cancer | ClinicalTrials.gov. Accessed on 04 March 2025.

147. A Study to Investigate the Efficacy and Safety of Tislelizumab Combined With Anlotinib as Maintenance Therapy for ES-SCLC. Full text: Study Details | A Study to Investigate the Efficacy and Safety of Tislelizumab Combined With Anlotinib as Maintenance Therapy for ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

148. A Study to Investigate the Efficacy and Safety of Tislelizumab Combined With Sitravatinib as Maintenance Therapy for ES-SCLC. Full Text: Study Details | A Study to Investigate the Efficacy and Safety of Tislelizumab Combined With Sitravatinib as Maintenance Therapy for ES-SCLC | ClinicalTrials.gov. Accessed on 04 Mrch 2025.

149. Combination of Atezolizumab With Dendritic Cell Vaccine in Patients With Lung Cancer (VENEZO-LUNG). Full Text: Study Details | Combination of Atezolizumab With Dendritic Cell Vaccine in Patients With Lung Cancer | ClinicalTrials.gov. Accessed on 04 March 2025.

150. Chemo-Immunotherapy Followed by Durvalumab and Ceralasertib in Treatment Naïve Patients With Extensive Stage Small Cell Lung Cancer. Full Text: Study Details | Chemo-Immunotherapy Followed by Durvalumab and Ceralasertib in Treatment Naïve Patients With Extensive Stage Small Cell Lung Cancer | ClinicalTrials.gov. Accessed on 04 March 2025.

151. A Phase III, Open-Label Study of Maintenance Lurbinectedin in Combination With Atezolizumab Compared With Atezolizumab in Participants With Extensive-Stage Small-Cell Lung Cancer (IMforte). Full Text: Study Details | A Phase III, Open-Label Study of Maintenance Lurbinectedin in Combination With Atezolizumab Compared With Atezolizumab in Participants With Extensive-Stage Small-Cell Lung Cancer | ClinicalTrials.gov. Accessed on 04 March 2025.

152. Olaparib and Durvalumab With Carboplatin, Etoposide, and/or Radiation Therapy for the Treatment of Extensive-Stage Small Cell Lung Cancer, PRIO Trial. Full Text: Study Details | Olaparib and Durvalumab With Carboplatin, Etoposide, and/or Radiation Therapy for the Treatment of Extensive-Stage Small Cell Lung Cancer, PRIO Trial | ClinicalTrials.gov. Accessed on 04 March 2025.

153. PD-L1 Inhibitor Combined With Apatinib as First-line Maintenance Treatment for Extensive-stage Small Cell Lung Cancer. Full Text: Study Details | PD-L1 Inhibitor Combined With Apatinib as First-line Maintenance Treatment for Extensive-stage Small Cell Lung Cancer | ClinicalTrials.gov. Accessed on 04 March 2025.

154. A Study to Compare the Efficacy and Safety of BMS-986489 (BMS-986012+ Nivolumab Fixed Dose Combination) in Combination With Carboplatin Plus Etoposide to That of Atezolizumab With Carboplatin Plus Etoposide as First-Line Therapy in Participants With Ex-

tensive-Stage Small Cell Lung Cancer (TIGOS). Full Text: Study Details | A Study to Compare the Efficacy and Safety of BMS-986489 (BMS-986012+ Nivolumab Fixed Dose Combination) in Combination With Carboplatin Plus Etoposide to That of Atezolizumab With Carboplatin Plus Etoposide as First-Line Therapy in Participants With Extensive-Stage Small Cell Lung Cancer (TIGOS). | ClinicalTrials.gov. Accessed on 04 March 2025.

155. Efficacy and Safety of Pembrolizumab Plus Investigational Agents in Combination With Chemotherapy as First-Line Treatment in Extensive-Stage Small Cell Lung Cancer (ES-SCLC) (MK-3475-B99/ KEYNOTE-B99). Full Text: Study Details | Efficacy and Safety of Pembrolizumab Plus Investigational Agents in Combination With Chemotherapy as First-Line Treatment in Extensive-Stage Small Cell Lung Cancer (ES-SCLC) (MK-3475-B99/ KEYNOTE-B99) | ClinicalTrials.gov. Accessed on 04 March 2025.

156. A Study to Investigate the Efficacy and Safety of Ivonescimab Combined With Irinotecan Liposome as Second-line Regimen for ES-SCLC. Full Text: Study Details | A Study to Investigate the Efficacy and Safety of Ivonescimab Combined With Irinotecan Liposome as Second-line Regimen for ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

157. Trilaciclib vs Placebo in Patients With Extensive Stage Small Cell Lung Cancer (ES-SCLC) Receiving Topotecan. Full Text: Study Details | Trilaciclib vs Placebo in Patients With Extensive Stage Small Cell Lung Cancer (ES-SCLC) Receiving Topotecan | ClinicalTrials.gov. Accessed on 04 March 2025.

158. Combined Simvastatin and Albumin Paclitaxel in Treating ES-SCLC Patients Relapsed From 1st Chemotherapy. Full Text: Study Details | Combined Simvastatin and Albumin Paclitaxel in Treating ES-SCLC Patients Relapsed From 1st Chemotherapy | ClinicalTrials.gov. Accessed on 04 March 2025.

159. SC0245 and Irinotecan in Treating Patients With Relapsed Extensive-Stage Small Cell Lung Cancer (ES-SCLC). Full Text: Study Details | SC0245 and Irinotecan in Treating Patients With Relapsed Extensive-Stage Small Cell Lung Cancer (ES-SCLC) | ClinicalTrials.gov. Accessed on 04 March 2025.

160. Study of Sacituzumab Govitecan Versus Standard of Care in Participants With Previously Treated Extensive Stage Small Cell Lung Cancer (EVOKE-SCLC-04). Full Text: Study Details | Study of Sacituzumab Govitecan Versus Standard of Care in Participants With Previously Treated Extensive Stage Small Cell Lung Cancer | ClinicalTrials.gov. Accessed on 04 March 2025.

161. Atezolizumab and Rechallenge Chemotherapy in Relapsed Patients With Extensive-stage Small Cell Lung Cancer (ES-SCLC). (CARRY-ON). Full Text: Study Details | Atezolizumab and Rechallenge Chemotherapy in Relapsed Patients With Extensive-stage Small Cell Lung Cancer (ES-SCLC). | ClinicalTrials.gov. Accessed on 04 March 2025.

162. Safety and Efficacy of Adebrelimab Plus Irinotecan Liposome (II) With or Without Famitinib in ES-SCLC Pre-treated With Immunotherapy. Full Text: Study Details | Safety and Efficacy of Adebrelimab Plus Irinotecan Liposome (II) With or Without Famitinib in ES-SCLC Pre-treated With Immunotherapy | ClinicalTrials.gov. Accessed on 04 March 2025.

163. Liposomal Irinotecan and Apatinib in ES-SCLC (LIAES). Full Text: Study Details | Liposomal Irinotecan and Apatinib in ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

164. Cadonilimab (AK104) With or Without CT as 2rd Line Treatment for ES-SCLC. Full Text: Study Details | Cadonilimab (AK104) With or Without CT as 2rd Line Treatment for ES-SCLC | ClinicalTrials.gov. Accessed on 04 March 2025.

165. MGC018 in Patients With Relapsed or Refractory Extensive-Stage Small-Cell Lung Cancer (MGC018-SCLC). Full Text: Study Details | MGC018 in Patients With Relapsed or Refractory Extensive-Stage Small-Cell Lung Cancer | ClinicalTrials.gov. Accessed on 04 March 2025.

166. Safety and Efficacy Study of Investigational Agents as Monotherapy or in Combination With Pembrolizumab (MK-3475) for the Treatment of Extensive-Stage Small Cell Lung Cancer (ES-SCLC) in Need of Second-Line Therapy (MK-3475-B98/KEYNOTE-B98). Full Text: Study Details | Safety and Efficacy Study of Investigational Agents as Monotherapy or in Combination With Pembrolizumab (MK-3475) for the Treatment of Extensive-Stage Small Cell Lung Cancer (ES-SCLC) in Need of Second-Line Therapy (MK-3475-B98/KEYNOTE-B98) | ClinicalTrials.gov. Accessed on 04 March 2025.

167. Roychoudhuri R, Putcha V, Møller H. Cancer and laterality: a study of the five major paired organs (UK). *Cancer Causes Control*. 2006;17(5):655–662.

168. Torres WE, Turner MA, Ernst RD. Anatomy and imaging of the tracheobronchial tree. *Radiol Clin North Am*. 1993;31(4):741–754.

169. Kim CS, Iglesias AJ, Garcia L. Deposition of aerosol particles in the human respiratory tract: comparison between experimental data and mathematical models. *J Aerosol Med*. 1996;9(1):23–41.

170. Vidic B, Obradovic V. Role of bronchial anatomy in pulmonary aspiration. *Acta Medica Okayama*. 1980;34(2):145–150.

171. Hogg JC, Chu F, Utokaparch S, et al. The nature of small-airway obstruction in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(26):2645–2653.

172. Cohen L, Lomas JQ. Foreign material in airways of patients dying in hospital: clinical and autopsy correlates. *Am J Forensic Med Pathol*. 1990;11(4):305–308.

173. Darquenne C. Aerosol deposition in health and disease. *J Aerosol Med Pulm Drug Deliv*. 2012;25(3):140–147.

174. Desai, K., & McKenna, L. (2013). Microsatellite instability in colorectal cancer: A review of the molecular mechanisms and the clinical relevance. World Journal of Gastroenterology, 19(29), 4622–4632. https://doi.org/10.3748/wjg.v19.i29.4622.

175. Lichtenstein, L., & Garofalo, A. (2014). BRAF mutations in colorectal cancer: Role in prognosis and therapy. Journal of Clinical Oncology, 32(9), 890–895. https://doi.org/10.1200/JCO.2013.53.7219.

176. Jass, J. R., & Leggett, B. (2008). Methylation and colorectal cancer: Insights into the molecular basis of colorectal carcinogenesis. Gut, 57(7), 979–988. https://doi.org/10.1136/gut.2007.145535.

177. Popat, S., & Hubner, R. (2012). Impact of left- versus right-sided primary tumors on survival in metastatic colorectal cancer: A retrospective study. Journal of Clinical Oncology, 30(19), 2350–2356. https://doi.org/10.1200/JCO.2011.40.7542.

178. Modest, D. P., et al. (2016). The role of EGFR inhibitors in the treatment of metastatic colorectal cancer: Impact of primary tumor location and RAS status. Journal of Cancer Research and Clinical Oncology, 142(3), 457–464. https://doi.org/10.1007/s00432-015-2077-6.

179. Schultheis, A.M.; Scheel, A.H.; Ozretic´, L.; George, J.; Thomas, R.K.; Hagemann, T.; Zander, T.; Wolf, J.; Buettner, R. PD-L1 expression in small cell neuroendocrine carcinomas. *Eur. J. Cancer* 2015, *3*, 421–426.

180. Marabelle A, Fakih M, Lopez J, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. *Lancet Oncol*. 2020; 21:1353–1365.

181. Bray F., Ferlay J., Soerjomataram I., Siegel R.L., Torre L.A., Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J.Clin. 2018; 68:394–424.

182. George J, Lim JS, Jang SJ, Cun Y, Ozretić L, Kong G, et al. Comprehensive genomic profiles of small cell lung cancer. Nature. 2015;524(7563):47–53.

183. Rudin CM, Durinck S, Stawiski EW, Poirier JT, Modrusan Z, Shames DS, et al. Comprehensive genomic analysis identifies SOX2 as a frequently amplified gene in small-cell lung cancer. Nat Genet. 2012; 44:1111–1116.

184. Gazdar AF, Bunn PA, Minna JD. Small-cell lung cancer: what we know, what we need to know and the path forward Nat Rev Cancer. Nat Publ Group. 2017;17(12):725–37.

185. Peifer M, Fernández-Cuesta L, Sos ML, et al. Integrative genome analyses identify key somatic driver mutations of small-cell lung cancer. Nat Genet. 2012; 44:1104–1110.

186. Arcaro A. Targeted therapies for small cell lung cancer: Where do we stand? Crit Rev Oncol Hematol. Elsevier Ireland Ltd. 2015; 95:154–64.

187. Bunn PA, Minna JD, Augustyn A, et al. Small cell lung cancer: can recent advances in biology and molecular biology be translated into improved outcomes? Journal of Thoracic Oncology. Lippincott Williams and Wilkins; 2016. 453–74.

188. Qu S, Fetsch P, Thomas A, Pommier Y, et al. Molecular subtypes of primary SCLC tumors and their associations with neuroendocrine and therapeutic markers. J Thorac Oncol. 2022; 17:141–53.

189. Longo V, Pizzutilo P, Catino A, et al.Prognostic factors for survival in extensive-stage small cell lung cancer: an Italian real-world retrospective analysis of 244 patients treated over the last decade. Thorac Cancer. 2022, 13:3486-95.

190. S.Y. Yang, M.S. Cho, N.K. Kim, et al. Difference between right-sided and left-sided colorectal cancers: from embryology to molecular subtype. Expert Rev. Anticancer. Ther. 2018: 18(4), 351–358.

191. S. Guo, K. Yao, X. He, S. Wu, Y. Ye, J. Chen, C.L. Wu, Prognostic significance of laterality in renal cell carcinoma: A population-based study from the surveillance, epidemiology, and end results (SEER) database. Cancer Med. 2019: 8(12), 5629–5637 .

192. C.J. Yang, S.A. Shah, B.K. Lin, et al. Right- sided versus left-sided pneumonectomy after induction therapy for non-small cell lung cancer. Ann. Thorac. Surg. 2019:107(4), 1074–1081.

193. La Salvia A, Faggiano AG, et al. Angioside: The role of Angiogenesis and Hypoxia in Lung Neuroendocrine Tumours According to Primary Tumour Location in Left or Right Parenchyma. J Clin Med. 2022 Oct 9;11(19):5958.

194. La Salvia A, Carletti R, Verrico M, et al. Angioside: The role of Angiogenesis and Hypoxia in Lung Neuroendocrine Tumours According to Primary Tumour Location in Left or Right Parenchyma. J Clin Med. 2022 Oct 9;11(19):5958. doi: 10.3390/jcm11195958. PMID: 36233825; PMCID: PMC9570740.

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Publikationsliste

1. Negrao MV, Araujo HA, Lamberti G, Cooper AJ, Akhave NS, Zhou T, Delasos L, Hicks JK, Aldea M, Minuti G, Hines J, Aredo JV, Dennis MJ, Chakrabarti T, Scott SC, Bironzo P, Scheffler M, Christopoulos P, Stenzinger A, Riess JW, Kim SY, Goldberg SB, Li M, Wang Q, Qing Y, Ni Y, Do MT, Lee R, Ricciuti B, Alessi JV, Wang J**, Resuli B**, Landi L, Tseng SC, Nishino M, Digumarthy SR, Rinsurongkawong W, Rinsurongkawong V, Vaporciyan AA, Blumenschein GR, Zhang J, Owen DH, Blakely CM, Mountzios G, Shu CA, Bestvina CM, Garassino MC, Marrone KA, Gray JE, Patel SP, Cummings AL, Wakelee HA, Wolf J, Scagliotti GV, Cappuzzo F, Barlesi F, Patil PD, Drusbosky L, Gibbons DL, Meric-Bernstam F, Lee JJ, Heymach JV, Hong DS, Heist RS, Awad MM, Skoulidis F. Co-mutations and KRAS G12C inhibitor efficacy in advanced NSCLC. Cancer Discov. 2023 Apr; CD-22-1420.
2. Walter J, Moeller C, **Resuli B**, Kauffmann-Guerrero D, Manapov F, Dinkel J, Neumann J, Kovacs J, Schneider Ch, Huber RM, Tufman A. Guideline adherence of tumor board recommendations in lung cancer and transfer into clinical practice. J Cancer Res Clin Oncol. 2023 Oct;149(13):11679-11688.
3. Orciuolo C, Cappuzzo F, Landi L, **Resuli B**, Carpano S, Vidiri A, Buglioni S, Mandoj CH, Ciliberto G, Minuti G. Pretreated EGFR del19/ BRAF V600E lung adenocarcinoma with leptomeningeal disease control on Osimertinib, Dabrafenib, and Trametinib: a case report. JTO Clinical Research Reports, Available online 30 June 2023, 100545.
4. Tufman A, Schneiderbauer S, Walter J, **Resuli B**, Kauffmann-Guerrero D, Mümmler C, Mertsch P, Götschke J, Kovács J, Manapov F, Schneider C, Sellmer L, Arnold P, Heinemann V, Behr J, Nasseh D. Early mortality in German patients with lung cancer: risk factors associated with 30- and 60-day mortality. Clin Exp Med. 2023 Dec;23(8):5183-5190.
5. Roberto M, Barchiesi G, **Resuli B**, Verrico M, Speranza I, Cristofani L, Pediconi F, Tomao F, Botticelli A, Santini D. Sarcopenia in Breast Cancer Patients: A Systematic Review and Meta-Analysis. Cancers (Basel). 2024 Jan 31;16(3):596.
6. **Resuli B**, Kauffmann-Guererro D. Novel immunotherapeutic approaches in lung cancer: driving beyond programmed death-1/programmed death ligand-1 and cytotoxic T-lymphocyte-associated Protein-4. Curr Opin Oncol. 2025 Jan 1;37(1):48-62.
7. **Resuli B**, Kauffmann-Guererro D, Behr J, Tufman A. Simultaneous Occurrence of *HER2* Mutations in *EGFR* Mutant NSCLC: Case Reports. JTO Clin Res Rep. 2024 Sep 7;5(12):100719.
8. **Resuli B**, Galarza H, Elsner L, Kauffmann-Guerrero D, Behr J, Tufman A. Safety of brigatinib following alectinib-induced-pneumonitis: Case report. Respir Med Case Rep. 2024 Dec 27; 53:102160.
9. **Resuli B**, Walter J, Kauffmann-Guerrero D, Mertsch P, Arredondo Lasso M, Arnold P, Schneider C, Behr J, Tufman A. Toxicity Profile and Efficacy of Docetaxel Following Paclitaxel- or Pemetrexed-Platinum Chemotherapy Alone or in Combination With Immune Checkpoint Inhibitors in NSCLC Patients: A Single Institution Retrospective Analysis. Cancer Control. 2025 Jan-Dec; 32:10732748251328618.
10. Resuli B, Kauffmann-Guerrero D. Will INSPIRE crown iruplinalkib as a new standard choice in first-line advanced *ALK*-positive non-small cell lung cancer? Transl Lung Cancer Res. 2025 Mar 31;14(3):653-656. doi: 10.21037/tlcr-24-655. Epub 2025 Mar 26.