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Lung Cancer, non small lung cancer (NSCLC)

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

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Lung Cancer, non small lung cancer (NSCLC)

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1 Summary

Lung carcinoma is the third most common malignant tumor in women and the second in men in the German-speaking countries. The median age of onset is between 68 and 70 years. The main risk factor is smoking.

Screening of asymptomatic high-risk individuals by low-dose computed tomography can detect lung cancer at early stages and reduce lung cancer mortality in smokers and to an even greater extent in female smokers but has not yet been implemented as a screening program in German-speaking countries.

Lung cancer is a prime example of the development of modern oncology. Until recently grouped into two main diagnoses (small cell and non-small cell lung carcinoma), lung carcinoma is now divided into numerous, biologically distinct entities with their own treatment concepts. Patients' prognosis is determined by stage, molecular subtype, histology, gender, general condition, and comorbidity, among other factors.

Treatment options include surgery, radiation, and systemic therapy, often combined as a multimodality approach. Patients with non-small cell lung cancer (NSCLC) are eligible for curative therapy in early stages and in some advanced stages. For the vast majority of stage IIIB/C and IV patients, therapy is not curative. In recent years, the integration of immune checkpoint and kinase inhibitors in conjunction with predictive biomarkers has significantly improved the prognosis of many patients. In addition, cytostatics, angiogenesis inhibitors, local endoscopic and percutaneous interventional therapies, and supportive care are available.

The treatment of patients with small cell lung cancer (SCLC) is the subject of Small Cell Lung Cancer.

2 Basics

2.1 Definition and basic information

Lung carcinomas are epithelial malignancies originating primarily in the lung. Therapy-oriented guidelines differentiate between small and non-small cell carcinomas, and in the case of non-

small cell carcinomas, further differentiation is made according to histological, genetic and immunohistochemical parameters.

The lung is a predilection site for metastases from numerous malignancies. These, other pulmonary tumors, and benign lesions must be excluded by history and, if necessary, cytologic or histologic assessment.

The following statements on epidemiology, risk factors, prevention and early detection refer to all forms of lung carcinoma. The other sections of this guideline deal with primary non-small cell lung cancer (NSCLC).

2.2 Epidemiology

The following results are based on cancer registry data from the individual German states, which are pooled for nationwide analyses at the Center for Cancer Registry Data [137].

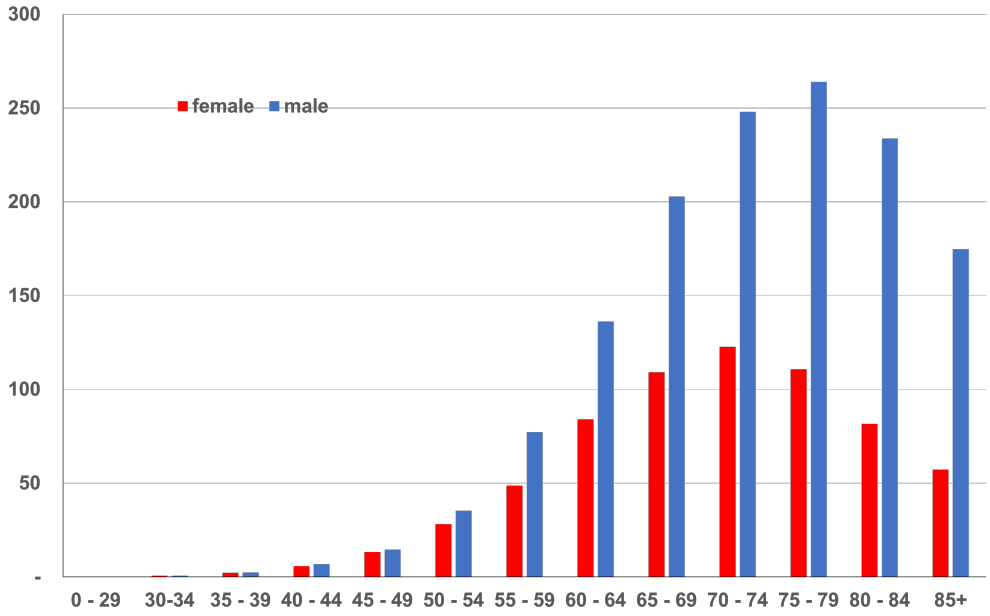
In 2017 - 2019, NSCLC accounted for approximately 79% of all lung cancer cases reported to cancer registries via hospitals, practices, or pathologies. 15% were SCLC, and in approximately 5% of cases, no assignment was possible due to nonspecific histology information. Adenocarcinomas formed the largest group within NSCLC at 54%, followed by squamous cell carcinomas (28%). The remaining cases were large cell or undifferentiated carcinomas (6%), carcinoid/neuroendocrine carcinomas (5%), or could not be clearly assigned to the above subgroups (7%, including 2% adenosquamous carcinomas).

The proportion of adenocarcinomas was higher in women (62%) than in men (49%), in whom, conversely, squamous cell carcinomas occupied a higher proportion (33% vs. 19%).

Approximately 14,500 women and 25,900 men develop NSCLC for the first time each year in Germany. Since about 12% of cases are reported through death certificates, which usually do not include histological differentiation, the reported incidence of NSCLC and SCLC is likely an underestimate of the true number of cases.

The age-specific incidence of lung cancer increases with age up to the 8th decade of life; the median age was most recently 69 years, and only about 2% of those affected develop the disease before the age of 50, see Figure 1.

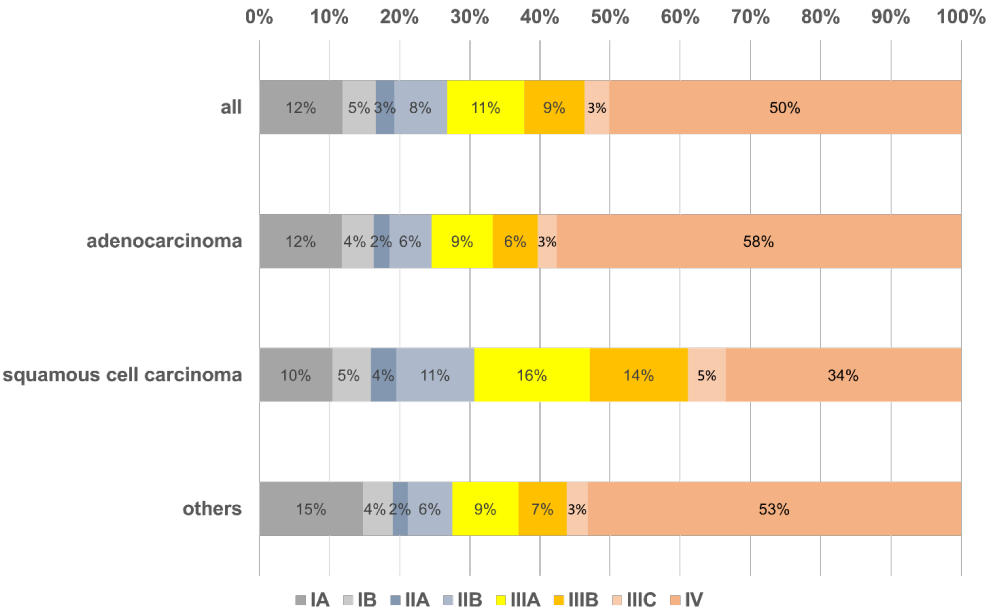
Figure 1: Annual incidence rates of NSCLC per 100,000 persons, by age and sex (Germany, 2017-2019).



Age-specific disease rates are declining in men at all ages and in younger women, and still increasing in women over 60 years of age. These developments reflect the gender-specific trends in smoking behavior with a latency of several decades; in the medium to long term, therefore, a decline can also be expected among women. The absolute number of cases has been almost constant since around 2015, with a total of around 40,000 cases per year, after a steady increase in previous years.

In 50% of new cases with sufficient documentation of tumor stages, distant metastases are already present at the initial diagnosis of NSCLC, and only 27% of cases are diagnosed in early stages I or II according to UICC. The distribution is slightly more favorable for squamous cell carcinomas than for adenocarcinomas, see Figure 2.

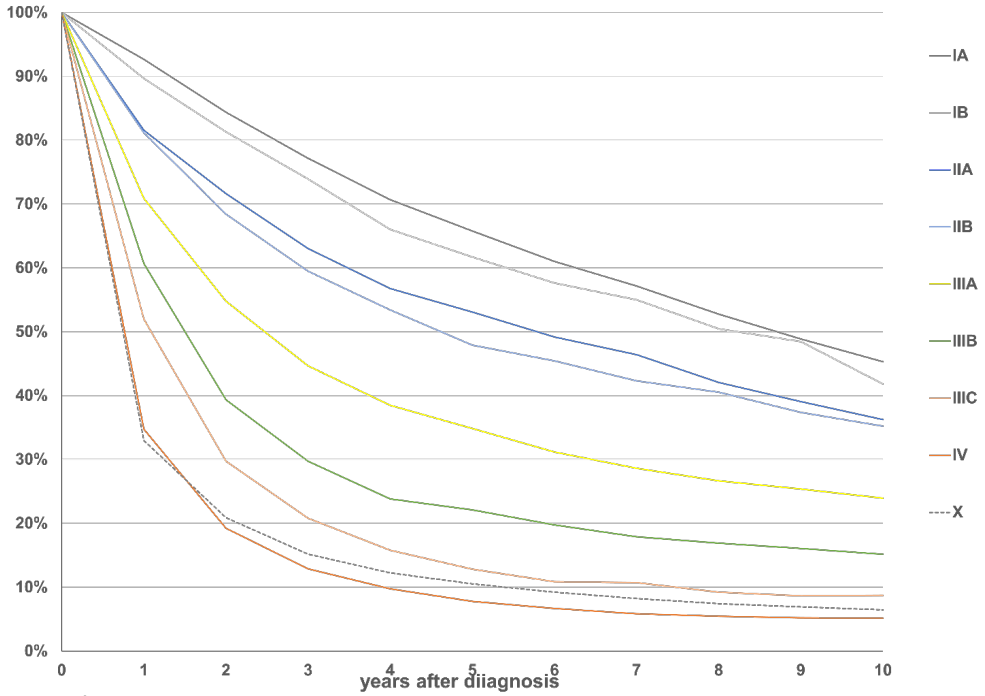
Figure 2: Relative distribution of stages and histology at initial diagnosis (Germany, 2017-2019).



Relative 5-year survival rates as an estimator of disease-specific survival for the 2017-2019 period for NSCLC are 21.7%, nearly four percentage points higher than 10 years earlier (17.9%).

Figure 3 illustrates the dependence of survival predictions on tumor stage.

Figure 3: Relative survival* to 10 years after initial diagnosis of NSCLC, period analysis (2017-2019).



Legend:
**relative to survival probabilities in the general population with the same age and gender distribution.*

Striking are the substantial differences within stage III (IIIA to IIIC), whereas the results for stage IA and IB or IIA and IIB are close. Despite the differences in stage distribution, survival rates for squamous cell and adenocarcinomas are almost identical; thus, at the same stage, adenocarcinomas usually have a slightly better prognosis. Especially for adenocarcinoma, the 5-year relative survival rates are higher in women than in men (27.4% vs. 21.0%).

In Austria, lung cancer ranked second among new cancer cases in 2019, with 2,061 cases (11% of all new cancer cases) in women and 2,770 cases (12%) in men, respectively. With approximately one in five cancer deaths, lung cancer ranked first among cancer-related causes of death in men (21%) and was second in women (17%) [116]. In Switzerland, lung cancer is also the second most common cancer in men and the third most common in women. The annual mean number of people diagnosed in 2014 - 2018 was 2758 for men and 1894 for women, and it is the most common cause of cancer death in men and the second most common cause of cancer death in women. The rate of new cases and death increase in men up to 84 years of age and in women up to 79 years of age. In men, the rates of new cases and deaths have been decreasing since 1989 (-33% and 47%, respectively), while in women both rates have been increasing (+82% and +62%, respectively) [12].

2.3 Pathogenesis

Lung carcinomas develop in a complex, stepwise process through the accumulation of altered molecules and deregulation of signal transduction pathways based on genetic aberrations. Lung carcinoma is among the malignancies with the highest mutational burden, although this is not true for all molecular subgroups. Molecular analyses are increasingly leading to a diversification of the previously histologically based subdivisions. They reveal different pathogenetic pathways, e.g. between smokers and nonsmokers, but also within histological subgroups. Targeted drugs are available for some of the key oncogenic driver mutations. Also relevant for the

spread of tumor cells is the interaction with the immune system. Here, drugs are available that interfere with immune regulation in a targeted manner.

2.4 Risk factors

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

acquired, exogenous:

- smoking, including passive smoking
- ionizing radiation (high environmental radon exposure, uranium mining, medical radiation exposure)
- fine dust
- diesel engine exhaust
- asbestos
- quartz dusts
- chronic infections

genetic, endogenous:

- Individuals with a positive lung cancer history in one or more first-degree relatives have an increased risk of developing the disease

Overall, smoking, especially in active form but also as passive smoking, is by far the most important risk factor. This includes all forms of inhaled tobacco use, including hookahs (shisha). The interaction of smoking with other exogenous or endogenous risk factors has not been conclusively clarified, with evidence of a superadditive effect, e.g., in asbestos exposure.

Lung cancer is recognized as an occupational disease in Germany for occupational exposure to arsenic, asbestos, beryllium, cadmium, chromium, coke oven raw gases, nickel, polycyclic aromatic hydrocarbons (PAHs), silica [48], and passive smoking. For some substances, the intensity of exposure (dose, duration) has been defined. Based on the results of the National Lung Cancer Screening Trial [1], the German Social Accident Insurance implemented a lung cancer screening program in 2014, using low-dose CT (LD-HRCT) to detect early tumors in at-risk individuals.

3 Prevention and early detection

3.1 Prevention

The general recommendations for prevention relate to the risk factors identified so far and to healthy lifestyle behaviours:

- Not smoking (by far the most important measure)
- avoid passive smoking
- avoid occupational exposure to carcinogens
- structural measures to reduce radon exposure in risk areas
- physical activity
- increased consumption of fruits and vegetables

Avoiding smoking is the key preventive measure (WHO Framework Convention on Tobacco Control) [49, 53]. Increased consumption of fruits and vegetables reduces the risk of lung cancer, especially in smokers [53].

Randomized trials in individuals at risk for lung cancer have not shown a positive preventive effect for intake of -carotene, various forms of retinoids, vitamin E, folic acid, tea extracts, selenium, N-acetylcysteine, acetylsalicylic acid, metformin, celecoxib, inhaled steroids, and other substances [117]. Specific forms of dietary supplementation or medications for the prevention of lung cancer are not recommended.

3.2 Early detection – Screening of asymptomatic persons

Since the prognosis of lung cancer is stage-dependent and curative local therapy is possible in the early stages, the rationale for early detection is given. Calculations of the median time between the first changes detectable by imaging and the clinical diagnosis of lung cancer (sojourn time) vary widely, ranging from 1.38 to 3.86 years for computed tomography [32].

In the German-speaking European area, there are no recommended measures for early detection so far, with the exception of a recommendation by SUVA (Swiss Accident Insurance Fund) for persons with asbestos contact and by the German Statutory Accident Insurance for occupationally exposed risk persons. Previous approaches to the use of chest radiography or sputum cytology have had no significant effect on reducing mortality. Screening with low-dose computed tomography (CT) of the thorax increases the detection rate of lung cancer in an at-risk population. In the US National Lung Cancer Screening Trial (NLST), CT-based screening significantly reduced cancer-specific mortality and all-cause mortality in a randomized trial of 53,454 heavy smokers or ex-smokers aged 55-74 years [1]. These data have recently been confirmed by the NELSON trial from the Netherlands and Belgium. Here, a significant reduction in lung cancer-specific mortality after 9 years was seen particularly in women (hazard ratio 0.52), but the difference was also clear and statistically significant in men (hazard ratio 0.76) [23]. In contrast, overall mortality was not affected by lung cancer screening, so the issue remains controversial. Data from a smaller German study also confirmed the value of screening by low-dose computed tomography in high-risk individuals [9]. Other studies with lower numbers of cases showed no significant differences.

Risks of screening are the high rate of false positive findings, complications of invasive diagnostics, and overdiagnosis of carcinomas with low progression [82]. These must be considered in a quality-assured introduction of screening.

Smoking cessation shows similar effects and should be combined with screening programs [119].

The goal of current efforts by scientific medical societies is the short-term implementation of a screening program in asymptomatic high-risk individuals in combination with smoking cessation. A positive benefit-risk assessment of low-dose CT screening by IQWIG has been available since October 2020. The Federal Office for Radiation Protection (BfS) also came to a positive assessment of the benefit-risk ratio in its scientific assessment published in December 2021, but under strict conditions. These are currently the subject of political discussions between the Federal Joint Committee and the BfS. The required approval by the German Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV) is still pending and is expected by the end of 2022. After that, the G-BA will have a maximum of 18 months to determine the exact implementation rules for the lung cancer screening measure using LDCT. Therefore, the start of a national screening program for lung cancer is not expected before 2024.

4 Clinical characteristics

Characteristic symptoms are summarized in Table 1. In the early stage, lung carcinoma is often asymptomatic. Symptoms such as pain often reflect advanced stages.

Table 1: Symptoms in patients with lung cancer

Cause	Symptom
Local tumor	• cough • dyspnea • chest pain • hemoptysis • bloody tinged sputum during coughing • upper influence congestion (superior vena cava syndrome) • dysphagia • stridor • hoarseness (vocal cord paresis with infiltration of the recurrent nerve) • Arm weakness (infiltration of the brachial plexus) • Horner syndrome (infiltration of the stellate ganglion)
Metastases	• pain, e.g. bone pain or headache • dizziness, headache, neurological deficits, confusion, seizures • swelling of lymph nodes (supraclavicular) • jaundice
General	• weight loss • weakness • fever • night sweats • paraneoplastic syndromes* ◦ autoimmune (collagenoses) ◦ endocrine ◦ hematological incl. coagulation ◦ cutaneous, e.g. dermatomyositis ◦ metabolic, e.g. SIADH (Schwartz-Bartter syndrome) with hyponatremia ◦ neurological, e.g. Lambert-Eaton syndrome, anti-Hu syndrome ◦ osseous, e.g. hypertrophic osteoarthropathy (Pierre-Marie-Bamberger syndrome) ◦ renal

Legend:
Paraneoplastic syndromes occur more frequently in patients with SCLC, see Onkopedia lung carcinoma, small cell (SCLC), and to a lesser extent in patients with adenocarcinomas.

In a proportion of patients, lung carcinoma is discovered incidentally during thoracic imaging for other indications.

5 Diagnosis

5.1 Diagnostics

5.1.1 Initial Diagnosis

The first step is to confirm the suspected clinical and/or imaging diagnosis, see Table 2.

Table 2: Diagnostics for new onset symptoms [115]

Examination	Recommendation
Laboratory	complete blood count, electrolytes, renal function, liver values, LDH, coagulation tests
CT[1] Thorax / upper abdomen with contrast medium, or FDG-PET-CT[2]	First-choice method
MRIT[3] Thorax / upper abdomen with contrast medium	Alternative to CT[1], if CT not feasible
Bronchoscopy with biopsy[4]	if imaging is suspicious and lesion is accessible
Transthoracic biopsy	in case of suspicious lesion at imaging, in particular peripheral pulmonary nodule inaccessible to endoscopic biopsy

Legend:
[1] CT - computed tomography;
[2] FDG-PET-CT- positron emission tomography with diagnostic CT, possible in Austria;
[3] MRI - magnetic resonance imaging;
[4] Alternative for peripheral masses: Brush, needle, or others;

After pathological confirmation of a primary lung carcinoma, an assessment of the extent of disease (staging) is indicated, taking into account clinical symptoms, see Table 3. Metastases in non-small cell lung carcinoma can occur in almost all regions of the body. The most common sites are lymph nodes, ipsi- or contralateral lung, skeleton, liver, adrenal glands, and CNS.

Table 3: Staging

Examination	Note
Sonography upper abdomen	
FDG-PET-CT[1]	in case of curative therapy concept
EUS / EBUS[2] with biopsy	in case of suspected mediastinal lymph node involvement
Mediastinoskopy (VAM[3], VAMLA[3]), if necessary video-assisted thoracoscopy (VATS[3])	If sufficient mediastinal staging cannot be reached by endoscopic examinations
MRI[4] brain	Method of first choice for diagnosis of cerebral metastases
CT[5] brain	if MRI[4] brain not feasible
Bone scintigraphy	if FDG-PET-CT[1] not feasible
CT[5] abdomen (incl. adrenal glands, lower liver margin and pelvis)	if FDG-PET-CT[1] not feasible
MRI[4] whole body	if FDG-PET-CT[1] not feasible; not indicated in the absence of curative therapeutic intent
Pleural puncture and, if necessary, videothoracoscopy	in case of pleural effusion; if necessary, pleural biopsy and thoracoscopy

Legend:
[1] FDG-PET-CT - positron emission tomography with computed tomography;
[2] EUS/EBUS - endobronchial or endoesophageal ultrasound with fine needle biopsy;
[3] VAM: video-assisted mediastinoscopy, VAMLA: video-assisted mediastinal lymphadenectomy,
[4] MRI - magnetic resonance imaging;
[5] CT - computed tomography;

5.3 Classification

5.3.1 stages

The classification was based on TNM and UICC criteria version 7 until 31. 12. 2016. Since 1. 1. 2017 the new staging according to IASLC/UICC8 is valid, see chapter 5.3.1.2.

5.3.1.1 TNM and IASLC / UICC8

The previous classification UICC7 has been revised based on data from nearly 100,000 patients and formally entered into force on 1/1/2017 with the collaboration of IASLC/AJCC and UICC. The current staging is based on the TNM and UICC8 criteria [6, 32, 42, 75, 91], see Table 4 and Table 5.

Table 4: Description of TNM stages according to IASLC Lung Cancer Staging Project.

Category	Stage	Brief description
T (Tumor)	Tis	• carcinoma in situ
	T1	• largest diameter <3 cm, surrounded by lung tissue or visceral pleura, main bronchus not involved
	• T1a (mi)	• minimally invasive adenocarcinoma
	• T1a	• largest diameter <1cm
	• T1b	• largest diameter >1 and < 2 cm
	• T1c	• largest diameter >2 and < 3 cm
	T2	• diameter >3 and <5 cm or • Infiltration of the main bronchus regardless of distance from the carina, but without direct invasion of the carina • infiltration of the visceral pleura or • tumor-related partial atelectasis or obstructive pneumonia extending into the hilus and involving parts of the lung or the entire lung
	• T2a	• largest diameter >3 and <4 cm
	• T2b	• largest diameter >4 and <5 cm
	T3	• largest diameter >5 but <7 cm or • infiltration of thoracic wall (including parietal pleura and superior sulcus), phrenic nerve, parietal pericardium, or • additional tumor nodule in the same lung lobe as the primary tumor
	T4	• largest diameter >7cm or with direct infiltration of diaphragm, mediastinum, heart, great vessels (v. cava, aorta, pulmonary artery, pulmonary vein intrapericardially), trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina or • additional tumor node in another ipsilateral lung lobe
N (lymph Node)	N0	• no lymph node metastases
	N1	• metastasis in ipsilateral, peribronchial, and/or ipsilateral hilar lymph nodes and/or intrapulmonary lymph nodes or direct invasion of these lymph nodes
	N2	• metastasis in ipsilateral mediastinal and / or subcarinal lymph nodes
	N3	• metastasis in contralateral mediastinal, contralateral hilar, ipsi or contralateral deep cervical, supraclavicular lymph nodes
M (Metastasis)	M0	• no distant metastases
	M1	• distant metastases
	• M1a	• separate tumor nodule in a contralateral lung lobe • pleura with nodular involvement • malignant pleural effusion • malignant pericardial effusion
	• M1b	• isolated distant metastasis in an extrathoracic organ
	• M1c	• multiple distant metastases (>1) in one or more organs

Table 5: Classification of tumor stages according to UICC 8 [42, 120]

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 T2a T2b T3	N1 N1 N1 N0	M0 M0 M0 M0
IIIA	T1a-c T2a-b T3 T4 T4	N2 N2 N1 N0 N1	M0 M0 M0 M0 M0
IIIB	T1a-b T2 a-b T3 T4	N3 N3 N2 N2	M0 M0 M0 M0
IIIC	T3 T4	N3 N3	M0 M0
IVA	each T each T	each N each N	M1a M1b
IVB	each T	each N	M1c

5.3.1.2 Stage IIIA N2 according to Robinson

Due to its therapeutic relevance, the very heterogeneous stage IIIA with ipsilateral mediastinal lymph node involvement is additionally classified according to Robinson [95], see Table 6.

Table 6: Subclassification of stage IIIA (according to Robinson) [95]

Stage	Description
$IIIA_1$	incidental lymph node metastases in one or more lymph node regions after postoperative workup in the specimen
$IIIA_2$	intraoperative evidence of lymph node metastases in a mediastinal lymph node station (intraoperative frozen section) and, if necessary, termination of the procedure without resection
$IIIA_3$*	preoperative detection of lymph node metastases in one or more lymph node stations (PET, mediastinoscopy, biopsy), potentially resectable
$IIIA_4$	IIIA4 extensive ('bulky') or fixed N2 metastases or metastases in multiple lymph node stations (mediastinal lymph nodes > 2 - 3 cm) with extracapsular infiltration; not resectable.

Legend:
** Clinically, a further subdivision into unilevel (U) and multilevel (M) is useful at this stage.*

In general, if N2 or N3 metastases are suspected, cytologic or histologic confirmation should be sought by EBUS/EUS or, failing that, by surgical biopsy, i.e., video-assisted mediastinoscopy (VAM), video-assisted mediastinoscopic lymphadenectomy (VAMLA), or video-assisted thoracoscopy (VATS). In cases of undoubtedly extensive mediastinal lymph node involvement ("bulky disease"), bioptic confirmation can be omitted by interdisciplinary consensus. FDG PET-CT assessment of tumour spread to regional lymph node may produce false positive results, espe-

cially in cases of retention pneumonia due to endobronchial tumor growth, carcinomas with a high degree of inflammation or coexistence of sarcoidosis.

5.3.2 Histology

The current histological classification according to WHO / IARC is summarized in Table 7.

Table 7: Histological classification of NSCLC according to WHO / IARC

Classification	Differentiation	Characterisation / Criteria
Squamous Cell Carcinoma	keratinizing	
	nonkeratinizing	(p40+, TTF1-)
	Basaloid	p40+/TTF1-
Adenocarcinoma	preinvasive	<3cm with <5mm invasion
	minimally invasive	
	invasive • G1 lepidic • G2 acinar, papillary • G3 micropapillary, solid	
	Variants	
Large cell carcinoma		
Neuroendocrine Tumors	Carcinoid • typical Carcinoid • atypical Carcinoid	
	small cell carcinoid (SCLC)	
	large cell neuroendocrine carcinoma (LCNEC)	

5.3.3 Molecular biology

5.3.3.1 Resectable stages

The diagnosis of therapy-relevant mutations and biomarkers should be performed in all patients in the operable stages for these markers:

- ALK translocations
- EGFR exon 18-21 mutations

The basis for this recommendation is that the use of adjuvant immunotherapy with atezolizumab excludes patients with EGFR and ALK alterations. For the adjuvant use of osimertinib we refer to chapter 6.1. An influence of the other driver mutations mentioned above on the efficacy of adjuvant immunotherapy is possible, but so far not confirmed.

5.3.3.2 Stage IV

Diagnosis of therapy-relevant mutations should be performed in all stage IV patients prior to initiation of first-line drug therapy. It should cover these aberrations (in alphabetical order):

- ALK translocations
- BRAF V600E mutation

- EGFR exon 18-21 mutations
- HER2 amplifications and mutations
- KRAS-G12C mutation
- c-MET exon 14 skipping mutations
- NTRK translocations
- RET translocations
- ROS1 translocations

Not all of these genetic aberrations are approved for first-line targeted therapy. However, early detection may be relevant for study inclusion, for a necessary change of therapy in case of chemo- or immunotherapy intolerance or in case of rapid progression.

For further alterations, specific therapy concepts are being developed, see chapter 6.1.6.2.4. These include, e.g.

- c-MET alterations with amplification and translocations
- NRG1 translocations

Molecular diagnostics should be targeted, comprehensive, tissue-sparing, integrated, quality assured, and timely (<10 working days).

5.3.4 Immunohistology

Immunohistochemical determination of PD-L1 should be performed in all patients in operable stages II-III, in stage III after definitive radiochemotherapy, and in all patients in stage IV before initiation of first-line drug therapy. Depending on the marketing authorization regulations, PD-L1 expression on tumor cells (Tumor Proportion Score, TPS) and/or on tumor-infiltrating immune cells (IC) is relevant.

5.6 General condition and comorbidity

Therapeutic options in patients with lung cancer are often limited by reduced general condition as well as cardiovascular, pulmonary or other comorbidities, including those related to age. This applies to both curative and palliative therapy.

5.6.1 Clinical and Functional Resectability

If there are no primary contraindications to surgery, the main factors to consider are the expected postoperative pulmonary function (see Table 8) and the perioperative cardiovascular risk (see Table 9). A differentiated algorithm for the pretherapeutic fitness of patients with lung cancer has been developed by the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) [11].

Table 8: Pulmonary function examinations [11, 53].

Examination	Note
Spirometry: FEV_1[1], TLCO[2]	First-line methods
Whole-body plethysmography	
Arterial blood gases at rest	
Cardiopulmonary exercise testing (spiroergometry)	in patients with limitation of FEV1 and / or diffusion capacity (TLCO), or other limiting cardiovascular risks or concomitant diseases

Legend:
[1] FEV_1 – forced expiratory 1-second volume;
[2] TLCO – CO transfer factor (CO diffusing capacity), formerly and in the USA also referred to as DLCO;
Clinical predictors of increased perioperative cardiovascular risk (according to American College of Cardiology (ACC) and American Heart Association (AHA)) [63]

Table 9: Clinical predictors of increased perioperative cardiovascular risk (according to American College of Cardiology (ACC) and American Heart Association (AHA)) [63]

Risk	Parameter
High	• unstable coronary artery disease ◦ recent myocardial infarction with evidence of relevant ischemic risk, based on clinical symptoms or non -invasive investigations ◦ unstable or severe angina (grade 3 or 4) • decompensated heart failure • significant arrhythmias ◦ AV block of grade II or III ◦ symptomatic ventricular arrhythmias in heart failure ◦ supraventricular arrhythmias with uncontrolled heart rate • severe valvular heart disease
Moderate	• moderate to mild angina pectoris (grade 1 or 2) • previous myocardial infarction, based on history or pathological Q waves • compensated heart failure or Z. n. decompensated heart failure • diabetes mellitus
Low	• advanced age (>70 years) • abnormal ECG (left ventricular hypertrophy, left bundle branch block, ventricular end part changes • absence of sinus rhythm with normal-frequency ventricular action (e.g., atrial fibrillation) • low exercise capacity • post apoplexy • poorly controlled arterial hypertension

5.6.2 Geriatric Assessment

The use of geriatric assessment instruments is recommended for objective assessment of general condition, see Geriatric Assessment Knowledge Base. Tests for objectifying mobility and comorbidity are particularly suitable. The indication for further tests is based on the clinical impression and the planned treatment.

5.6.3 Nutritional status

About one third of all patients with lung cancer are malnourished [67]. All patients should be offered repeated screening for malnutrition with a validated tool [60]. If there is a risk constellation in the screening, further diagnostics and professional nutritional counseling should be offered. All patients should be motivated and instructed in regular muscle training to support body cell mass.

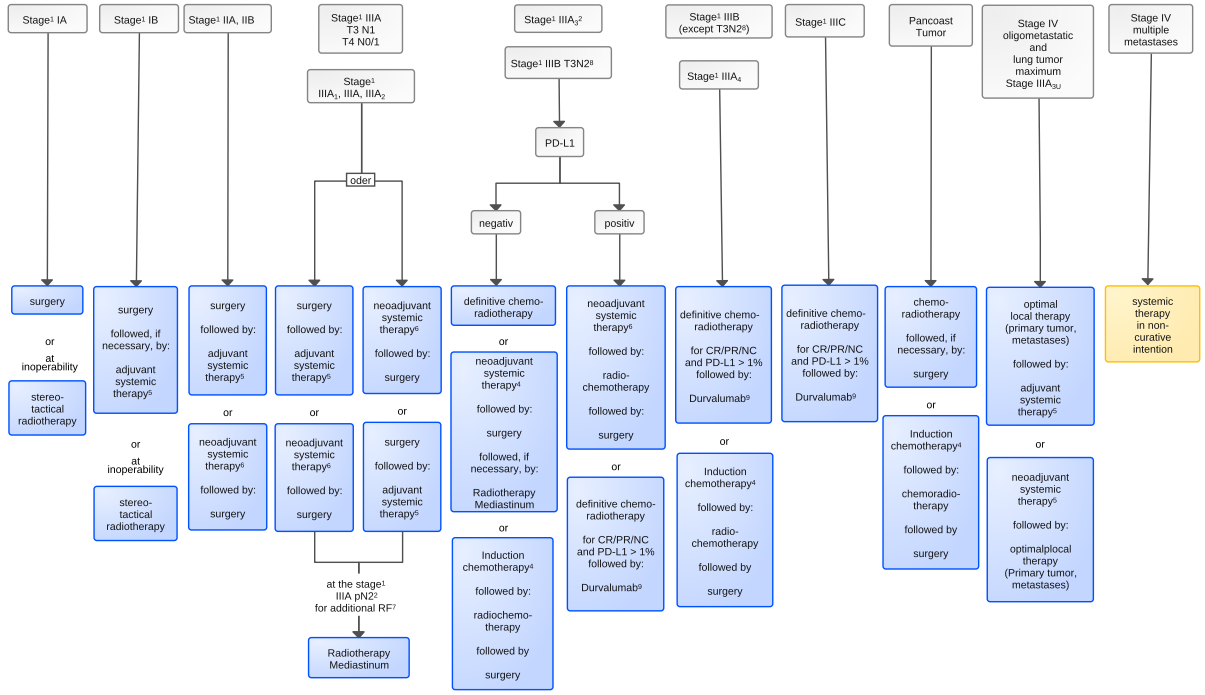
6 Therapy

6.1 Structure

Treatment is stage-dependent [53, 76], see Figure 4. The basis of the initial therapy decision is the clinical staging, taking into account the general condition, pulmonary functional reserve, and comorbidities. After surgery, further therapy is determined by the results of pathologic examinations and lymph node status.

The task of interdisciplinary tumor conferences is to critically weigh the differential therapeutic options as the basis for the physician's recommendation. Comprehensive information of the patient is a prerequisite for his autonomous decision. An algorithm for primary therapy is shown in Figure 4. Whenever possible, patients should be treated in clinical trials.

Figure 4: Therapy structure for non-small cell lung cancer (NSCLC)



Legend:

curative intent therapy; non-curative intent therapy;

[1] clinical stages;

[2] Individual therapy should be determined in an interdisciplinary tumor board involving all diagnostic and therapeutic disciplines;

[3] negative: PD-L1 <1%; positive ≥1%;

[4] surgery - umbrella term for all forms of tumor resection or ablation

[5] adjuvant systemic therapy after resection includes
- platinum-containing chemotherapy in stages IIA - IIIA and
- in case of EGFRmut (del 19, L858R) in stages IB - IIIA: osimertinib (for classification change from UICC 7th edition or according to UICC 8th edition see chapter 6.1.2.) and
- for PD-L1 expression on tumor cells ≥50% in stages IIA - IIIA in EGFR/ALK wild-type: atezolizumab;
- or a combination of these options

[6] platinum-containing combination chemotherapy + nivolumab; for divergent approvals in respective countries.

[7] Additional risk factors: multiple N2 infestations and capsular overgrowth;

[8] pT3 criterium based on extent of the tumor, infiltration of the chest wall or size between 5-7 cm

[9] see currently valid marketing authorization information; approval in Switzerland independent of PD-L1 status.

Recommendations for local therapy with curative intent apply to the entire group of non-small cell lung cancers. Histological, immunological and genetic markers are used to guide the choice of systemic therapy in advanced disease. The introduction of systemic, molecular stratified therapy, immune checkpoint inhibitors and multimodal treatment may lead to an individual overall survival time beyond 5 years. This applies especially to patients with oligometastatic disease.

6.1.1 Stage IA

The therapeutic intent is curative. Surgery is the therapy of choice if there are no contraindications. Postoperative 5-year survival rates are 80-93% for stage IA [42, 53, 100, 132]. Adjuvant

chemotherapy does not improve 5-year survival in this stage. In the postoperative setting after R0 resection, radiotherapy has a negative impact on prognosis and is not indicated.

Ablative radiotherapy (SABR or SBRT) is a potential alternative as a primary treatment modality, especially in functionally inoperable patients. In a cohort comparison from the US National Cancer Database, stereotactic is superior to conventional fractionated radiotherapy in terms of overall survival [45]. Stereotactic methods can achieve local control rates comparable to those of surgery [131]. Two randomized trials (STARS, ROSEL) comparing stereotactic radiotherapy versus surgical resection were terminated early due to slow recruitment. The results were summarized in a pooled analysis [16]. The data are insufficient to demonstrate equivalence of surgery and SABR in terms of disease-free and overall survival.

6.1.2 Stage IB

The therapeutic intent is curative. Surgery is the treatment of choice in the absence of contraindications. The postoperative 5-year survival rate for stage IB in the now valid TNM edition is 73% [42, 53, 100, 132]. The change in classification also affected stage IB, with tumors >4 cm now classified as stage II.

Adjuvant chemotherapy may be considered for stage IB patients. Recommendations from various guidelines derived from the data are not consistent [53, 76]. Retrospective analyses suggest that possibly stage IB (TNM, version 7) patients with additional risk factors such as micropapillary or solid subtyping of adenocarcinomas, pleural infiltration, lymphatic (L1) or vascular (V1) infiltration may also benefit from adjuvant chemotherapy [122]. These additional parameters have not been prospectively validated. In this context, special attention should be paid to potential contraindications and comorbidities. Recommendations for the implementation of adjuvant chemotherapy can be found in chapter 6.2.3.1. and in Lung Cancer Therapy Protocols.

In stage IB patients with an EGFR mutation del19 or L8585R, adjuvant therapy with osimertinib may also be considered, see chapter 6.1.3. It should be noted that the inclusion criteria of the ADAURA trial were based on the UICC 7 criteria. The majority of patients classified according to UICC 7 are also stage IB according to UICC 8 [59]. This must be taken into account when determining the indication.

Adjuvant radiation is only indicated after incomplete resection (R1, R2) when re-excision is not possible. In the postoperative situation after R0 resection, it has a negative impact on prognosis and is not indicated [62].

Radiotherapy is an alternative as a primary therapeutic measure in inoperable patients

6.1.3 Stages IIA and IIB

The therapeutic intent is curative. Surgery is the key curative therapeutic modality in the absence of contraindications. Postoperative 5-year survival rates range from 60 to 65% for stage IIA and from 53 to 55% for stage IIB [42, 53, 76, 77, 120, 132]. In stage IIA and IIB, systemic therapy, adjuvant or induction, should be given.

After R0 resection, adjuvant chemotherapy is recommended. It resulted in a 5% absolute improvement in 5-year survival in a meta-analysis of 34 trials with different chemotherapy protocols [26]. In the long-term meta-analysis of patients treated with cisplatin / vinorelbine, the 5-year survival rate was 11.6% higher than in the control group.

The value of adjuvant systemic therapy with molecular-targeted and immune checkpoint inhibitors is currently the subject of numerous studies. Results available to date that are relevant to therapy are:

- EGFR mutations
  - In the ADAURA trial, adjuvant therapy with osimertinib for 3 years in patients with an EGFR common mutation (del19, L858R) in stages IB, II, and IIIA (UICC7) after R0 resection versus placebo resulted in significant prolongation of disease-free survival (HR 0.17; p<0.001) and a 90% reduction in the risk of CNS metastasis [130]. 76% of the patients had additionally received adjuvant chemotherapy. Mature data on the impact of adjuvant osimertinib on overall survival are not yet available. The data from ADAURA confirm the results of a phase III trial in Chinese patients with activating EGFR mutations in stage II/IIIA, in which adjuvant therapy with gefitinib versus cisplatin/vinorelbine resulted in a prolongation of disease-free survival (HR 0.60; median 10.7 months) [139]. However, overall survival was not prolonged by 2 years of gefitinib administration, which may be partially explained by the use of EGFR TKIs at progression. In another randomized trial comparing gefitinib vs cisplatin/vinorelbine conducted in Japan, gefitinib resulted in a lower rate of early relapse, but the final analysis showed no significant difference between the two study arms in terms of disease-free and overall survival [118].
- Immune checkpoint inhibitors
  - In the IMpower 010 trial in patients with NSCLC in stages IB-IIIA (TNM 7) after adjuvant chemotherapy, subsequent immunotherapy with atezolizumab for 16 cycles significantly prolonged progression-free survival (HR 0.81). The differences were more pronounced in patients in the higher disease stages with a trend towards prolongation of overall survival, and in patients with expression of PD-L1. The approval limits the indication to patients with PD-L1 expression >50%, high risk of recurrence, and exclusion of EGFR or ALK alteration). Data on the impact of atezolizumab on overall survival are immature [35, 134].

An alternative to adjuvant systemic therapy is induction chemotherapy, also referred to as preoperative or neoadjuvant therapy, see also chapter 6.2.3.1. The basis of induction chemotherapy in NSCLC before surgery was two randomized trials published in 1994 comparing this new form of therapy versus surgery alone. The results suggested a survival advantage for induction chemotherapy in stage IIIA patients. The largest meta-analysis based on individual data from 2,385 patients included clinical stages IB (according to UICC7, 46% of patients), IIB (26%), and IIIA (21%), and showed a significant prolongation of overall survival and 5-year overall survival with combined therapy (HR 0.87; p = 0.0007) [78]. In an indirect comparison, the data of this combined therapy are similar to those of adjuvant chemotherapy. However, the collectives are not identical. The inclusion criteria for induction chemotherapy are based on clinical staging, whereas the indication for adjuvant chemotherapy is based on pathologic classification.

Results of direct randomized trials comparing induction chemotherapy versus adjuvant chemotherapy are largely lacking. Only one Spanish study performed a three-arm comparison of surgery alone versus neoadjuvant or adjuvant therapy, with no difference in overall survival between study arms [36]. The argument for induction therapy is the higher treatment adherence, relative to systemic therapy. Also, the morbidity of postoperative chemotherapy after pneumonectomy is increased. For further details of induction chemotherapy, see chapter 6.2.3.1.

Currently, the first data on the combination of neoadjuvant chemotherapy with an immune checkpoint inhibitor are available, see chapter 6.1.4.1 [38]. The CheckMate 816 trial also enrolled stage II patients; however, the data are not yet mature for evaluation in this stage of disease.

In the postoperative setting after R0 resection, radiotherapy has a negative impact on prognosis and is not indicated. Radiation therapy is an alternative as a primary therapeutic measure in inoperable patients It may also be indicated in an R1 or R2 situation when reoperation is not possible.

6.1.4 Stage III - Overview

Stage III comprises a very heterogeneous group of patients, see Table 5. In principle, cure remains the goal of treatment. The 5-year survival rates for stage IIIA are between 15 and 40%, for stage IIIB between 5 and 10% [42, 53, 76, 77, 120, 132]. Above all, the extent and localization of lymph node metastases are prognostically relevant. For stage IIIA lymph node status N2, Robinson's subclassification allows therapy depending on mediastinal lymph node involvement, see Table 6. However, it must be critically noted that Robinson's subclassification predates the wider use of sensitive and specific imaging techniques such as PET. Consultation in an interdisciplinary tumor board is essential, also for clinical classification of imaging findings.

The value of induction therapy with immunologically active drugs in combination with platinum-containing chemotherapy is currently being reevaluated. For the option of adjuvant therapy with osimertinib when an EGFR-del19 or an L858R mutation is detected, or for the use of atezolizumab, we refer to chapter 6.1.3.

A conceptual alternative to adjuvant chemotherapy is induction or neoadjuvant chemotherapy.

6.1.4.1 Stage IIIA T3 N1, T4 N0, T4 N1

The treatment recommendations for clinical stage T3 N1, T4 N0 and T4 N1 patients are essentially the same as for stage IIB. Surgery is the local therapy of choice if there are no contraindications due to tumor location or comorbidities. In general, patients with infiltration of thoracic wall (T3), vertebral body, pulmonary artery, mediastinum, trachea, or bifurcation (T4 extension (T4 Ext)) should be presented to an experienced thoracic surgeon for evaluation of potential resectability. In cases of infiltration of the aorta or esophagus (T4 extension (T4 Ext)), surgical procedures should be evaluated with caution because of the highly complex procedures with high mortality. It is strongly recommended to discuss the procedure in an interdisciplinary tumor conference. In the case of a T4 stage caused by involvement of multiple ipsilateral lobes of the lung, the integration of surgery should be considered. In this case, lung-sparing procedures should be preferred.

After R0 resection, adjuvant chemotherapy is recommended, followed by adjuvant therapy with atezolizumab if PD-L1 expression is high and EGFR/ALK WT is present. Patients with a common EGFR mutation should be treated with osimertinib after chemotherapy. According to the design of the pivotal trial, osimertinib administration is recommended until recurrence, unacceptable toxicity, for a maximum of 3 years. Recommendations for the administration of adjuvant chemotherapy can be found in chapter 6.2.3.1.

An alternative to adjuvant is induction chemotherapy, see chapter 6.1.3. and chapter 6.2.3.2. Meta-analysis of 3 prospective randomized trials showed that induction chemotherapy and induction radiochemotherapy have a favorable impact on response, mediastinal downstaging, and pathologic CR of mediastinal lymph nodes without affecting periinterventional mortality. More patients in the radiochemotherapy group achieved R0 resection. However, no long-term differences were found between chemotherapy and radiochemotherapy in terms of progression-free and overall survival at 2, 4, and 6 years [17, 88].

Currently, the first data on the combination of neoadjuvant chemotherapy with an immune checkpoint inhibitor are available. In the CheckMate 816 trial, the combination of platinum-containing chemotherapy with nivolumab versus chemotherapy resulted in an increase in the rate of pathohistologic complete remission from 2.2 to 24.0%, prolongation of event-free survival (HR 0.63; p=0.005), and overall survival (HR 0.57; p=0.008) [38], but the data are immature. Nivolumab has not yet been approved in this indication. In the current evaluation, the positive effect in terms of event-free survival and overall survival is limited to stage IIIA patients and to patients with PD-L1 expression >1% on tumor cells. 83.2% of patients in the immunochemotherapy arm and 75.4% of patients in the chemotherapy arm underwent surgery with curative intent. An advantage of neoadjuvant therapy is that potentially all patients can be directed to such, ICI-containing therapy. Close monitoring is critical in order to identify non-responders in time and not to miss the window for curative surgery.

The basic prerequisite for interdisciplinary discussion and critical evaluation in the presence of thoracic surgeons should always be the likelihood of achieving complete tumor resection (R0) by surgery. If the risk of R1 or R2 resection is high, definitive simultaneous radiochemotherapy with ablative intensity should be chosen as the definitive local therapy for these patients (with the alternative of definitive or induction treatment).

6.1.4.2 Stage $IIIA_1$, $IIIA_2$, $IIIA_{3U}$

Patients in stages $IIIA_1$ and $IIIA_2$ are by definition diagnosed with stage N2 only during histological workup or intraoperatively; these patients entered surgery as N0 or N1. Adjuvant chemotherapy is indicated postoperatively in these patients. It resulted in 5% improvement in 5-year survival in meta-analysis of differently treated stage IIIA patients [26], and 14.7% improvement in long-term analysis of patients treated with cisplatin / vinorelbine adjuvant. Adjuvant chemotherapy is recommended after R0 resection. If PD-L1 expression is high and EGFR/ALK WT, adjuvant therapy with atezolizumab should follow [35, 124]. In patients with an *EGFR* common mutation (*del19, L858R*) adjuvant chemotherapy should be followed by osimertinib [130]. Based on the design of the pivotal trial, treatment with Osimertinib is recommended until relapse, inacceptable toxicity or over a period of 3 years. Recommendations for the implementation of adjuvant chemotherapy can be found in chapter 6.2.3.1. Critically, the comorbidity profile of the patients must be considered in any decision to use adjuvant chemotherapy.

If N2 involvement was confirmed intraoperatively by frozen section diagnosis ($IIIA_2$) and surgery was subsequently aborted without resection, the originally planned therapy regimen must be reevaluated. An interdisciplinary decision must be made whether, knowing the new findings, a protocol with induction chemotherapy followed by surgical resection or definitive radiochemotherapy should now be chosen.

Additional postoperative radiotherapy of the mediastinum after R0 resection is not generally recommended. In this setting, radiation has been shown reduced local recurrence risk but not prolong overall survival [62]. In the Lung Art study, 501 post-operative patients with N2 disease were included; 249 did not receive adjuvant radiotherapy, and 252 patients received postoperative radiotherapy (PORT). Neither the primary study endpoint of disease-free survival nor overall survival was improved by PORT. However, the PORT arm showed an increased risk of lethal cardiopulmonary toxicity and an increased number of second tumors. The evaluation must take into account that the rate of mediastinal recurrence was reduced by 50% in the PORT arm and that more precise irradiation methods are currently available. However, even these have not yet led to a prolongation of survival. This was confirmed by the randomized PORT-C trial conducted in China in stage pIIIA N2 patients who received predominantly intensity-modulated radiotherapy (IMRT). Here, too, postoperative radiotherapy after complete resection and adju-

vant chemotherapy did not prolong disease-free or overall survival in the overall evaluation [52].

In clinical practice, a pragmatic decision algorithm has proven to be effective, albeit without a hard evidence base. In the case of unilevel N2, PORT is usually not recommended; in the case of multilevel N2, postoperative radiotherapy is recommended, taking into account the individual risk profile and also in the case of capsular invasion with extranodal extension of lymph node metastases. The prerequisite is that a systematic lymph node dissection with radical clearance of the mediastinal compartments was performed. If this was not possible and tumor had to be left behind at one or more lymph node stations, this is to be considered locally as an R1 or R2 situation and taken into account accordingly for the further therapy decision.

After R1 resection - without the option of resection - radiotherapy may be indicated as primary adjuvant therapy. Additional decision factors for the interdisciplinary tumor conference are the local situation and the N-status.

6.1.4.3 Stage $IIIA_3$

The optimal therapeutic concept in these patients is still controversial. The decisive question is whether, for the individual tumour and patient, curative therapy is possible. A special situation arises for T3N2 tumors, which had been categorizied as Stage IIIA according to TNM7 and are now entirely categorized as stage IIIB following the recent TNM8 version. Presumably some of these T3N2 patients had been included in clinical trials with new drugs such as CheckMate 816. Therefore, we have included the subgroup also in this section. Especially relevant are tumors who fulfilled the T3 criterium on the basis of thoracic wall infiltration or a size between 5-7 cm.

The approach is determined pre-therapeutically in the context of interdisciplinary tumor conferences. Options are

- Primary surgery at unilevel-N2 ($IIIA_{3U}$), followed by adjuvant systemic therapy. Several recent studies highlight the association between extent of mediastinal lymph node involvement and prognosis with a favorable overall survival rate of ≥ 60% at 3 years after primary surgery and adjuvant CTx [18, 136]. Adjuvant concepts are the same as those described in chapter 6.1.4.2.
- Definitive, curatively intended, concurrent radiochemotherapy followed by durvalumab as consolidative immunotherapy in patients with PD-L1 positive tumors without disease progression. This definitive radiochemotherapy is considered the standard of care internationally. The value of consolidating chemotherapy after radiochemotherapy has not been established [37]. In a randomized trial in stage III patients with non-resectable lung cancer after definitive radiochemotherapy, consolidative immunotherapy with the anti-PD-L1 antibody durvalumab significantly prolonged progression-free survival (HR 0.52; median 11.2 months) and overall survival (HR 0.71; median 18.4 months) [3]. EMA approval is limited to patients with PD-L1 expression >1%; in Switzerland this limitation does not apply (see the currently valid marketing authorization information) . Retrospective data show worse efficacy of durvalumab in tumors with activating EGFR mutation [5]. Whether such patients should be treated with osimertinib instead of durvalumab is currently being investigated by the LAURA trial.
- Induction chemotherapy followed by surgery and/or radiation. Induction chemotherapy resulted in a 6-7% absolute increase in 5-year survival compared with surgery alone in a meta-analysis of 7 trials [13]. Another recent meta-analysis examined the different modalities in stage III [138]. 18 studies with a total of 13 different treatment strategies were included. Regarding the overall survival endpoint, induction chemotherapy followed by surgery and adjuvant chemotherapy or radiotherapy, if necessary, was slightly supe-

rior to the other treatment strategies (HR 1.14). Induction therapy followed by surgery and radiotherapy was superior to surgery alone with a HR of 0.38. In the CheckMate 816 trial, combining platinum-containing chemotherapy with nivolumab increased the rate of pathohistologic complete remission compared to chemotherapy alone, and prolonged event-free and overall survival in stage IIIA patients and those with PD-L1 expression >1% [38]. Nivolumab has not yet been approved in this indication.
Thus, induction chemotherapy, immunochemotherapy, or radiochemotherapy represent further options in stage IIIA, see Figure 4. Whether surgery, radiation, or combined induction chemotherapy or immunotherapy and radiotherapy is the best approach for optimal local tumor control has not been conclusively determined. The tumor board decision is largely determined by functional operability, general condition, existing comorbidities, and local expertise of the multimodality treatment team. If surgery is performed, it should preferentially be a lobectomy. Complex procedures such as pneumonectomy after induction therapy are associated with increased morbidity and mortality and require that the local multidisciplinary team has sufficient experience with such a procedure.

- Another alternative is trimodal therapy with consecutive use of induction chemotherapy followed by radiochemotherapy (concurrently) and then surgery [33].

6.1.4.4 Stage IIIA$_4$, Stage IIIB

For specific aspects of stage IIIB we also refer to chapter 6.1.4.3. Combined definitive radiochemotherapy followed by durvalumab as consolidative immunotherapy is recommended in patients with PD-L1 positive tumors without disease progression. In Switzerland, the limitation to PD-L1 positive tumors does not apply. RCT resulted in an 8% absolute increase in 2-year survival compared with radiotherapy alone in a meta-analysis of 9 trials. For radiochemotherapy, a simultaneous treatment schedule is superior to sequential application. In meta-analyses, simultaneous treatment increases 2-year survival by 10% and 5-year survival by 4.5% [79].

Chemotherapy during radiochemotherapy is platinum-based, see drug tumor therapy - protocols. Commonly used combinations are cisplatin / vinorelbine and cisplatin / etoposide. The decision should depend on the patients' general condition as well as the size of the radiotherapy target volume. In a recently published study in elderly Japanese patients (>70 years), combined radiochemotherapy with low-dose carboplatin resulted in prolonged survival [8]. However, these data contradict older, clearly negative study results on the use of carboplatin as a radiosensitizer [7]. Moreover, the Japanese study showed significant hematologic toxicity.

Definitive radiochemotherapy is followed by durvalumab as consolidative immunotherapy in patients without disease progression, without signs of pneumonitis, and with PD-L1 expression >1%, see chapter 6.1.4.3.

The inclusion of a surgical procedure in stage IIIA$_4$ and IIIB cannot be ruled out in principle and may be considered, especially in the case of a good response to induction therapy in young and fit patients, when R0 resection seems realistic [33].

In patients who cannot be treated locally curatively or whose tumors do not "fit into a radiation field", therapy is performed with non-curative intent.

6.1.4.5 Stage IIIC

Combined definitive radiochemotherapy is recommended, see chapter 6.1.4.4, followed by durvalumab as consolidative immunotherapy in patients without disease progression, without signs of pneumonitis and with PD-L1 expression >1%, see chapter 6.1.4.4.

Patients who cannot be treated locally with curative therapy or whose tumors cannot be irradiated within the limits of normal tissue tolerance are treated with non-curative intent.

6.1.5 Pancoast tumor

Pancoast tumors (synonym: superior sulcus tumor) are a distinct entity [96]. Characteristic symptoms result from the consequences of local growth, starting from the lung apex, with infiltration of neural (brachial plexus, stellate ganglion) or osseous structures (ribs, vertebral bodies). Optimal local imaging by thoracic MRI is crucial for therapy planning. It is the basis for assessing operability, especially the relationship to the brachial plexus, neuroforamina or vertebral bodies.

Prospective randomized trials of Pancoast tumor therapy are lacking. The best results are achieved by primary induction chemotherapy and radiotherapy, followed by surgery with curative intent. Prognosis is largely determined by initial lymph node status and achievement of R0 resection.

Radiotherapy is given with 40-50 Gy, conventionally dosed or hyperfractionated accelerated. Chemotherapy is given simultaneously, analogous to the use in stage III, see chapter 6.1.4. Close coordination between the conservative and surgical disciplines (thoracic surgery and, if necessary, neurosurgery) is crucial, especially on the question of operability after induction radiochemotherapy. In many patients a local surgical approach is not possible, these patients should receive maintenance therapy with durvalumab after radio-chemotherapy if PD-L1 expression is >1%.

Another alternative is trimodal therapy with consecutive use of induction chemotherapy or induction immunochemotherapy followed by radiochemotherapy (concurrently) and subsequent surgery [33]. Regarding a possible use of osimertinib in adjuvant therapy, we refer to chapter 6.1.3.

6.1.6 Stage IV

More than 50% of patients with non-small cell lung cancer are diagnosed in stage IV. In the majority of patients in this stage the therapeutic intent is not curative [42, 53, 76, 77, 120, 132]. Patients in the newly defined, so-called oligometastatic stage M1b, e.g., with solitary adrenal, CNS, lung, or bone metastases, in whom a potentially curative therapeutic approach may be considered, are an exception. However, they challenge the formal dichotomy of “curative” and “non-curative (paliiative)”.

6.1.6.1 Stage IV A with oligometastatic disease

The treatment of patients with oligometastatic disease (OMD) is also the subject of intense debate in NSCLC. The definition of OMD is already controversial [44, 64]. Here, we particularly point out the need for an individualized therapy recommendation based on an interdisciplinary tumor board.

Patients with limited organ metastasis can be offered a therapeutic concept with a potentially curative approach. The prerequisite for this is a locally curatively treatable disease, i.e. a local tumor extension up to $IIIA_3$ or $IIIA_4$. Background is among others a phase II study with 49 patients with up to 3 metastases (a positive N-status was counted as one localization) without progression after systemic induction therapy, who were randomized between local consolidative therapy and waiting or maintenance therapy. Here, progression-free survival (median 9.8 months, p=0.02) and overall survival (median 24.2 months; p=0.017) were found to be pro-

longed in the arm with the active approach, i.e. surgery or radiation [43]. Diagnosis in OMD should be performed with adequate imaging to exclude further metastases but also adequate diagnosis of mediastinal involvement, see Table 3. In case of isolated pulmonary (contralateral) metastasis, histological confirmation should be performed to exclude a second carcinoma,f supplemented by molecular genetic studies if necessary. In the situation of a synchronous second tumor or a solitary contralateral metastasis, a potentially curative approach as described above is also possible.

Patients should receive optimal local ablative therapy of the solitary metastases and optimal systemic therapy analogous to stage IV B in the course of the multimodal treatment protocol in addition to therapy of the primary tumor. This means

- Organ metastasis: surgery; alternatively: stereotactic radiotherapy
- CNS metastasis: surgery + tumor bed irradiation or isolated radiosurgery; whole-brain irradiation is not recommended in these patients because of long-term cognitive and neurological side effects [10].
- Primary tumor: see chapter 6.1.3. and chapter 6.1.4.

The new staging classification UICC8 classifies every solitary metastasis the same, i.e. not only a CNS or adrenal metastasis, but a solitary metastasis of all organs is classified as Oligometastastic Disease (OMD).

The application of the most effective systemic therapy in this treatment concept seems to be a prerequisite for long-term remission, but it is not evidence-based for the different initial situations. This includes the use of immune checkpoint inhibitors or targeted therapy approaches when predictive genetic aberrations or other biomarkers are present. However, confirmatory data on optimal sequencing are also lacking.

Application of systemic therapy prior to surgery/local therapy of the lung tumor is recommended for evaluation of the response of the primary tumor, for more favorable compliance with systemic therapy, and to create a bridging window of time between surgical/local therapy measures. During this time interval, it is also possible to check whether the patients develop new metastases in the short term. This limits definitive ablative local therapy (primary tumor and metastasis) to those patients who also have a longer-term survival prognosis. Favorable results are known from cisplatin/taxane combinations such as cisplatin/paclitaxel or cisplatin/docetaxel analogous to stage III [33]. The role of immunotherapies and molecularly targeted therapies in the context of curatively intended approaches in OMD is currently being investigated in clinical trials. Since these patients are in Stage IVA or IVB, the approved drugs for immunochemotherapy can be used, if no contraindications apply.

6.1.6.2 Stage IV B with multiple metastases

In these patients the therapeutic goal is not curative [42, 53, 76, 77, 120, 132]. The therapy includes the treatment of physical and psychological complaints. It is carried out in an interdisciplinary manner. Diagnosis is symptom- and therapy-oriented, see Table 2. The median survival time was between 8 and 12 months just a few years ago. In patients with activating exon 19 or exon 21 and some of the so-called "uncommon" EGFR mutations or with ALK, ROS1 and BRAF V600 alterations under targeted therapy, it is significantly longer. With EGFR mutations, ALK or ROS1 translocations, median survival times are in the range of several years. Comutations may also be prognostically and predictively relevant.

For many years, systemic therapy in patients with non-small cell lung cancer was based solely on clinical criteria such as comorbidity and general condition. Current recommendations are

based on predictive histologic, immunohistochemical, and genetic markers. Algorithm for systemic therapy are shown in Figure 5, Figure 6 and Figure 7.

Figure 5: Algorithm for drug therapy in advanced stages - overview.

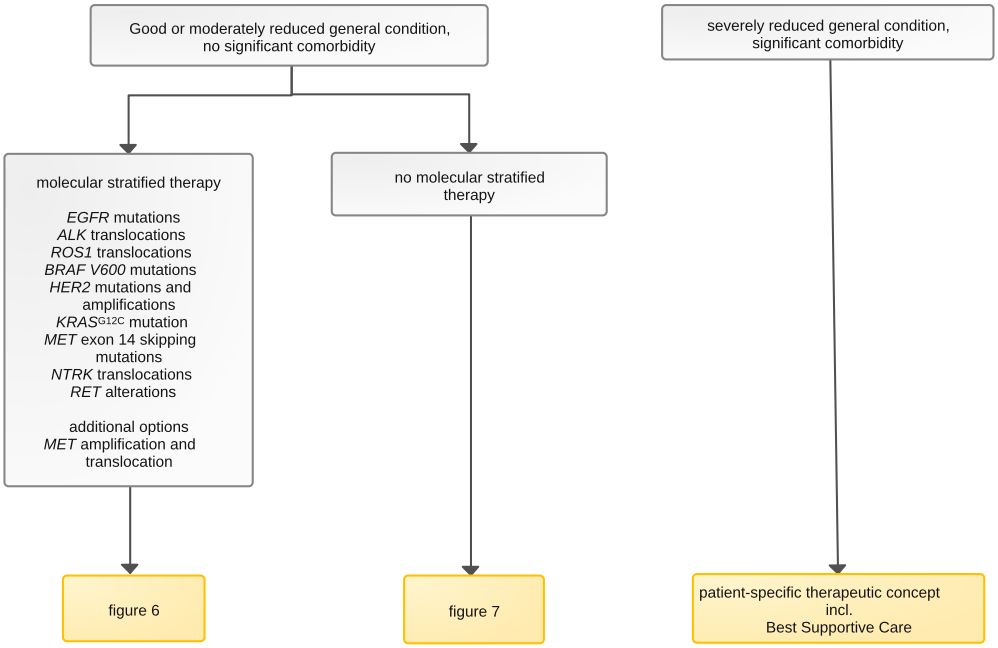
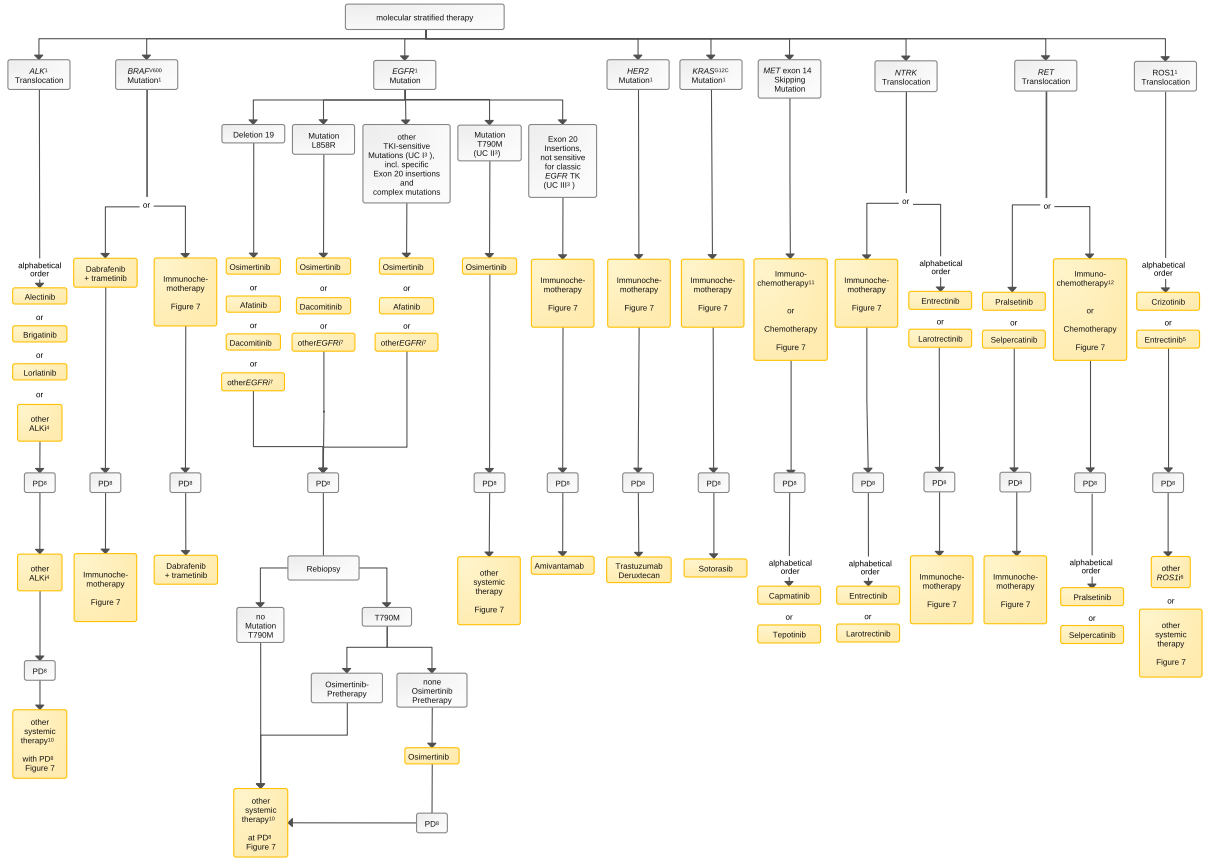


Figure 6: Algorithm for molecular stratified therapy in advanced stages



Legend:

[1] ALK - anaplastic lymphoma kinase; ROS1 - tyrosine protein kinase ROS; EGFR - epidermal growth factor receptor gene; BRAF V600 - in majority V600E, but also other activating V600 mutations; NTRK alterations - gene fusions involving NTRK genes (NTRK1, NTRK2, NTRK3); RET alterations - gene fusions involving RET; additional alterations: e.g. HER2 amplifications and mutations, KRAS G12C mutations, c-MET exon alterations - c-MET 14 skipping mutation or MET amplification;

[2] see current applicable regulatory information;

[3] UC - uncommon mutations, UC I - EGFR TKI-sensitive point mutations or duplications in exons 18-21, specific EGFR TKI-sensitive exon 20 insertions, and double mutations with typical EGFR mutations or TKI-sensitive uncommon mutations ; UCII - mutation T790M in exon 20 alone or in combination with other mutations; UC III - non-EGFR TKI-sensitive exon 20 insertions;

[4] ALKi - ALK inhibitor: Alectinib, brigatinib, ceritinib, crizotinib, lorlatinib, see current applicable regulatory information;

[5] primarily for CNS metastases;

[6] ROSi - ROS1 inhibitor: crizotinib, entrectinib;

[7] EGFR-TKI - afatinib, dacomitinib, erlotinib in combination with bevacizumab resp. ramucirumab, osimertinib;

[8] CR - complete remission, PR - partial remission, SD - stable disease, PD - progressive disease;

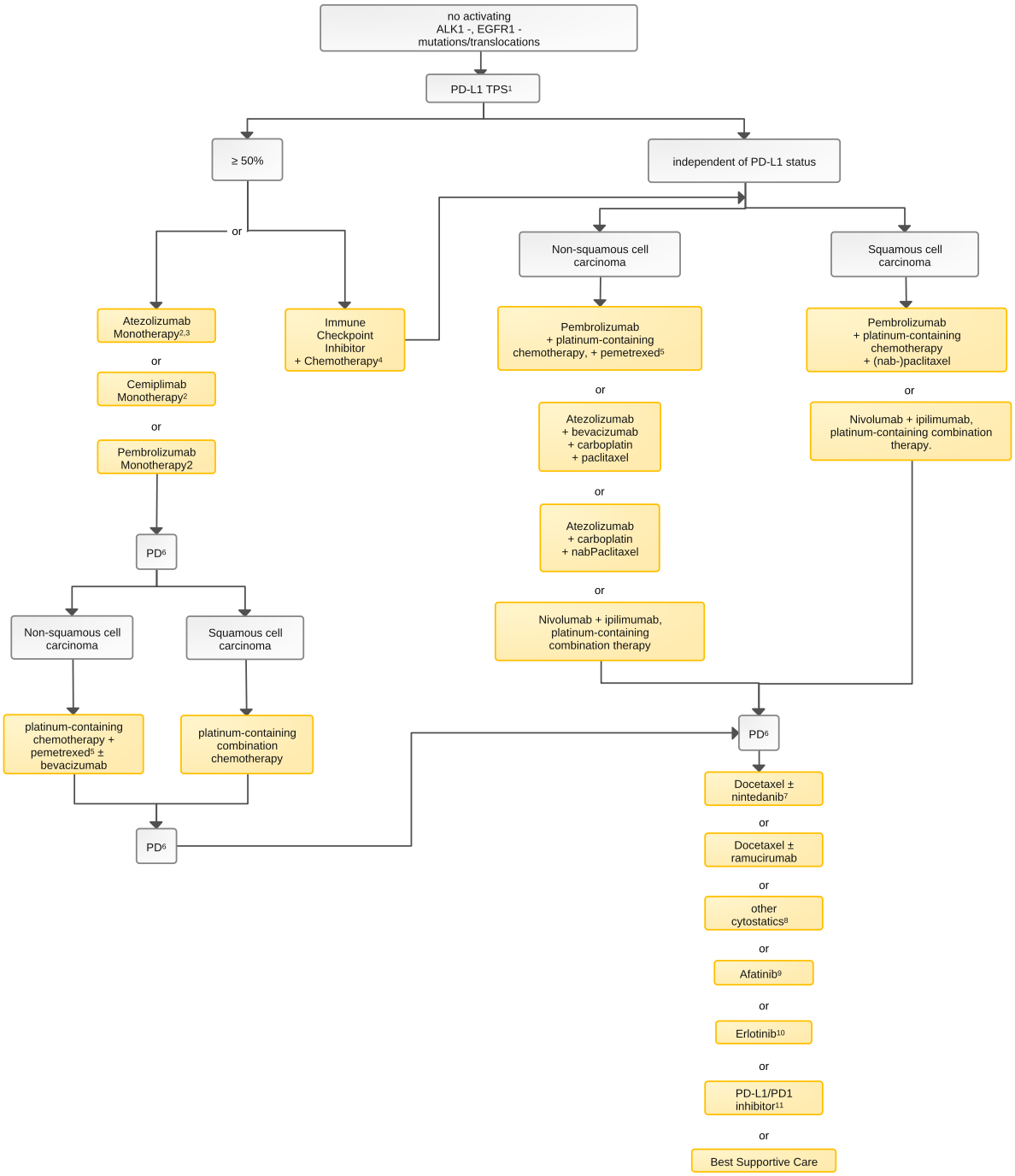
[9] BRAFi - BRAF inhibitor, NTRKi - NTRK inhibitor, RETi - RET inhibitor;

[10] in the pivotal IMpower 150 trial of carboplatin/paclitaxel/bevacizumab/atezolizumab, patients with ALK and EGFR mutations included;

[11] it is not certain whether chemotherapy or immunochemotherapy is the better option in first-line therapy, see chapter 6.1.6.2.6;

[12] it is not certain whether chemotherapy or immunochemotherapy is the better option in first-line therapy, see chapter 6.1.6.2.8;

Figure 7: Algorithm for non-molecular stratified drug therapy in advanced stages



Legend:

1 PD-L1 TPS - expression of PD-L1 on tumor cells quantified according to the Tumor Progression Score (TPS);
2 if suitable for immunotherapy and no relevant contraindications exist; see also the currently valid regulatory information;
3 alternatively IC>10%;
4 from an anti-PD1/-PD-L1 antibody and chemotherapy, differentiated by histology;
5 TTF1 negativity is a negative predictor of pemetrexed efficacy;
6 PD - progressive disease;
7 Nintedanib only in adenocarcinoma;
8 3rd generation cytostatic. Generation: gemcitabine, pemetrexed, vinorelbine; pemetrexed only in non-squamous cell carcinoma;
9 afatinib only in squamous cell carcinoma;
10 the indication was removed by the FDA in 2016;
11 PD-1/PD-L1 inhibitor: atezolizumab (independent of PD-L1 expression), nivolumab (independent of PD-L1 expression), pembrolizumab (only in TPS >1%); evidence of efficacy is not established in patients, who have been pre-treated with an immune checkpoint inhibitor in first-line therapy;

The decision to offer systemic therapy is based on general condition, prior treatment, symptomatology, specific comorbidity, and patient preference; agent selection is determined by tumor histologic classification, molecular pathologic alterations (molecular stratified therapy), and degree of PD-L1 expression on tumor cells and immune cells. The lack of expression of TTF1 is a negative predictive factor, and in a retrospective analysis also a negative predictive factor for pemetrexed. For this reason, pemetrexed-free regimens should be considered in this situation [39]. Knowledge of therapeutic options allows for optimal management.

6.1.6.2.1 ALK translocations

In 4-5% of all patients with non-small cell lung cancer, a rearrangement (gene translocation or inversion) involving the ALK gene is detectable in the tumor cells. The most frequent translocation partner is EML4. This acquired genetic alteration leads to overexpression of ALK (anaplastic lymphoma kinase). ALK is a tyrosine kinase that is not active in normal lung tissue. Constant ALK activation can lead to uncontrolled cell division involving complex signal transduction pathways. Detection of ALK translocations is associated with non-smoking, adenocarcinoma, younger age, and lack of detection of other targetable markers.

ALK translocated NSCLC may present with a thrombotic diathesis of unclear etiology, which should be detected and treated early [141], and is likely to be improved by effective therapy of the underlying NSCLC.

6.1.6.2.1.1 First-line therapy for ALK translocations

There are 5 approved tyrosine kinase inhibitors available for first-line therapy of patients with activating ALK translocations. The use of a second- or third-generation TKI in first-line therapy is recommended, see Figure 6. Regarding the choice of TKI, toxicity, PFS and CNS activity should be considered. Results of direct comparisons of second- and third-generation TKIs are not yet available. Meta-analyses provide evidence for different efficacy, especially also in CNS metastases, and for differences in the spectrum of side effects [86]. Options for first-line therapy are (alphabetical order):

- Alectinib resulted in prolonged progression-free survival (hazard ratio 0.50) in a head-to-head comparison with crizotinib, also with a significant reduction in the incidence of CNS metastases [73]. Survival is significantly prolonged compared to crizotinib arm (HR 0.67, 95% CI 0.46-0.98, p=0.0376) in however not yet final data, see also drug alectinib.
- Brigatinib significantly increased remission rates and significantly prolonged progression-free survival with a hazard ratio of 0.48 in the ALTA-L1 trial compared with crizotinib [74, 75]. Brigatinib did not significantly prolong overall survival in the overall population with data, however, not yet final, see Drug Brigatinib.
- Lorlatinib was evaluated in the CROWN phase III trial versus crizotinib in the first-line setting and was significantly superior in terms of progression-free survival (HR 0.28). In terms of CNS progression, lorlatinib had an HR of 0.07 (p<0.001) [104]. Lorlatinib did not significantly prolong overall survival in the overall population, albeit with relatively short follow-up.

Also approved are (alphabetical order):

- Ceritinib versus platinum-based chemotherapy resulted in an increase in remission rate and prolongation of progression-free survival (HR 0.55; median 8 months) [114]. The impact of ceritinib on overall survival prolongation is not statistically significant (p=0.056), however, the data are influenced by a high crossover rate, see Drug Product Ceritinib.

- Crizotinib significantly prolonged progression-free survival (HR 0.45; median 3.9 months), increased remission rates, reduced disease-associated symptoms, improved quality of life, and reduced side effects compared with platinum- and pemetrexed-containing chemotherapy [114]. Overall survival is not prolonged, but data are affected by a high crossover rate, see Drug Crizotinib.

6.1.6.2.1.2 Second- and third-line therapy

The choice of second-line therapy is dependent on first-line therapy and is also influenced by the detection of secondary resistance mutations in the ALK gene. In cases of progression on an ALK inhibitor, the mechanism of resistance can be investigated by liquid biopsy or tissue biopsy, if feasible with acceptable morbidity. If the liquid biopsy is negative, tissue biopsy should be performed. Tissue rebiopsy should be performed on a manifestation that is progressive and clinically relevant. Data and recommendations for systemic therapy in the second-line setting are (alphabetical order):

- Alectinib resulted in prolonged progression-free survival, increased remission rates, and decreased rates of serious adverse events after pretreatment with crizotinib versus docetaxel or pemetrexed [133]. Alectinib has high efficacy in CNS metastases. Overall survival is not prolonged, but data are affected by a high crossover rate, see Drug product alectinib.
- Brigatinib resulted in a response rate of 54%, progression-free survival of 16.7 months, and median overall survival of 34.1 months after pretreatment with crizotinib at the approved dose of 180 mg, also with high CNS efficacy [57]. Brigatinib has not been studied in head-to-head comparison with alectinib or ceritinib, see drug brigatinib, see current valid regulatory information.
- Lorlatinib resulted in a response rate of 42.9%, and a median progression-free survival of 5.5 months in a phase I/II trial after pretreatment with an ALK TKI; after pretreatment with at least 2 ALK TKIs, it resulted in a response rate of 39.6% and a median progression-free survival of 9.9 months [113]. Lorlatinib is approved for therapy after first-line pretreatment with alectinib or ceritinib, or after first-line crizotinib and at least one other ALK inhibitor in the second line, see the currently valid regulatory information. Lorlatinib has high efficacy in the ALK-G1202R mutation compared with the other approved ALK-TKIs.

Also approved are (alphabetical order):

- Ceritinib resulted in increased remission rate, prolonged progression-free survival, and improved clinical symptoms after pretreatment with crizotinib versus docetaxel or pemetrexed [106]. There was no difference in overall survival compared with chemotherapy, Overall survival was not prolonged, but the data were influenced by a high crossover rate, see Drug product ceritinib.
- Crizotinib was studied in the second-line setting only after prior therapy with platinum-containing chemotherapy. Compared with docetaxel or pemetrexed, crizotinib resulted in prolonged progression-free survival, an increase in remission rate, relief of disease-associated symptoms, and fewer side effects [105]. There was no difference in overall survival compared with chemotherapy; this endpoint had limited evaluability because of a high crossover rate; see Drug Crizotinib.

Special attention should be paid to CNS metastases in ALK+ lung carcinomas. Diagnostic imaging by MRI is indicated if clinical symptoms are present. A structured imaging examination, e.g. every 3-6 months, should also be offered to asymptomatic patients.

Further therapies are based on the recommendations for patients without molecular stratification features, see Figure 7, chapter 6.1.6.2.4. and chapter 6.1.6.2.5.

6.1.6.2.2 BRAF V600 mutations

BRAF mutations are detected in 1-2% of all patients with non-small cell lung cancer. About half of these are V600 mutations, the vast majority of which are V600E, rarely V600G. In previously untreated patients the BRAF inhibitor dabrafenib resulted in a remission rate of 64% and a median overall survival of 24.6 months in a single-arm phase II study in combination with the MEK inhibitor trametinib [87], see Drug Dabrafenib and Drug Trametinib. In patients pretreated with chemotherapy, the remission rate was 63%. In indirect comparison, the rate of severe adverse events is lower than with chemotherapy. Data from randomized trials are not available. Dabrafenib/trametinib can be used in first- or second-line therapy for BRAFV600 mutations. For other point mutations outside the V600 position, the situation is complex because kinase-inactivating mutations also occur. In this case, a molecular tumor board should be consulted [68]. Direct comparisons versus immunochemotherapy are not available. Tumors with BRAF V600E may respond to immunotherapy [69], so chemo-immunotherapy is also a reasonable option.

6.1.6.2.3 EGFR mutations

For the therapy of patients with activating EGFR mutations, data on first-generation (erlotinib, gefitinib), second-generation (afatinib, dacomitinib) and third-generation (osimertinib) tyrosine kinase inhibitors are available, see the currently valid regulatory information. The TKI itself and the type of mutation are critical to efficacy. TKIs are more effective than platinum-containing chemotherapy and are associated with fewer side effects. Combinations with angiogenesis inhibitors also have efficacy in the advanced stages.

Here, the results of systemic therapy in the different activating mutations are presented. In the relevant pivotal studies, patients with the so-called classical mutations del19 and L858R were grouped together, and the studies were not designed to demonstrate differences in the subgroups.

6.1.6.2.3.1 Exon 19 deletion (del19)

Exon 19 deletions represent the most common activating EGFR aberration. Patients with del19 have the longest remission duration and survival. Afatinib significantly prolonged survival compared with platinum-containing chemotherapy in the pivotal trial (hazard ratio 0.55; median 12 months). In subgroup analysis of a randomized phase II trial comparing afatinib versus gefitinib, progression-free survival was significantly prolonged (hazard ratio 0.73; median 0.1 month). Overall survival and rates of treatment discontinuation were not significantly different; see Drug Afatinib.

In the randomized FLAURA trial, osimertinib significantly prolonged progression-free survival (hazard ratio 0.46; 18.9 vs 10.2 months) and overall survival (38.6 vs 31.8 months; HR 0.80; p = 0.046) in first-line therapy compared with erlotinib or gefitinib. The survival benefit for patients with del19 was particularly pronounced with HR 0.68. Also, the benefit was higher in the Caucasian population than in the Asian population. Follow-up of patients in the control arm of the study was similar to European standards in terms of T790M testing rates and availability of osimertinib in the presence of T790M [90].

In the ARCHER 1050 randomized trial in patients with del19 or L858R, first-line dacomitinib versus gefitinib resulted in prolonged progression-free survival (hazard ratio 0.59; median 5.5 months) and overall survival (hazard ratio 0.76, median 7.3 months) [129]. Patients with brain metastases were excluded. The difference in survival in the subgroup of patients with del 19

was not significant (HR 0.847; p = 0.3021), see drug dacomitinib. Data comparing dacomitinib versus osimertinib or afatinib are not available.

In cases of progression on TKIs and suspected resistance, the mechanism of resistance should be comprehensively investigated by tissue rebiopsy or liquid biopsy (e.g., panel diagnostics), particularly with the question of an EGFR T790M resistance mutation or other targetable alteration after treatment with a first- or second-generation TKI, see chapter 6.1.6.2.3.3. Tissue rebiopsy should be performed on a progressive manifestation.

One of the most common resistance mutations under osimertinib is c-MET amplification, therefore the addition of a MET inhibitor might be of perspective benefit, see chapter 6.1.6.2.6.

6.1.6.2.3.2 L858R mutation

L858R mutation in exon 21 is the second most common activating EGFR aberration. In patients with mutation L858R, TKIs result in remission rates of 40-70% and significant prolongation of progression-free survival compared to platinum-containing chemotherapy. Afatinib did not prolong overall survival compared with chemotherapy in this subgroup of the pivotal trial.

In the randomized FLAURA trial, osimertinib versus erlotinib or gefitinib resulted in a significant prolongation of progression-free survival (hazard ratio 0.51; median 4.9 months) and a lower rate of CNS progression (6 vs 15%), see the currently applicable regulatory information. Overall survival was also prolonged in the overall group, but the difference was not detectable in the L858R subgroup (HR 1.00).Follow-up therapies in the control arm of the study were similar to European standards in terms of T790M testing rates and availability of osimertinib in the presence of T790M [90].

In the ARCHER 1050 randomized trial in patients with del19 or L858R, first-line dacomitinib versus gefitinib resulted in prolonged progression-free survival (hazard ratio 0.59; median 5.5 months) and overall survival (hazard ratio 0.76, median 7.3 months) [129]. Patients with brain metastases were excluded. The difference in survival in the subgroup of patients with L858R mutation was statistically significant (HR 0.665; p = 0.0203). Data for direct comparison versus osimertinib or afatinib are not available.

In cases of progression on TKIs and suspected resistance, the mechanism of resistance should be comprehensively investigated by tissue rebiopsy or liquid biopsy (e.g., panel diagnostics), especially with the question of EGFR T790M resistance mutation after treatment with a first- or second-generation TKI, see chapter 6.1.6.2.6. Tissue rebiopsy should be performed on a progressive manifestation.

6.1.6.2.3.3 Atypical/Uncommon Mutations (UC)

In patients with other genetic EGFR aberrations, so-called Uncommon Mutations (UC), a distinction is made between TKI-sensitive and -resistant mutations. Uncommon mutations account for 30% of EGFR mutations [93]. As these are heterogeneous and often include complex aberrations with multiple mutations, case-by-case decisions are required regarding their activating function [55]. The EMA's formulation for approved EGFR TKIs is "activating EGFR mutations." These case-by-case decisions should be made in interdisciplinary molecular tumor boards. A retrospective evaluation of the clinical response of atypical EGFR mutations and the classification based on this with regard to their TKI sensitivity can be found [55].

6.1.6.2.3.3.1 TKI-sensitive atypical EGFR mutations (UC I)

Atypical EGFR mutations can also be responsive to TKIs. In general, UC1 mutations are numerically less responsive than classical EGFR mutations [55]. Data from randomized clinical trials are not available.

TKI-sensitive EGFR mutations include:

- Complex mutations containing a classic (exon19 Del or L858R) EGFR mutation.
- G719X, L861Q, and S768I mutation alone or complexed with atypical EGFR mutations
- Exon 19 insertion mutations
- Specific exon 20 insertion mutations (e.g., Y763_V764insFQEV, H773_V774ins) [55].
- Specific, very rare point mutations [55].

The most data for uncommon mutations are for afatinib and osimertinib [19, 55, 134]. In the EU, "activating" mutations are broadly covered by the approval of the two TKIs. In the US and Switzerland, separate approvals exist for afatinib in G719X, L861Q, and S768I mutations.

6.1.6.2.3.3.2 T790M Mutation (UC II)

The T790M mutation in EGFR exon 20 is detectable in only 0-3% of patients with EGFR mutations prior to therapy with EGFR TKIs [134, 135], often in combination with other EGFR mutations. It occurs much more frequently in resistance under first- or second-generation EGFR TKI therapy (approximately 60%). Therefore, rebiopsy or liquid biopsy is recommended in case of progression. If the liquid biopsy is negative, a tissue biopsy should be performed. If a T790M mutation is detected, treatment with osimertinib is recommended. Remission rates are 65-70% and progression-free survival is 9 to 11 months. In case of non-response or progression under third-generation EGFR TKIs or progression under osimertinib in first-line therapy and exclusion of targetable resistance mechanisms, platinum-based chemotherapy is the therapy of choice. Data are available on paclitaxel, carboplatin in combination with bevacizumab, and atezolizumab [112].

6.1.6.2.3.3.3 Exon 20 insertions (UC III)

This group was previously referred to as "TKI resistant", but this only referred to the first TKIs used here, which were developed for classic EGFR mutations. Exon 20 insertions are found in up to 12% of all patients with EGFR mutations. The collective is heterogeneous, with over 60 different mutations detected to date, some of which are internal duplications. Response rates to first- and second-generation TKIs are less than 15% in the overall group, and median progression-free survival is 2-3 months [97]. One exception is the EGFR-A763_Y764insFQEA mutation, among others. It occurs at a frequency of 5-6% of exon 20 insertion mutations and shows a comparable clinical response to the classic TKI-sensitive mutations [123].

In patients with exon 20 insertions other than specific EGFR TKI-sensitive mutations of the UC I group (see chapter 6. 1. 6. 2. 3. 3. 1.), initial administration of classical EGFR TKIs is not indicated.

A newly approved drug for patients with evidence of an EGFR exon 20 insertion mutation is the bispecific antibody amivantamab. Amivantamab inhibits the EGF and MET receptors and activates the immune system. After failure of platinum-containing chemotherapy, amivantamab induced remission in 38.8% of patients in the non-randomized CHRYSALIS trial. Median progression-free survival was 6.7 months, and median overall survival was 22.8 months [81]. Indirect comparison with German registry data more than doubled overall survival, also confirmed by international real-world data [72]. In August 2022 the pharmaceutical company withdrew amivantamab from the German market for commercial reasons. Start of a new treatment with amivantamab is now an off label use. If further study inclusion is not possible after failure of amivantamab, systemic therapy as in wild-type patients is recommended, see chapter chapter 6.1.6.2.4.

Exon20 insertion-specific EGFR TKIs are currently in clinical development. These include mobocertinib. This oral kinase inhibitor is already approved in the USA and Switzerland for platinum-containing chemotherapy failure. Approval was based on data from a non-randomized phase I/II trial in 114 patients after platinum-containing prior therapy. The remission rate was 28%, median PFS was 7.3 months, and median overall survival was 24.5 months [140].

6.1.6.2.3.3.4 other EGFR mutations (UC IV)

The group of UC IV mutations includes all other rare EGFR mutations, especially very rare (ultrarare) point mutations of exons 18-21 of EGFR. In the overall group of very rare EGFR mutations, a retrospective analysis showed a PFS and OS benefit of EGFR TKIs over chemotherapy over chemotherapy (n=82 patients) [55]. Due to their rarity, the majority of single mutations occurred only once in the studied collective, which is why decision making for this group in particular should be made in molecular tumor boards.

6.1.6.2.4 HER2 amplifications and mutations

HER2 (Human Epidermal Receptor 2) is mutated in 1-4% of NSCLC and overexpressed in 30%. Underlying genetic aberrations include mutations and amplifications, or overexpression of the protein. Retrospective data suggest the efficacy of chemo-immunotherapy in this patient population [98].

Strategies for targeted therapy include monotherapy with trastuzumab, combination chemotherapy with trastuzumab, double antibody blockade with trastuzumab/pertuzumab, and use of the antibody conjugates trastuzumab emtansine and trastuzumab deruxtecan [70]. When refractory to standard therapy, therapy with trastuzumab deruxtecan resulted in a remission rate of 55%, a median progression-free survival of 8.2 months, and a median overall survival of 17.8 months in a phase II study of 91 patients [65]. A particular side effect is interstitial lung disease; it occurred in 26% of patients.

Trastuzumab deruxtecan is not approved in this indication for the EU, nor are other targeted anti-HER2 drugs.

6.1.6.2.5 KRAS mutations

Oncogenic KRAS mutations occur in approximately 30% of cases in NSCLC, especially in adenocarcinomas, depending also on ethnicity and smoking status. The most common, oncogenic KRAS variants in NSCLC are: G12C ~53%, G12V ~27%, G12D~6%, G12A ~6%, G12S ~4%, others ~4%. In the phase II CodeBreak 100 trial, 124 patients with second-line KRASG12C mutations were given sotorasib 960 mg/day after platinum-containing chemotherapy or immunochemotherapy. The response rate was 37.1% and median progression-free survival (PFS) was 6.3 months. The 2-year survival rate was 32.5% [30, 111]. Sotorasib is approved for KRASG12C-mutated NSCLC patients after failure of standard first line therapy, see Drug Product Sotorasib. There are no approvals for the other mutated KRAS alleles.

In a recent analysis of the randomized phase III CodeBreak 200 trial comparing sotorasib vs docetaxel in patients with KRASG12C-mutated NSCLC patients sotorasib led to prolongation of progression-free survival (median 1.1 months; HR 0.66; p=0.002), but not in overall survival. Comparison of toxicity showed advantages for sotorasib in alopecia, anemia, fatigue and stomatitis, disadvantages for diarrhea and elevated transaminases [56].

Other, KRASG12C-specific TKIs are in clinical development. This includes also combination therapies.

6.1.6.2.6 c-MET alterations

Deregulation of c-MET is a common phenomenon in non-small cell lung cancer and is associated with an unfavorable prognosis. Causes may include MET amplification (frequency 1-6%), the MET exon 14 skipping mutations (frequency 3-4%), and, although very rare, MET fusions (frequency < 1%). These aberrations are found in both adenocarcinomas and squamous cell carcinomas. Two specific MET inhibitors, capmatinib and tepotinib, are newly approved; see Drug Approval.

Tepotinib resulted in a response rate of 42-45%, a median progression-free survival of 7.6-7.9 months, and a median overall survival of 13.1 months in 142 patients with METex14 NSCLC and 1-2 pretreatments, as well as relief of disease-associated symptoms (cough, chest pain) [80].

For capmatinib, the response rate of non-pretreated patients was 68%, median PFS was 12.5 months and median OS was 25.5 months; for pretreated patients response rate was 44%, with a median PFS of 5.5 months [50, 128]. In the capmatinib trial, MET amplified patients were also studied. Here, therapeutic activity was found only at a copy number (GCN; gene copy number) of ≥10. The results were: non-pretreated patients with a response rate of 40%, a median PFS of 4.2 months; pretreated patients with a response rate of 29%, a median PFS of 4.1 months a median OS of 13.6 months [127]. Capmatinib and tepotinib are not approved in c-MET-amplified patients.

Both agents have shown efficacy in CNS metastases. Data on direct comparison versus immunochemotherapy are not yet available.

Retrospective analyses debate whether chemotherapy or immunochemotherapy is the better option in first-line therapy of patients with c-MET alterations when molecularly targeted therapy is not used [61]. Data from prospective studies are lacking.

6.1.6.2.7 NTRK translocations

Gene fusions involving the NTRK genes (NTRK1, NTRK2, NTRK3) have been identified as a very rare subset in a variety of malignant tumors, including NSCLC with an incidence of 0.1 to 0.3%. Targeted drugs are larotrectinib and entrectinib. In a phase I/II trial of larotrectinib, 5 of 7 patients responded [27], and 7 of 10 patients responded to entrectinib [25]. Remissions are sustained. Larotrectinib has been approved by the EMA since September 2019 and entrectinib since 2020 for NTKR fusion gene-positive tumors when no satisfactory alternative therapy is available, see the currently valid marketing authorization information. Chemotherapy is also an option; the role of immunotherapy is unclear.

6.1.6.2.8 RET translocations

The RET gene encodes a receptor tyrosine kinase that is active in different cells. RET can fuse with different genes in NSCLC. The most common fusion partner is KIF5B, and other genes include CCDC6, NCOA, TRIM33, CUX1, KIAA1217, FRMD4A, and KIAA1468. The specific fusion partner may play a role in the prognosis of the disease and in the effectiveness of therapy. RET gene rearrangements are detected in 1-2% of NSCLC patients. They are associated with adenocarcinomas, younger age, and nonsmoking history. RET gene rearrangements rarely occur with other driver mutations.

Selpercatinib and pralsetinib, two highly effective, specific RET inhibitors in advanced NSCLC from first-line, are approved for use in the EU; for divergent approvals in respective countries. Pralsetinib resulted in a remission rate of 70% in 27 non-pretreated patients and a remission duration of >6 months in 80%. In 87 cisplatin-pretreated patients, the remission rate was 57% [40, 51]. In 69 patients without systemic pretreatment, selpercatinib achieved a response rate of 84%, mostly partial remissions. The median progression-free survival was 22 months, the overall survival rate after 2 years was 70% [28].

Retrospective analyses debate whether chemotherapy or immunochemotherapy is the better option in first-line therapy of patients with RET translocations when molecularly targeted therapy is not used [46]. Data from prospective studies are lacking.

Some of the multikinase inhibitors approved for other tumor entities are also effective in patients with RET gene alterations. Their use may be considered after failure of pralsetinib or selpercatinib. These include cabozantinib, vandetanib, lenvatinib, and sunitinib.

6.1.6.2.9 ROS1 translocations

In 1-2% of all patients with non-small cell lung cancer (NSCLC), a rearrangement involving the ROS1 gene is genetically detectable in tumor cells. At least 10 ROS1 fusion variants are clinically relevant. They lead to overexpression of ROS1 (proto-oncogene tyrosine-protein kinase). CD74-ROS1 gene fusions are most common in NSCLC. ROS1 translocations are associated with non-smoking status, adenocarcinoma, and younger age. ROS1 translocations define a distinct genetic subtype but may co-occur with other oncogenic aberrations.

ROS1-translocated NSCLC have increased thrombotic-embolic events compared with other NSCLC subgroups, which should be detected and treated early [141], and is likely to improve during effective therapy of the underlying NSCLC.

In patients with the rare activating ROS1 translocations, crizotinib and entrectinib are approved in first-line therapy:

- Crizotinib resulted in a 72% remission rate and a median progression-free survival of 19.3 months in the Profile 1001 trial of 53 patients [107]. Another study in East Asian patients showed a remission rate of 71.7% and a median PFS of 15.9 months. The EUCROSS study showed a remission rate of 69% and a median PFS of 20 months [71].
- Entrectinib showed a median PFÜ of 16.8 months in ROS1-positive NSCLC, similar efficacy to crizotinib in an indirect comparison. There are also CNS response data for entrectinib, with a remission rate of 79.2%. The median PFS of patients with CNS metastases was 11.9 months, and 28.3 months without CNS metastases [29].

Thus, crizotinib and entrectinib are alternatives in first-line treatment. Crizotinib shows better tolerability, while entrectinib is favored for its better CNS efficacy, especially in the presence of pre-existing CNS metastases.

After failure of first-line therapy, rebiopsy should be sought. If no G2032R mutation is found in the ROS1 gene or if rebiopsy is not possible, lorlatinib is the therapy of choice, especially in the presence of CNS metastases [108]. Lorlatinib is not approved in this indication.

Other agents that are effective but not approved in this indication are ceritinib and cabozantinib, the latter agent also effective in the G2032R mutation. In clinical development is repotrectinib, a TKI also effective in G2032R with good CNS efficacy.

After failure of targeted therapies, platinum- and pemetrexed-containing chemotherapy or a regimen as in nontargeted NSCLC is recommended, see chapter 6.1.6.2.11.

6.1.6.2.10 Additional predictive genetic markers for targeted therapy

In NSCLC, numerous other genetic aberrations can be detected. Here, options for targeted therapies often exist. Effective inhibitors are available in trials. Due to the rarity of the aberrations, data are often only available from phase I/II trials, alone or as part of basket studies. Randomized trials comparing these targeted drugs versus modern chemotherapy or immunotherapy are lacking, including the positioning of targeted drugs in first- or second-line therapy.

6.1.6.2.11 Non-small cell lung cancer without activating EGFR, ROS1 or ALK aberrations

The previous predictive importance of histological classification has been increasingly superseded by biological parameters. The histological classification into adenocarcinoma, squamous cell carcinoma or non- squamous cell carcinoma is relevant if this classification was the basis of registration studies.

6.1.6.2.11.1 First-line therapy for NSCLC without activating EGFR-, ROS1-, or ALK aberrations

In patients without genetic aberrations for whom targeted drugs are approved, the following recommendations apply:

- Expression of the immune marker PD-L1 on >50% of tumor cells.
    - Monotherapy with the anti-PD1 antibody pembrolizumab versus platinum-containing chemotherapy resulted in prolonged overall survival (hazard ratio 0.62; 26.3 vs 13.4 months), prolonged progression-free survival (HR 0.50; median 4.3 months), and reduced rates of serious adverse events; see Drug Pembrolizumab [92]. These data are supported by the results of the KEYNOTE-042 trial. Data from a direct comparison of pembrolizumab monotherapy versus pembrolizumab + combination chemotherapy are not yet available.
    - Monotherapy with the anti-PDL1 antibody atezolizumab was tested in patients with PD-L1 on ≥50% of tumor cells or a rate of PD-L1 positive tumor-infiltrating immune cells (IC) of ≥10%. Compared with platinum-containing chemotherapy, atezolizumab prolonged overall survival (HR 0.59; 20.2 vs 13.1 months), and progression-free survival (HR 0.63; median 3.1 months), and reduced the rate of serious adverse events (52.5 vs 30.1%) [47].
    - Monotherapy with the anti-PDL1 antibody cemiplimab resulted in prolongation of overall survival (HR 0.57; median not reached vs 14 months), prolongation of progression-free survival (HR 0.63; median plus 2.5 months), and in the overall study, a reduction in the rate of serious adverse events (28 vs 39%) in patients with PD-L1 expression >50% vs platinum-containing chemotherapy [103].
    - The combination of an immune checkpoint inhibitor with chemotherapy is a potential alternative especially in patients in urgent need of treatment due to distressing symptoms, high tumor burden and/or rapid tumor growth. A meta-analysis by the FDA showed no significant differences in overall survival between monotherapy and combination therapy, but a slight numerical advantage in favor of immunochemotherapy and a significant advantage in progression-free survival. In patients > 75 years, there is evidence of an advantage in favor of immunomonotherapy [2]. In addition, there appears to be an impact of gender on

the efficacy of immune checkpoint inhibitor monotherapy vs. ICI + chemotherapy. Women appear to consistently benefit less than men from ICI monotherapy [21], as do non-smokers [58]. These observations require confirmation to guide treatment decisions.

- Independent of PD-L1 expression on tumor cells or tumor-infiltrating immune cells.
  - In non-squamous cell carcinoma, the combination of pembrolizumab with chemotherapy (platinum/pemetrexed) versus chemotherapy resulted in prolonged overall survival (HR 0.56; median 11.3 months) and prolonged progression-free survival (HR 0.48; median 3.9 months) [41], see Drug Product Pembrolizumab. The relative gain by pembrolizumab increases with the degree of PD-L1 expression, but is also significant in terms of overall survival (HR 0.52) in the group of PD-L1 negative patients [41]. In the subgroup of TTF1 negative patients the use of other cytostatic agents instead of pemetrexed should be considered [39].
  - In squamous cell carcinoma, the combination of pembrolizumab with chemotherapy (platinum/(nab)paclitaxel) versus chemotherapy was shown to prolong overall survival (HR 0.63; median 4.6 months) and progression-free survival (HR 0.56; median 1.6 months) [84], see Drug Product Pembrolizumab. Thereby, no significant benefit was seen for the subgroup of patients with PD-L1 expression <1% in the final survival analysis of the KEYNOTE-407 trial [85].
  - In non-squamous cell carcinoma, the combination of atezolizumab with carboplatin/paclitaxel/bevacizumab (BCP) versus BCP resulted in prolonged overall survival (HR 0.78; median 5.5 months) and progression-free survival (HR 0.62; median 1.5 months) [112]. The need for bevacizumab in this combination is unclear. This combination is the only approved combination therapy with immune checkpoint inhibitors for patients with EGFR and ALK alterations. There is no approval in Switzerland. However, this combination should only be used in this indication if the options for targeted therapy have been exhausted. One group of patients who may particularly benefit from atezolizumab-BCP therapy versus BCP are patients with liver metastases.
  - In non-squamous cell carcinoma, the combination of atezolizumab with carboplatin / nab-paclitaxel also resulted in prolonged overall survival (HR 0.79; median 4.7 months) and progression-free survival (HR 0.64; median 1.5 months) [125].
  - In squamous or non-squamous cell carcinoma regardless of PD-L1 expression, the combination of nivolumab / ipilimumab in combination with chemotherapy for 2 cycles and continuation of immune combination therapy versus conventional chemotherapy for 4 cycles resulted in significant prolongation of overall survival (HR 0.66; median 15.6 vs 10.9 months) [83], for approval see the currently valid regulatory information. Side effects of immunocombination therapy are higher than with immunomonotherapy or combination of immunotherapy with chemotherapy and mainly involve liver, skin, and endocrine toxicities. In the study, patients with low PD-L1 expression and squamous histology benefited particularly well. A direct comparison of dual immune checkpoint inhibitor (I/O-I/O) chemotherapy versus single immune checkpoint inhibitor (I/O) chemotherapy is not available.
- When chemotherapy alone is chosen, combination chemotherapy with two cytostatic agents is more effective than monotherapy in terms of remission rate, progression-free survival, and overall survival. Combinations are burdened with higher therapy-associated toxicity. Most experience is with platinum-containing combinations. Previous studies have shown that significantly higher remission rates are achieved with cisplatin than with carboplatin; however, these differences are not evident in combinations with third-generation drugs. In terms of overall survival, the two platinum derivatives are equieffective

[4, 22]. The choice is mainly based on the individual expected toxicity. Non-platinum combinations have lower remission rates than platinum-containing combinations.

- In patients with non-squamous cell carcinoma, the combination of bevacizumab with carboplatin/paclitaxel, cisplatin/gemcitabine, or another platinum-containing two-drug combination increased remission rates and prolonged progression-free survival compared with chemotherapy alone, but also increased the rate of side effects. The paclitaxel/carboplatin/bevacizumab combination also resulted in an increase in overall survival.
- In stable disease, first-line platinum-containing therapy should be stopped after 4 cycles. If there is a response, combination therapies should be stopped after 4-6 cycles.
- If disease is at least stable, therapy with single agents can be continued in terms of maintenance therapy. In some randomized trials, survival was significantly prolonged compared to controls. Current options are
  - Pemetrexed for non-squamous cell carcinoma.
  - Pembrolizumab - monotherapy (for TPS >50%) every 3 or every 6 weeks in continuation of the induction immunomonotherapy; in the pivotal trial, pembrolizumab was given for up to 35 cycles
  - Pembrolizumab + pemetrexed every 3 or every 6 weeks following combination immunochemotherapy; in the pivotal study, pembrolizumab was given for up to 35 cycles
  - Nivolumab + ipilimumab following induction with combination immunotherapy and chemotherapy; in the pivotal trial, nivolumab + ipilimumab was given for 2 years.
- An alternative to maintenance chemotherapy is the initiation of second-line therapy at progression. Close monitoring, e.g., at 6-8 week intervals, is necessary to diagnose progression early. However, in this concept only about 60% of patients receiving first-line therapy are treated with second-line therapy.

6.1.6.2.11.2 Second-line therapy

The options for second-line therapy of patients without evidence of genetic markers for molecularly targeted therapy are diverse. The majority were tested against docetaxel, following first-line chemotherapy alone. The background to these comparative therapies is that an increase in survival had been shown over best supportive care for docetaxel, erlotinib, as well as pemetrexed. Data from direct comparative trials or from trials of sequential therapies with the new agents are not yet available. None of the second-line therapy trials have been tested according to the current standard, chemotherapy + immune checkpoint inhibitor. The current results can be summarized as follows:

- The immune checkpoint inhibitors atezolizumab, nivolumab, and pembrolizumab, which target PD-1 or PD-L1, respectively, prolong survival compared with docetaxel monotherapy, but do not prolong progression-free survival in the majority of studies. The rate of serious adverse events is lower with checkpoint inhibitors than with docetaxel. Efficacy is unclear when a checkpoint inhibitor has been used in an earlier phase of therapy. Therefore, second-line therapy with a checkpoint inhibitor after first-line therapy with a drug from this class is currently not recommended.
- In patients with adenocarcinoma, the combination of docetaxel with the antiangiogenic inhibitor nintedanib resulted in a statistically significant prolongation of survival (hazard ratio 0.83; median 2.3 months), see Drug Nintedanib. The impact of nintedanib on clinical symptoms is small.
- The antiangiogenic antibody ramucirumab, in combination with docetaxel, resulted in a statistically significant prolongation of survival time (hazard ratio 0.86; median 1.2

months) in patients receiving second-line therapy for NSCLC, regardless of histology; see Drug Product Ramucirumab. Symptoma and quality of life are not significantly affected.

- Afatinib and erlotinib are approved, regardless of EGFR mutation status, for patients with squamous cell carcinoma after failure of platinum-containing chemotherapy. A randomized trial tested afatinib versus erlotinib. Afatinib significantly increased survival (hazard ratio 0.82; median 1.1 months) and progression-free survival, not remission rate. Diarrhea and stomatitis in CTCAE grade >3/4 occurred more frequently with afatinib, and exanthema (rash) occurred more frequently with erlotinib. The FDA removed this indication for erlotinib in 2016.
- Oligoprogression on ongoing maintenance therapy with an immune checkpoint inhibitor (pembrolizumab, atezolizumab, cemiplimab, nivolumab+ipilimumab) may be offered continuation of ICI and radiation to the oligoprogressive metastasis.

6.2 Therapeutic options

6.2.1 Surgery

6.2.1.1 Primary tumor

Surgery is the main curative treatment modality. Anatomical lung resections are preferred, with lobectomy being the standard form of resection [53, 76]. If a minimally invasive surgical procedure is possible (cT1-3, cN0-1), lobectomy should be performed using video-assisted techniques (VATS lobectomy). This has now become the standard of care for stage I tumors and is associated with lower postoperative morbidity and less impairment of exercise capacity [66]. Long-term data from comparative randomized trials on the oncologic outcome of the two methods are pending.

For tumors <2 cm in diameter, anatomic segment resection is an alternative to lobectomy. Currently, data are available from the Japanese JCOG0802 trial, in which n=1106 stage IA patients were randomized to lobectomy or anatomic segment resection. The 5-year recurrence-free survival rate was not different between the groups, 87.9% and 88.0%, respectively. However, 5-year overall survival showed a significant advantage in favor of segmental resection, 94.3% versus 91.1%. This advantage was predominantly due to lower mortality from second malignancies and a higher rate of curative therapy for second malignancies in the segment group. In both groups combined, 4.9% of patients died from their primary lung cancer and 7.8% from another cause of death, predominantly second malignancy, during the observation period (median 7.3 years) [100].

If the tumor is centrally located, pneumonectomy is rarely indicated. The mortality after pneumonectomy is two- to threefold higher than after lobectomy, partly because of the greater loss of lung parenchyma and an intrinsic right heart burden. One way to achieve radical resection and avoid pneumonectomy even in the presence of central tumor growth is lobectomy with bronchus or vascular cuff resection. The operative risk is approximately the same as that of simple lobectomy.

6.2.1.2 Lymph nodes

The aim of lymph node removal as part of tumor surgery is to improve the prognosis by precisely determining the tumor stage (N status) as the basis for stage-adapted postoperative therapy. Depending on the extent of lymph node removal, a distinction is made between:

- Systematic lymph node dissection: in this procedure, all lymph node stations and the lymph nodes present there are completely removed in predefined compartments (interlobar, hilar and mediastinal). This procedure has the highest sensitivity for diagnosing existing lymph node involvement. It is recommended as the standard [53].
- Systematic lymph node sampling: in this procedure, individual lymph nodes are removed from the predefined lymph node stations.
- Punctate lymph node sampling: removal of individual conspicuous lymph nodes.

There is no evidence of an increase in postoperative morbidity or lethality associated with lymph node dissection. Even in the case of PET-negative mediastinum, tumor-involved lymph nodes are detected in 10-16% during systematic intraoperative lymph node dissection, depending on tumor location and size.

6.2.2 Radiation therapy

6.2.2.1 Radiation therapy alone

Radiation is an effective therapy for non-small cell lung cancer. It is indicated in non-operable patients in stages I and II, and in selected patients in stage III. Options are

- hyperfractionated (CHART)
- conventional fractionation with >60 Gy
- stereotactic

In operated patients irradiation is indicated after incomplete resection. In the postoperative situation after R0 resection in N0 or N1 status, it has an unfavorable impact on prognosis and is not indicated. In higher N stages, postoperative radiotherapy improved local control, but not disease-free survival or overall survival, and therefore can no longer be regularly recommended [62]. The evaluation of mediastinal involvement should be differentiated and discussed in a multidisciplinary manner.

Prophylactic cranial irradiation of stage III patients reduces the incidence of brain metastases but has no effect on disease-free or overall survival at 1 year and is not recommended in non-small cell lung cancer.

Radiation pneumonitis is a critical side effect. It becomes symptomatic in 5-15% of patients. Time of onset and severity depend on the total dose, irradiated volume, fractionation, concurrent chemotherapy, and other individual factors [126]. Signs of illness range from cough irritation to respiratory insufficiency. Acute pneumonitis is often followed by transition to pulmonary fibrosis with secondary complications. It may occur within 6-24 months after the end of radiation. Thoracic CT is suitable for the diagnosis of radiation pneumonitis, see chapter 8 Follow-up. Functional limitation is assessed and quantified by pulmonary function testing including diffusion capacity.

6.2.2.2 Combined radiochemotherapy

The combination of radiotherapy with tumor drug therapy is more effective than radiotherapy alone and indicated in stage III patients [17, 79, 89]. Effective drugs and combinations for radiochemotherapy include.

- Cisplatin / etoposide

- Cisplatin / vinorelbine
- Cisplatin monotherapy
- Carboplatin monotherapy in elderly patients
- carboplatin / paclitaxel
- Cisplatin / pemetrexed in non-squamous cell carcinoma, refer to current valid regulatory information.

The value of adding immune checkpoint inhibitors simultaneously to systemic therapy is uncertain, and this combination is not recommended outside of clinical trials. Recommendations for consolidative immunotherapy in stages $IIIA_3$ multilevel ($IIIA_{3m}$), $IIIA_4$, and IIIB are summarized in chapter 6.1.4.3. and chapter 6.1.4.4.

Recommended dosages are summarized under Lung Cancer Therapy Protocols. In the absence of comparative studies, no universally applicable standard has been defined. Monochemotherapy or lower doses reduce efficacy. The choice of drugs depends on the comorbidity of the patients Taxane-containing combinations may be associated with increased toxicity.

6.2.3 Systemic therapy

6.2.3.1 Adjuvant systemic therapy

Numerous randomized trials have been conducted over the past 35 years to improve survival rates after surgical resection. Inclusion criteria, composition of the study cohorts, treatment protocols, and follow-up periods vary. The following conclusions can be drawn from the results of individual studies, from meta-analyses, and from subgroup analyses:

- Adjuvant chemotherapy significantly increased 5-year survival rates in patients with stage II-III non-small cell lung cancer after R0 resection and may also be considered in stage IB (UICC 7th edition) with additional risk factors.
- The benefit of adjuvant chemotherapy is not limited to certain age groups. However, there are insufficient data for patients >75 years of age.
- Adjuvant chemotherapy should start 4-8 weeks after surgery. A benefit is only proven if chemotherapy is started within 60 days after surgery
- Adjuvant chemotherapy should consist of a cisplatin-containing combination. The efficacy of carboplatin has been prospectively demonstrated in only one study in stage IB (UICC 7th edition).
- Most data are available for the combination of cisplatin and vinorelbine, given over 4 courses of treatment. Depending on comorbidity, side effects, and approval status, other cisplatin-containing combinations may be chosen, e.g., with docetaxel, etoposide, gemcitabine, or pemetrexed; see also the currently valid Approval Information and Drug Therapy for Tumors - Protocols.
- Combining chemotherapy with an anti-angiogenesis inhibitor did not prolong survival or increase survival.
- Data on the value of immune checkpoint inhibitors in adjuvant systemic therapy are available with the Impower 010 trial using atezolizumab. Here, an improvement in disease-free survival was shown. The approval is limited to patients with a high risk of recurrence after R0 resection, a PD-L1 expression on tumor cells of >50% and an EGFR/ALK WT constellation after adjuvant chemotherapy.
- - Regarding the use of osimertinib, please refer to chapter 6.1.3.

6.2.3.2 Neoadjuvant therapy / induction therapy

Induction chemotherapy is an alternative to adjuvant chemotherapy in stages II and III, based on randomized trials and meta-analyses. The results can be summarized as follows:

- Randomized trials and meta-analyses show no difference between preoperative versus postoperative chemotherapy.
- Therapy adherence may be higher preoperatively than postoperatively.
- Postoperative chemotherapy after pneumonectomy is associated with significantly lower treatment adherence, and has a significantly higher morbidity rate than after lobectomy.

Effective combinations of drug tumor therapy for the induction modality include:

- cisplatin / paclitaxel
- cisplatin / docetaxel
- cisplatin / gemcitabine
- cisplatin / pemetrexed
- cisplatin / vinorelbine
- carboplatin / paclitaxel
- The above combination chemotherapies plus nivolumab [38]; not approved in this indication.

Recommended dosages are summarized under Lung Cancer Therapy Protocols. The choice of drugs is based on the comorbidity of the patients Generally, four cycles of induction chemotherapy (as in adjuvant therapy) are applied and surgery is scheduled approximately 4 weeks after day 1 of the 3rd or 4th cycle of chemotherapy. Molecular-targeted therapies (kinase inhibitors and antibodies) do not, at this time, replace perioperative chemotherapy in patients with a curative approach to therapy. Such therapeutic approaches should be applied within clinical trials. Data on induction chemotherapy in combination with the immune checkpoint inhibitor nivolumab show a significant increase in the rate of pathological complete remissions and event-free survival as well as a numerical prolongation of overall survival, see chapter 6.1.4.1.

6.2.3.3 Substances (by substance class and in alphabetical order)

Systemic tumor therapy is used in non-small cell lung cancer in the primary (neoadjuvant) and adjuvant setting, in combination with radiotherapy and in the non-curative intent treatment setting, see Figure 4, Figure 5, Figure 6 and Figure 7. For further information, please refer to the current approval status.

6.2.3.3.1 Cytostatic drugs

6.2.3.3.1.1 Carboplatin

Carboplatin is a platinum derivative. It has a more favorable side effect spectrum than cisplatin, but is also somewhat less effective. Remission rates are significantly lower, and survival times are comparable. Specific serious side effects include hematotoxicity (thrombocytopenia, anemia, neutropenia), nausea and vomiting, neurotoxicity. The decision of the platinum component

(carboplatin or cisplatin) should be based on the different toxicity profile of the two substances and the existing comorbidities in each individual case.

6.2.3.3.1.2 Cisplatin

Platinum derivatives are among the most effective single substances. In combination with other cytostatic drugs, cisplatin is part of the drug standard in primary (neoadjuvant), adjuvant and palliative therapy as well as in combination with radiotherapy. In palliative therapy, cisplatin in combination with taxanes, gemcitabine, vinorelbine, or pemetrexed achieves remission rates of 15-30% and median progression-free survival of 3-5 months. Specific serious adverse events (grade 3/4) include nausea and vomiting, nephrotoxicity, polyneuropathy, ototoxicity, hematotoxicity, electrolyte shifts, cardiotoxicity, and diarrhea. The decision of the platinum component (carboplatin or cisplatin) should be based on the different toxicity profiles of the two agents and existing comorbidities on a case-by-case basis.

6.2.3.3.1.3 Docetaxel

Docetaxel belongs to the group of taxanes. Taxanes are effective combination partners of platinum derivatives in neoadjuvant, adjuvant and palliative therapy as well as in combination with radiotherapy. However, they can also be used in other combinations, e.g., with gemcitabine; see Lung Cancer Therapy Protocols. For second-line monotherapy, docetaxel is more effective than vinorelbine or ifosfamide. In the ECOG study comparing four platinum-containing combination therapies, the following serious adverse events (CTCAE grade 3/4) occurred with cisplatin/docetaxel: Neutropenia (69%), febrile neutropenia (11%), anemia (15%), thrombocytopenia (3%), vomiting (21%), diarrhea (10%), nephrotoxicity (3%), and neuropathy (5%) and fatigue (16%). Other side effects include edema, alopecia, onychodystrophy, and allergic reactions.

6.2.3.3.1.4 Gemcitabine

Gemcitabine is a pyrimidine analogue and, along with the taxanes, vinorelbine, irinotecan, and pemetrexed, is one of the so-called third-generation cytostatics. Gemcitabine is an effective combination partner of the platinum derivatives in neoadjuvant, adjuvant and palliative therapy. In palliative platinum-containing combination therapy, it is as effective as taxanes, but can also be used in non-platinum-containing therapy, see Lung Cancer Therapy Protocols. In the ECOG study comparing four platinum-containing combination therapies, the following serious adverse events (grade 3/4) occurred with cisplatin/gemcitabine: Neutropenia (63%), febrile neutropenia (4%), anemia (28%), thrombocytopenia (50%), vomiting (35%), nephrotoxicity (9%), neuropathy (9%), and fatigue (17%).

6.2.3.3.1.5 Paclitaxel / nab-paclitaxel

Paclitaxel belongs to the taxanes. Taxanes are effective combination partners of platinum derivatives in neoadjuvant, adjuvant and in palliative therapy as well as in combination with radiotherapy. However, they can also be used in other combinations, e.g., with gemcitabine; see Drug Therapy for Tumors - Protocols. In the ECOG study comparing four platinum-containing combination therapies, the following serious adverse events (grade 3/4) occurred with cisplatin/paclitaxel: Neutropenia (65%), febrile neutropenia (16%), anemia (13%), thrombocytopenia (6%), vomiting (24%), diarrhea (7%), nephrotoxicity (3%), neuropathy (5%), and fatigue (14%). Other side effects include edema, alopecia, onychodystrophy, and allergic reactions.

An alternative to solvent-based paclitaxel (sbPaclitaxel) is albumin-bound paclitaxel (nabPaclitaxel). In patients with advanced NSCLC, nabPaclitaxel in combination with carboplatin vs sbPaclitaxel/carboplatin resulted in a significant increase in response rate (33 vs 25%). Serious adverse events (grade 3/4) that occurred more frequently with nabPaclitaxel/carboplatin were

thrombocytopenia (47%) and anemia (27%). Neuropathy and neutropenia occurred less frequently than with paclitaxel, as did the administration of high-dose steroids.

6.2.3.3.1.6 Vinorelbine / vinca alkaloids

Vinorelbine is a semisynthetic derivative of the vinca alkaloid vinblastine. Vinca alkaloids are effective combination partners of platinum derivatives in neoadjuvant, adjuvant and in palliative therapy as well as in combination with radiotherapy. In palliative monotherapy, it achieves remission rates of 10%; see Drug Therapy for Tumors - Protocols. Vinorelbine can be administered orally or intravenously. In adjuvant chemotherapy trials, it was one of the most frequently chosen combination partners of cisplatin. In the LACE adjuvant chemotherapy efficacy trial, the following serious adverse events (grade 3 / 4) occurred with cisplatin/vinorelbine: Neutropenia (80%), febrile neutropenia (9%), thrombocytopenia (3%), nausea/vomiting (20%), constipation (4%), nephrotoxicity (1%), and neuropathy (3%).

6.2.3.3.2 Immunotherapy

6.2.3.3.2.1 Atezolizumab

Atezolizumab is a monoclonal anti-PD-L1 antibody and belongs to the substance class of immune checkpoint inhibitors. Monotherapy with the anti-PDL1 antibody atezolizumab resulted in prolongation of overall survival (HR 0.59; 20.2 vs 13.1 months), prolongation of progression-free survival (HR 0.63; median 3.1 months) in patients with PD-L1 on >50% of tumor cells or a rate of PD-L1 positive tumor-infiltrating immune cells (IC) of >10% compared to platinum-containing chemotherapy [47]. In non-squamous cell carcinoma, the combination of atezolizumab with carboplatin/paclitaxel/bevacizumab (BCP) versus BCP resulted in prolongation of overall survival (HR 0.78; median 5.5 months) and progression-free survival (HR 0.62; median 1.5 months) [112]. In non-squamous cell carcinoma, the combination of atezolizumab with carboplatin / nabPaclitaxel also resulted in prolonged overall survival (HR 0.79; median 4.7 months) and progression-free survival (HR 0.64; median 1.5 months) compared with carboplatin / nabPaclitaxel [125]. Atezolizumab resulted in prolonged overall survival (OAK: HR 0.73; median 4.2 months; POPLAR: HR 0.73; median 2.9 months) in the second-line treatment of patients with locally advanced or metastatic NSCLC compared with docetaxel in the pivotal trial and another randomized trial, regardless of the detection of PD-L1 expression on tumor cells, see Drug Product Atezolizumab. Atezolizumab did not increase remission rates or prolong progression-free survival. The rate of serious adverse events with atezolizumab is lower than with docetaxel. CTCAE grade ¾ adverse events occurred significantly less frequently with atezolizumab (37% overall) than with docetaxel (54%). Fatigue (14%), nausea (9%), loss of appetite (9%), and asthenia (8%) were the most common side effects, as were immune-mediated side effects [102].

Atezolizumab results in highly statistically significant improvement in DFS in patients with PD-L1 expression of >50% and an EGFR/ALK WT constellation after R0 resection and after adjuvant cisplatin-containing chemotherapy for NSCLC stage IB- III (UICC 7th edition), OS data are not available. Adjuvant atezolizumab therapy was approved in June 2022.

6.2.3.3.2.2 Durvalumab

Durvalumab is a monoclonal anti-PD-L1 antibody and belongs to the substance class of immune checkpoint inhibitors. In a randomized trial in stage III patients with non-resectable NSCLC after definitive radiochemotherapy, consolidative immunotherapy with the anti-PD-L1 antibody durvalumab significantly prolonged progression-free survival (HR 0.52; median 11.2 months) and overall survival (HR; median), see Drug Product Durvalumab. CTCAE grade 3/4 adverse events

that occurred more frequently in the durvalumab arm than in the control arm were pneumonia (4.4 vs 3.8%) and pneumonitis (3.4 vs 2.6%).

6.2.3.3.2.3 Ipilimumab

Ipilimumab is a drug from the group of monoclonal antibodies. It blocks the inhibitory T cell regulator CTLA-4 and thereby enhances the autologous immune response. For the approval conditions, please refer to the currently valid approval information. In this combination, ipilimumab/nivolumab significantly prolonged overall survival (HR 0.66; median 15.6 vs 10.9 months) compared with conventional chemotherapy, independent of PD-L1 expression [83]. The rate of severe therapy-associated adverse events was increased with the addition of immune checkpoint inhibitors (24.5 vs 13.9%), as was the rate of treatment discontinuation due to adverse events (18.1 vs 9.1%). Most common immune-mediated side effects were related to skin (34% of patients) and endocrine functions (23.8%). For management of immune checkpoint inhibitor side effects.

6.2.3.3.2.4 Nivolumab

Nivolumab is an anti-PD-1 monoclonal antibody and belongs to the immune checkpoint inhibitor class. Ipilimumab was approved by the EMA in October 2020 for the first-line treatment of advanced/metastatic NSCLC in combination with nivolumab and chemotherapy. In this combination, ipilimumab/nivolumab significantly prolonged overall survival (HR 0.66; median 15.6 vs 10.9 months) compared with conventional chemotherapy, regardless of PD-L1 expression [83]. The rate of severe therapy-associated adverse events was increased with the addition of immune checkpoint inhibitors (24.5 vs 13.9%), as was the rate of treatment discontinuation due to adverse events (18.1 vs 9.1%) [102]. Most common immune-mediated side effects were related to skin (34% of patients) and endocrine functions (23.8%). For management of immune checkpoint inhibitor side effects.

In a randomized trial of second-line therapy, nivolumab significantly prolonged survival (HR 0.59; median 3.2 months), progression-free survival (HR 0.62; median 0.7 months), increased remission rates, and reduced treatment side effects in patients with squamous cell carcinoma compared with docetaxel; see Drug Product Nivolumab. In patients with non-squamous cell carcinoma, nivolumab also led to a significant improvement in overall survival (hazard ratio 0.73; median 2.8 months), an increase in remission rate, not a prolongation of progression-free survival in a randomized comparison with docetaxel monotherapy, see Drug Nivolumab.

The CheckMate 816 trial tested the efficacy of neoadjuvant chemoimmunotherapy with combination platinum-containing chemotherapy + nivolumab versus chemotherapy. Chemoimmunotherapy resulted in an increase in the rate of pathohistological complete remissions from 2.2 to 24.0%, prolongation of event-free survival and overall survival [38]. In stage IIIA, the differences were statistically significant, although the data are immature. Nivolumab has not yet been approved in this indication.

Side effects in CTCAE grade 3/4 with nivolumab monotherapy were fatigue (1%), nausea (1%), loss of appetite (1%), diarrhea (1%), and leukocytopenia (1%). Fatigue was also the most common of all side effects (16%) with nivolumab, followed by loss of appetite (10-11%), asthenia (10%), nausea (9-12%), and diarrhea (8%); immune-mediated side effects also occurred.

6.2.3.3.2.5 Pembrolizumab

Pembrolizumab is an anti-PD-1 monoclonal antibody and belongs to the immune checkpoint inhibitor class of compounds. In first-line therapy, pembrolizumab as monotherapy resulted in prolongation of overall survival (hazard ratio 0.63; median 16 months), prolongation of progression-free survival (HR 0.50 median 4.3 months;), and a reduction in the rate of serious adverse

events in patients with PD-L1 expression >50% versus platinum-containing chemotherapy, see Drug Product Pembrolizumab.

In patients with non-squamous cell carcinoma (KEYNOTE-189), combination of pembrolizumab with platinum-containing chemotherapy, regardless of PD-L1 expression, versus combination chemotherapy resulted in improved survival at 12 months (HR 0.49; OR +19.8%) and prolonged progression-free survival (HR 0.52; median 3.9 months). The relative gain with pembrolizumab increases with the degree of PD-L1 expression, but is also significant in the group of PD-L1 negative patients (HR 0.59). In patients with squamous cell carcinoma, the combination of pembrolizumab with platinum-containing chemotherapy and (nab-)paclitaxel versus combination chemotherapy (KEYNOTE-407) resulted in prolonged overall survival (HR 0.64; median 4.6 months) and progression-free survival (HR 0.56; median 1.6 months).

In second-line therapy, pembrolizumab monotherapy versus docetaxel significantly prolonged survival (HR 0.71; median 1.9 months), increased remission rates, and reduced severe treatment side effects. Progression-free survival was not significantly prolonged. Pembrolizumab is approved in second-line therapy only in patients with immunohistochemical evidence of PD-L1 expression in at least 1% of tumor cells.

Side effects in CTCAE grade 3/4 with pembrolizumab include loss of appetite (1%), fatigue (1%), diarrhea (1%), anemia (1%), nausea (<1%), rash (<1%), and asthenia (<1%). Loss of appetite and fatigue were also the most common of all side effects (14% each) with pembrolizumab, followed by nausea (11%), rash (9%), and diarrhea (7%); other immune-mediated side effects also occurred.

6.2.3.3.3 Molecular targeted therapy

6.2.3.3.3.1 Afatinib

Afatinib is an irreversible inhibitor of EGFR tyrosine kinases. In the pivotal study in patients with adenocarcinoma and activating EGFR mutations in first-line therapy, afatinib resulted in a significant increase in remission rate, significant prolongation of progression-free survival, and better tolerability compared to chemotherapy with cisplatin/pemetrexed. The same results were obtained when compared with cisplatin/gemcitabine. In the LUX-Lung 3 and LUX-Lung 6 trials, a survival benefit of about 12 months was achieved for afatinib compared with chemotherapy (pemetrexed and cisplatin in LUX-Lung 3, gemcitabine and cisplatin in LUX-Lung 6) in patients with del19; overall survival was not prolonged in patients with mutation L858R. In a randomized trial of afatinib versus gefitinib, progression-free survival was longer and remission rates were higher in the afatinib arm; the rate of treatment discontinuation due to adverse events was the same.

Afatinib also shows efficacy in the rare EGFR mutations G719X, L861Q, and S768I. Approval in the EU is not limited to specific mutations. In Switzerland, afatinib is also approved for the treatment of tumors with the atypical EGFR mutations G719X, S768I and L861Q.

In patients with squamous cell carcinoma and progression after or on first-line platinum-containing therapy, afatinib significantly prolonged overall survival (HR 0.81; median 1.1 months) and progression-free survival (HR 0.82; median 0.5 months) compared with erlotinib.

Afatinib side effects are drug class effects. Side effects in CTCAE grade 3/4 occurring in more than 5% of patients are diarrhea (5-14%), skin exanthema/acne (6-16%), and stomatitis/mucositis (4-11%).

6.2.3.3.3.2 Alectinib

Alectinib is a second-generation ALK inhibitor with higher specificity for ALK kinase than crizotinib. In first-line therapy, alectinib at a dose of 1,200 mg/day versus crizotinib resulted in prolonged progression-free survival (hazard ratio 0.50) and a significant reduction in the incidence of CNS metastases, see Drug Product Alectinib. Results from a second, Japan-only study at 600 mg/day confirmed the data. In second-line therapy, alectinib resulted in a response rate of 51.3% and progression-free survival of 8.2 and 8.9 months, respectively, in two nonrandomized phase II studies with a total of 225 patients; see Drug Alectinib. Serious CTCAE grade 3/4 adverse events primarily involve elevated laboratory values (data from second-line therapy): Creatine kinase (CK) (8%), GPT (6%), and GOT (5%). Most common side effects in CTCAE grade 1/2 are constipation (33-36%), fatigue (26-33%), peripheral edema (23-25%), and myalgia (24%). Severe CTCAE grade 3-5 adverse events occurred in 41% of patients on alectinib in first-line therapy. Side effects that occurred more frequently with alectinib than with crizotinib were anemia, myalgia, elevated bilirubin, weight gain, musculoskeletal pain, and photosensitivity.

6.2.3.3.3.3 Amivantamab

Amivantamab is a bispecific antibody against MET and EGFR. It is approved as monotherapy in patients with NSCLC and evidence of an activating EGFR exon 20 insertion mutation after failure of platinum-based therapy. Amivantamab achieved a response rate of 40%, a median duration of response of 11.1 months, and a median PFS of 8.3 months in the Chrysalis trial in patients with exon 20 insertions and prior therapy with chemotherapy (100% of patients) and immune checkpoint inhibitors (46% of patients) [81]. Side effects were essentially class effects of EGFR and MET inhibition. Infusion-related side effects occurred at 94% during the first infusion and were compatible with continued therapy.

6.2.3.3.3.4 Brigatinib

Brigatinib is an inhibitor of ALK and of EGFR. It is approved for first- and second-line treatment of ALK+ NSCLC. Brigatinib resulted in a significant increase in remission rate and a significant prolongation of progression-free survival with a hazard ratio of 0.48 in the ALTA-L1 trial compared with crizotinib. Brigatinib did not lead to a significant prolongation of overall survival in the overall population with, however, not yet final data and a high crossover rate, see Drug Brigatinib. In the group of patients with primary CNS metastasis, a significant survival benefit over crizotinib was shown (HR 0.43; p=0.02) [15]. Two different doses were tested in the pivotal second-line therapy trial. At the approved dose of 180 mg/day, brigatinib resulted in a response rate of 54%, and 67% for CNS metastases. Median progression-free survival was 16.7 months, and median overall survival was 34.1 months; see Drug Product Brigatinib. Brigatinib was not evaluated in head-to-head comparison with alectinib or ceritinib. In first-line therapy, brigatinib versus crizotinib resulted in a reduction in the combined endpoint of progression-free survival and death (HR 0.49; median not yet reached). Serious adverse events in CTCAE grade 3/4 occurred in 69.1% of patients taking brigatinib in the pivotal study. Serious adverse events occurring in more than 5% of patients were hypertension and elevation of CK. Also observed were elevation of amylase and lipase. Pulmonary grade 3/4 adverse events occurred early in treatment in 2.7% of patients For the approval conditions in D-A-CH, please refer to the approval status.

6.2.3.3.3.5 Capmatinib

Capmatinib is a MET inhibitor, an approval was granted based on the Geometry study starting in the second line for patients with a MET exon 14 skipping mutation. The response rate was 66.7% in the treatment-naive cohort, 51.6% in the second-line pre-treated cohort, and 40.6% in the second- and third-line cohorts [128]. The PFS for the first-line cohort was 12.4 months, and the PFS for the second- and further-line cohorts was 6.9 and 5.1 months, respectively. The adverse event rate was low. Edema is a clinically relevant adverse and should be treated prophylactically if possible. Edema occurred with all grades in 54% of patients, of which 9.7% were

grade 3. Other side effects included nausea and vomiting, elevated creatinine, dyspnea, fatigue, and loss of appetite. Discontinuation of therapy due to treatment-related adverse events was seen in 9.7% of patients

6.2.3.3.3.6 Ceritinib

Ceritinib is a second-generation ALK inhibitor with higher specificity for ALK kinase than crizotinib. Ceritinib resulted in an increase in remission rate (72.5 vs. 26.7%) and prolongation of progression-free survival (HR 0.55; median 8 months) in first-line therapy versus platinum-based chemotherapy. The impact of ceritinib on overall survival was not statistically significant in this trial (p=0.056), possibly due to the high crossover rate from the chemotherapy to the ceritinib arm, see Drug Product Ceritinib. In second-line therapy, ceritinib versus chemotherapy resulted in an increase in remission rate from 6.9% to 39.1% and prolonged progression-free survival (hazard ratio 0.49; median 3.8 months). Overall survival was not prolonged; see Drug Product Ceritinib. Serious side effects of ceritinib include hepatotoxicity, gastrointestinal toxicity, QT time prolongation, and bradycardia. Other side effects include diarrhea, nausea/vomiting, fatigue, elevated transaminases, abdominal pain, and loss of appetite. The lower dosage now approved is associated with fewer side effects.

6.2.3.3.3.7 Crizotinib

Crizotinib is an oral inhibitor of the phosphorylation of tyrosine kinases such as ALK, MET, and ROS1. In first-line therapy in patients with ALK mutations, crizotinib significantly prolonged progression-free survival (hazard ratio 0.454; median 3.9 months), increased remission rates (74 vs. 45%), reduced disease-associated symptoms, and reduced side effects compared with platinum-containing chemotherapy + pemetrexed. Survival was not significantly different in the two study arms; however, switching to crizotinib occurred in 70.2% of patients in the chemotherapy arm; see Drug Product Crizotinib. In a direct comparative study of first-line therapy, alectinib versus crizotinib resulted in prolonged progression-free survival but not overall survival.

In the pivotal study in second-line ALK mutation patients, crizotinib resulted in higher response rate, better symptom control, longer progression-free survival, and better quality of life than the control group receiving chemotherapy with docetaxel or pemetrexed, see Drug Product Crizotinib. Side effects in CTCAE grade 3/4 occurring in more than 5% of patients treated with crizotinib include transaminase elevation (14-16%), neutropenia (11-13%), and pulmonary embolism (5%). Characteristic side effects of crizotinib include visual disturbances and taste changes.

Crizotinib is also approved in patients with ROS1 translocation and resulted in disease control in over 90% of patients.

6.2.3.3.3.8 Dabrafenib

Dabrafenib is a BRAF inhibitor. Dabrafenib, in combination with trametinib, resulted in a 64% remission rate and a median overall survival of 24.6 months in first-line treatment of patients with BRAFV600 mutation in a single-arm phase II study, and a 63% remission rate and a median overall survival of 18.2 months in second-line treatment, see Drug Product Dabrafenib. In indirect comparison, the rate of serious adverse events is lower than with chemotherapy. Data from randomized trials are not available. Side effects that occurred with dabrafenib+trametinib in more than 5% of patients in CTCAE grade 3/4 were neutropenia (5%), hyponatremia (7%), and anemia (5%). The most common adverse event was fever (16%). Squamous cell carcinoma of the skin occurred in two patients (4%). Severe side effects occurred in 56% of the patients

6.2.3.3.3.9 Dacomitinib

Dacomitinib is an irreversible inhibitor of EGFR tyrosine kinases. In the randomized pivotal ARCHER 1050 trial, dacomitinib resulted in prolonged progression-free survival (hazard ratio 0.59; median 5.5 months) and significantly prolonged overall survival (hazard ratio 0.76, median 7.3 months) compared with gefitinib in first-line therapy, drug dacomitinib. The difference in survival was significant in the overall study, not in the subgroups of patients with del19, but in the group with L858R. Patients with brain metastases and with other activating EGFR mutations were not included. Severe adverse events in CTCAE grade 3/4 occurred in 53% of patients in the pivotal study. Most common adverse events in all severity grades were acne (14%), diarrhea (8%), and paronychia (7%).

6.2.3.3.3.10 Entrectinib

Entrectinib is an inhibitor of neurotrophic tyrosine receptor kinases (NTRK) and an inhibitor of ROS1. Entrectinib is used as monotherapy for the treatment of adult and pediatric patients with solid tumors and evidence of neurotrophic tyrosine receptor kinase (NTRK) gene fusion. It is approved for locally advanced or metastatic disease for which no satisfactory treatment options are available; see Drug Product Entrectinib. In the pivotal trial, 8 of 12 NSCLC patients achieved remission, and the median progression-free survival was 14.9 months [29]. The safety of entrectinib was recorded in all patients in the pivotal trials. Serious adverse events in CTCAE grade >3 occurred in 68.5% of patients The most common adverse events were fatigue, dysgeusia, edema with weight gain, confusion, diarrhea, nausea, dysesthesia, dyspnea, anemia, creatinine increase, and cognitive impairment.

Entrectinib is also approved in patients with ROS1 translocation and resulted in remission in 65.5% of patients. The median progression-free survival was 13.6 months, and the median overall survival was 30.5 months; see Drug Product Entrectinib.

6.2.3.3.3.11 Erlotinib

Erlotinib is an oral inhibitor of EGF receptor (EGFR) tyrosine kinase activity. In a head-to-head comparative study of first-line therapy in patients with activating EGFR mutation, osimertinib versus erlotinib or gefitinib resulted in prolonged progression-free and survival and overall survival (38.6 vs 31.8 months; HR 0.80; p = 0.046) [90]. The efficacy of erlotinib is enhanced by combination with antiangiogenic antibodies, regardless of the type of EGFR mutation. Both the combination of erlotinib with the anti-VEGF antibody bevacizumab significantly prolonged progression-free survival (HR 0.605; median 3.6 months) compared with erlotinib in a Japanese study [99] and the combination of erlotinib with the VEGFR antibody ramucirumab (HR 0.59; median 7 months) [74]. In both studies, overall survival at the time of publication was not prolonged by combination therapy.

Erlotinib is also effective in maintenance after first-line platinum-containing chemotherapy in patients without activating EGFR mutations. Compared with placebo, it significantly prolonged overall survival (median 1 month) and progression-free survival (median 0.3 months).

In patients with squamous cell carcinoma, erlotinib is inferior to afatinib therapy in second-line therapy in terms of overall survival and progression-free survival.

The characteristic side effect is an acne-like rash. It occurs in 60% of patients, and in severity grade 3/4 in 9%. Other severe side effects (grade 3/4) that occurred in large randomized trials were diarrhea (4%), anorexia (1-9%), and fatigue.

6.2.3.3.3.12 Gefitinib

Gefitinib is an oral inhibitor of EGF receptor (EGFR) tyrosine kinase activity. In a randomized trial of afatinib versus gefitinib, progression-free survival was shorter and remission rates were lower in patients with del19 and L858R in the gefitinib arm, and the rate of treatment discontin-

uation due to adverse events was the same. In a direct comparative study of first-line therapy, osimertinib versus erlotinib or gefitinib resulted in prolonged progression-free and overall survival.

The characteristic side effect is an acne-like rash. It occurs in 66% of patients, and in severity grade 3/4 in 3%. Other severe side effects (grade 3/4) that occurred in large randomized trials were diarrhea (4%), anorexia (1-5%), and anemia (2%).

6.2.3.3.3.13 Larotrectinib

Larotrectinib is an inhibitor of neurotrophic tyrosine receptor kinases (NTRK). Larotrectinib is used as monotherapy for the treatment of adult and pediatric patients with solid tumors and evidence of neurotrophic tyrosine receptor kinase (NTRK) gene fusion. It is approved for locally advanced or metastatic disease for which no satisfactory treatment options are available, see Drug Product Larotrectinib. In the pivotal trial, 5 of 7 NSCLC patients achieved remission. Safety of larotrectinib was recorded in all patients in pivotal trials; 30% of patients were pediatric. Grade 3/4 adverse events occurred in 5% of patients The most common side effects were (in descending frequency): Fatigue (32%), increased ALT (31%), dizziness (30%), increased AST (29%), constipation (29%), nausea (26%), anemia (24%), and vomiting (20%). Larotrectinib is a weak inhibitor of CYP3A, an inducer of CYP2B6, and an inhibitor of OATP1B1.

6.2.3.3.3.14 Lorlatinib

Lorlatinib is an inhibitor of Anaplastic Lymphoma Kinase, specifically designed to cross the blood-brain barrier. Lorlatinib is approved in patients with ALK+ NSCLC NSCLC in first-line therapy and after prior therapy with alectinib, ceritinib or crizotinib, see also the currently valid regulatory information. In the CROWN trial, a response rate of 67 vs. 58% was observed for lorlatinib vs. crizotinib, and the primary endpoint of progression-free survival was statistically significant in favor of lorlatinib with a HR of 0.28 (median PFS not reached vs. 9.3 months). The intracranial remission rate was improved with 66 (CR 61%) vs. 20% (CR 15%) for non-measurable and measurable CNS metastases, respectively; for measurable CNS metastases, the response rate was 82% (CR 71%) vs. 23% (CR 8%). The risk of intracranial progression was improved with a HR of 0.07 in favor of lorlatinib. Survival data are immature; quality of life was statistically significantly improved. The discontinuation rate due to treatment-associated adverse events was 7% for lorlatinib and 9% for crizotinib. The spectrum of side effects is different from all ALK inhibitors and includes hypercholesterolemia (81%), hypertriglyceridemia (60%), edema, weight gain (not water retention), peripheral neuropathy, cognitive and neuropsychiatric changes. Lorlatinib is also effective in ROS1-positive patients, and resulted in a response rate of about 50%, see also the currently valid regulatory information.

6.2.3.3.3.15 Osimertinib

Osimertinib is a third generation oral EGFR tyrosine kinase inhibitor. It was first approved for its high efficacy in patients with a T790M mutation. In these patients, osimertinib versus combination therapy with cis- or carboplatin/pemetrexed resulted in increased remission rates (71 vs 31%) and progression-free survival (HR 0.37; median 5.7 months). Osimertinib-associated adverse events in CTCAE grade 3/4 occurred in more than 13% of patients. The most common side effects with osimertinib were diarrhea (42%), exanthema (24%), nausea (17%), and loss of appetite (16%) and constipation (15%).

In the randomized FLAURA trial, osimertinib in first-line therapy versus erlotinib or gefitinib significantly prolonged progression-free survival (hazard ratio 0.46; 18.9 vs 10.2 months) and overall survival (38.6 vs 31.8 months; HR 0.80; p = 0.046). The survival benefit for patients with del19 was particularly pronounced with HR 0.68 [90].

In the ADAURA trial stage II and IIIA (UICC7) patients with an EGFR common mutation (del19, L858R) were treated with adjuvant therapy with osimertinib versus placebo for 3 years following R0 resection. In this trial, osimertinib significantly prolonged disease-free survival (HR 0.17; $p < 0.001$) and reduced the risk of CNS metastasis by 90% [130]. Mature data on the impact of adjuvant osimertinib on overall survival are not yet available. Regarding the conditions of approval, we refer to the currently valid regulatory information.

A recent observation is the frequent occurrence of severe immune-mediated adverse events such as pneumonitis when osimertinib is used after therapy with PD-(L)1 inhibitors. These side effects were not observed to increase when TKIs were used before PD-(L)1 inhibitors [102].

6.2.3.3.3.16 Pralsetinib

Pralsetinib is approved for the first- and second-line treatment of RET translocated NSCLC (and RET mutated other tumors). The compound was evaluated in a single-arm phase II study in different patient populations (treatment-naive and not chemotherapy-naive, treatment-naive and chemotherapy-naive, pre-treated). It resulted in an overall response rate of 69%, in patients with measurable disease 79%, in therapy-naive and non-chemotherapy-eligible patients 74%, in therapy-naive and chemotherapy-eligible patients 88%, and in pre-treated patients 62% (with platinum) and 73% (without platinum). Median PFS was particularly high in non-pretreated patients at 16.4 vs 13.0 vs 10.9, vs NR, vs 16.5 vs 12.8 months. Side effects were mainly neutropenia (42% all grades, 20% in CTCAE grade >3), anemia (38/13%), hypertension (25/12%). Other side effects were dysgeusia (grade 1,2) in 15%, and dry mouth (15% grade 1,2). Febrile neutropenia was not observed.

6.2.3.3.3.17 Selpercatinib

105 platinum-pretreated and 39 therapy-naive patients were enrolled in the single-arm phase I/II pivotal study of selpercatinib [28]. All patients had RET translocation. The response rate was 64% in pretreated patients median duration of response was 17.5 months, and median PFS was 16.5 months. The response rate of CNS metastases was 91% (10/11 patients). The median response duration of CNS metastases was 10.1 months. In 69 patients without systemic pretreatment, selpercatinib achieved a response rate of 84%, mostly partial remissions. The median progression-free survival was 22 months, the overall survival rate after 2 years was 70% [28]. The most common adverse events were arterial hypertension (14%), ALT elevations (13%), AST elevations (10%, hyponatremia (6%), and lymphocytopenia (6%). In 30% of the patients a dose reduction had to be performed, 2% of the patients discontinued the therapy because of therapy-associated side effects.

6.2.3.3.3.18 Sotorasib

Sotorasib is a specific KRAS G12C inhibitor that was tested in the Codebreak 100 trial in pretreated patients with NSCLC. The response rate in pretreated patients (chemotherapy +/- immunotherapy) was 37.1%, median PFS was 6.8 months, and median overall survival was 12.5 months. Adverse events occurred in 99.2% of patients, the most common being diarrhea (50.8%), nausea (31%), fatigue (25.4%), arthralgia (21.4%), AST and ALT (21.4 and 20.6%). Dose modifications were necessary in 22% of patients due to treatment-related side effects, and discontinuation of therapy occurred in 7.1%. In a recent analysis of the randomized phase III CodeBreak 200 trial comparing sotorasib vs docetaxel in patients with KRASG12C-mutated NSCLC patients sotorasib led to prolongation of progression-free survival (median 1.1 months; HR 0.66; p=0.002), but not in overall survival. Comparison of toxicity showed advantages for sotorasib in alopecia, anemia, fatigue and stomatitis, disadvantages for diarrhea and elevated transaminases [56].

6.2.3.3.3.19 Tepotinib

Tepotinib is a MET inhibitor that was approved in the second-line treatment of NSCLC with MET exon 14 skipping mutation based on the VISION study. Patients with histologic or liquid biopsy evidence of MET exon 14 skipping mutation were included in the study. The response rate for these groups was 50%, 48%, or 46% and was not dependent on comutation or line of therapy. The median PFS was 11.0 and 8.5 and 8.5 months, respectively. The median duration of response ranged from 12.4 to 17.1 months. Peripheral edema was the most common adverse event, occurring in 63%, grades 1-2 56%, grade 3 7%. Patients with MET exon 14 skipping mutations are often older than the median NSCLC patients (median age in the study 74 years), and, in contrast to other driver mutated lung carcinomas, 50% are men (48% in the VISION study) and many are burdened with comorbidities because of smoking status (40 to 50%).

6.2.3.3.3.20 Trametinib

See chapter 6.2.3.3.3.8.

6.2.3.3.3.21 Trastuzumab deruxtecan

Trastuzumab deruxtecan is the conjugate of an anti-Her2 antibody and the topoisomerase inhibitor SN38, which has a significantly higher "drug load" compared to trastuzumab emsantine, which is approved for breast cancer. A phase II study included 91 NSCLC patients with HER2 mutations and pretreatment across multiple lines of therapy. The primary endpoint of the study was response rate. Central confirmed response was achieved in 55% of patients, median PFS was 8.2 months, and median survival was 17.8 months. The most common grade 3 side effect was neutropenia (19%), ILD (interstitial lung disease) was observed in 26% of patients, and 2 patients had a fatal course of ILD. Approval is available for breast cancer, so the substance may be offered in off-label use in pretreated NSCLC patients. Trastuzumab Deruxtecan is approved in the EU for breast cancer. In the US it’s also approved for patients with NSCLC at at a dose of 5.4mg/kg. It should be offered to relapsed or refractory NSCLC patients after systemic pretreatment.

6.2.3.3.4 Angiogenesis inhibitors

6.2.3.3.4.1 Bevacizumab

Bevacizumab is a monoclonal antibody with anti-angiogenic activity. In first-line therapy of patients with non-squamous cell carcinoma, bevacizumab in combination with platinum-containing combination chemotherapy increased remission rates and prolonged progression-free survival (hazard 0.79; median 2 months). After severe hemoptysis occurred in squamous cell carcinoma in an early phase II study, these patients were excluded from pivotal trials. In a more recent study of first-line treatment of non-squamous cell carcinoma, the combination of atezolizumab with carboplatin/paclitaxel/bevacizumab (ABCP) versus BCP prolonged overall survival (HR 0.78; median 5.5 months) and progression-free survival (HR 0.62; median 1.5 months) [112]. Serious adverse events in CTCAE grade 3/4 in the pivotal trials were: Bleeding (4%), Hypertension (5-9%), Asthenia (15-17%), Fatigue (5%), Proteinuria (1-4%) and Neutropenia in combination with chemotherapy.

6.2.3.3.4.2 Nintedanib

Nintedanib is an oral VEGFR and FGFR inhibitor. A phase III trial evaluated the combination of docetaxel + nintedanib versus monochemotherapy with docetaxel in second-line NSCLC. The subgroup of patients with adenocarcinoma had a higher response rate, a prolongation of median progression-free survival, and a statistically significant prolongation of overall survival by 2.3 months, see Drug Product Nintedanib. Adverse events in CTCAE grade 3/4 that occurred in more than 5% of patients on nintedanib combination were diarrhea (6.6%) and reversible

elevations in transaminases (7.8%). For the conditions of approval, please refer to the currently valid regulatory information.

6.2.3.3.4.3 Ramucirumab

Ramucirumab is a human IgG1 antibody that binds specifically and with high affinity to the extracellular domain of vascular endothelial growth factor receptor-2 (VEGFR2). For the conditions of approval, please refer to the currently valid marketing authorization information. In patients in progression after or on first-line platinum-containing therapy, ramucirumab in combination with docetaxel versus docetaxel monotherapy significantly prolonged survival (hazard ratio 0.86; median 1.4 months), progression-free survival (hazard ratio 0.76; median 1.5 months), and remission rate from 14 to 23%, see Drug Product Ramucirumab. CTCAE grade 3/4 adverse events that occurred in more than 5% of patients in the docetaxel + ramucirumab combination and more frequently than in the control arm were neutropenia (49%), febrile neutropenia (16%), fatigue (14%), and hypertension (6%).

In patients with EGFR mutations, the combination of erlotinib + ramucirumab versus erlotinib significantly prolonged progression-free survival (HR 0.59; median 7 months), but not overall survival [74].

6.3 Special situations

6.3.1 Bronchus and tracheal stenosis

Endoluminal tumor growth or external compression may cause hemorrhage, dyspnea, and/or retention symptoms in the trachea and central bronchi. Depending on the findings, tumor-ablating methods such as the Nd-YAG laser, argon beamer or cryotherapy, endoluminal small-area radiation, or prosthetic methods (endoluminal stents) are appropriate for symptom relief.

Stent implantation can be combined with other physical procedures such as endoscopic laser therapy or endoluminal brachytherapy. The goal is to prolong the time to symptom recurrence.

Results of randomized studies comparing local therapy methods are not available.

6.3.2 Malignant pleural effusion

Unilateral or bilateral malignant pleural effusion is a frequent complication in patients with advanced lung cancer. Prerequisites for local therapy are

- symptomatic malignant effusion and
- expandable lung and
- non-response to systemic drug therapy or
- Contraindications to systemic drug therapy.

Based on a meta-analysis of 36 randomized trials with a total of 1499 patients, thoracoscopic talcum pleurodesis has become the standard of care [109]. More recent studies show that other concepts such as talcum application via a catheter or long-term insertion of tunneled pleural drains (indwelling pleural catheters) can also achieve comparable results in symptom relief. Results of large, randomized trials to establish a new standard are pending.

6.3.3 Bone metastases

Local and systemic measures are available for the treatment of patients with bone metastases. In case of pain symptoms or fracture risk, radiation is the therapy of choice. It can be performed hypofractionated under continuous systemic therapy. An additional option is surgical treatment for pathologic fractures, unstable vertebral body fractures, or as a relief for spinal compression.

Systemic measures include causal therapy and the administration of bone-modifying substances (bisphosphonates, RANKL antibodies). Bone-modifying agents may reduce the risk of skeletal complications in osseous metastasis of solid tumors. In subgroup analysis of a multicenter study comparing zoledronate and denosumab in solid tumors, patients with NSCLC treated with denosumab showed no significant difference in skeletal-related events but significantly longer survival [54].

Bisphosphonates are additionally indicated in hypercalcemia.

6.3.4 CNS metastases

The initial acute treatment of symptomatic metastasis is the administration of steroids to reduce perifocal edema. For isolated, resectable brain metastases, local surgical therapy or targeted local radiation (Gamma-Knife, Cyber-Knife, stereotactic radiation) are recommended. In patients with solitary brain metastases, a curative therapeutic approach exists in combination with optimal local therapy of the lung tumor, see Figure 4 and chapter 6.1.6.1. In patients with small and asymptomatic brain metastases, a wait-and-see approach with repeated MRI imaging under system therapy is an alternative to primary local therapy [94]. Especially some of the molecularly targeted drugs have high efficacy in the CNS.

6.3.5 Isolated liver metastases

Isolated liver metastases are rare in NSCLC patients Therefore, systemic therapy is the main focus. The benefit of locoregional therapy for liver metastases has not been established in lung cancer patients

6.3.6 Isolated adrenal metastases

Patients with isolated adrenal metastases are a distinct group. With resection of the adrenal metastasis as well as optimal local therapy of the primary tumor, treatment with curative intent may be possible, see Figure 4 and chapter 6.1.6.1. The benefit of locoregional therapy of adrenal metastases has been shown in patients in retrospective analyses, results of prospective studies are not available.

6.3.7 HIV-associated lung cancer

Among the non-AIDS-defining malignancies (NADM), lung carcinoma is one of the most common tumors and contributes significantly to morbidity and mortality in HIV-positive patients [110]. The risk of developing lung cancer is approximately 2-7 times higher in the HIV-positive population than in the general population [34]. The median age of onset is 45 years, which is significantly lower than in HIV-negative patients [14]. More than half of patients have stage III or IV disease at the time of diagnosis. Histologically, adenocarcinoma is most commonly found, followed by squamous cell carcinoma, large cell carcinoma, and small cell lung cancer. HIV-typical histologies do not occur.

It is expected that most patients with HIV-associated lung carcinoma are already receiving HAART. This should be continued. In the case of antitumor drug therapy, HAART should be switched to an unboosted regimen without ritonavir or cobicistat prior to initiation of tumor therapy. Potential interactions with other antiretroviral agents should be reviewed. If the patient has not previously received HAART at the time of diagnosis of lung cancer, it should be started prior to initiation of oncologic therapy.

During oncologic therapy, measurements of CD4 positive helper cell counts and HIV viral load should be performed at regular intervals. In particular, if the helper cell count falls below 200/µl, prophylaxis for pneumocystis jirovecii pneumonia should be started with cotrimoxazole and for herpes zoster with aciclovir.

7 Rehabilitation

Surgery, radiotherapy, medical tumor therapy and comorbidity can lead to therapy sequelae of different severity in patients with non-small cell lung cancer. They can be alleviated by targeted rehabilitative measures in the somatic and psychosocial areas.

Patients should be informed at an early stage about the possibilities of outpatient and inpatient rehabilitation measures as well as other claims arising from social law. With regard to the rehabilitation clinic, the patient's wishes should be taken into account (§9 SGB IX). Nevertheless, a recommendation for a clinic with an oncological focus should be made in order to ensure optimal rehabilitation success.

8 Monitoring and Follow-up

8.1 Curative Therapy

The goals of follow-up care are early diagnosis of recurrence with the aim of prolonging survival / increasing the chance of cure, detection of side effects of therapy and preventive care. In patients with lung cancer, the value of intensive, structured follow-up in terms of prolonging survival is not certain. After curative therapy, the goal of follow-up is also the early diagnosis of a second tumor. Some patients with recurrence or a second carcinoma have a curative potential [20]. In these patients, the follow-up interval can be shortened to 6-8 weeks [53].

Recommendations for conventional structured follow-up after therapy with curative intent are summarized in Table 10.

Table 10: Structured follow-up after curative therapy

Examination	Months 3	6	12	18	24	36	48	60
Medical history, physical examination	X	X	X	X	X	X	X	X
Thoracic CT	X*	X*	X	X*	X	X	X	X
Pulmonary function testing	X	X	(X)	(X)	(X)			

Legend:
(X) after radiotherapy;

In patients after radiotherapy alone or after radiochemotherapy, pulmonary function testing should be continued until the risk of pneumonitis has ended [101]. In patients with an individually high risk of developing cerebral metastasis (e.g., large cell carcinomas, undifferentiated adenocarcinomas, small cell carcinomas or mixed tumors, rare lung tumor histologies), one

should certainly consider including MRI cranial examinations in the follow-up plan at realistic intervals (6-9 months), but only in the first three years after local therapy.

8.2 Non-curative therapy

Patients in a palliative situation have the option of early initiation of second-line therapy in the event of disease progression during follow-up after first-line drug therapy. Expert consensus in the S3 guideline recommends shortening the three-month intervals to shorter, 6-8-week intervals [53]. Data from prospective studies on the optimal follow-up interval using current treatment options are not yet available.

A promising new option in patients in the palliative setting is long-term monitoring of patients and disease progression using a web-based tool. In a French study, patients in advanced stages without disease progression were randomized between weekly web-based self-assessment and standardized 3- or 6-monthly CT monitoring. Patients in the experimental arm had significantly longer median survival (HR 0.32; median 7 months) [24].

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16 Disclosure of Potential Conflicts of Interest

according to the rules of DGHO, OeGHO, SGH+SSH, SGMO

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Absenger, Gudrun	Steiermärkische Krankenanstaltengesellschaft m. b. H.	**Yes** Beratertätigkeit für folgende Firmen: Amgen, AstraZeneca, BMS, Böhringer Ingelheim, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, Takeda	**No**	**No**	**Yes** Vortragstätigkeit für folgende Firmen: Amgen, AstraZeneca, BMS, Böhringer Ingelheim, Janssen, Lilly, MSD, Novartis, Pfizer, Roche, Sanofi, Takeda	**No**	**No**	**No**
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