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Small-Cell Lung Cancer (SCLC)

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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DGHO Deutsche Gesellschaft für Hämatologie und
Medizinische Onkologie e.V.
Bauhofstr. 12
D-10117 Berlin

Executive chairwoman: Prof. Dr. med. Claudia Baldus

Phone: +49 (0)30 27 87 60 89 - 0

info@dgho.de
www.dgho.de

Contact person

Prof. Dr. med. Bernhard Wörmann
Medical superintendent

Source

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Small-Cell Lung Cancer (SCLC)

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Authors: Annalen Bleckmann, Volkmar Borrass, Wilfried Eberhardt, Martin Eichhorn, Nikolaj Frost, Martin Früh, Oliver Gautschi, Frank Griesinger, Hans Hoffmann, Felix John, Philipp Jost, Barbara Kiesewetter-Wiederkehr, Wolfgang Johannes Köstler, Klaus Kraywinkel, Sonja Loges, Christoph Pöttgen, Martin Reck, Niels Reinmuth, Wolfgang Schütte, Martin Sebastian, Cornelius Waller, Martin Wolf
Previous authors: Wolfgang Hilbe, Rudolf Maria Huber, Robert Pirker, Ron Pritzkuleit, Jan Stöhlmacher, Michael Thomas, Dieter Ukena, Jürgen Wolf, Bernhard Wörmann

1 Summary

Lung cancer is the third most common malignant tumor in women and the second most common in men in German-speaking countries. Lung cancer is the most common cause of cancer-related death in both men and women. The median age of onset is approximately 70 years. The main risk factor is smoking.

Small cell lung cancer (SCLC) accounts for approximately 12-15% of lung cancers. In Germany, approximately 7,000-8,000 people are diagnosed with SCLC each year. The disease is characterized by a high cell division rate and rapid growth progression. These biological characteristics explain the tumor's high sensitivity to chemotherapy and radiotherapy. On the other hand, they also lead to early dissemination and high recurrence rates. According to the American Cancer Society, the 5-year survival rate for SCLC is 9% (for non-SCLC: 32%) [76]. In stages I-III (very limited disease, limited disease), curative therapy is possible. Treatment in these stages is multimodal, involving surgery, systemic tumor therapy, and radiation. For adult patients in the limited disease stage, whose disease is not progressive after platinum-based chemoradiotherapy, consolidation with durvalumab for 2 years is recommended. The combination of chemotherapy and immunotherapy is the current standard in the first-line study of extensive disease (ED) SCLC. With combined chemo-immunotherapy, 15-20% of patients achieve a 3-year survival.

2 Basics

2.1 Definition and basic information

Lung carcinomas are malignancies that arise from the epithelial cells of the respiratory tract. Based on cell line differentiation, a distinction is made between small cell and non-small cell carcinomas. Non-small cell carcinomas (NSCLC) are further differentiated according to immunohistochemical and, more recently, molecular parameters, so that this term is to be understood as a summary for mainly adenocarcinomas and squamous cell carcinomas. SCLC, on the other hand, is a separate entity from the group of neuroendocrine neoplasms (NEN) [57].

The lungs are a predilection site for metastases from numerous malignancies. These, as well as other rare pulmonary tumors and benign lesions must be ruled out based on medical history and, if indicated, histopathologically.

SCLC develops from neuroendocrine cells in the bronchi. These cells have a regulatory function in the lungs and produce hormones and peptides. Contact with carcinogens (tobacco components, radon, arsenic, etc.) leads to mutations in tumor suppressor genes and/or proto-oncogenes, which play a central role in aggressive tumor growth [62]. SCLC is characterized by biallelic inactivating mutations in the two tumor suppressor genes *TP53* and *RB1*, which are found in almost all patients affected [5, 6]. In addition, SCLC often involves mutations in the *NOTCH* gene family or amplifications of the *MYC* gene [3, 56, 61].

Microscopically, SCLC typically presents as a small, blue, round-cell tumor and must be distinguished histologically from other such tumors such as Ewing's sarcoma or lymphomas. The tumor cells are small and have a high nucleus-to-cytoplasm ratio. The cell nuclei are hyperchromatic with fine-grained chromatin (so-called "salt and pepper" pattern), and a nucleolus is usually barely visible. Due to the high mitotic activity, there are high rates of apoptosis and pronounced areas of necrosis. The growth pattern is nest-like, diffuse, or trabecular. To confirm the diagnosis, neuroendocrine markers are typically stained in immunohistochemistry. SCLC tumor cells are usually positive for CD56 (NCAM), synaptophysin, chromogranin A, and TTF-1. Characteristically, a high Ki-67 proliferation rate of over 80% is often observed. In contrast to NSCLC, there are no glandular structures (adenocarcinomas) or keratinization (squamous cell carcinomas). Due to the high proliferation rate, elevated levels of neuron-specific enolase (NSE) and lactate dehydrogenase (LDH) are often found in the blood as markers of the high apoptosis rate.

The following statements on epidemiology, risk factors, prevention, and early detection refer to all forms of lung cancer. The subsequent sections of this guideline focus on primary SCLC.

The first description of SCLC is based on observations made among workers in the Schneeberg mines in the German Erzgebirge (Ore mountains) [1].

2.2 Epidemiology of SCLC in Germany

The following results are based on data from cancer registries in all German federal states, which are regularly compiled at the Center for Cancer Registry Data for nationwide evaluations.

In the period 2020-2022, SCLC accounted for about 15% of all lung cancer cases reported to cancer registries by clinics, practices, or pathology departments in Germany; in about 5% of cases, no classification was possible due to a lack of specific information on histology.

During the same period, approximately 3,500 women and 4,500 men were diagnosed with SCLC for the first time each year. Since the approximately 12% of cases known to the registry only through death certificates (DCO) do not usually allow for histological differentiation, they are therefore included in the incidence of lung cancer but not in that of the two subgroups. The figures quoted should be understood as minimum estimates.

Age-standardized incidence rates are declining among men, while among women they appear to have reached a plateau (Figure 1). Age-specific incidence increases with age up to the eighth decade of life. The median age most recently was 68 years, with only about 2% of those affected developing the disease before the age of 50 (Figure 2). Incidence rates are declining in men in all age groups and in younger women, but are still rising in women over 60. These developments reflect gender-specific trends in smoking behavior with a latency of several decades, so a decline is also expected in women in the medium to long term. The absolute number of cases has also been declining slightly overall recently.

In around 75% of new cases (women: 73%, men: 76%) with sufficient documentation of the tumor stages, distant metastases are already present at the time of initial diagnosis of SCLC. The most commonly affected organs are the liver (44% of cases with distant metastases), the

brain (34%), and the bones (27%). On average, two metastatic sites are reported per case. Only slightly less than 5% of cases are diagnosed in the early UICC stages I or II.

The relative 5-year survival rate as an estimator for disease-specific survival for the period 2020-2022 for SCLC is 8.9%, only slightly higher than 10 years ago (8.5%).

Figure 3 illustrates survival by tumor stage. The significantly worse prognosis compared to NSCLC can be explained in part by the more unfavorable tumor stage distribution, but even in the rare cases of early stages, the results are worse than for NSCLC.

Figure 1: Age-standardized incidence of SCLC in Germany, 2010-2022 (new cases per 100,000 persons, old European standard)

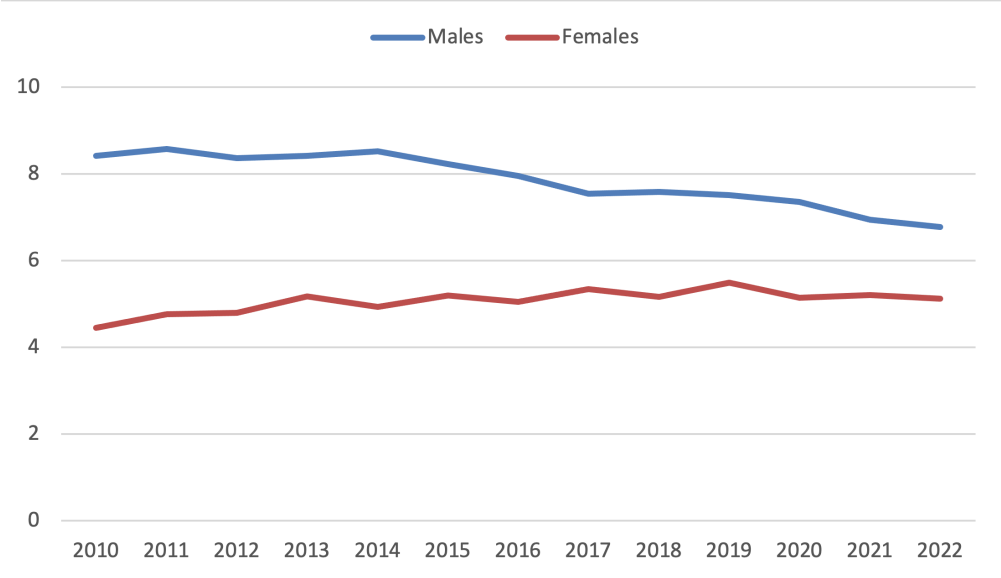


Figure 2: Annual incidence rates of SCLC per 100,000 persons, by age (in years) and sex (Germany, 2020-2022)

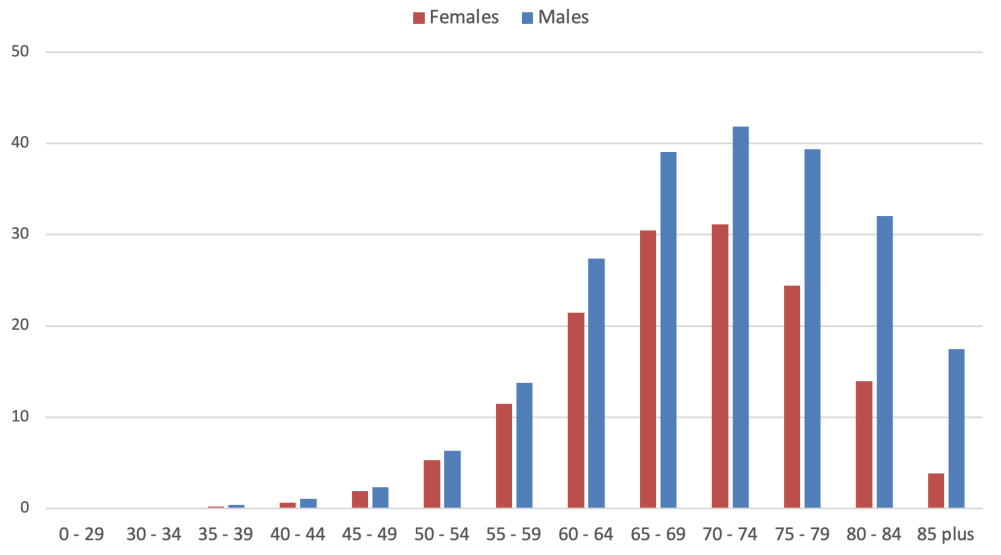
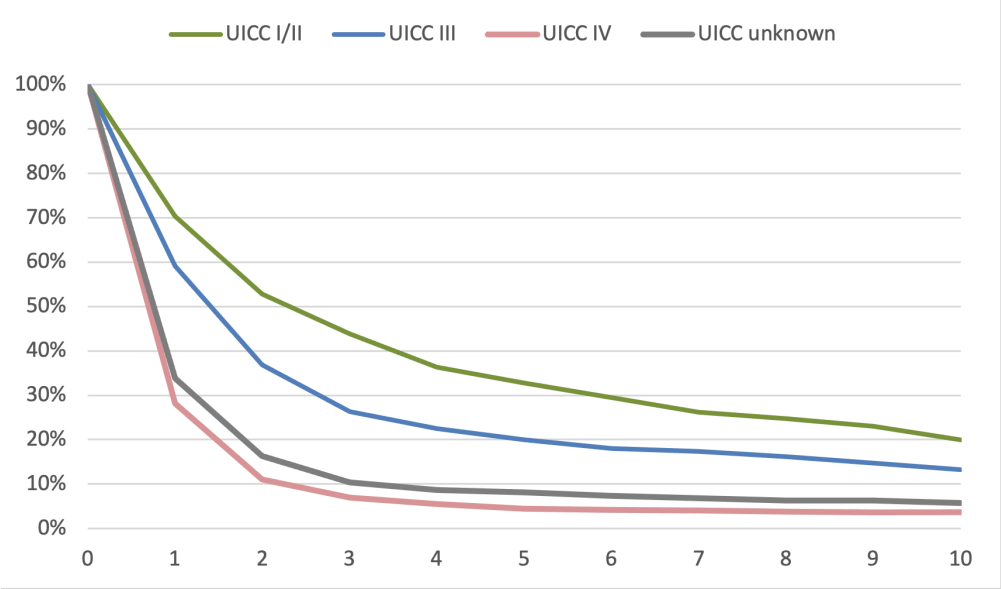


Figure 3: Relative survival (compared to the age-matched general population) up to 10 years after initial diagnosis of SCLC, period analysis (2020-2022)



2.4 Risk factors

The risk of developing lung cancer is increased by the following factors:

- Acquired, exogenous
  - Smoking, including passive smoking
  - Inhalation of vapors ("vaping") from electronic cigarettes containing liquids that contain chemical carcinogens such as acetaldehyde and formaldehyde
  - Ionizing radiation (high environmental radon exposure, uranium mining, medical radiation exposure)
  - Fine dust
  - Diesel exhaust fumes
  - Asbestos
  - Quartz dust
  - Chronic lung infections
- Genetic, endogenous
  - individuals with a positive history of lung cancer in one or more first-degree relatives have an increased risk of developing the disease.

Further information on risk factors for lung cancer can be found in Lung cancer, non-small cell (NSCLC).

2.5 Histopathology and molecular subgroups

Neuroendocrine tumors (NET) store active neuropeptides such as bombesin, calcitonin, or serotonin in intracytoplasmic granules and release them in response to neural, chemical, or mechanical stimuli. They often occur in the gastrointestinal tract, but also in the lungs. SCLC is the most common type of primary pulmonary neuroendocrine tumor (pNET; [55]). Another type of high-grade pNET, which is rarer, accounting for approximately 3% of all lung cancers, is large cell neuroendocrine carcinoma (LCNEC). There are also low-grade carcinoids (approx. 2% with a ratio of typical to atypical of 10:1). The criteria for the classification of neuroendocrine tumors of the lung and gastrointestinal tract do not match.

For the diagnosis of small cell neuroendocrine lung carcinoma from biopsies, endobrochial ultrasound (EBUS), or cytology, immunohistochemical detection of at least two neuroendocrine markers (TTF-1, CD 56, synaptophysin, chromogranin) is required. The proliferation rate with Ki67 should be above 70% Ki67-positive cells. Differential diagnosis from small cell basaloid squamous cell carcinomas or non-Hodgkin's lymphomas is particularly important.

Inactivating mutations in the tumor suppressor genes *TP53* and *RB1* are found in almost all SCLCs and can be understood here as a fundamental causal mechanism in malignant transformation. Further molecular aberrations found in some cases include mutations in *TP73, CREBB* genes from the *NOTCH* family and, less frequently, in other oncogenes and suppressor genes [3]. The molecular aberrations identified are not yet amenable to targeted therapy.

Based on gene expression analyses in human and murine tumors, differential expression of the four central transcription factors achaete-scute homologue 1 (ASCL1/ASH1), neurogenic differentiation factor 1 (NeuroD1), and POU class 2 homeobox 3 (POU2F3) has been found and a new classification has been proposed accordingly [4, 65]. This classification cannot yet be used to make treatment decisions.

EGFR-mutated NSCLC with secondary SCLC transformation is discussed in the Onkopedia guideline NSCLC.

3 Prevention and early detection

3.1 Prevention

The general recommendations for prevention refer to the risk factors identified to date and private lifestyle, see Lung cancer, non-small cell (NSCLC):

- Not smoking is by far the most important measure
- Avoid passive smoking and e-cigarettes
- Avoid occupational exposure to hazardous substances
- Structural measures to reduce radon exposure in risk areas
- Physical activity
- High consumption of fruit and vegetables

Avoiding smoking is the most important preventive measure (WHO Framework Convention on Tobacco Control) [6]. Increased consumption of fruit and vegetables reduces the risk of lung cancer, especially in smokers.

3.2 Early detection

There is no generally accepted method for early detection of SCLC in Europe in terms of national screening programs, see non-small cell lung cancer (NSCLC). In Switzerland, the Swiss Accident Insurance Fund (SUVA) offers insured persons with occupational asbestos exposure a screening program in accordance with National Lung Screening Trial (NLST) criteria.

4 Clinical characteristics

The clinical symptoms of patients with SCLC do not differ substantially from those of patients with NSCLC, see Non-small cell lung cancer (NSCLC). Typical features include primary growth in the central airways and often a short medical history with tumor-related symptoms such as dyspnea, cough, or signs of upper respiratory congestion. A special feature of SCLC is the more fre-

quent occurrence of paraneoplastic syndromes, most commonly with endocrine clinical pictures. Table 1 shows the frequency and distribution of paraneoplastic syndromes in patients with lung cancer. The main symptom of the syndrome of inadequate antidiuretic hormone secretion (SIADH) is hyponatremia, while in ACTH syndrome, the characteristic clinical picture of Cushing's syndrome is often not fully developed due to the clinically short development time. Lambert-Eaton syndrome manifests clinically as muscle weakness with dysarthria, swallowing disorders, and proximal limb paresis. Antibody testing (anti-Hu-ANNA-1, anti-neuronal antibody type 1), anti-Ri (ANNA-2, anti-neuronal antibody type 2), anti-CRMP5, anti-Ma1, anti-amphiphysin, etc. [7]) can confirm the clinical suspicion of a neurological paraneoplastic syndrome.

Table 1: Paraneoplastic syndromes in patients with lung cancer [6]

Syndrome	SCLC (% of patients)	NSCLC (% of patients)
SIADH	10	< 0.1
Cushing's (ACTH)	2	< 0.1
Lambert-Eaton syndrome	1	< 0.1
Other neuropathies	up to 5	< 0.1
clubbed fingers	< 1	5
Osteoarthropathy	< 1	5
Hypercalcemia	< 1	Up to 10

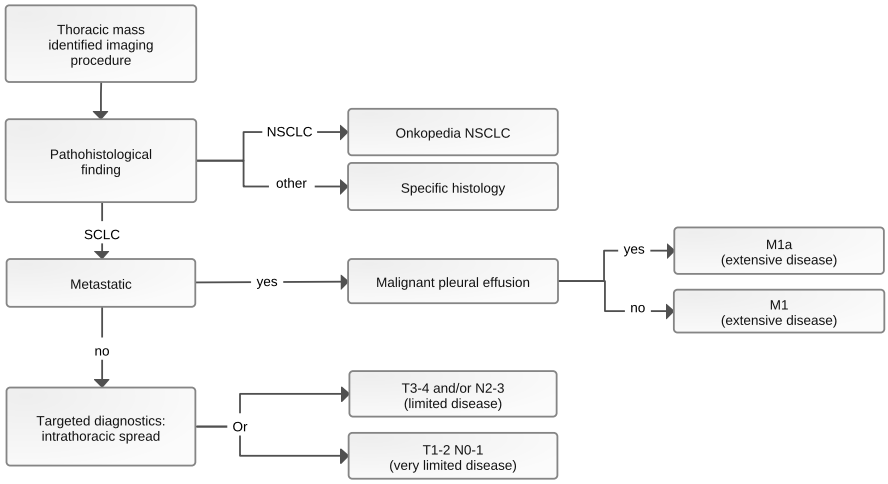
5 Diagnosis

5.2 Diagnostics

5.2.1 First diagnosis

The first step is to confirm the suspected diagnosis based on clinical and/or imaging findings, see Figure 4.

Figure 4: Diagnostic algorithm for SCLC



Diagnostics should be performed until metastasis is detected or ruled out and, in the absence of metastasis, until TNM criteria are specified, see Table 2.

Table 2: Diagnostic pathway for suspected lung tumor

Procedure	Recommendation
Stage 1 Imaging evidence of a thoracic mass	
Chest X-ray overview in 2 planes	
Labor	Complete blood count, electrolytes, uric acid, kidney parameters, liver parameters, LDH, coagulation, NSE± CEA
CT[1] Chest/abdomen with contrast medium[6] / FDG-PET-CT[7]	Method of first choice
MRI[2] Chest / upper abdomen with contrast medium[6]	Alternative to CT[1]
Stage 2 Histological or cytological confirmation	
Bronchoscopy with biopsy[3]	If imaging suggests a diagnosis
Transthoracic biopsy, mediastinoscopy, thoracoscopy	If bronchoscopy is negative, alternative to histology if necessary
Stage 3 Exclusion of organ metastasis	
If not already performed in stage 1: CT scan of the abdomen or MRI scan of the abdomen	Alternatively, upper abdominal ultrasound if there is clear evidence of abdominal metastasis Alternatively, PET-CT, especially in the case of a curative approach
Cranial MRI	Alternatively, CT scan of the skull if there is clear evidence of intracerebral metastasis
Bone scintigraphy	Alternatively, PET-CT, especially in the case of a curative approach
Stage 4 Determination of intrathoracic tumor spread	
FDG-PET-CT[4]	In non-metastatic SCLC to rule out distant metastasis. Only if PET-CT is not available, chest/abdominal CT and bone scintigraphy are the alternative); PET-positive findings should be confirmed histologically or cytologically if they change the treatment concept.
EUS/EBUS[5] with biopsy	Diagnostic significance in very limited disease (VLD) SCLC
Mediastinoscopy	No longer relevant in SCLC (EUS/EBUS is appropriate and reliable)
Thoracocentesis	In cases of pleural effusion and no organ metastasis
Thoracoscopy	In the absence of organ metastasis to detect carcinomatous pleurisy in cases of pleural effusion and negative pleural puncture

Legend:
[1] CT = computed tomography;
[2] MRI = magnetic resonance imaging;
[3] Alternative for peripheral lesions: brush, needle, or similar;
[4] FDG-PET-CT = 18F-fluorodeoxyglucose positron emission tomography with computed tomography;
[5] EBUS = endobronchial or endoesophageal ultrasound with fine needle biopsy;
[6] CM = contrast medium;
[7] if there is a high probability of a diagnosis of NSCLC or SCLC

FDG-PET-CT results in a significant percentage of patients being upgraded from stage LD to ED. In 8 studies with a total of 138 LD SCLC patients, the stage changed to ED in 29 cases, i.e., on average in 20% of patients [8]. This justifies PET-CT before planned curative therapy using concurrent chemoradiotherapy or surgery [9, 66].

5.3 Classification

5.3.2 Stages

Since January 1, 2025, the criteria of the 9th edition of the TNM classification for lung cancer are effective [53, 54], see Tables 3 and 4.

Table 3: Lung TNM definitions (9th edition) according to the IASLC Lung Cancer Staging Project [53, 54]

Category	Stadium	Description
T (tumor)	Tx	Primary tumor cannot be assessed[a]
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ[b]
	T1	Tumor surrounded by lung or visceral pleura, or in a lobar or more peripheral bronchus[c]
	• T1mi	Minimally invasive adenocarcinoma[d]
	• T1a	Tumor ≤1 cm in greatest dimension
	• T1b	Tumor >1 cm but ≤2 cm in greatest dimension
	• T1c	Tumor >2 cm but ≤3 cm in greatest dimension
	T2	Tumor with any of the following features:
	• T2a	• Tumor >3 cm but ≤4 cm in greatest dimension; • invades visceral pleura; • invades an adjacent lobe; • involves main bronchus (up to but not including the carina) or is associated with atelectasis or obstructive pneumonitis extending to the hilar region, involving either part of or the entire lung
	• T2b	Tumor >4 cm but ≤5 cm in greatest dimension
	T3	Tumor with any of the following features: • tumor >5 cm but ≤7 cm in greatest dimension; • invades parietal plaura or chast wall; • invades pericardium, phrenic nerve, or anzygos vein;[e] • invades thoracic nerve roots (i.e. T1, T2) or stellate ganglion; • separate tumor nodule(s) in the same lobe as the primary
	T4	Tumor with any of the following features: • tumor >7 cm in greatest dimension; • invades mediastinum, thymus, trachea, carina, recurrent laryngeal nerve, vagus nerve, esophagus or diaphragm; • invades heart, great vessels (aorta, superior / inferior vena cava, intrapericardial pulmonary arteries / veins), supra-aortic arteries, or brachiocephalic veins; • invades subclavian vessels, vertebral body, lamina, spinal canal, cervical nerve roots, or brachial plexus (i.e. trunks, divisions, cords, or terminal nerves); • separate tumor nodule(s) in a different ipsilateral lobe than that of the primary
N (lymph nodes)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metasstasis in ipsilateral peribronchial and/or ipsilateral hilar and/or intrapulmonary lymph nodes, including involvement by direct extension
	N2	Metasstasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
	• N2a	Single N2 station involvement
	• N2b	Multiple N2 station involvement
	N3	Metasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene or supraclavicular lymph node(s)
M (metastasis)	M0	No distant metastasis
	M1	Distant metastasis

Category	Stadium	Description
	• M1a	Tumor with pleural or pericardial nodules or malignant pleural or pericardial effusions, separate tumor nodule(s) in a contralateral lobe
	• M1b	Single extrathoracic metastasis in a single organ system
	• M1c	Multiple extrathoracic metastases
	• M1c1	Multiple extrathoracic metastases in a single organ system
	• M1c2	Multiple extrathoracic metastases in multiple organ systems

Legend:
[a] This includes tumors proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.
[b] This includes adenocarcinoma in situ – Tis (AIS) – and squamous cell carcinoma in situ – Tis (SCIS).
[c] uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a.
[d] Solitary adenocarcinoma (not more than3 cm in greatest dimension), with a predominantly lepidic pattern and not mor than 5 mm invasion in greatest dimension.
[e] Although these structures lie within the mediastinum, the degree of mediastinal penetration by the tumor needed to invade these structures is not counted as T4.

Table 4: Definition of tumor stages according to UICC-9 (current changes highlighted in blue)

Stage	Primary tumor	Lymph nodes	Distant metastases
0	Tis	N0	M0
IA1	T1a(mi) T1a	N0 N0	M0 M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB*	T1a-c	N1	M0
	T1a-c	N2a	M0
	T2a	N1	M0
	T2b	N1	M0
	T3	N0	M0
IIIA*	T1a-c	N2b	M0
	T2a-b	N2a	M0
	T3	N1	M0
	T3	N2a	M0
	T4	N0	M0
	T4	N1	M0
IIIB*	T1a-b	N3	M0
	T2 a-b	N2b	M0
	T2 a-b	N3	M0
	T3	N2b	M0
	T4	N2a/b	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	any T	any N	M1a
	any T	any N	M1b
IVB*	any T	any N	M1c1
	any T	any N	M1c2

Legend:
** Changes in UICC9 compared to UICC8 are highlighted in blue.*

For many decades, the classification developed in 1957 by the Veterans Administration Lung Study (VALS), which divided the disease into limited and extensive disease, was used [11], see Table 5.

Table 5: Classification of the Veterans Administration Lung Study (VALS)

Stage	Description
Limited Disease (LD)	Tumor limited to the initial hemithorax with or without ipsilateral or contralateral mediastinal or supraclavicular lymph node metastases* and with or without ipsilateral pleural effusion regardless of cytological results*
Extensive Disease (ED)	Any spread beyond "limited disease"

Legend:
** Supraclavicular lymph nodes and cytologically malignant pleural effusion are also classified as extensive disease by some groups.*

This classification was primarily based on the feasibility of radiation therapy. "Limited Disease" (LD) is defined as tumor spread that can be completely covered and irradiated using a tolerable radiation therapy target volume. A supplement to this is the subdivision of the LD stage into a "very limited disease" (VLD) group without evidence of mediastinal lymph node involvement and an LD group with mediastinal lymph node involvement.

Although the VALS classification is usually sufficient for clinical purposes, the more differentiated classification based on the TNM and UICC criteria [10] is now recommended for standardization of staging and due to its more accurate prognostic significance, see above. The assignment of TNM characteristics to the VALS classification is summarized in Table 6.

Table 6: Assignment of TNM characteristics to the VALS classification [9]

VALS stages	Assignment to the TNM classification
Very Limited Disease	T1-2 N0-1
Limited Disease	T3-4 and/or N2-3
Extensive Disease	M

More recently, a new classification has been proposed based on gene expression analyses in human and murine tumors [4]. This is based on the differential expression of four central transcription factors: achaete-scute homologue 1 (ASCL1/ASH1), neurogenic differentiation factor 1 (NeuroD1), and POU class 2 homeobox 3 (POU2F3).

Accordingly, the new classification divides SCLC into the types SCLC-A, SCLC-N, SCLC-P, and SCLC-Y. SCLC-I (inflamed gene signature) has been proposed as a further subtype [5]. The distinctiveness of these subtypes and their therapeutic relevance are the subject of current research and discussion. Initial data suggest that immunotherapy is more effective in the "inflamed" subgroup.

5.6 General condition and comorbidity

Treatment options for patients with lung cancer are often limited by reduced general condition and cardiovascular, pulmonary, or other comorbidities, including age-related comorbidities. This applies to both curative and palliative therapy. Parameters for assessing operability can be found in Lung cancer, non-small cell (NSCLC).

For objective assessment of the general condition of older patients, the use of geriatric assessment tools is recommended; see the Geriatric Assessment knowledge database. Tests for objectively assessing mobility and comorbidity are particularly suitable. The indication for further tests is based on clinical impression and the planned treatment.

6 Therapy

6.1 Treatment structure

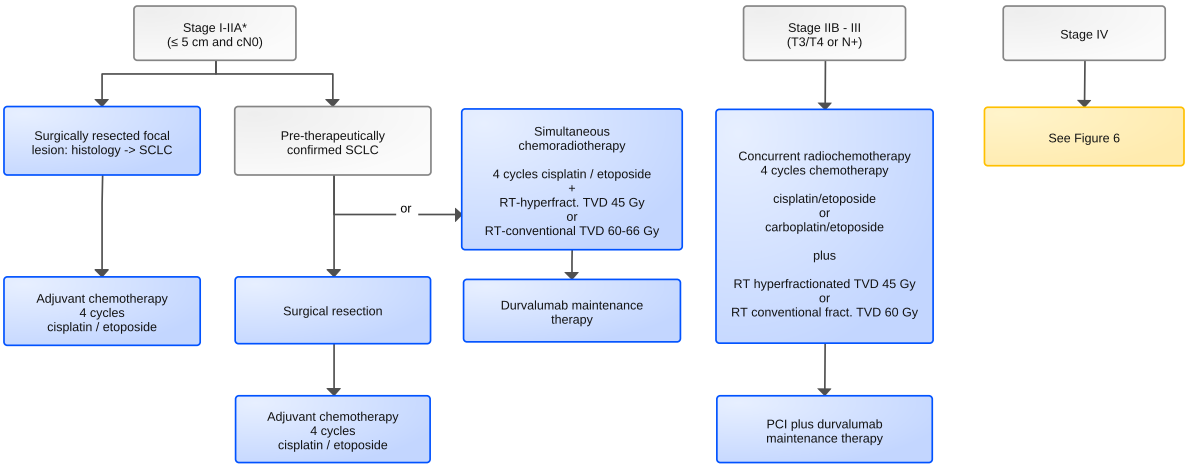
6.1.1 First-line therapy

Treatment recommendations are based on the UICC staging system. However, the conventional classification into very limited, limited, and extensive disease (VLD, LD, and ED) is still in use in the consideration of therapy options, as clinical studies have generally been conducted on the basis of this classification and it therefore forms the basis for therapy recommendations.

Treatment varies depending on the stage. In VLD, the most effective form of treatment is surgery with chemotherapy with curative intent. In combination with surgery and/or radiotherapy, LD can also be treated with curative intent using chemoradiotherapy followed by immunotherapy. In ED, in addition to palliative symptom improvement, a significant improvement in survival time is now also achieved for some patients.

An algorithm for primary therapy is shown in Figure 5. Whenever possible, patients should be treated within the framework of clinical trials.

Figure 5: Treatment structure for first-line treatment of small cell lung cancer (SCLC)



Legend:
**** The value of PCI is unclear for patients with stage I–II disease [77].***
curative intent *palliative intent*
PCI = prophylactic cranial irradiation; RT = Radiotherapy; hyperfractionated RT = hyperfractionated radiotherapy twice daily, conventional RT = conventionally fractionated radiation therapy once daily, Gy = Gray, TVD = target volume delineation

6.1.1.1 Stage I-IIA (very limited disease, VLD)

Only about 5% of patients with SCLC are diagnosed in stages I and IIA (tumors smaller than 5 cm without lymph node involvement). Most of these are patients who undergo surgery for a peripheral round lesion and histopathology reveals the presence of SCLC. In an analysis of the US National Cancer Database, 1,574 patients were recorded and evaluated who underwent various forms of further treatment after such a resection [12]. After surgery alone, the 5-year survival rate was 40% (n=388), after additional adjuvant chemotherapy 52% (n=544), and after additional prophylactic cranial irradiation (PCI) just under 70% (n=99). Mediastinal radiotherapy did not result in any further survival benefit. Based on the retrospective data, adjuvant chemotherapy with 4 cycles of cisplatin/etoposide can be recommended after surgical resec-

tion. The significance of PCI is limited due to the small number of cases and possible patient selection.

The database analysis by Raman et al [13] examined the required extent of resection in a total of 1948 surgically operated SCLC patients in stage T1-2N0. These patients underwent either wedge resection (n=609), segment resection (n=96), or lobectomy (n=1233). Seventy-five percent of patients were stage IA, 10% were stage IB, and 15% were stage II. Thirty-five percent of patients received adjuvant chemotherapy, and 10% received additional cranial radiation. The 5-year survival rates were 31% and 35% for wedge resection and segment resection, respectively, and were significantly higher for lobectomy at 45%. Therefore, for primary surgery a lobectomy with systematic lymphadenectomy is recommended.

If SCLC in stage VLD is detected using classic diagnostic methods before the start of therapy, combined concurrent chemoradiotherapy is a treatment option in addition to primary surgery with adjuvant therapy.

This treatment modality and its results are discussed in detail in chapter 6.1.1.2.

Unfortunately, there are no stage-related randomized comparisons between the two treatment modalities of surgery or concurrent chemoradiotherapy. Two older randomized studies allocated patients after neoadjuvant chemotherapy alone to surgery followed by radiotherapy or radiotherapy alone. In 146 and 69 randomized patients, respectively, no difference between the arms could be detected. In case series and phase II studies, 5-year survival rates of 50-70% were observed for such a neoadjuvant therapy strategy in patients with stage N0 and 35-40% in patients with N1.

The benefit from prophylactic cranial irradiation (PCI) in stages N0-1 has not been established. However, registry data suggest an increase in the 5-year survival rate after surgical resection with PCI. Its use must be discussed on a case-by-case basis. The benefit from adjuvant immunotherapy with durvalumab has not been tested in the postoperative setting, but can be considered in analogy to the procedure for LD after chemoradiotherapy.

6.1.1.2 Stage IIB and III (limited disease, LD)

Approximately one-third of patients with SCLC are in LD stage at initial diagnosis (tumors with T3 or T4 characteristics or N1/N2/N3 involvement). In these cases, a curative treatment approach is indicated. The 5-year survival rates are in the range of 30–35%. Concurrent chemoradiotherapy is the standard treatment.
The most effective chemotherapy is a combination of cisplatin and etoposide over 4 cycles. Cisplatin/etoposide can be used concurrently with radiotherapy without dose restriction and with a tolerable side effect profile. Cisplatin has a well-documented radiosensitizing effect; less data is available on carboplatin, but cohort studies show at least no clear inferiority [67]. The standard dose of cisplatin should be 75-90 mg/m^2 on day 1, but can also be divided into 25-30 mg/m²/day on days 1-3 for better tolerability. Carboplatin is an alternative for patients who are cisplatin-ineligible. Radiotherapy should be started no later than with the beginning of the third cycle.
The preferred radiotherapy options are hyperfractionated, accelerated radiotherapy with 1.5 Gy twice daily up to a total dose of 45 Gy (up to 60 Gy in phase II studies) or conventionally fractionated, once-daily radiotherapy with 1.8-2.0 Gy ED and a total dose of up to 66 Gy. The randomized comparison of these two options in the CONVERT study by Faivre-Finn et al. [15] did not show any significant improvement over the conventional regimen; the 3-year survival rate in the study was 43% for hyperfractionated RT and 39% for conventional RT. The CALGB study by Bogart et al. [16] also showed no significant differences. 638 patients received either concurrent chemoradiotherapy with twice daily RT up to 45 Gy or once daily RT with a target vol-

ume dose (TVD) of 70 Gy. 60% received radiotherapy using IMRT technology. Radiotherapy was started with the first cycle of chemotherapy in 45% of patients, and cisplatin was used as the basis for chemotherapy in 81%. Median survival was slightly less than 2.5 years, with a 5-year survival rate of 29% in the twice-daily radiation arm and 34% in the once-daily radiation arm. The rate of side effects did not differ, with esophageal complications occurring in 17% of patients.

Dose-escalated hyperfractionated radiotherapy with twice daily hyperfractionated RT up to 60 Gy was used in the randomized phase II study by Grønberg et al [17]. A total of 176 patients were treated, with 2-year survival rates of 74% at 60 Gy compared to 48% at 45 Gy. The most common side effects were hematological, with neutropenia occurring in 80% of cases and a neutropenic infection in 27%. The esophagitis rate was 21% vs. 18%. In both treatment arms, three patients died from treatment-related complications. The concept is not yet standard practice; a confirmatory, randomized phase III study is pending.

Dose-intensified, accelerated-hyperfractionated radiotherapy can contribute to improved survival [17, 64]. This opens up the possibility of increasing the effectiveness of treatment for selected patients, e.g., those with bulky tumors.

Table 7 below provides an overview of the results of randomized studies comparing conventional vs. hyperfractionated radiotherapy.

Table 7: Controlled studies on concurrent chemoradiotherapy for locally limited SCLC

Authors	n	Radiotherapy	3-year OS	5-year OS
Turrisi [14]	206	RT 45 Gy, 1.8 Gy daily x 25	3%	16%
	211	RT 45 Gy, 1.5 Gy twice daily x 15	27%	26%
Faivre-Finn CONVERT [15]	270	RT 66 Gy, 2 Gy daily x 33	39%	27%
	273	RT 45 Gy, 1.5 Gy twice daily x 15	43%	33%
Bogart CALGB [16]	325	RT 70 Gy, 2 Gy daily x 35	44%	34%
	313	RT 45 Gy, 1.5 Gy twice daily x 15	42%	29%
Grønberg [17]	89	RT 60 Gy, 1.5 Gy twice daily x 20	74% (2 years)	42% (4 years)
	81	RT 45 Gy, 1.5 Gy twice daily x 15	48% (2 years)	28% (4 years)
Yu TRISS [64]	108	RT 54 Gy, 1.8 twice daily Gy x 15	76% (2 years)	NA
	116	RT 45 Gy, 1.5 Gy twice daily x 15	54% (2 years)	NA

Legend:
RT = radiotherapy, Gy = gray, OS = overall survival, NA = not available

6.1.1.2.1 Immunotherapy maintenance after concurrent chemoradiotherapy

The results of the ADRIATIC study in SCLC stage I-III showed that durvalumab as consolidation therapy in patients without progression after cCRT led to a statistically significant and clinically meaningful improvement in both progression-free survival (PFS) and overall survival (OS) compared to placebo. Median OS was 55.9 months in the durvalumab arm versus (vs.) 33.4 months in the placebo arm (hazard ratio [HR] 0.73; 95% confidence interval [CI] 0.57-0.93; p = 0.0104). Median PFS was 16.6 months for durvalumab and 9.2 months for placebo (HR 0.76; 95% CI 0.61-0.95). The safety analysis showed that the rate of pneumonitis was slightly increased with durvalumab (38% vs. 30% in the placebo arm). The ADRIATIC study thus demonstrates that consolidation therapy with durvalumab for 2 years after successful cCRT in patients with LD-SCLC leads to a significant OS prolongation and has an acceptable safety profile [54].

The ADRIATIC regimen can therefore be considered the standard therapy for LD-SCLC stage I-III after chemotherapy and radiotherapy. Approval by the EMA for combined and sequential chemoradiotherapy has been granted. In patients irradiated according to Turrisi [14], durvalumab did not lead to a clear survival benefit.

6.1.1.2.2 Annotations to concurrent chemoradiotherapy

Concurrent chemoradiotherapy is superior to the consecutive approach and is therefore the preferred treatment approach, provided it can be administered in a timely manner and at the planned dosage [68]. A consecutive approach should only be used as part of individual treatment concepts in patients with contraindications to concurrent chemoradiotherapy.

Carboplatin-containing protocols are primarily used in the adjuvant setting and have not been sufficiently tested in the context of concurrent chemoradiotherapy concepts. They should therefore only be used here in patients with unequivocal contraindications to cisplatin. Initial chemotherapy with carboplatin and etoposide followed by consolidating radiotherapy may be a treatment option for patients in significantly compromised general condition, if standard therapy with cisplatin and etoposide is not feasible.

Another possible treatment option is concurrent hyperfractionated chemoradiotherapy with cisplatin/etoposide in the first cycle and parallel RT with 1.5 Gy twice daily from the first day of treatment, up to a total dose of 45 Gy, followed by a switch to the combination of cisplatin/irinotecan for the remaining three cycles of chemotherapy alone. In a Japanese patient cohort, this approach was equivalent to the standard approach with continuation of cisplatin/etoposide [19].

The use of anthracycline-containing protocols should be avoided in concurrent chemoradiotherapy due to their poorer efficacy and higher toxicity. Similarly, dose intensification concepts are not recommended outside of studies.

6.1.1.3 Prophylactic cranial irradiation in stage LD

Prophylactic cranial irradiation (PCI) reduces the risk of brain metastases from 40% in non-irradiated patients to less than 10% in irradiated patients and improves the 5-year survival rate by 5% [20]. PCI is therefore an established part of therapy for patients after concurrent CT-RT.

PCI may be associated with cognitive impairment. Several studies have therefore attempted to reduce this side effect by sparing the hippocampus. A Spanish study by Rodríguez de Dios et al. [21] included 150 patients, 75 of whom received classic PCI with 25 Gy in 10 fractions and the other half received the same PCI with hippocampal sparing. Here, better protection of neurocognitive abilities was demonstrated through hippocampal sparing. The rates of significant neurocognitive deterioration were 8.7% vs. 20.6%. A second study from the Netherlands by Belderbos et al [22] included 168 patients. Here, too, 25 Gy in 10 fractions with and without hippocampal sparing was used. The rates of significant deterioration in neurocognitive abilities were 29% vs. 28% and were therefore not different. In both studies, the rate of new brain metastases was not different and survival was also the same. Preserving the hippocampus therefore does not reduce the effectiveness of PCI and does not impair survival. However, the impact on the preservation of neurocognitive abilities is not clearly established [79].

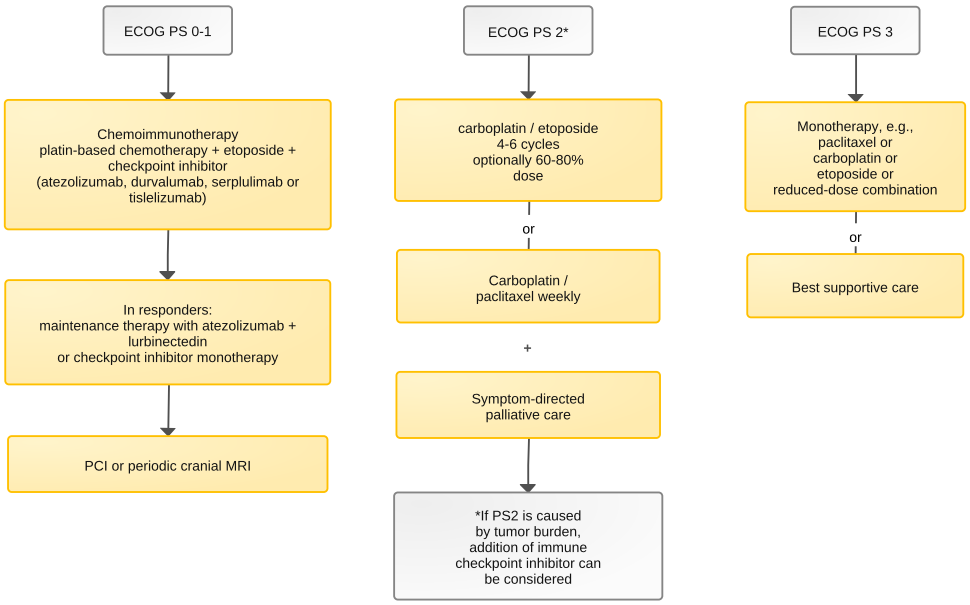
6.1.1.4 Extensive Disease (ED)

60–70% of patients with SCLC cancer are in ED stage at initial diagnosis. Here, the standard treatment is systemic tumor treatment using chemotherapy and immunotherapy. In addition to improving symptom control and thus quality of life, this leads to prolonged survival compared to chemotherapy alone. With chemoimmunotherapy, the median survival time for ED patients is approximately 12 months, the 2-year survival rate is 20–25%, and the 3-year survival rate is 15–20%. The addition of immunotherapy has tripled the 3-year survival rates of patients compared to chemotherapy alone.

6.1.1.4.1 Systemic tumor therapy for ED-SCLC

An algorithm for selecting chemoimmunotherapy in stage IV is shown in Figure 6.

Figure 6: Algorithm for first-line therapy in stage IV SCLC



Legend:
palliative intent
**ECOG PS = general performance score*

The results of systemic therapy for extensive disease can be summarized as follows:

6.1.1.4.1.1 Chemotherapy

- Platinum-based therapy regimens achieve significantly higher complete remission rates than non-platinum combination therapies. In meta-analyses, the results regarding overall survival are not consistent. In a meta-analysis of 5,530 patients, no significant difference in survival rates was found after 6, 12, or 24 months [23].
- When selecting the platinum derivative, the majority of studies showed that cisplatin is slightly more effective than carboplatin. In a relatively small meta-analysis based on individual patient data with heterogeneous treatment regimens, cisplatin and carboplatin were equally effective and the remission rates were the same. The side effect profile of carboplatin is more favorable. The two platinum derivatives are equally effective in the treatment of stage ED.
- Achieving the full platinum target dose is an important prognostic factor.
- Anthracycline-containing protocols such as ACO, EpiCO, or ACE (adriamycin/doxorubicin or epirubicin plus cyclophosphamide/vincristine or etoposide) are generally effective, but

are no longer used in primary therapy due to anthracycline-associated cardiotoxicity, which may be further pronounced by radiotherapy.

- Dose intensification increases remission rates but does not prolong overall survival.
- Alternating administration of different combination therapies also does not improve survival time compared to sequential therapy.

6.1.1.4.1.2 Immunotherapy

Several randomized phase III studies are now available comparing chemotherapy alone with chemotherapy plus PD-(L)1 monoclonal antibodies.

- The IMpower 133 study [25] randomized 403 patients to either 4 cycles of carboplatin/etoposide alone or the same regimen plus the PD-L1 antibody atezolizumab, followed by maintenance therapy with atezolizumab in responders. The remission rates were not different (60% vs. 64%), but the 12-month PFS rate was significantly higher in the atezolizumab arm at 12.6% vs. 5.4%. Median survival was significantly prolonged by 2 months from 10.3 to 12.3 months (HR 0.76). The 2-year survival rates were 22% vs. 18%. Long-term follow-up is not yet available.
- In the CASPIAN study [26], the anti-PD-L1 antibody durvalumab in combination with 4 cycles of platinum/etoposide followed by maintenance therapy with durvalumab in responders to 4-6 cycles of platinum/etoposide also led to an improvement of overall survival from 10.3 to 13.0 months (HR 0.73). The 2-year survival rates were 22% vs. 14%, and the 3-year survival rates 18% vs. 6%.
- The addition of tremelimumab (a CTLA-4 antibody) to platinum/etoposide plus durvalumab did not improve patient survival in the CASPIAN study.
- The KEYNOTE-604 study [27] evaluated pembrolizumab as an addition to platinum and etoposide. Although the results of this study were not statistically significant in terms of overall survival (HR 0.80, p=0.016), the 2-year survival rates were also 23% vs. 11%.
- The ASTRUM study [28, 70] tested the PD-1 antibody serplulimab in combination with platinum/etoposide. A total of 585 patients, preferably from Asia, were recruited to this study. Median survival was significantly prolonged at 15.8 vs. 11.1 months, and remission rates were also higher with immunotherapy. The 4-year survival rates are 21.9% vs. 7.2%, respectively.
- The CAPSTONE-1 [29] phase III study, also conducted exclusively in China, showed an OS advantage for the anti-PD-L1 antibody adebrelimab in combination with carboplatin/etoposide compared to chemotherapy alone (15.3 months vs. 12.8 months; HR 0.72). To date, there is no approval for Europe (as of August 2025).
- The phase III RATIONALE-312 study [69], also conducted exclusively in China, showed an OS advantage for the anti-PD-L1 antibody tislelizumab in combination with etoposide and cisplatin or carboplatin compared to chemotherapy alone (15.5 months vs. 13.5 months, HR 0.75).
- All studies with PD-(L)-1 addition thus show an advantage for immunotherapy, so that the combination of approved PD-(L)-1 inhibitors is now standard in first-line therapy.
- Atezolizumab is approved for first-line therapy in combination with carboplatin and etoposide, and durvalumab is approved in combination with cisplatin or carboplatin plus etoposide. In the CASPIAN study, the addition of durvalumab to cisplatin/etoposide was 10% more effective than carboplatin/etoposide. Whether selection effects or interaction contribute to this is not clear from this setting. Serplulimab is approved in combination with carboplatin and etoposide; tislelizumab is approved in combination with etoposide and platinum chemotherapy.

- According to the approval, the duration of therapy is not limited; the combination of chemotherapy and immunotherapy should be administered over 4 (up to a maximum of 6 cycles), after which immunotherapy is continued until progression.
- In patients with humoral paraneoplasia (Lambert-Eaton, other neuropathies), the indication for immune checkpoint inhibitor therapy should be viewed with caution; if required, treatment should only be started after the paraneoplasia has subsided.
- The study results for primary combined chemo-immunotherapy are shown in Table 8.

Table 8: Controlled studies on combined chemoimmunotherapy in advanced SCLC

Study	Arms	n	RR	PFS (mo)	HR PFS	OS (mo)	OS 24 mo	OS 36 mo	HR OS
IMpower-133 [25]	Atezolizumab	201	60	5.2	0.72	12.3	22		0.76
	Placebo	201	64	4.3	0.62-0.96	10.3	18		0.6-0.95
CASPIAN [26]	Durvalumab	268	68	5.1	0.80	12.9	22	18	0.75
	Placebo	269	58	5.4	0.70-1.01	10.6	14	6	0.68-1.00
KEYNOTE-604 [27]	Pembrolizumab	228	71	4.5	0.75	10.8	23		0.80 n.s.
	Placebo	225	62	4.3	0.61-0.91	9.7	11		0.64-0.98
ASTRUM-005 [28, 70]	Serplulimab	389	80	5.7	0.46	15.8	31.7		0.63
	Placebo	196	70	4.3	0.38-0.59	11.1	18.7		0.49-0.82
CAPSTONE-1 [29]	Adebrelimab	230	70.4	5.8	0.67	15.3	31.3		0.72
	Placebo	232	65.9	5.6	0.54-0.83	12.8	17.2		0.58-0.9
RATIONALE-312 [69]	Tislelizumab	227	68.3	4.7	0.65	15.5	33.2		0.78
	Placebo	230	61.7	4.3	0.53-0.80	13.5	22.4		0.63-0.95

Legend:
n = number of patients, RR = response rate, PFS = progression-free survival, OS = overall survival, mo = months, HR = hazard ratio, n.s. = not significant

The results of the recently published phase III IMforte study [75] showed a significant prolongation of PFS and OS with lurbinectedin plus atezolizumab compared to atezolizumab alone. Lurbinectedin in combination with atezolizumab can be considered a new option for maintenance therapy in patients with ECOG status 0 or 1 and without brain metastases, but it is not yet approved for this indication and the potential survival benefit must be weighed against the higher rate of side effects.

The BEAT-SC study is currently investigating the combination of bevacizumab (angiogenesis inhibitor) with atezolizumab + carboplatin/cisplatin + etoposide (ACE) compared to placebo + ACE Q3W x 4 cycles followed by maintenance Q3W bevacizumab + atezolizumab vs. placebo + atezolizumab. The addition of bevacizumab to ACE was generally well tolerated, and the safety profile was consistent with the known risks of the individual drugs and the underlying disease. The primary endpoint PFS was achieved and showed a statistically significant improvement in PFS in favor of bevacizumab + ACE compared to placebo + ACE. OS data were still immature at the first interim analysis and showed no improvement in favor of bevacizumab + ACE. OS follow-up is ongoing [51].

6.1.1.4.1.3 Patients with CNS metastases

The efficacy of systemic chemotherapy is lower intracerebrally than outside the CNS. In earlier studies, chemotherapy alone was associated with shorter survival compared to additional radiotherapy.

As a rule, evidence of intracerebral metastasis is therefore an indication for additional radiotherapy. The extent and timing of additional local therapy have been challenged by recent study results. The FIRE study [30] is a case collection of 710 patients with brain metastases in SCLC who were treated with stereotactic radiotherapy. Approximately one-third of the patients had 1 or 2-4 brain metastases, and one-third had more than 4 brain metastases. The median OS times in the respective groups were 11 months, 8.7 months, and 8.0 months. New brain metastases developed in 55% of patients with initial metastasis and 70% of patients with multiple brain metastases. A matched-pair analysis of patients who underwent stereotactic cerebral radiotherapy and those who underwent whole-brain radiation (187 vs. 178 patients) showed a survival advantage for patients who underwent stereotactic radiotherapy, even though the intracerebral recurrence rate was approximately 60%, which was twice as high as the 30% rate after whole-brain radiation. Stereotactic radiotherapy alone is associated with significantly less impairment of neurocognitive abilities than stereotactic plus whole brain irradiation in patients with 1-3 brain metastases of different etiology (60% lung carcinomas) [31]. Whole brain radiotherapy can also be performed in the form of hippocampal-sparing radiation in patients without metastases in the hippocampal region. The NRG study [32] showed better preservation of neurocognitive abilities along with same efficacy and survival in over 500 patients with brain metastases of various etiologies (60% lung carcinomas).

In the IMpower 133 study, patients with brain metastases did not benefit from atezolizumab administration, and in the KEYNOTE-604 study, patients with brain metastases were even at a disadvantage in the pembrolizumab group. In CASPIAN, progression-free survival is identical in patients with and without brain metastases, while median survival is more favorable for the durvalumab group (8.7 vs. 11.8 months), but the curves converge over time.

While IMpower 133 and KEYNOTE-604 included pretreated (mostly irradiated) and stable brain metastases, 90% of patients with brain metastases in CASPIAN were not pretreated.

Neither atezolizumab nor durvalumab reduced the incidence of new brain metastases. Approximately 15% of patients without initial brain metastases developed new brain metastases during the course of therapy.

In CASPIAN, 3 patients in the durvalumab arm and 4 patients in the durvalumab + tremelimumab arm achieved 3-year survival in the presence of brain metastases, whereas this was not observed in any of the patients receiving chemotherapy alone [32].

The use of combined chemo-immunotherapy and the initial avoidance of additional radiotherapy is therefore an option in asymptomatic patients, as is the use of stereotactic radiotherapy in patients with a limited number of brain metastases. Symptomatic patients with multiple intracerebral lesions, on the other hand, should continue to receive early whole-brain radiation.

6.1.1.4.1.4 Older patients with a performance score of 2

In older patients in good general condition, treatment results are comparable to those in younger patients. Age by itself is therefore not a negative prognostic parameter. There is no evidence to date that immunotherapy is less effective in older patients. It should be noted that the therapy has higher hematological toxicity in older patients, which requires dose adjustments.

Only patients with a performance score (PS) of 0 and 1 were included in the studies on combined chemo-immunotherapy. It is unclear whether PS2 patients benefit from the addition of immunotherapy. Further studies are needed in this patient population. Current drug approval does not exclude PS2 patients. In the case of a PS2 situation caused by tumor burden, the administration of additional immunotherapy is justified despite the lack of study data.

For patients in reduced general condition due to significant comorbidity, purely symptom-directed therapy or, at most, monotherapy with a chemotherapeutic agent is recommended. Mono-immunotherapy has not been elucidated and should not be used.

6.1.1.4.1.5 Predictors of immunotherapy efficacy

Predictors for the efficacy of immunotherapy have not yet been sufficiently defined. Tumor cells in SCLC rarely express PD-L1; immune cells in the peripheral areas of the tumor are more likely to be positive. PD-L1 expression was not predictive of PD-L1 antibody efficacy in either IMpower 133 or CASPIAN; in IMpower 133, PD-L1-negative patients even tended to benefit more from atezolizumab. In CASPIAN, PD-L1 positivity and the HLA trait DQB1*03:01 were favorable parameters for achieving 3-year survival under durvalumab + tremelimumab. The HLA marker DQB1*03:01 was not predictive for durvalumab alone. Tumor mutational burden was also not a predictive factor for the efficacy of the PD-L1 antibody in either IMpower 133 or CASPIAN.

6.1.1.4.1.6 Maintenance therapy

After combined chemo-immunotherapy, immunotherapy should be continued as maintenance therapy for at least 2 years or until progression, in accordance with the current approval.

6.1.1.4.1.7 Administration of therapy and duration of therapy

- The response to chemo-immunotherapy can be assessed after a minimum of 2 cycles of therapy, usually after 3 to 4 cycles. If there is a response, combination therapy should be continued for a total of 4 cycles. If tolerability is good and further clinical benefit is expected, it is also possible to extend the treatment to up to 6 cycles, followed by maintenance immunotherapy.
- If there is no response to first-line therapy, the prognosis is very poor. An early switch to second-line therapy may be made. The DeLLphi-304 study [63] compared tarlatamab, a bispecific T-cell engager, with chemotherapy in patients with SCLC who were progressive during or after initial platinum-based chemotherapy. Tarlatamab resulted in longer survival than chemotherapy (13.6 months vs. 8.3 months, HR 0.6). Approval in Europe is still pending, but inclusion in the PEI's compassionate use program is expected.
- An important negative prognostic factor is an increased serum LDH.
- Tumor lysis syndrome may occur or worsen at the start of chemotherapy.

6.1.1.5 Local therapeutic measures in stage IV (ED)

- In patients without primary chemo-immunotherapy, thoracic re-irradiation in patients without progression after first-line therapy did not lead to a significant improvement in the primary study endpoint of overall survival (HR 0.84; p=0.066), but did lead to an increase in the 2-year survival rate from 3% to 13%. Female patients under the age of 70 with residual thoracic tumor benefited particularly from follow-up radiation.
- Consolidative tumor radiotherapy has not been tested in the setting of primary combined chemoimmunotherapy. This was not planned in either IMPOWER-133 or CASPIAN. It is unclear whether consolidating radiotherapy in patients with residual thoracic tumor and very good remission of distant metastasis also results in an increased long-term survival rate when combined chemo-immunotherapy is used as primary treatment. In view of the expected thoracic and pulmonary toxicity under ongoing immune maintenance therapy, this approach is not standard practice and is being tested in studies (e.g., Maverick, NCT04155034).
- There are varying study results for prophylactic cranial irradiation (PCI) in extensive disease. In the EORTC study [36] in patients without progression after first-line therapy and

without clinical signs of brain metastasis, PCI led to an improvement in OS compared to observation (HR 0.68; median 1.3 months). However, no systematic cranial MRI checks were performed in this study, and cranial irradiation in the control arm was only initiated when clinical symptoms of CNS involvement occurred. Only 45% of patients in the non-PCI arm received second-line chemotherapy vs. 68% in the PCI arm; data on the frequency of cranial irradiation in the control arm are lacking.

- A randomized Japanese study [37] only included patients without MRI-based evidence of brain metastases. In this study, a cranial MRI scan was performed every 3 months in the control arm, and cranial radiotherapy was initiated if brain metastases were detected on imaging. In this study, 89% of non-PCI patients received second-line chemotherapy, and of 51 patients with newly diagnosed brain metastases, 81% were treated with radiotherapy or surgery. In this study, a slight, statistically insignificant survival disadvantage was observed with PCI, with a median of 11.6 vs. 13.7 months (HR 1.27; p=0.094).

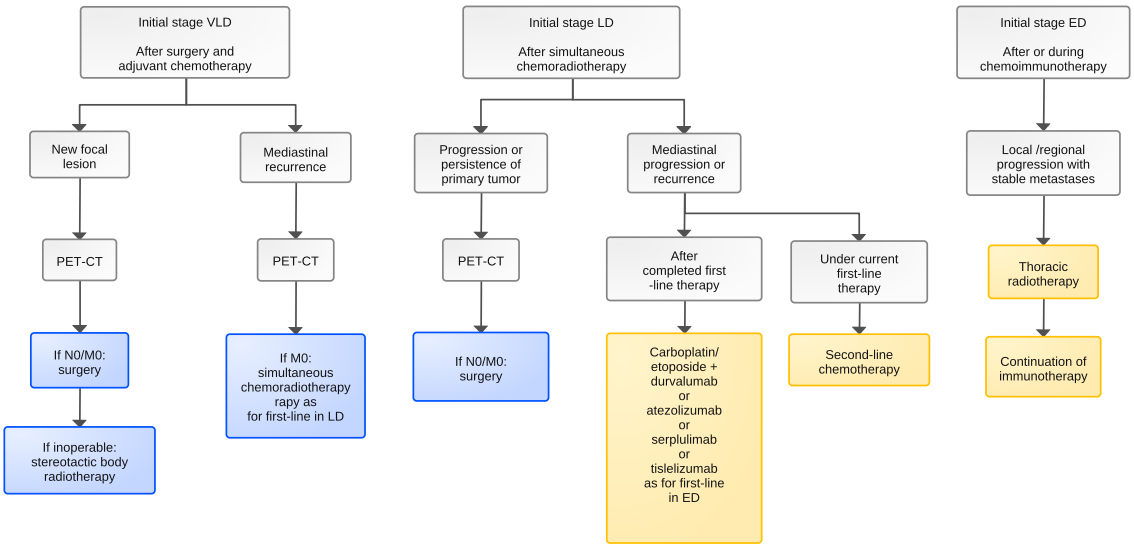
In selected patients, PCI can be offered as an alternative to monitoring with MR follow-up after response to systemic therapy and should be discussed on an individual basis.

6.1.2 Second-line therapy

Indication and selection of second-line therapy depend on the stage, patient performance, and comorbidity, the previous therapy, and the time to progression (or therapy-free period). Treatment algorithms are shown in Figure 7, Figure 8, and Figure 9, distinguishing between local progression (Figure 7) and systemic progression (Figure 8 and Figure 9).

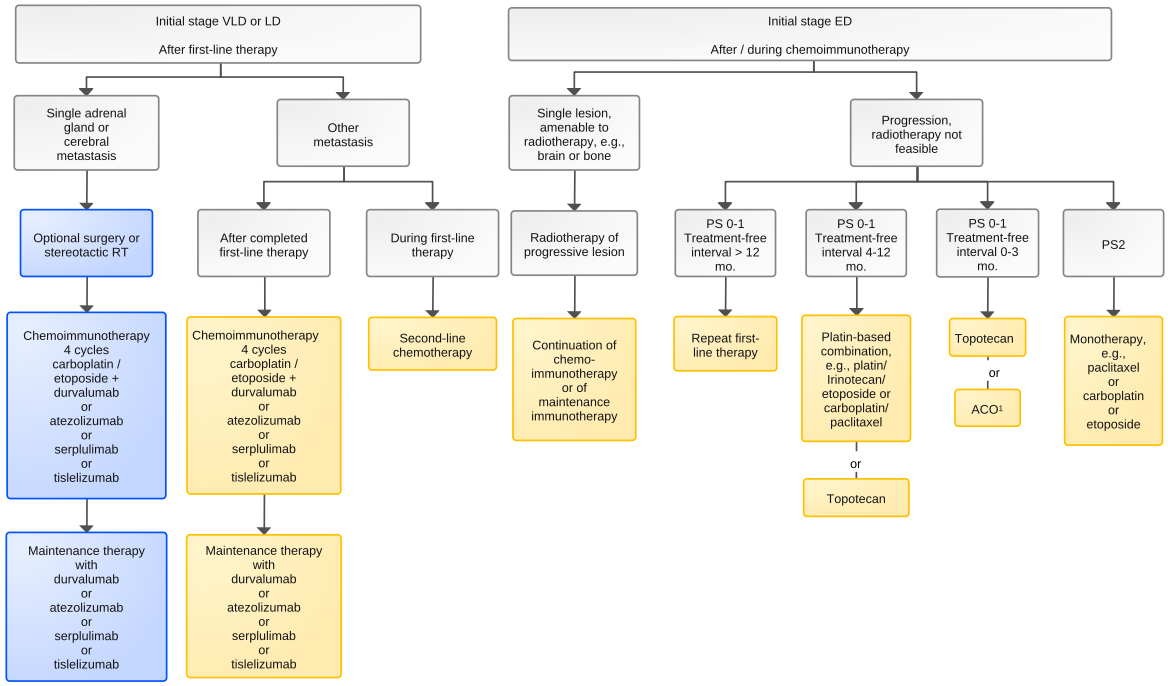
For local recurrence settings in particular, only retrospective analyses, case compilations, and clinical experience are available. The recommendations are therefore not supported by prospective studies, but represent a clinical-practice approach.

Figure 7: Algorithm for the treatment of relapsed SCLC – Part 1: Local progression/relapse



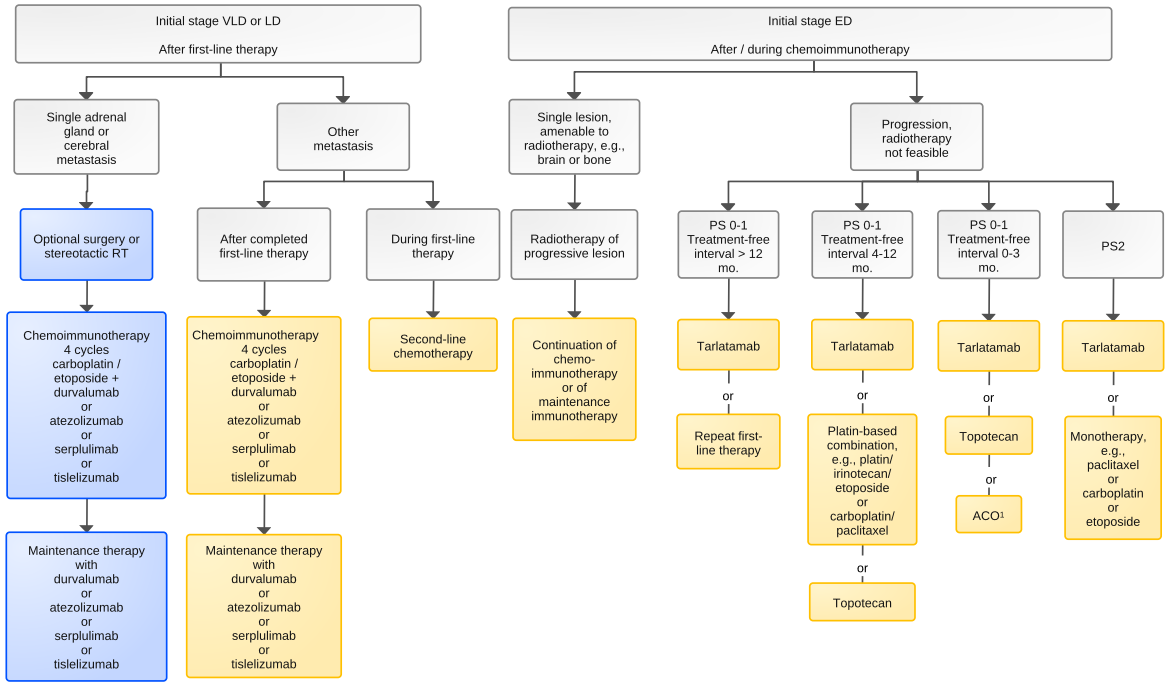
Legend:
curative intent *palliative intent*
Note: Thoracic radiotherapy during ongoing immunotherapy has not yet been sufficiently tested in studies. A potentially higher risk of pulmonary toxicities should be considered.

Figure 8: Algorithm for the treatment of relapsed SCLC – Part 2: disseminated progression; recommendations without the availability of tarlatamab



Legend:
curative intent *palliative intent*

Figure 9: Algorithm for the treatment of relapsed SCLC – Part 2: disseminated progression; recommendations when tarlatamab is available



Legend:
curative intent *palliative intent*
[1] Treatment regimens : ACO = Adriamycin (doxorubicin)/epirubicin, cyclophosphamide, vincristine; see SCLC treatment protocols

Note: The recommendation to opt for surgical resection or stereotactic radiotherapy of an isolated adrenal or brain metastasis is based on individual case reports and clinical experience. It is not supported by prospective studies or case compilations with a large number of patients.

In Switzerland, in addition to topotecan, lurbinectidine is also approved as a second-line treatment if there are no brain metastases and platinum-based therapy was terminated at least 30 days prior.

6.1.2.1 Local and regional progression – second-line therapy

If patients develop an intrapulmonary tumor after surgical resection and adjuvant chemotherapy, the possibility of a second tumor of a different histopathology must also be considered. In the case of a new round focal lesion without lymph node involvement or distant metastasis, based of PET-CT and, if indicated, further mediastinal staging, a repeat surgical resection can be performed. If SCLC is confirmed histologically, it is unclear whether repeat adjuvant chemotherapy is beneficial.
If primary resection is not performed, histological confirmation should be sought prior to treatment. If SCLC histology is confirmed prior to treatment, concurrent chemoradiotherapy can be performed as an alternative to surgery. If the histology is different, histology- and stage-specific therapy should be initiated.

If patients develop a locoregional relapse with mediastinal lymph node involvement after surgical resection and adjuvant chemotherapy, concurrent chemoradiotherapy similar to the procedure for LD is recommended, after histopathological confirmation and exclusion of distant metastasis by PET-CT.

If complete remission of lymph node involvement is achieved in stage LD after completion of concurrent chemoradiotherapy, but the primary tumor persists or shows local progression again, surgical resection of the primary tumor may be considered in individual cases. Before doing so, N2 or N3 involvement should be ruled out by means of PET-CT and, if required, further mediastinal staging, as should cerebral metastasis by means of cranial MRI. Pneumonectomy should be avoided. Stereotactic radiotherapy may also be considered in individual cases.

If locoregional relapse with mediastinal lymph node involvement occurs after completion of concurrent chemoradiotherapy, systemic therapy with chemotherapy and immunotherapy as for first-line therapy in ED-SCLC is recommended.

If local progression is observed in primary metastatic disease with stable distant metastasis, local radiotherapy of the progressive tumor may be applied. In this case, chemoimmunotherapy or immunotherapy can be continued initially, and a switch to second-line chemotherapy may only be given if systemic progression recurs. It should be noted that primary tumor radiotherapy during ongoing immunotherapy has not yet been investigated in larger studies and may carry a higher risk of pulmonary toxicity.

6.1.2.2 Systemic progression – second-line therapy

If a solitary adrenal or brain metastasis occurs as a relapse in the initial VLD or LD stage, local therapy is an option. In the case of adrenal metastasis, resection is the preferred treatment, while in the case of brain metastasis, stereotactic radiotherapy is preferred. It is unclear whether subsequent systemic chemotherapy improves the prognosis. Due to the now metastatic disease situation and the positive data on chemoimmunotherapy, additional chemoimmunotherapy as for primary therapy in stage IV is recommended.

As an alternative to a local approach followed by systemic chemo-immunotherapy, the latter can also be used as primary therapy. There are no prospective studies on the value of the local approach; the optional recommendation is based on individual case descriptions and clinical experience.

In the event of disseminated progression or relapse, systemic second-line therapy is indicated in patients with ECOG PS 0-2 and disease-related ECOG PS 3. It leads to symptom relief and prolongs survival time. Depending on the time to progression, it can be referred to as chemotherapy-sensitive or chemotherapy-refractory progression. While data from the period before PD-L1 inhibition in first-line therapy indicate chemotherapy-sensitive progression after a 60-day platinum-free interval (the period between the last administration of platinum-based chemotherapy and detected progression), retrospective data from Japan after the introduction of PD-L1 inhibition show a shift in the timing to a 75-day platinum-free interval.

The later the progression or relapse occurs, the more effective is the second-line chemotherapy and the longer is the survival benefit that can be achieved.

The results for second-line systemic therapy in extensive disease can be summarized as follows:

6.1.2.2.1 Chemotherapy

- Drugs with proven efficacy in the second line are topotecan, irinotecan including the liposomal formulation, paclitaxel, ifosfamide, anthracyclines (including amrubicin), and lurbinectedin.
- Topotecan vs. best supportive care has been tested in a randomized trial [38]. Topotecan led to a significant prolongation of OS from 14 to 26 weeks. The benefit was observed in both sensitive and refractory relapse. Oral and intravenous administration of topotecan is equieffective. Topotecan is currently the only therapy specifically approved for second-line treatment of SCLC and was therefore used as the standard in the comparator arm in studies.
- In a study comparing cisplatin/etoposide/irinotecan vs. topotecan in patients with sensitive relapse [39], combination therapy prolonged median survival from 12 to 18 months, but without increasing or achieving long-term survival beyond 3 years, and with significantly higher toxicity.
- Similarly, in the French study by Baize et al [40], an advantage was observed for renewed therapy with carboplatin/etoposide over topotecan in patients with sensitive relapse and more than 90 days of therapy-free survival.
- Further studies showed no superiority for the ACO protocol and for single agents such as amrubicin and liposomal irinotecan compared to topotecan therapy.
- The Atlantis study [41], which compared adriamycin (doxorubicin) plus lurbinectedin vs. topotecan or ACO in the control arm in 600 patients, also showed no advantage for the combination. The therapy-free interval had to be at least 30 days. Median survival was 8.6 months in the lurbinectedin arm and 7.6 months in the control arm. The OS curves were almost identical.
- The RESILIENT study comparing liposomal irinotecan vs. topotecan in 461 patients also showed no advantage for the liposomally encapsulated agent [42].

6.1.2.2.2 Immunotherapy

- Although the administration of immunotherapy with a PD-L1 checkpoint inhibitor in the second line achieved remission rates of approximately 12% in phase II studies (Checkmate 032) [43], it was not successful in randomized studies. In the CheckMate 331 study,

there was no difference between nivolumab and topotecan in PFS and OS in the overall population [44].

- In the phase III DeLLphi-304 study, tarlatamab, a bispecific antibody (BiTE molecule) targeting CD3 and DLL3, showed a significant prolongation of PFS and OS compared to second-line chemotherapy (OS 13.6 months vs. 8.3 months, HR 0.6) with an overall response rate (ORR) of 35%. There was a significant reduction in serious side effects associated with tarlatamab compared to standard chemotherapy. The most common adverse events were cytokine release syndrome (CRS), fatigue, and fever, with CRS decreasing significantly in frequency after dose adjustment. Side effects led to discontinuation of treatment in 5% of patients (vs. chemotherapy 12%). The data available to date indicate that tarlatamab is effective intracranially [71].
- Based on phase II data, the FDA granted accelerated approval for tarlatamab in May 2024 for the treatment of adults with ED-SCLC, regardless of DLL3 expression, whose disease has progressed after platinum-based chemotherapy and PD-L1 inhibition [48]. Approval in Europe is currently pending. Phase III studies are currently investigating the combination of tarlatamab with durvalumab as first-line maintenance therapy after platinum-based chemoimmunotherapy for ED-SCLC (NCT06211036, DeLLphi 305) and the use of tarlatamab as maintenance therapy after concurrent chemoradiotherapy in the first line of LD-SCLC (NCT06117774, DeLLphi 306). Studies on the practicability of tarlatamab application in an outpatient setting have been published [78].

Based on the results of the DeLLphi 301 study [48], tarlatamab is the preferred option for non-radiation-eligible relapses after chemoimmunotherapy.

7 Targeted agents

Antiangiogenic substances are not indicated in either first-line or second-line treatment, following negative studies on aflibercept, bevacizumab, thalidomide, vandetanib, and other agents.

Furthermore, negative randomized phase II studies are available for mTOR inhibitors, HDAC inhibitors, BCL-2 antisense agents, and PARP inhibitors. The maintenance therapy study with the PARP inhibitor niraparib showed no difference between the two treatment arms in terms of PFS or OS.

7.1 Treatment concepts in development

7.1.1 Innovative immunotherapies

- With obrixtamig [73], another bispecific antibody targeting DLL3 and CD3 showed a preliminary ORR of 17% and a DCR of 43% in phase I (NCT04429087). while another study combining obrixtamig and topotecan (NCT05990738) showed a preliminary ORR of 70% and a DCR of 87%.
- Ivonescimab, a bispecific antibody targeting PD-1 and VEGF, showed an ORR of 80% across all dose levels with an acceptable side effect profile in a first-line phase I study in combination with carboplatin and etoposide [74]. Bispecific antibodies directed against PD-1 and VEGF are currently being tested in randomized phase III trials (NCT06712355).
- Other innovative immunotherapies are currently in early clinical phases, including trispecific antibodies targeting two distinct epitopes of DLL3 on tumor cells and CD3 on T cells (NCT06440057) and CAR-T cells directed against DLL3 (NCT03392064, NCT05680922).

7.1.2 Antibody-drug conjugates (ADC)

- Ifinatamab deruxtecan (I-DXd, DS-7300) is a novel ADC that targets B7-H3. B7-H3 is a transmembrane protein that is overexpressed in various solid tumors, including SCLC, and is associated with a poor prognosis. [72]. In preclinical studies, DS-7300 showed specific binding to B7-H3 and inhibited the growth of B7-H3-expressing cancer cells in vitro. In vivo, it showed significant antitumor activity in various xenograft models, including patient-derived xenograft (PDX) models of SCLC [72]. DS-7300 was evaluated in a phase 1/2 study (NCT04145622) in patients with advanced solid tumors, including SCLC. At a median follow-up of 11.7 months, the ORR in evaluable SCLC patients was 52.4%, with a median PFS of 5.6 months. The median OS was 12.2 months. Treatment was generally well tolerated, with a safety profile consistent with previous reports [50]. Based on these promising results, the phase 3 IDeate-Lung02 trial (NCT06203210) was initiated to further evaluate the efficacy and safety of DS-7300 in patients with recurrent SCLC. The first patient was enrolled in this trial in August 2024. In summary, DS-7300 shows promising efficacy and an acceptable safety profile in the treatment of SCLC in preclinical and previous clinical studies.
- ZL-1310 is a novel ADC that targets DLL3. The ADC consists of a humanized anti-DLL3 monoclonal antibody conjugated to a novel camptothecin derivative, a topoisomerase I inhibitor. This design aims to overcome the challenges of previous ADCs, such as nonspecific toxicity. In an ongoing phase 1a/1b trial (NCT06179069), ZL-1310 is being evaluated in patients with previously treated ED-SCLC who have received at least one platinum-based chemotherapy. Preliminary results from the dose escalation phase (part 1a) were presented at the EORTC-NCI-AACR (ENA) Symposium 2024. In this study, 25 patients received ZL-1310 at four different doses (0.8 mg/kg, 1.6 mg/kg, 2.0 mg/kg, and 2.4 mg/kg). Of the 19 patients available for efficacy assessment, 74% (n=14) achieved partial remission. It is noteworthy that all six evaluable patients with brain metastases also showed partial remission. In terms of safety, ZL-1310 was well tolerated. Most treatment-emergent adverse events (TEAEs) were grade 1 or 2. Grade 3 or higher TEAEs occurred in 20% of patients, with neutropenia being the most common event (12%). A dose-limiting toxicity event (grade 4, transient neutropenia/thrombocytopenia) was observed in the 2.4 mg/kg cohort. There were no treatment-related deaths or discontinuations due to TEAEs. Based on these promising data, ZL-1310 was granted orphan drug status by the FDA. In summary, ZL-1310 shows promising efficacy and an acceptable safety profile in early clinical trials in patients with pretreated ED-SCLC.
- Sacituzumab govitecan is an ADC that targets the Trop-2 protein, which is overexpressed in many solid tumors, including SCLC. The phase II TROPiCS-03 study evaluated the efficacy and safety of sacituzumab govitecan in patients with ED-SCLC who showed disease progression after platinum-based chemotherapy and anti-PD-(L)1 therapy [58]. Patients received 10 mg/kg of the drug on days 1 and 8 of a 21-day cycle. The study reported an ORR of 41.9%, with a median DOR of 4.7 months. The safety profile was manageable and consistent with previous studies. Based on these results, in December 2024, the FDA granted breakthrough therapy designation to sacituzumab govitecan for the treatment of adults with ED-SCLC whose disease has progressed after platinum-based chemotherapy. In summary, sacituzumab govitecan shows promising efficacy and an acceptable safety profile in the treatment of ED-SCLC after prior therapy.
- ABBV-011 is a novel ADC that targets the protein SEZ6 (Seizure-Related Homolog Protein 6), which is overexpressed in SCLC. The ADC consists of a monoclonal antibody that specifically binds to SEZ6, coupled to the cytotoxic agent calicheamicin via a stable, non-cleavable linker [59]. In preclinical studies, ABBV-011 showed strong binding to SEZ6-positive SCLC cells, followed by internal uptake and release of the active agent, resulting in significant inhibition of tumor growth in vitro and in vivo [59]. A phase I study

(NCT03639194) investigated the safety, tolerability, and preliminary efficacy of ABBV-011 in patients with recurrent or refractory SCLC. Patients received ABBV-011 intravenously every 3 weeks at doses ranging from 0.3 to 2.0 mg/kg. The maximum tolerated dose was not reached, but dose-dependent side effects such as fatigue, nausea, and thrombocytopenia occurred. At a dose of 1.0 mg/kg, the ORR was 25%, with a median DOR of 4.2 months and a median PFS of 3.5 months [60]. Since ABBV-011 has a manageable safety profile and promising antitumor activity in pretreated SCLC patients, SEZ6 represents a potential therapeutic target for the treatment of SCLC and warrants further clinical investigation.

8 Indication for therapy and differential therapy

- In PS 0-1 patients, the use of a second-line combination treatment is justified after considering the treatment goals and treatment-associated toxicity.
- If progression occurs after a treatment-free interval of more than (6 to) 12 months, the first-line regimen can be used again.
- For a therapy-free interval of 4–12 months, a combination of cisplatin/irinotecan and etoposide can be used. Alternative combinations include cisplatin or carboplatin with irinotecan or topotecan, but also carboplatin with paclitaxel. Repeated therapy with carboplatin/etoposide is also an option. Platinum-free combinations include ACO or AIO (adriamycin/doxorubicin, ifosfamide, vincristine) or ACE (adriamycin/doxorubicin, cyclophosphamide, etoposide).
- In cases of treatment refractoriness with progression during therapy or within 3 months after the end of therapy, topotecan is the only tested substance with an advantage over best supportive care. The value of repeated combination therapy is not certain in this case.
- In patients with reduced general performance or conscious decision not to undergo renewed combination therapy, topotecan as monotherapy is the approved standard. Myelosuppression must be monitored. An alternative is weekly paclitaxel treatment. If available, lurbinectedin and liposomal irinotecan are also alternatives.
- In cases of severely reduced general performance, best supportive care is usually indicated. Another possible option here is oral administration of etoposide or trofosfamide with the aim of improving symptoms.

8.1 Surgery

If surgery is performed to remove a peripheral round lesion without knowledge of the histology and the histopathological examination reveals SCLC, these patients should receive adjuvant chemotherapy and, if necessary, PCI postoperatively (see Figure 5). Postoperative mediastinal radiotherapy should be avoided in patients with pN0 disease, as retrospective studies have shown a negative effect on long-term survival.

In patients with preoperatively diagnosed SCLC and very limited disease, especially in N0 patients, resection with adjuvant chemotherapy is an alternative to chemoradiotherapy. Resection should be performed according to the same standard as in patients with NSCLC. After lobectomy in stage pT1/2, 5-year survival rates of 53% and a median survival of 65 months can be achieved.

Prior to surgery, it is necessary to rule out distant metastasis as far as possible and to carefully examine the mediastinal lymph nodes. Patients with pre-therapeutic N2 or N3 involvement should not undergo surgery in the first instance. The value of surgery in patients with stage N1 disease is controversial. The exclusion of mediastinal lymph node involvement should be per-

formed using PET-CT, EUS/EBUS, or mediastinoscopy. The goal of surgery is R0 resection. Lobectomy is recommended. Pneumonectomy should be avoided in SCLC. Postoperatively, adjuvant chemotherapy and PCI should be performed in cases of LD.

A neoadjuvant approach is justified in the VLD group. Surgery is particularly important here if residual tumor is still present after concurrent chemoradiotherapy and no mediastinal lymph node involvement is detectable. Pneumonectomy should also be avoided in this case.

Local therapy of a solitary adrenal metastasis is an option, especially for patients who achieved complete remission after combined chemoradiotherapy and who, after a longer period without therapy, have a solitary adrenal metastasis as their relapse manifestation.

8.2 Radiotherapy

8.2.1 Thorax

Radiotherapy is an effective therapy for SCLC. In stage VLD after primary surgery and adjuvant chemotherapy, registry data from the National Cancer Database show no advantage for consolidative mediastinal radiation. It should not be performed in N0 and N1, but in N2, mediastinal follow-up radiation may be performed. Controlled studies on this issue are not available.

In patients with LD and in VLD without surgery, radiotherapy is used in combination with chemotherapy.

Chemotherapy should consist of cisplatin and etoposide whenever possible. Carboplatin is less effective in combination with radiotherapy and has not been sufficiently tested. Concurrent chemotherapy and radiation therapy results in 5-year survival rates of 20–30% and is therefore a potentially curative treatment. Compared to sequential therapy, the 5-year survival rate is increased by approximately 5–10%. With concurrent administration, early initiation of radiation should be aimed for, with radiation starting no later than the beginning of the third cycle. This ensures that two complete cycles of cisplatin/etoposide are administered in parallel with radiation therapy. Early initiation of radiation therapy is associated with a higher rate of neutropenia. It is essential to ensure that no dose reductions or even discontinuation of therapy are carried out when concurrent chemoradiotherapy is used early on. Failure to follow the treatment protocol will worsen the results. Therefore, optimal supportive care is of great importance in the context of concurrent chemoradiotherapy protocols.

With conventional fractionation using daily single doses of 1.8–2.0 Gy, a total radiation therapy dose of 60–66 Gy is recommended. In a randomized study, accelerated hyperfractionation with twice daily doses of 1.5 Gy was superior to conventional fractionation with the same total dose of 45 Gy. However, the biologically effective dose differs significantly between the two treatment approaches. Comparisons of accelerated hyperfractionated radiotherapy (AHF) with 1.5 Gy twice daily up to a total dose of 45 Gy vs. conventionally fractionated radiotherapy with daily single doses of 1.8–2.0 Gy up to 66–70 Gy show no statistically significant difference. Both treatment methods are appropriate, although the impact on normal tissue may occasionally suggest an advantage for the AHF regimen.

Patients with ED usually receive primary chemoimmunotherapy with immunotherapy maintenance. The use of consolidating primary tumor irradiation has not been tested in the context of such a treatment strategy and should therefore be reserved for clinical studies.

8.2.2 Prophylactic cranial irradiation

Prophylactic cranial irradiation (PCI) leads to a significant reduction in brain metastases as a site of recurrence. In the LD stage, this is reduced from approximately 40% to 10%. PCI also leads to an extension of OS and a 5% increase in the 5-year OS rate. In a meta-analysis of 7 studies with 987 limited disease patients, the OS rate after 3 years was 20.7% compared to 15.3% in the control arm. Possible PCI regimens are:

- 25 Gy in 10 fractions
- 30 Gy in 10-15 fractions

A randomized study comparing a PCI dose of 25 Gy in 10 fractions to a dose of 36 Gy in 18 fractions showed a reduction in the intracranial recurrence rate from 30% to 24% with the higher dose in 760 patients, but was associated with a less favorable survival curve. Surprisingly, the intrathoracic recurrence rate was increased in the group receiving the higher PCI dose. Doses above 30 Gy are therefore not standard practice and are also associated with a higher risk of CNS toxicities, including cognitive deficits. These are less pronounced with smaller single doses and lower total doses.

In patients with extensive disease who responded to induction chemotherapy, there are divergent study results on PCI. The EORTC study [36], which was based exclusively on clinical symptoms, showed an increase in median survival from 5.4 to 6.7 months, while the MRI-based study from Japan showed a statistically insignificant survival disadvantage with PCI, with a median of 11.6 vs. 13.7 months (HR 1.27; p=0.094). In the EORTC study, the rate of patients receiving second-line chemotherapy in the non-PCI arm was significantly lower at 45% than in the PCI arm at 69%. This may have contributed to the survival advantage for PCI in this study. In the MRI-guided Japanese study, the rate of second-line therapies in both arms was between 80% and 90%, and overall survival times were also significantly more favorable. PCI for ED may be an option if regular cranial MRI studies are not performed.

8.2.3 Symptom-directed radiotherapy

Local radiation is an effective therapy for symptom relief, e.g., in cases of multiple brain metastases or symptomatic bone metastases. Radiotherapy should be considered as an emergency measure in cases of Vena cava superior syndrome and acute paraplegia symptoms in cases of spinal compression on a multidisciplinary basis.

8.3 Systemic tumor therapy

Chemotherapy is the basis of treatment for patients with SCLC. It is used at every stage of the disease, see Figure 5, Figure 6, Figure 7, Figure 8 and Figure 9.

8.3.1 Systemic anticancer agents (in alphabetical order)

8.3.1.1 Amrubicin

Amrubicin is a fully synthetic anthracycline with potentially less pronounced cardiotoxicity. It is effective in SCLC, but the randomized second-line study failed to demonstrate any advantage over topotecan. Therefore, the substance is not approved for the treatment of SCLC.

8.3.1.2 Atezolizumab

Atezolizumab is a monoclonal anti-PD-L1 antibody and belongs to the class of immune checkpoint inhibitors. In first-line therapy of patients with extensive disease SCLC, atezolizumab in combination with carboplatin/etoposide led to an improvement in OS compared to therapy with carboplatin/etoposide alone (improvement in OS 2.0 months; HR 0.70; p=0.007). Clinically relevant side effects included an increase in grade 3/4 diarrhea (2% vs. 0.5%) and infusion-related reactions (2% vs. 0.5%). Atezolizumab may cause an exacerbation of paraneoplastic phenomena, which must be monitored closely.

8.3.1.3 Carboplatin

Carboplatin is a platinum derivative. It has a more favorable side effect profile than cisplatin. In stage ED, the remission rates are the same as those for cisplatin, and the survival rates are probably no different (chapter 8.3.1.4). A specific severe side effect is hematotoxicity with thrombocytopenia, anemia, and neutropenia. Nausea, vomiting, and neurotoxicity occur, but are less pronounced than with cisplatin. Carboplatin is administered intravenously.

8.3.1.4 Cisplatin

Platinum derivatives are among the most effective single substances. The combination of cisplatin and etoposide is the global standard protocol in stage VLD and LD and, in patients in stage ED, the most commonly used regimen with carboplatin/etoposide. Specific severe side effects (grade 3/4) include nausea and vomiting, nephrotoxicity, polyneuropathy, ototoxicity, hematotoxicity, electrolyte imbalance, cardiotoxicity, and diarrhea. Cisplatin is administered intravenously.

8.3.1.5 Cyclophosphamide

Cyclophosphamide is mainly used in combination with anthracyclines, see doxorubicin.

8.3.1.6 Doxorubicin (adriamycin), epirubicin

Anthracycline-containing regimens are an alternative in first-line therapy for ED in cases where platinum-containing combinations are contraindicated. They are also frequently used as second-line treatment. Doxorubicin (adriamycin) and epirubicin have been tested in studies. Anthracyclines are used in combination with cyclophosphamide plus etoposide or vincristine (ACE, EpiCO, or ACO), see Systemic Tumor Therapy - Protocols. The remission rates for first-line therapy are 50-60%, and for second-line therapy 20%. Severe side effects (grade 3/4) of combination therapy, which occurred in more than 5% of patients in randomized studies, are primarily hematological: neutropenia (52-87%), febrile neutropenia (5-10%), anemia (5-15%), thrombocytopenia (1-20%). Doxorubicin/adriamycin is administered intravenously.

8.3.1.7 Durvalumab

Durvalumab is a monoclonal anti-PD-L1 antibody from the class of immune checkpoint inhibitors. In first-line therapy of patients with extensive disease SCLC [52], durvalumab in combination with cisplatin/carboplatin + etoposide led to an improvement in OS compared to chemotherapy alone (improvement in OS of 2.3 months; HR 0.75; p=0.007). The 3-year OS rates were 18% vs. 6%. Based on the results of the ADRIATIC study, consolidation with durvalumab is recommended for adult patients with limited disease whose disease is not progressive

after platinum-based chemoradiotherapy. The median OS was 55.9 months in the durvalumab arm vs. 33.4 months in the placebo arm (HR 0.73; 95% CI 0.57-0.93; p = 0.0104). The median PFS was 16.6 months for durvalumab and 9.2 months for placebo (HR 0.76; 95% CI 0.61-0.95). The safety analysis showed that the rate of pneumonitis was slightly increased with durvalumab (38% vs. 30% in the placebo arm). Immunotherapy-related side effects should be monitored.

8.3.1.8 Etoposide

Etoposide is a topoisomerase II inhibitor. Etoposide in combination with cisplatin is a treatment standard. In patients with extensive disease, the response rates of combination therapy are 60–70%. Oral monotherapy with etoposide is less effective than intravenous combination therapy and has poorer bioavailability. In first-line palliative therapy, the following severe side effects (grade 3–4) occurred with cisplatin/etoposide: neutropenia (68–76%), anemia (11–12%), thrombocytopenia (8–15%), nausea/vomiting (11–12%), fatigue (11%), and anorexia (5%). Etoposide can be administered intravenously or orally.

8.3.1.9 Ifosfamide

Ifosfamide is an alkylating agent approved for combination therapy of SCLC. It was used in combination with adriamycin/doxorubicin and etoposide in the "AIO" protocol (analogous to the "ACO" protocol with cyclophosphamide instead of ifosfamide) for chemotherapy in patients with SCLC, but is now rarely used. The clinically significant side effects are (dose-limiting) bone marrow depression, nausea, hair loss, and encephalopathy, which occurs in up to 50% of patients. Due to the risk of hemorrhagic cystitis, MESNA (mercaptoethanesulfonate sodium) is administered in parallel with ifosfamide. Deterioration of renal function is to be expected, particularly in patients with pre-existing renal impairment (dose reduction may be necessary according to the product information). Particular attention should be paid to numerous drug interactions due to common metabolism via cytochrome p450 isoenzymes such as CYP3A4. Relevant interactions exist, for example, with sorafenib, fluconazole, itraconazole, ketoconazole, carbamazepine, glucocorticosteroids, St. John's wort, phenobarbital, phenytoin, and rifampicin.

8.3.1.10 Irinotecan

Irinotecan is a topoisomerase I inhibitor. In combination with cisplatin, remission rates of 60–70% are achieved in first-line therapy, with OS rates comparable to those of the cisplatin/etoposide combination. Severe side effects (grade 3-4) occurring in more than 5% of patients receiving this combination therapy include neutropenia (34%), febrile neutropenia (5%), diarrhea (19%), nausea/vomiting (14%), fatigue (14%), anorexia (13%), dyspnea (8%), and anemia (5%). Irinotecan is administered intravenously.

The liposomal formulation of irinotecan was not superior to topotecan in a randomized phase III study in the second line (see above) and will therefore not be available for second-line treatment.

8.3.1.11 Lurbinectedin

Lurbinectedin is structurally similar to trabectedin. It inhibits the transcription of tumor cell genes. Phase II studies demonstrated the efficacy of lurbinectedin in second-line SCLC treatment, with remission rates of 35% and PFS of 5.3 months. The drug was subsequently approved in the US for second-line therapy. However, the subsequent randomized phase III study failed to show any advantage over topotecan. The IMforte study [75] demonstrated a sig-

nificant improvement in PFS (8.6 vs. 5.3 months, HR 0.54) and OS (16.4 vs. 13.8 months, HR 0.73) in patients who received lurbinectedin in addition to PD-L1 inhibition (atezolizumab) for maintenance therapy and who had no progression after completion of induction therapy and no brain metastases. In the EU, the combination of lurbinectedin + atezolizumab is not yet approved for the treatment of SCLC (August 2025).

8.3.1.12 Paclitaxel

Paclitaxel belongs to the taxane family. Taxanes are effective drugs in advanced/metastatic stages. They are used in combination with platinum derivatives or as monotherapy. Side effects include neutropenia, anemia, thrombocytopenia, nausea/vomiting, diarrhea, nephrotoxicity, neuropathy, and fatigue. Other side effects include edema, alopecia, onychodystrophy, and allergic reactions requiring appropriate premedication. Paclitaxel is administered intravenously.

8.3.1.13 Serplulimab

Serplulimab is a PD1-targeted monoclonal humanized IgG4 antibody from the class of immune checkpoint inhibitors. It has been approved by the EMA in February 2025 for first-line treatment of adults with extensive disease SCLC, in combination with carboplatin and etoposide. Compared to combination chemotherapy alone, the ASTRUM-005 study showed an overall survival benefit of 15.4 vs. 10.9 months (HR 0.63, $p < 0.001$) [28, 70]. When using this drug, attention must be paid to side effects that are also relevant for other PD1/PD-L1 inhibitors, particularly autoimmune-related side effects such as pneumonitis, colitis, or hepatitis. Relevant drug interactions are not to be expected, as there is no metabolism via cytochrome P450 isoenzymes. The simultaneous administration of immunosuppressive drugs such as glucocorticoids weakens the effect of serplulimab.

8.3.1.14 Tarlatamab

Tarlatamab is a bispecific antibody directed against CD3 and DLL3 that, compared to second-line chemotherapy in patients with SCLC, shows significantly prolonged PFS (5.3 vs. 4.3 months, HR 0.71) and OS (13.6 vs. 8.3 months, HR 0.6). While a significant reduction in serious side effects was observed with tarlatamab compared to standard chemotherapy, cytokine release syndrome (CRS) (56%), loss of appetite (35%), fever (27%), and taste disturbances (24%) were more common with tarlatamab. With increasing duration of therapy with tarlatamab, CRS gradually decreased in severity and frequency; the majority of patients were monitored as inpatients during the first two doses as part of the study. Data from the phase I study indicate intracranial efficacy. Based on the phase II data, the FDA granted accelerated approval in May 2024 for the treatment of ED-SCLC regardless of DLL3 expression in patients whose disease has progressed after platinum-based chemotherapy and PD-(L)1 inhibition. Approval in Europe is currently (August 2025) pending.

8.3.1.15 Tislelizumab

Tislelizumab is a humanized IgG4 mAb with high affinity and binding specificity against PD-1 that has been specifically engineered to minimize binding to FcγR on macrophages. The binding surface of tislelizumab to PD-1 largely overlaps with that of PD-L1, resulting in complete blockade of the PD-1/PD-L1 interaction (>99%). Tislelizumab has been EMA-approved since May 2025 in combination with etoposide and platinum chemotherapy for the first-line treatment of advanced SCLC.

8.3.1.16 Topotecan

Topotecan is a topoisomerase I inhibitor and a standard drug for second-line therapy of SCLC. Remission rates of 20% are achieved here. In combination with cisplatin, topotecan is also effective in first-line therapy and achieves comparable survival times to cisplatin/etoposide. Severe side effects (grade 3-4) occurring in more than 5% of patients receiving this combination therapy include neutropenia (33-88%), anemia (25-31%), thrombocytopenia (7-43%), fatigue (8%), and dyspnea (10%). Topotecan can be administered intravenously or orally.

8.3.1.17 Vinca alkaloids

Vinca alkaloids, most commonly vincristine, are mainly used in combination with anthracyclines, see doxorubicin.

8.4 Palliative therapy – symptom-directed

Palliative care includes the treatment of physical and psychological symptoms. It is carried out on a multidisciplinary basis. The indication and possibilities of palliative therapy should be discussed comprehensively with all those affected at an early stage of SCLC. The following specific symptoms occur particularly frequently in patients with SCLC.

8.4.1 Bone metastases

Local and systemic measures are available for the treatment of patients with bone metastases. Radiotherapy is the treatment of choice for pain symptoms or risk of fracture. It can be administered in hypofractionated doses alongside ongoing systemic therapy. An additional option is surgical treatment for pathological fractures, instable vertebral fractures, or to relieve spinal compression. Systemic options include causal therapy and the administration of bone-modifying substances (bisphosphonates, RANKL antibodies). Bone-modifying substances can reduce the risk of skeletal complications in cases of osseous metastasis of solid tumors. Results from prospective randomized studies in patients with SCLC are not available. Bisphosphonates are also indicated for hypercalcemia.

8.4.2 Brain metastases

The first measure in symptomatic metastasis is the administration of glucocorticosteroids to reduce perifocal edema. In symptomatic patients with multiple foci, whole brain radiation is the treatment of choice. Depending on the overall situation, chemotherapy can also be used as the primary treatment for SCLC, see Figure 6. Stereotactic radiotherapy may also be considered for single metastases or a small number of well-defined metastases. In individual cases, local surgical therapy or targeted local radiation (stereotactic radiotherapy) may be discussed for isolated, resectable brain metastases that persist or progress again after whole brain radiation.

9 Rehabilitation

Systemic tumor therapy, surgery, radiotherapy, and comorbidity can lead to therapy-related disorders of varying severity in patients with SCLC. These can be alleviated by focused rehabilitative measures in somatic and psychosocial aspects.

Patients should be informed at an early stage about the options for outpatient and inpatient rehabilitation measures as well as other entitlements under social welfare law. The wishes of patients should be taken into account with regard to the choice of the rehabilitation facility (§9,

German SGB IX). Nevertheless, a recommendation for a clinic with a focus on oncology should be provided in order to support optimal rehabilitation success.

10 Monitoring and follow-up

10.2 Follow-up

The goals of follow-up care are the early diagnosis of relapse with the aim of prolonging survival, the early diagnosis of secondary neoplasia, the detection of side effects of therapy, and prevention. This applies to patients in localized stages. Structured follow-up care can be based on the recommendations for NSCLC, see Table 9.

Table 9: Structured follow-up care after curative therapy

Procedure	Months 3	6	9	12	18	24	36	48	60
Medical history, physical examination	X	X	X	X	X	X	X	X	X
Thoracic CT	X	X	X	X	X	X	X	X	X
Lung function	X	X	X	(X)	(X)	(X)			
Cranial MRI in LD without PCI	X	X	X	X	X	X	X	(X)	(X)

Legend:
CT = computed tomography, MRI = magnetic resonance imaging, LD = limited disease, PCI = prophylactic cranial irradiation
Note: If follow-up examinations of the suspected reveal a localized relapse or a relapse situation that may be treatable locally, the diagnosis should be supplemented by further imaging, including PET-CT and/or methods for histological confirmation, if required.

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16 Links

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17 Authors' Affiliations

Univ.-Prof. Dr. med. Annalen Bleckmann
Uniklinikum Münster
Medizinische Klinik A
Hämatologie, Onkologie, Pneumologie
Albert-Schweitzer-Campus 1
48149 Münster
annalen.bleckmann@ukmuenster.de

Dr. Volkmar Borrass
volkmarborrass@web.de

PD Dr. med. Wilfried Eberhardt
Universitätsklinikum Essen
Westdeutsches Tumorzentrum
Innere Klinik und Poliklinik
Hufelandstr. 55
45147 Essen
Wilfried.Eberhardt@uk-essen.de

PD Dr.med. Martin Eichhorn
Chirurgische Abteilung
Thoraxklinik
Universitätsklinikum Heidelberg
Röntgenstr. 1
69126 Heidelberg
martin.eichhorn@med.uni-heidelberg.de

PD Dr. Nikolaj Frost
Charité Universitätsmedizin Berlin
Klinik für Infektiologie und Intensivmedizin
Augustenburger Platz 1
13353 Berlin
nikolaj.frost@charite.de

Dr. med. Martin Früh
Kantonsspital St. Gallen
Departement Innere Medizin
Fachbereich Onkologie/Hämatologie
CH-9007 St. Gallen
martin.frueh@kssg.ch

PD Dr. med. Oliver Gautschi
Luzerner Kantonsspital
Medizinische Onkologie
CH-6000 Luzern
oliver.gautschi@luks.ch

Prof. Dr. med. Frank Griesinger
Pius Hospital Oldenburg
Universitätsklinik Innere Medizin-Onkologie
Klinik für Hämatologie und Onkologie
Georgenstr. 12
26121 Oldenburg
frank.griesinger@pius-hospital.de

Prof. Dr. med. Hans Hoffmann
Klinikum rechts der Isar
der Technischen Universität München
Sektion für Thoraxchirurgie
Ismaninger Str. 22
81675 München
thoraxchirurgie@mri.tum.de

Dr. med. Felix John
Universitätsklinikum Köln
Medizinsche Klinik I
Kerpener Str. 62
50937 Köln
felix.john@uk-koeln.de

Univ. Prof. Dr. med. Philipp Jost
Medizinische Universität Graz
Klinische Abteilung für Onkologie
Auenbruggerplatz 15
A-8036 Graz
philipp.jost@medunigraz.at

Prof. Dr. Dr. Barbara Kiesewetter-Wiederkehr
Medizinische Universität in Wien
Universitätsklinik für Innere Medizin I
Klinische Abteilung für Onkologie
Währinger Gürtel 18-20
A-1090 Wien
barbara.kiesewetter-wiederkehr@meduniwien.ac.at

Univ.-Prof. Dr. med. Wolfgang Johannes Köstler
Wiener Privatklinik
Pelikangasse 15/OG
A-1090 Wien
wolfgang.koestler@meduniwien.ac.at

Dr. med. Klaus Kraywinkel
Zentrum für Krebsregisterdaten
Robert Koch-Institut
General-Pape-Straße 62-66
12101 Berlin
k.kraywinkel@rki.de

Prof. Dr. med. Dr. rer. nat. Sonja Loges
Medizinische Fakultät Mannheim der Universität Heidelberg
Universitätsklinikum Mannheim
III. Medizinische Klinik
Theodor-Kutzer-Ufer 1-3
68167 Mannheim
Sonja.Loges@umm.de

Prof. Dr. med. Christoph Pöttgen
Universitätsklinikum Essen
Westdeutsches Tumorzentrum
Klinik für Strahlentherapie
Hufelandstr. 55
45147 Essen
Christoph.Poettgen@uk-essen.de

Prof. Dr. med. Martin Reck
LungenClinic Grosshansdorf GmbH
Onkologischer Schwerpunkt
Wöhrendamm 80
22927 Großhansdorf
m.reck@lungenclinic.de

Prof. Dr. med. Niels Reinmuth
Asklepios Fachkliniken München-Gauting
Thorakale Onkologie
Robert-Koch-Allee 2
82131 München-Gauting
n.reinmuth@asklepios.com

Prof. Dr. med. Wolfgang Schütte
Krankenhaus Martha-Maria
Klinik für Innere Medizin II Pneumologie
Röntgenstr. 1
06120 Halle (Saale)
wolfgang.schuette@martha-maria.de

Dr. med. Martin Sebastian
Universitätsklinik Frankfurt
Medizinische Klinik II
Bereich Hämatologie/Onkologie
Theodor-Stern-Kai 7
60590 Frankfurt / Main
martin.sebastian@unimedizin-ffm.de

Prof. Dr. med. Cornelius Waller
Universitätsklinikum Freiburg
Klinik für Innere Medizin I
Hämatologie, Onkologie und Stammzelltransplantation
Hugstetter Str. 55
79106 Freiburg
cornelius.waller@uniklinik-freiburg.de

Prof. Dr. med. Martin Wolf

18 Disclosure of Potential Conflicts of Interest

according to the rules of the responsible Medical Societies.