Chapter 152: Lung Cancer

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UPDATE SUMMARY

Update Summary

June 21, 2023

The following sections, tables, and figures were made:

- Key Concept 1: updated 5-year survival rate
- Introduction and Epidemiology: updated estimated 2023 statistics
- Non-Small Cell Lung Cancer, Local Disease (Stages I-II): updated adjuvant osimertinib and pembrolizumab paragraph
- Table 152-6: added adagrasib
- Non-Small Cell Lung Cancer, Advanced (Stage IV) and Relapsed Disease, Targetable Genetic Mutation: added adagrasib

CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Chapter 63, Lung Cancer.

KEY CONCEPTS

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1. Lung cancer is the leading cause of cancer deaths in both men and women in the United States. The overall 5-year survival rate for all types of lung cancer is approximately 23%.

2. Cigarette smoking is responsible for most lung cancers. Smoking cessation should be encouraged, particularly in those receiving curative treatment (ie, Stages I to IIIA non-small cell lung cancer [NSCLC] and limited-stage small cell lung cancer [SCLC]).

3. NSCLC is the most commonly diagnosed type of lung cancer (about 80%). NSCLC typically has a slower growth rate and doubling time than SCLC.

4. Annual screening with low-dose computed tomography (LDCT) imaging is recommended to identify lung cancer in high-risk individuals.

5. The treatment goals for lung cancer are cure (early-stage disease), prolonged survival, and maintenance of, or improved quality of life through alleviation of symptoms. Early-stage lung cancer has the highest cure rates, following surgical resection of the tumor with or without chemotherapy for NSCLC and chemoradiotherapy for SCLC.

6. Treatment decisions for NSCLC are guided by the stage of disease, histology (squamous or nonsquamous), targetable mutations such as epidermal growth factor (EGFR) exon 19 deletion or L858R, EGFR exon 20 insertion, Kirsten rat sarcoma viral oncogene homologue (KRAS), anablastyic lymphoma kinase (ALK), B-rapidly accelerated fibrosarcoma (BRAF), neurotrophic receptor kinase (NTRK), rearranged during transfection (RET), mesenchymal epithelial transition factor (MET), and receptor tyrosine kinase (ROS1), and programmed death ligand (PD-L1) expression levels of the tumor. Patient-specific factors (eg, performance status, comorbid conditions) must also be considered when developing a treatment plan.

7. Targeted therapies for advanced-stage NSCLC are preferred over platinum-based doublets or immunotherapy as first-line therapy in patients whose tumors harbor targetable genetic mutations such as EGFR exon 19 deletions or exon 21 (L858R) substitution mutations, EGFR exon 20 insertion mutations, or mutations in ALK, BRAF, NTRK, KRAS, MET, RET, or ROS1.

8. For patients without a targetable mutation, immunotherapy with anti-programmed-death 1 (PD-1) targeting monoclonal antibody is recommended as first-line treatment of metastatic NSCLC that is PD-L1 positive (tumor proportion score [TPS] ≥50%). Immunotherapy can be added to a platinum doublet in patients with tumors that do not have a targetable genetic mutation and/or are PD-L1 negative. Patients with extensive-stage SCLC may receive immunotherapy either with a platinum doublet as first-line therapy or alone as second-line therapy.

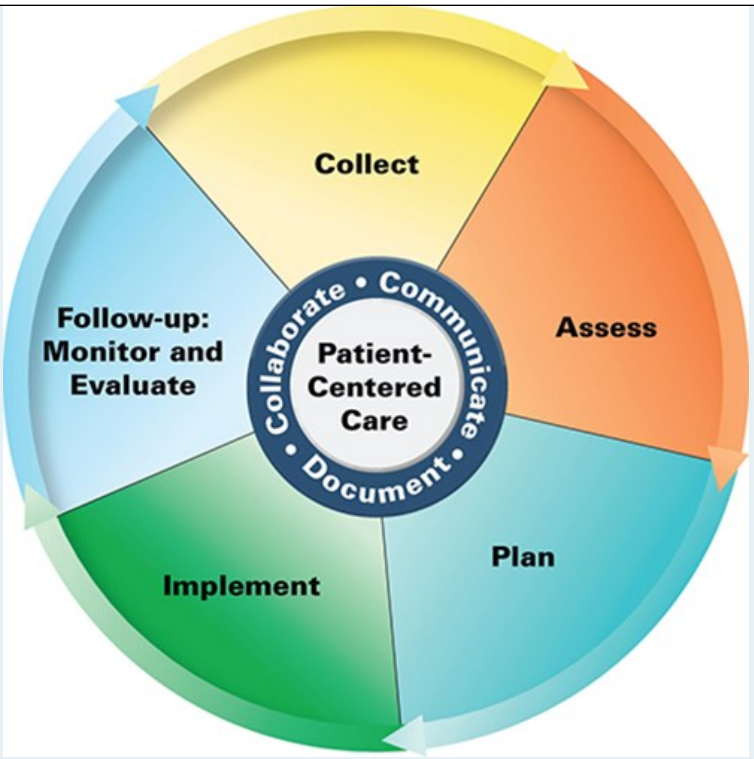
9. In the treatment of limited stage SCLC, thoracic radiation is always combined with chemotherapy and the regimen of choice is etoposide and cisplatin. Prophylactic cranial irradiation is added in patient who achieve a completion response.

10. Treatment approach for patients who experience relapsed SCLC include repeating initial chemotherapy regimen (if >6 months since end of therapy) or second-line therapy with topotecan or lurbinectidin.

11. Optimal patient care includes the management of adverse drug reactions from drug therapy. Adverse drug reactions may cause delays in treatment administration, increase morbidity, and contribute to treatment failure.

PATIENT CARE PROCESS

Patient Care Process for Lung Cancer



Collect

- Patient characteristics (eg, age, ancestry)
- Patient history (past medical, family, social—dietary habits, tobacco use)
- Current medications and any prior anticancer therapy
- Symptoms of pain, pain score, pain management
- Clinical and objective evaluation of tumor status
- Objective data
  - BP, HR, height, weight, respiratory rate
  - Labs (eg, serum electrolytes, complete blood count, Scr, BUN)
  - Imaging scans (CT scan, endobrachial ultrasound)
  - Biopsy to obtain histology (Table 152-1) and biomarkers (PD-1, EGFR, ALK, etc.)

Assess

- Type of and response to any prior treatments
- Stage of tumor (Table 152-2)
- Anticancer treatment options based on the cancer's histology, stage, and biomarkers
- Need for any dose adjustments (renal/hepatic function, drug interaction)
- Adverse drug reactions from current anticancer regimen if this is second dose or second cycle

- Barriers to adherence for oral anticancer regimens
- Emotional status (eg, presence of anxiety, depression)

Plan*

- Goals of treatment (curative or palliative)
- Drug therapy regimen including drugs, dose, route, frequency, and duration (Tables 152-3 to 152-7)
- Supportive care plan (eg, antiemetics, premedications, infection prophylaxis, and medications for specific drugs [eg, folic acid and vitamin B_{12} for pemetrexed])
- Patient education (eg, treatment plan and schedule, adverse drug reactions and how to manage them)
- Provide tools to support adherence to anticancer treatments and supportive care medications
- Encourage use of a diary to track pain medication and diarrhea/constipation medications

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up for assessment of adverse drug reactions and timing of next cycle

Follow-up: Monitor and Evaluate

- Presence of adverse drug reactions
- Measure appropriate laboratory values to determine the presence of serious adverse drug reactions that warrant dose adjustments, delays, or discontinuation at the next cycle
- Assess for signs/symptoms of infection
- Inquire about pain symptoms
- Verify patient adherence to the treatment plan

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

View the video “Lung Cancer Screening”. Detect Lung Cancer early (https://www.youtube.com/watch?v=2cZWXC077L8&t=143s) regarding the use of low-dose computed tomography (CT) scans for early detection in patients at an increased risk of lung cancer. What are some consequences of lung cancer screening in patients who are not at high risk for the disease? Consider the process for low-dose CT scan and the characteristics of appropriate candidates for screening. What are some difficulties patients may have while undergoing this exam? The information is useful to enhance understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION AND EPIDEMIOLOGY

1 Lung cancer is a leading cause of morbidity and mortality. It has reached epidemic proportions in many industrialized countries and is the most common cause of cancer-related death in the world. About 238,340 new cases of lung cancer were diagnosed in the United States in 2023.[1] This represents a continued decline in new lung cancer diagnoses that began more than 30 years ago. Despite major advances in the understanding and management of lung cancer, the overall 5-year survival rate for lung cancer remains low at only 23%. In the United States, lung cancer accounts for about 12% of newly diagnosed cancers and is the leading cause of cancer death in adult men and women, with about 127,070 deaths in 2023. The incidence and mortality related to lung cancer are declining, which has been attributed to decreased tobacco use over the last 50 years as well as the development of new therapies. The incidence of lung cancer increases with age, with 61% of deaths occurring between ages 65 and 85 years.[1] Lung cancer incidence and mortality are higher in Black men and slightly lower in Black women compared to White counterparts.[1] The cure rate is highest with early-stage disease treated with surgical resection; however, most patients present with metastatic disease.[1]

Two leading oncology groups in the United States have published clinical practice guidelines for the treatment of lung cancer. The National Comprehensive Cancer Network (NCCN) has developed consensus-based guidelines that provide recommendations regarding the screening, staging, and treatment of both non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC).[2,3] The American Society of Clinical Oncology (ASCO) publishes several evidence-based guidelines that are regularly updated regarding the care of patients with lung cancer.[4,5] ASCO also has endorsed the guidelines of other organizations including guidelines on the use of molecular testing for NSCLC[6] and guidelines on the treatment of SCLC.[7]

ETIOLOGY

Lung carcinomas arise from normal bronchial epithelial cells that have acquired multiple genetic lesions and express a variety of phenotypes.[8] Important advances have been made in our understanding of the molecular genetic changes involved in lung cancer pathogenesis.[8] A large variety of molecular lesions result in the abrogation of key cellular regulatory and growth control pathways. Mutations cause activation of proto-oncogenes, inhibition of tumor suppressor genes, and production of autocrine (self-stimulatory) growth factors contributing to cellular proliferation and malignant transformation.[8]

Many of these molecular alterations are common to both SCLC and NSCLC, but certain mutations are found more frequently in specific subtypes of lung cancer and can be potentially treated with targeted interventions. In autocrine loop abnormalities, SCLC frequently overexpresses C-KIT, a protein tyrosine kinase receptor that is specific for stem cell factor. For NSCLC, multiple mutations have been identified that can drive tumor growth and survival. These biomarkers serve as targets of drug therapy. Multiple targetable mutations have been identified in NSCLC including EGFR, ALK, KRAS, BRAF, NTRK, MET, RET, ROS1, and HER2.[8–10]

2 Smoking is a major cause of lung cancer, with about 80% of lung cancer deaths in the United States directly attributed to tobacco use. Tobacco smoke contains many substances, including tumor promoters, carcinogens, and cocarcinogens.[11] The association between environmental tobacco smoke (ETS; also referred to as passive smoking) and lung cancer risk in nonsmokers is clear. Studies show that spouses of smokers have a 25% higher risk of lung cancer than spouses of nonsmokers. In addition, workplace exposure to ETS increases the risk of lung cancer by about 17%. ETS contributes to about 3,000 lung cancers annually. Although these studies are observational, they consistently show a dose-risk relationship, with no safe level of exposure.[11] Smoking cessation is associated with a gradual decrease in the risk, but more than 5 years is necessary before an appreciable decline in risk occurs and the risk never returns to that of a nonsmoker.[11] Because of the public health implications, the United States has several tobacco control efforts, including antismoking campaigns, increased tobacco taxes, and smoke-free areas in many public areas. Although the prevalence of cigarette smoking has slowly decreased, it remains at about 14% in 2019.[12]

Although most cases of lung cancer are attributable to cigarette smoking, less than 20% of smokers develop lung cancer, suggesting other risk factors are relevant. An increased risk of lung cancer has been associated with exposure to other environmental respiratory carcinogens (eg, asbestos, benzene, and arsenic). Genetic risk factors are also important, with an increased risk of lung cancer observed in those with first-degree relatives diagnosed with the disease. Lung cancer risk is associated with polymorphisms that affect the expression and/or function of enzymes regulating the metabolism of tobacco carcinogens, DNA repair, or inflammation. Patients with a history of chronic obstructive airway disease and adults with asthma

are at an increased risk of lung cancer.[8,10]

HISTOLOGIC CLASSIFICATION

Before treatment begins, it is critical that an experienced lung cancer pathologist reviews the pathologic material to confirm malignancy, characterize the tumor histology, and identify targetable molecular characteristics of the tumor.

3 NSCLC is diagnosed in most (80%) lung cancer patients. NSCLC typically has a slower growth rate and doubling time than SCLC. The histologic classification of NSCLC is well defined and widely accepted (Table 152-1).[13] Histologic types, subtypes, and identifiable variants provide information about the prognosis and can influence therapeutic decisions.[13,14]

TABLE 152-1

Histologic Classification of Non-Small Cell Lung Carcinomas

1. Squamous cell carcinoma
    - Papillary
    - Clear cell
    - Small cell
    - Basaloid
2. Adenocarcinoma
    - Minimally invasive adenocarcinoma
    - Invasive adenocarcinoma
    - Lepidic predominant (previously classified as bronchioalveolar carcinoma)
    - Acinar predominant
    - Papillary predominant
    - Micropapillary predominant
    - Solid predominant with mucin
    - Variants of invasive adenocarcinoma
    - Invasive mucinous adenocarcinoma (previously classified as bronchioalveolar carcinoma)
    - Colloid
    - Fetal (low and high grade)
    - Enteric
3. Large cell carcinoma
    - Large cell neuroendocrine carcinoma
    - Combined large cell neuroendocrine carcinoma
    - Basaloid carcinoma
    - Lymphoepithelioma-like carcinoma
    - Clear cell carcinoma
    - Large cell carcinoma with rhabdoid phenotype
4. Adenosquamous carcinoma
5. Sarcomatoid carcinomas
    - Pleomorphic carcinoma
    - Spindle cell carcinoma
    - Giant cell carcinoma
    - Carcinosarcoma
    - Pulmonary blastoma
    - Other
6. Carcinoid tumor
    - Typical carcinoid
    - Atypical carcinoid
7. Carcinomas of salivary gland type
    - Mucoepidermoid carcinoma
    - Adenoid cystic carcinoma
    - Epimyoepithelial carcinoma

Adapted from 2004 WHO classification and the 2011 IASCL/ATS/ERS classification.

Four major cell types of carcinomas (squamous cell, adenocarcinoma, large cell, and small cell) account for more than 90% of lung tumors. Early

studies with localized disease demonstrated that radiation could cure SCLC, while surgery could not. Studies with the other histologic types demonstrated better outcomes with surgery than with radiation, which provided the basis for the general classification of SCLC and NSCLC. Historically, systemic treatment for NSCLC histologies was the same and resulted in a similar overall prognosis, which supported a general classification of SCLC and NSCLC. Incorporation of genetics in NSCLC and the availability of targeted therapies have led to personalized treatment. Optimal therapy requires knowledge of histology, immunotherapy marker expression, and genetic mutational status.[6,8]

Squamous cell carcinoma, one of the most common histologies of all lung cancers, now represents less than 30% of cases. It has a much higher incidence in males and smokers, with a strong dose-response relationship to tobacco exposure. Studies of the natural history of lung cancer in show a relatively constant tumor volume doubling time (104-122 days).[15] Squamous cell tumors are slower to metastasize with eventual spread to the hilar and mediastinal lymph nodes, liver, adrenal glands, kidneys, bone, and gastrointestinal tract.

Other histologies occurring in NSCLC are collectively referred to as nonsquamous NSCLC. Adenocarcinoma accounts for half of lung cancers and is increasing in frequency. It is the most common histology in nonsmoking patients. The natural history of adenocarcinoma in the lung shows that small tumors discovered through screening are relatively slow growing and tumor doubling time increases as they enlarge. Doubling time of tumors discovered with screening is about 576 days, while those found only with routine patient care grew more rapidly, doubling in size every 169 days.[15] This histology is likely to metastasize from a relatively small tumor (often before diagnosis) and spread widely to distant sites, including the contralateral lung, liver, bone, adrenal glands, kidneys, and CNS. Table 152-1 shows several subclassifications and variants of adenocarcinoma. Large cell carcinomas are infrequently occurring, undifferentiated epithelial tumors, which tend to be large and bulky tumors arising in the periphery of the lung. Large cell carcinomas have a propensity to metastasize in a pattern like adenocarcinomas and are associated with a similar prognosis.[3,10]

SCLCs account for 15% of all lung tumors. They are distinguished by their appearance as small cells with round to oval nuclei. Historically, SCLC was referred to as “oat cell” carcinoma due to its appearance. These tumors occur in major bronchi and the periphery of the lung. SCLC is aggressive and rapidly growing, with 60% to 70% of patients initially presenting with disease outside the hemithorax. SCLC commonly expresses neuroendocrine differentiation, which may account for some of the paraneoplastic syndromes frequently associated with this disease. SCLC secretes gastrin-releasing peptide that acts as an autocrine growth factor. The secretion of other peptide hormones, cytogenetic abnormalities, and amplification and increased expression of oncogenes are also common. SCLC typically metastasizes to the lymph nodes, opposite lung, liver, adrenal glands and other endocrine organs, bone, bone marrow, and CNS.[2,9] Unlike NSCLC, SCLC treatment is not guided by specific biomarkers due to their lack of clinical data demonstrating efficacy with targeted agents. However, genetic studies may be performed should new targeted therapies be developed.

Lung tumors can exhibit more than one cell type (eg, adenosquamous). Mixed histology tumors should also undergo genetic testing.[6,8] Patients can have multiple lung nodules arising in different lobes or the contralateral lung. This is referred to as synchronous tumors, and the nodules can be the same or different cell types. Synchronous tumors worsen overall prognosis.[3]

CLINICAL PRESENTATION

At the time of diagnosis, 16% of lung cancers are localized, 22% have regional spread, and 57% have distant metastases (some patients are not staged). Location and extent of the tumor determine presenting signs and symptoms. A lesion in the central portion of the bronchial tree is more likely to cause symptoms at an earlier stage as compared with a lesion in the periphery of the lung, which may remain asymptomatic until the lesion is large or has spread. The most common initial signs and symptoms include cough, dyspnea, and chest pain or discomfort, with or without hemoptysis.[10] Many patients with lung cancer also have chronic pulmonary and/or cardiovascular diseases (usually related to smoking), and such symptoms may go unnoticed or be attributed to concomitant diseases. Many patients also exhibit systemic symptoms of malignancy such as anorexia, weight loss, and fatigue. Disseminated disease can cause extrapulmonary signs and symptoms such as neurologic deficits resulting from CNS metastases, bone pain or pathological fractures secondary to bone metastases, or liver dysfunction resulting from tumor involvement in the liver.[10]

Paraneoplastic syndromes are signs and symptoms that occur at sites away from the tumor location(s) and are not associated with direct tumor involvement. They may be caused by the production of biologically active substances (eg, peptide hormones) or antibodies or by other undefined mechanisms. Paraneoplastic syndromes occur more frequently with lung cancer than with any other tumor, and more frequently with SCLC than with NSCLC. These syndromes may be the first signs of a tumor and may prompt the search for an underlying malignancy.[9]

CLINICAL PRESENTATION: Lung Cancer

Local signs and symptoms

- Cough
- Hemoptysis
- Dyspnea
- Rust-streaked or purulent sputum
- Chest, shoulder, or arm pain
- Wheeze and stridor
- Superior vena cava obstruction
- Pleural effusion or pneumonitis
- Dysphagia (secondary to esophageal compression)
- Hoarseness (secondary to laryngeal nerve paralysis)
- Horner's syndrome
- Phrenic nerve paralysis
- Pericardial effusion/tamponade
- Tracheal obstruction

Extrapulmonary signs and symptoms

- Bone pain and/or pathologic fractures
- Liver dysfunction
- Neurologic deficits
- Spinal cord compression

Paraneoplastic syndromes

- Weight loss
- Cushing's syndrome
- Hypercalcemia (most commonly in squamous cell lung cancer)
- Syndrome of inappropriate secretion of antidiuretic hormone (most commonly in SCLC)
- Pulmonary hypertrophic osteoarthropathy
- Clubbing
- Anemia
- Eaton-Lambert myasthenic syndrome

- Hypercoagulable state

SCREENING AND PREVENTION

Most patients with lung cancer have advanced disease at the time of diagnosis, which contributes to the poor prognosis associated with this disease. Surgery and radiation are the most effective treatment modalities in NSCLC and SCLC, respectively. Only patients diagnosed in early clinical stage can be cured with these treatment modalities alone.[2,3,16,17] The need to diagnose lung cancer earlier provides rationale for screening.

The survival benefits of screening with low-dose computed tomography (LDCT) were first documented in the National Lung Cancer Screening Trial, which enrolled more than 54,000 high-risk smokers. Screening discovered 70% of tumors at stage I or II, when they were potentially curable with surgical resection. The study reported a decrease in overall mortality (7% vs 7.5%) and lung cancer-specific mortality (1.3% vs 1.7%) with LDCT versus control.[18]

The evidence-based recommendation is to offer annual screening with LDCT to high-risk individuals, defined as aged 50 to 80 years with a 20-pack-year history who are still smoking or have quit for less than 15 years.[19] This recommendation comes with a few caveats, including the fact that the most important step is for current smokers to quit. Follow-up trials to the National Lung Cancer Screening Trial validated the earlier onset of screening[20] and the pack year criteria.[21]

C*hemoprevention* (the use of prophylactic medications to prevent the development of cancer) has failed to show benefit for lung cancer. Many studies of potential chemopreventive agents, including nonsteroidal anti-inflammatory drugs, retinoids, inhaled glucocorticoids, vitamin E, selenium, and green tea extracts, have been conducted, but none have been successful.[22] In summary, the most effective prevention/early intervention approach is to avoid tobacco, maintain a healthy diet with high amounts of fruits and vegetables, and offer screening to high-risk individuals.

DIAGNOSIS

A patient suspected of having lung cancer should undergo a diagnostic evaluation. Diagnosis of lung cancer requires visualization of the cancerous lesion and tissue sampling for pathologic assessment. Patients must have a thorough history and physical examination with emphasis on detecting signs and symptoms of the primary tumor, regional spread, distant metastases, and paraneoplastic syndromes. Performance status should be assessed to determine if a patient is a candidate for aggressive therapy.[2,3,9,10]

Visualization of suspected tumor(s) provides information necessary to choose the most appropriate sampling technique. Computed tomography (CT) scans of the chest and upper abdomen are the most common initial radiologic evaluations. The staging workup can include an endobronchial ultrasound, positron emission tomography (PET) scan, or other tests.[9,10] The use of integrated CT-PET technology has been reported to improve the diagnostic accuracy in the staging of NSCLC over either test alone.[10]

Once located, pathologic examination of tumor tissue is necessary to establish the diagnosis of lung cancer. Tissue is usually obtained through the least invasive method most likely to result in an adequate sample; methods include sputum cytology, tumor biopsy by bronchoscopy, mediastinoscopy, percutaneous needle biopsy, or open lung biopsy. The tissue sample not only confirms malignancy, it is also necessary to determine the specific tumor type and to provide tissue for molecular analysis including testing for PD-L1 and genetic mutations that drive tumor growth.[4,5] Once the diagnosis is established, additional radiologic tests may be required to evaluate lymph nodes and potential metastatic sites for complete staging.[2,3,9,10]

STAGING

Once the diagnosis of lung cancer is confirmed, the extent of disease must be determined to estimate prognosis and guide therapy. For NSCLC, tumor growth and spread are staged with the American Joint Committee on Cancer, tumor, node, and metastasis (TNM) staging system. SCLC is typically staged with the Veterans Administration Lung Cancer Study Group method.[13,23]

Non-Small Cell Lung Cancer

Clinical staging of NSCLC with the TNM system incorporates the size of the tumor, extent of nodal involvement, and presence of metastatic sites.[13] Clinical stages and associated survival rates are described in Table 152-2. For comparison of various therapeutic modalities, a simpler stage grouping system is used in which stage I refers to tumors confined to the lung without lymphatic spread, stage II refers to large tumors with ipsilateral peribronchial or hilar lymph node involvement, stage III includes other lymph node and regional involvement that may or may not involve both lungs, and stage IV includes tumor with distant metastases. Local disease is associated with the highest cure and survival rates, while advanced disease results in 5-year survival of less than 5%. Once evidence of metastatic disease has been identified, further evaluation is not necessary.

TABLE 152-2

Tumor (T), Node (N), Metastasis (M) Staging for Non-Small Cell Lung Cancer

Primary Tumor (T)		Description
T_1		Tumor ≤3 cm in diameter, surrounded by lung or visceral pleura, without invasion more proximal than lobar bronchus
	T_{1mi}	Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in diameter) with a predominately lepidic pattern
	T_{1a}	Tumor ≤1 cm in diameter
	T_{1b}	Tumor >1 cm but ≤2 cm in diameter
	T_{1c}	Tumor >2 cm but ≤3 cm in diameter
T_2		Tumor >3 cm but ≤5 cm, or tumor with any of the following features: - Involves main bronchus, without involvement of the carina - Invades visceral pleura - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung
	T_{2a}	Tumor >3 cm but ≤4 cm
	T_{2b}	Tumor >4 cm but ≤5 cm
T_3		Tumor >5 cm but ≤7 cm or directly invading the parietal pleura, chest wall, phrenic nerve, parietal pericardium, or with separate tumor nodule(s) in the same lobe as the primary tumor
T_4		Tumor >7 cm or tumor of any size that invades the diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or with separate tumor nodules in a different ipsilateral lobe
Regional Lymph Nodes (N)		
N_0		No regional lymph node metastases
N_1		Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N_2		Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N_3		Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
Distant Metastasis (M)		
M_0		No distant metastasis
M_1		Distant metastasis
	M_{1a}	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules, or malignant pleural or pericardial effusion
	M_{1b}	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
	M_{1c}	Multiple extrathoracic metastases

Stage	T	N	M	5-Year Survival (%)
IA1	T_{mi}-T_{1a}	N_0	M_0	92%
IA2	T_{1b}	N_0	M_0	83%
IA3	T_{1c}	N_0	M_0	77%
IB	T_{2a}	N_0	M_0	68%
IIA	T_{2b}	N_0	M_0	60%
IIB	T_{1a}, T_{1b}, T_{1c}, T_{2a}, T_{2b}	N_1	M_0	53% (all IIB)
	T_3	N_0	M_0	
IIIA	T_{1a}, T_{1b}, T_{1c}, T_{2a}, T_{2b}	N_2	M_0	36% (all IIIA)
	T_3	N_1	M_0	
	T_4	N_0, N_1	M_0	
IIIB	T_{1a}, T_{1b}, T_{1c}, T_{2a}, T_{2b}	N_3	M_0	26% (all IIIB)
	T_3, T_4	N_2	M_0	
IIIC	T_3, T_4	N_3	M_0	13%
IVA	Any T	Any N	M_{1a} or M_{1b}	10%
IVB	Any T	Any N	M_{1c}	<1%

Small Cell Lung Cancer

The most commonly used system of staging SCLC was developed originally by the Veterans Administration Lung Cancer Study Group.[23] This system categorizes SCLC into two stages: limited and extensive disease. When evidence of the tumor is confined to a single hemithorax and can be encompassed by a single radiation field, the disease is considered limited. Progression beyond this point is extensive disease. About 60% to 70% of patients initially present with extensive-stage disease. The initial pretreatment evaluation of an SCLC patient should include a medical history, a clinical examination, and laboratory survey, as well as a CT scan of the chest, abdomen, and head. The typical approach is to identify tumor spread that would demonstrate extensive stage, at which time the workup can stop. For patients without extrathoracic disease, a bone scan and bone marrow biopsy should be performed to confirm limited-stage disease.[2,9]

TREATMENT

Desired Outcomes

5 The treatment goals for lung cancer include cure, prolonged survival when cure is not possible, and maintenance of/improved quality of life through symptom alleviation. The ability to achieve these goals depends on tumor histology, extent of disease, and patient characteristics such as age, history, and performance status.[2,3] Stages I and II (NSCLC) or limited-stage (SCLC) diseases are commonly referred to as early-stage disease, while stages III and IV (NSCLC) or extensive-stage (SCLC) diseases are referred to as advanced-stage disease. In patients with early-stage disease who can tolerate aggressive treatment, a definitive cure is the desired outcome of treatment. In patients with advanced-stage disease who can tolerate aggressive therapy, the desired outcome is prolongation of survival. Regardless of treatment goals, all therapies should improve quality of life. Patients should carefully weigh the potential benefits of treatment against the significant toxicities associated with an aggressive approach. Treatment decisions must include the healthcare team and an informed, well-counseled patient.

Non-Small Cell Lung Cancer

6 If left untreated, patients with advanced NSCLC will die within months.[10] Surgery, radiation, and systemic therapies with cytotoxic chemotherapy, immunotherapy, or targeted therapies are used in the management of NSCLC. The applications of these treatment modalities are determined by stage- and patient-specific factors.[3,10]

Local Disease (Stage I-II)

Local disease is associated with a favorable prognosis and the treatment goal is cure. A multimodal approach involving surgery, radiation, and systemic treatments is utilized for early-stage disease. Surgery is the primary treatment and may be used alone or in combination with radiation and/or systemic therapy.[3] Patients who are not surgical candidates or refuse surgical interventions can be treated with radiation, although cure rates are lower. Stage IA and IB tumors are treated with surgery.[3,24] If surgical margins are positive, re-resection is recommended. Alternatively, patients may receive radiotherapy with or without chemotherapy. Although controversial, patients with IB tumors and high-risk features (eg, poorly differentiated tumors, vascular invasion, large tumors, visceral pleural involvement) may also receive adjuvant chemotherapy.[3,24,25]

The primary treatment of stage IIA and IIB diseases is surgery followed by adjuvant chemotherapy, typically for four cycles. The optimal adjuvant chemotherapy regimen is not clear. Positive clinical trials used platinum-based regimens, with arguably the best clinical trial data coming from cisplatin–vinorelbine (Table 152-3).[14] The absolute benefit in 5-year overall survival ranges from no benefit to 15%, with a recent systematic review reporting an absolute difference of 4%. The analysis suggested little effect of the chemotherapy regimen.[14] Although genetics and histology influence systemic treatment and outcomes in advanced disease, this approach has not been tested in large, randomized trials of adjuvant chemotherapy.

TABLE 152-3

Common Chemotherapy Regimens Used in the Adjuvant Treatment of Non-Small Cell Lung Cancer

Regimen	Drugs and Doses	Frequency and Number of Cycles
Cisplatin/etoposide	Cisplatin 100 mg/m^2 IV day 1 Etoposide 100 mg/m^2 IV daily on day 1, 2, and 3	Every 28 days for 4 cycles
Cisplatin/vinorelbine	Cisplatin 50 mg/m^2 IV day 1 and 8 Vinorelbine 25 mg/m^2 IV day 1, 8, 15, and 22	Every 28 days for 4 cycles
	Cisplatin 100 mg/m^2 IV day 1 Vinorelbine 30 mg/m^2 IV day 1, 8, 15, and 22	Every 28 days for 4 cycles
Carboplatin/paclitaxel	Carboplatin AUC 6 IV day 1 Paclitaxel 200 mg/m^2 IV day 1	Every 21 days for 4 cycles
Cisplatin/pemetrexed	Cisplatin 75 mg/m^2 IV day 1 Pemetrexed 500 mg/m^2 IV day 1	Every 21 days for 4 cycles (for nonsquamous histology only)

The benefits of adjuvant targeted therapy in patients who have undergone a complete resection of their NSCLC has been identified. In patients with stage Ib to IIIa disease whose tumors test positive for sensitizing EGFR mutations, the kinase inhibitor, osimertinib, improved 5-year overall survival from 78% to 88% compared to placebo.[26] Benefit was demonstrated in patients regardless of chemotherapy use after surgery. The study was planned for a 3-year duration of treatment; however, it was stopped early due to clinical benefit, leaving the optimal duration of therapy in the adjuvant setting unknown. Program death pathway inhibitors pembrolizumab and atezolizumab have also demonstrated benefit in the adjuvant treatment of NSCLC following complete resection and chemotherapy. In patients with stage II-IIIA disease whose tumors have a PD-L1 expression of at least 1%, 1 year of atezolizumab resulted in improved disease-free survival at 2 years (74.6% vs 61.0%) and at 3 years (60% vs 48.2%).[27] It is important to note atezolizumab is not approved for use in patients with stage IB disease. In patients with stage IB-IIIA disease, regardless of PD-L1 expression, 1 year of pembrolizumab resulted in improved median disease-free survival from 34.9 months to 58.7 months compared to placebo.[28] Targeted therapies are discussed in further detail in the section of this chapter covering treatment of advanced stage and relapsed NSCLC, information on proper dosing can be found in Tables 152-4, 152-5, and 152-6.

TABLE 152-4

Selected Regimens for the First-Line Treatment of Advanced-Stage Non-Small Cell Lung Cancer

	Nonsquamous		Squamous	
Place in Therapy	PD-L1 ≥50%	PD-L1 1%-49%	PD-L1 ≥50%	PD-L1 1%-49%
First Line	Pembrolizumab 200 mg IV on day 1 every 21 days or 400 mg IV on day 1 every 42 days Repeat until disease progression or	Platinum + pemetrexed + pembrolizumab Cisplatin 75 mg/m^2 or Carboplatin AUC 5 IV on day 1 Pemetrexed 500 mg/m^2 IV on day 1 Pembrolizumab 200 mg IV on day 1 Repeat cycle every 3 weeks × 4 cycles—	Pembrolizumab 200 mg IV on day 1 every 21 days or 400 mg IV on day 1 every 42 days Repeat until disease progression, or	Carboplatin + paclitaxel + pembrolizumab Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m^2 IV on day 1 or nab-paclitaxel 100 mg/m^2 IV on day 1, 8, and 15 Pembrolizumab 200 mg IV on day 1

	unacceptable toxicity for a maximum of 2 years	Pembrolizumab maintenance up to 31 additional doses or until progression	unacceptable toxicity for a maximum of 2 years	Repeat cycle every 3 weeks × 4 cycles– Pembrolizumab maintenance up to 31 additional doses or until progression
	Atezolizumab 840 mg IV on day 1 repeat every 14 days or 1,200 mg IV on day 1 repeat every 21 days or 1,680 mg IV on day 1 repeat every 28 days Continue until disease progression or unacceptable toxicity	Atezolizumab + carboplatin + paclitaxel + bevacizumab Atezolizumab 1,200 mg IV on day 1 Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m^2 IV on day 1 Bevacizumab 15 mg/kg IV on day 1 Repeat cycle every 3 weeks × 6 cycles Atezolizumab and bevacizumab maintenance until progression	Carboplatin + taxane + pembrolizumab Carboplatin AUC 6 IV on day 1 Paclitaxel 200 mg/m^2 IV on day 1or nab-paclitaxel 100 mg/m^2 IV on day 1, 8, and 15 Pembrolizumab 200 mg IV on day 1 Repeat cycle every 3 weeks × 4 cycles Pembrolizumab maintenance up to 31 additional doses or until progression	Nivolumab + ipilimumab + carboplatin + paclitaxel Nivolumab 360 mg IV on day 1 and 22 Ipilimumab 1 mg/kg IV on day 1 Paclitaxel 200 mg/m^2 on day 1 and 22 Carboplatin AUC 6 IV on day 1 and 22 Followed by nivolumab and ipilimumab maintenance every 42 days until disease progression or unacceptable toxicity for a maximum of 2 years
	Cemiplimab 350 mg IV on day 1 Repeat every 21 days until disease Continue until disease progression or unacceptable toxicity	Nivolumab + ipilimumab + platinum + pemetrexed Nivolumab 360 mg IV on days 1 and 22 Ipilimumab 1 mg/kg IV on day 1 Pemetrexed 500 mg/m^2 on days 1 and 22 Carboplatin AUC 6 IV or cisplatin 75 mg/m^2 on day 1 and 22 Followed by nivolumab and ipilimumab maintenance every 42 days until disease progression or unacceptable toxicity for a maximum of 2 years	Atezolizumab 840 mg IV on day 1, repeat every 14 days or 1,200 mg IV on day 1 repeat every 21 days or 1,680 mg IV on day 1 repeat every 28 days Continue until disease progression or unacceptable toxicity	Nivolumab + ipilimumab Nivolumab 3 mg/kg IV on day 1, 15, and 29 Ipilimumab 1 mg/kg IV on day 1 Repeat every 42 days until disease progression or unacceptable toxicity for a maximum of 2 years
	Platinum + pemetrexed + pembrolizumab Cisplatin 75 mg/m^2 or carboplatin AUC 5 IV on day 1 Pemetrexed 500 mg/m^2 IV on day 1 Pembrolizumab 200 mg IV on day 1 Repeat cycle every 3 weeks × 4 cycles Pembrolizumab	Nivolumab + ipilimumab Nivolumab 3 mg/kg IV on day 1, 15, and 29 Ipilimumab 1 mg/kg IV on day 1 Repeat every 42 days until disease progression or unacceptable toxicity for a maximum of 2 years	Cemiplimab 350 mg IV on day 1 Repeat every 21 days until disease progression or unacceptable toxicity	Pembrolizumab 200 mg IV on day 1 every 21 days or 400 mg IV on day 1 every 42 days Repeat until disease progression, or unacceptable toxicity for a maximum of 2 years

	maintenance up to 31 additional doses or until progression			
First-line: Contraindications to PD-1 or PD-L1 Inhibitors	Carboplatin + pemetrexed Carboplatin AUC 5 IV on day 1 Pemetrexed 500 mg/m^2 IV on day 1 Repeat cycle every 3 weeks × 4 or 6 cycles followed by pemetrexed maintenance		Gemcitabine + cisplatin Gemcitabine 1,000 mg/m^2 IV on day 1, 8, and 15 Cisplatin 100 mg/m^2 IV on day 1 Repeat cycle every 28 days	

TABLE 152-5

Selected Regimens for the Second-Line Treatment of Advanced-Stage Non-Small Cell Lung Cancer

Second Line: No previous checkpoint inhibitor	Nivolumab 240 mg IV on day 1 repeat every 14 or 480 mg IV on day 1 repeat every 28 days Continue until disease progression or unacceptable toxicity
	Atezolizumab 840 mg IV on day 1, repeat every 14 days or 1,200 mg IV on day 1 repeat every 21 days or 1,680 mg IV on day 1 repeat every 28 days Continue until disease progression or unacceptable toxicity
	Pembrolizumab 200 mg IV on day 1 every 21 days or 400 mg IV on day 1 every 42 days Repeat until disease progression, or unacceptable toxicity
Second Line: Other recommend	Docetaxel + ramucirumab Docetaxel 75 mg/m^2 IV day 1 Ramucirumab 10 mg/kg IV day 1 Repeat every 21 days

TABLE 152-6

Selected Oral Targeted Therapies for Advanced, Mutation-Driven NSCLC

Drug and Dosing	Adverse Reactions		Monitoring Parameters	Comments
	Common	Rare but Serious		
EGFR Exon 19 Deletion or *EGFR l858R* Mutation				
Osimertinib 80 mg (1 × 80 mg tablet) once	• Anorexia • Dermatologic reactions including dry skin and rash	• Cardiomyopathy • Interstitial lung disease • Keratitis	• Signs and symptoms of interstitial lung disease (dyspnea, cough, and fever) • Skin exam	• Can be taken without regard to meals • Increase dose by 50% if patient taking strong

daily	• Diarrhea • Fatigue • Myelosuppression • Paronychia • Stomatitis	• QTc interval prolongation	• CMP at baseline and periodically • Ophthalmic exam periodically and at the onset of any vision changes • CBC at baseline and periodically • ECG periodically in patients with congenital long QTc syndrome, heart failure, electrolyte abnormalities, or concomitantly receiving other QT prolonging agents • Ejection fraction at baseline and periodically in patients at risk for developing heart failure or if patients develop cardiac symptoms	cytochrome P4503A4 inducer • Activity not effected by T790M mutation • Improved CNS activity compared to other EGFR targeting agents • Can be used in patients who have progressed while receiving earlier generation inhibitors (erlotinib, gefitinib, dacomitinib)
Erlotinib 150 mg (1 × 150 mg tablet) once daily	• Anorexia • Cough • Fatigue • Diarrhea • Dyspnea • Nausea and vomiting • Rash	• Cerebrovascular accident • Gastrointestinal perforation • Hemolytic anemia with thrombocytopenia • Hepatotoxicity including hepatorenal syndrome • Interstitial lung disease • Ocular disorders including corneal perforation, ulceration, or severe keratitis • Severe rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis	• Signs and symptoms of interstitial lung disease • Skin exam • CMP at baseline and periodically • Ophthalmic examinations periodically and at the onset of any changes in vision • Signs and symptoms of hemorrhage if patients receiving warfarin	• Should be taken 1 hour before or 2 hours after meals • Best absorbed in acidic gastric environment • Cytochrome P450 3A4 substrate, use with caution with 3A4 inducers/inhibitors • Increased hemorrhage risk with warfarin • Resistance caused by T790M mutation • Has been studied in combination with bevacizumab or ramucirumab
Afatinib 40 mg (1 × 40 mg tablet) once daily	• Anorexia • Dermatologic reactions including dry skin and rash • Diarrhea • Nausea and vomiting	• Hepatotoxicity • Interstitial lung disease • Keratitis • Renal impairment from dehydration	• Signs and symptoms of interstitial lung disease • Skin exam • CMP at baseline and periodically • Ophthalmic examinations periodically and at onset of any	• Should be taken 1 hour before or 2 hours after meals • Dose reduction recommended for severe renal impairment

	• Paronychia • Pruritus • Stomatitis	due to diarrhea • Severe rash, including Stevens-Johnson syndrome and toxic epidermal necrolysis	changes in vision	• Diarrhea can be severe and require dose reductions • Pharmacokinetics may be affected by P-glycoprotein inhibitors and inducers • Resistance caused by T790M mutation • Patients with reduced ejection fraction excluded from clinical trials
ALK Rearrangement				
Alectinib 600 mg (4 × 150 mg capsules) twice daily	• Anemia • Constipation • Edema • Fatigue • Hepatotoxicity • Leukopenia • Myalgia • Photosensitivity	• Bradycardia • Endocarditis • Gastrointestinal perforation • Increased creatine kinase • Interstitial lung disease • Pulmonary embolism • Renal impairment	• Signs and symptoms of interstitial lung disease • CMP at baseline and periodically • CBC with differential monthly • Liver function tests every 2 weeks for the first 3 months of treatment then monthly • Heart rate and blood pressure should be monitored regularly • CPK every 2 weeks for the first month of treatment and with patient reports of unexplained muscle pain, tenderness, or weakness	• Should be taken with meals • Counsel regarding appropriate precautions to protect from UVA/UVB exposure
Brigatinib 90 mg (1 × 90 mg tablet) orally once daily for 7 days then increase to 180 mg (1 × 180 mg tablet) daily if tolerated	• Cough • Diarrhea • Fatigue • Hyperglycemia • Increased creatine kinase • Increased serum lipase and amylase • Nausea	• Bradycardia • Hypertension • Interstitial lung disease • Pneumonitis, including pneumonia • Visual disturbances	• Signs and symptoms of interstitial lung disease • Ophthalmic examinations periodically and at the onset of any changes in vision • Blood pressure should be monitored after 2 weeks then monthly • Heart rate and blood pressure should be monitored regularly • CPK levels should be monitored regularly • Fasting serum glucose at baseline and regularly • Lipase and amylase levels monitored regularly	• Can be taken without regard to meals • Dose reduction recommended for severe renal or hepatic impairment • Cytochrome P450 3A4 substrate, should not be used with moderate-to-strong inhibitors or inducers of 3A4

Lorlatinib 100 mg (1 × 100 mg tablet) once daily	• Arthralgia • Diarrhea • Dyslipidemia • Dyspnea • Edema • Fatigue • Peripheral neuropathy • Weight gain	• Atrioventricular block • CNS effects such as mood disorders or seizures • Hepatotoxicity • Hyperglycemia • Hypertension • Interstitial lung disease	• Signs and symptoms of interstitial lung disease • Blood pressure should be monitored after 2 weeks then monthly • Heart rate and blood pressure should be monitored regularly • Fasting serum glucose at baseline and regularly • Serum cholesterol and triglycerides at baseline, 1 month and 2 months after initiation then periodically • ECG at baseline and periodically	• Can be taken without regard to meals • Dose reduction recommended for severe renal impairment • Has demonstrated efficacy after the failure of previous ALK targeted therapies • Patients with severe psychiatric illness excluded from clinical trials
ROS1 Rearrangement				
Crizotinib 250 mg (1 × 250 mg capsule) twice daily	• Anorexia • Constipation • Diarrhea • Dizziness • Edema • Fatigue • Hepatotoxicity • Lymphopenia and neutropenia • Nausea and vomiting • Neuropathy • Upper respiratory infection, including possible pneumonia • Vision disorders	• Bradycardia • Interstitial lung disease • Pulmonary embolism • QTc interval prolongation	• Signs and symptoms of interstitial lung disease • CMP at baseline and periodically • Ophthalmic evaluation in patients with new-onset vision changes • CBC with differential monthly • ECG should be monitored periodically in patients with heart failure, bradyarrhythmias, electrolyte abnormalities, or concomitantly receiving other QT prolonging agents • Heart rate and blood pressure should be monitored regularly	• Can be taken without regard to meals • Dose reduction recommended for severe renal or hepatic impairment • Cytochrome P450 3A4 substrate, should not be used with strong inhibitors or inducers of 3A4 • Fatal hepatoxicity has occurred • Ocular toxicity can lead to severe vision loss
Entrectinib 600 mg (3 × 200 mg capsules) once daily	• Arthralgia/myalgia • Constipation • Edema • Fatigue • Nausea/vomiting/diarrhea • Vision disorders • Weight gain	• Fractures • Heart failure • Hepatoxicity • Hyperuricemia • Mood disorder • QT prolongation	• Liver function tests every 2 weeks for the first month of therapy then monthly • Uric acid level at baseline and periodically • CMP at baseline and periodically to anticipate risk of QT prolongation • Ejection fraction at baseline and periodically	• Also indicated for *NTRK* mutation positive NSCLC • Can be taken without regard to meals
BRAF V600E Mutation				
Trametinib 2 mg	• Edema • Fatigue	• Cutaneous or other malignancy	• Signs and symptoms of interstitial lung disease	• Should be used with dabrafenib

(1 × 2 mg tablet) once daily	• Fever • Nausea/vomiting/diarrhea • Rash	• Hemorrhagic events • Cardiomyopathy • Colitis with or without perforation • Hyperglycemia • Interstitial lung disease • Ocular toxicity • Venous thromboembolism	• Fasting serum glucose at baseline and regularly • Dermatologic evaluations at baseline and every 2 months • Ejection fraction at baseline, 1 month after initiation of therapy then every 2-3 months • Ophthalmic evaluation at baseline and within 24 hours of any visual disturbances	• Can be taken without regard to meals • Permanently discontinue if symptomatic cardiomyopathy or decrease in ejection fraction by greater than 20% (0.20)
Dabrafenib 150 mg (2 × 75 mg capsules) twice daily	• Edema • Fatigue • Fever • Nausea/vomiting/diarrhea • Rash	• Cardiomyopathy • Cutaneous or other malignancy • Hemorrhagic events • Hyperglycemia • Uveitis	• Fasting serum glucose at baseline and regularly • Dermatologic evaluations at baseline and every 2 months • Ejection fraction at baseline, 1 month after initiation of therapy then every 2-3 months	• Should be used with trametinib • Should be taken 1 hour before or 2 hours after meals • Permanently discontinue if symptomatic cardiomyopathy or decrease in ejection fraction by greater than 20% (0.20) • Hemolytic anemia can occur if patient has glucose-6-phosphate dehydrogenase deficiency
MET exon 14 Mutation				
Capmatinib 400 mg (2 × 200 mg tablets) twice daily	• Edema • Decreased appetite • Dyspnea • Fatigue • Nausea/vomiting	• Hepatotoxicity • Interstitial lung disease • Photosensitivity	• Signs and symptoms of interstitial lung disease • Liver function tests at baseline then every 2 weeks for 3 months, then monthly	• Can be taken without regard to meals • Avoid coadministration of strong CYP3A inducers or inhibitors • Patients should be counseled regarding appropriate precautions to protect from ultraviolet light A/B exposure
Tepotinib 450 mg (2 × 225 mg	• Dyspnea • Edema • Fatigue	• Hepatoxicity • Interstitial lung disease	• Signs and symptoms of interstitial lung disease (dyspnea, cough, and fever)	• Should be taken with meals

tablets) once daily	• Myalgias • Nausea/diarrhea		• Liver function tests at baseline then every 2 weeks for 3 months, then monthly	
RET Rearrangement				
Selpercatinib 160 mg (2 × 80 mg capsules) twice daily	• Diarrhea • Edema • Fatigue • Hepatotoxicity • Hyperglycemia • Hypertension • Hypocalcemia • Leukopenia • Rash • Thrombocytopenia • Xerostomia	• Hemorrhage • Hypersensitivity • Impaired wound healing • QT prolongation • Tumor lysis syndrome	• Liver function tests at baseline then every 2 weeks for 3 months, then monthly • Electrolytes, including calcium, at baseline and periodically • Blood pressure at baseline, 1 week after therapy initiation, then monthly • ECG at baseline and periodically	• Can be taken without regard to meals • Dose reduce to 120 mg if patient is less than 50 kg • Dose reduction recommended for severe hepatic impairment • Patients should watch for signs/symptoms of hypersensitivity • Hold therapy for planned surgical procedures
Pralsetinib 400 mg (4 × 100 mg capsules) once daily	• Constipation • Edema • Fatigue • Hepatotoxicity • Hypertension • Musculoskeletal pain • Myelosuppression	• Hemorrhage • Impaired wound healing • Interstitial lung disease • Tumor lysis syndrome	• Signs and symptoms of interstitial lung disease • Liver function tests at baseline then every 2 weeks for 3 months, then monthly • Blood pressure at baseline, 1 week after therapy initiation, then monthly	• Should be taken 1 hour before or 2 hours after meals • Dosing modifications required if used concomitantly with strong P-glycoprotein inhibitors or strong CYP3A inhibitors or inducers • Hold therapy for planned surgical procedures
NTRK Gene Fusion Positive				
Larotrectinib 100 mg (1 × 100 mg capsule) twice daily	• Constipation or diarrhea • Dizziness • Fatigue • Hepatotoxicity • Hypocalcemia • Musculoskeletal pain • Myelosuppression • Nausea/Vomiting	• CNS effects including cognitive impairment or mood disorders • Fractures	• Liver function tests at baseline then every 2 weeks for 1 month, then monthly	• Can be taken without regard to meals • Dosing modification required if used concomitantly with strong CYP3A4 inhibitors or inducers • Dose reduction recommended for patients with severe hepatic impairment

				• Inform patients to report signs/symptoms of possible fracture
KRAS G12C Mutation				
Sotorasib 960 mg (8 × 120 mg tablets) once daily	• Diarrhea • Fatigue • Hepatotoxicity • Musculoskeletal pain • Nausea	• Interstitial lung disease	• Signs and symptoms of interstitial lung disease • Liver function tests at baseline then every 3 weeks for 3 months, then monthly	• Can be taken without regard to meals • Avoid administration with drugs that decrease gastric acid • Has only been evaluated after progression on other therapies for advanced disease
Adagrasib 600 mg (3 x 200 mg tablets) twice daily	• Diarrhea • Fatigue • Hepatotoxicity • Musculoskeletal pain • Nausea • Fatigue • Renal impairment • Edema • Dyspnea • Decreased appetite	• Interstitial lung disease • QT prolongation • Gastrointestinal bleeding and obstruction	• Signs and symptoms of interstitial lung disease • Liver function tests at baseline then monthly for 3 months, then as clinically indicated	

Some patients with early-stage NSCLC receive neoadjuvant therapy, therapy before surgery. Such patients could include those with tumors that are considered operable but may be difficult to resect due to the tumors size, location, involvement of other structures, or extent of lymph node involvement. Typically, these patients would receive the same regimens used in the adjuvant setting, but given before surgery. The addition of immunotherapy to chemotherapy in this setting improves outcomes. In patients with resectable NSCLC with a tumor size greater than 4 cm or having positive lymph node involvement, adding the PD-L1 inhibitor nivolumab to standard chemotherapy every 3 weeks for 3 cycles improves the median event free survival (31.6 vs 20.8 months) and rate of pathologic complete response prior to surgery (24% vs 2.2%).[29] The use of adjuvant targeted therapy in patients received neoadjuvant nivolumab has not been studied.

Adjuvant radiation should generally be avoided in patients with local disease who have complete resection and clean margins as it does not improve survival. However, radiation, or more commonly chemoradiotherapy, can be indicated in specific situations. Patients who are medically inoperable should receive chemoradiotherapy if they can tolerate the combined modality. Patients who have positive margins after resection should ideally undergo “re-resection”; if that is not possible, then radiation to the positive margin(s) with or without chemotherapy can be given. Concurrent rather than sequential administration of chemotherapy and radiation therapy is preferred when both are used.[3] Recommended regimens combined with radiation include cisplatin with either gemcitabine or docetaxel for patients with squamous histology or cisplatin combined with pemetrexed in patients with nonsquamous histology. Carboplatin may be substituted in patients who cannot tolerate cisplatin.

Locally Advanced Disease (Stage III)

Patients with more advanced local disease have large tumors, multiple tumors, and/or nodal involvement. This group of patients is heterogeneous,

and few large clinical trials are available to guide treatment. Treatment is best planned by a multidisciplinary team where individual features and patient preferences are considered. Optimal outcomes are achieved with multimodality therapy that typically includes systemic chemotherapy. For patients with stage III disease (large tumor [T_3 or T_4] or mediastinal node positive), radiation in the adjuvant or neoadjuvant setting with or without chemotherapy is recommended. Patients with operable disease should be considered for surgery preceded or followed by systemic chemotherapy. Adjuvant chemotherapy after surgery prolongs overall survival in patients with completely resected stage III disease (Table 152-3).[3,14] Two meta-analyses have reported that neoadjuvant chemotherapy improves 5-year survival by 5% compared to surgery alone.[30,31] The stage most likely to benefit, what regimen is best, or how it would compare to surgery followed by adjuvant therapy were not evaluated. The potential benefit of reducing tumor size to make the surgery more feasible is attractive for patients with large tumors. A trial of neoadjuvant versus adjuvant therapy has not been reported; however, both approaches are equivalent and superior to surgery alone.[3] If neoadjuvant chemotherapy is to be utilized in stage III disease, consideration should be given to the inclusion of nivolumab as described earlier.

Radiation may be given in place of surgery as the local treatment modality combined with chemotherapy. Although a large definitive trial has not been performed to compare radiation and surgery in this subset of patients, several small randomized trials have shown no difference in outcomes, such as overall survival, event-free survival and local failure rates.[32,33] Therefore, it is recommended that patients with resectable stage IIIA NSCLC be treated with chemotherapy followed by surgery or radiation, depending on patient and tumor features.[3,24] As with local disease, the use of targeted therapy with atezolizumab or osimertinib with appropriate biomarker expression is recommended for patients with resectable stage IIIa disease.

Patients with stage IIIA disease who are not surgical candidates are typically treated with both a platinum-containing regimen and concurrent radiotherapy. Patients with tumors that cannot fit safely in a radiation field may receive induction chemotherapy followed by chemoradiotherapy. Responding patients may then become surgical candidates.

Stage IIIB and IIIC NSCLC are generally considered unresectable. These patients should receive induction therapy with chemoradiation. Patients who respond to chemoradiation (about 80% of patients) should then receive consolidation therapy with the PD-L1 inhibitor, durvalumab, for 1 year. In a large clinical trial, durvalumab demonstrated significantly sustained benefits over placebo in progression-free survival (16.9 vs 5.6 months) and overall survival (47.5 vs 29.1 months).[34] Durvalumab should not be used if a patient undergoes surgical resection. Patients with stage III disease who are not candidates for radiation are treated like those with stage IV disease.[3–5,24]

Advanced (Stage IV) and Relapsed Disease

About 56% of NSCLC patients have advanced disease (stage IV) at diagnosis.[1,3,10] Typically, these patients are not surgical candidates; however, those who harbor a single metastatic site may undergo resection of the primary tumor and the metastatic site.[4,5] Chemoradiotherapy can be considered for patients with a tumor that fits in a tolerable radiation field. However, for most patients systemic therapy is the primary treatment modality.

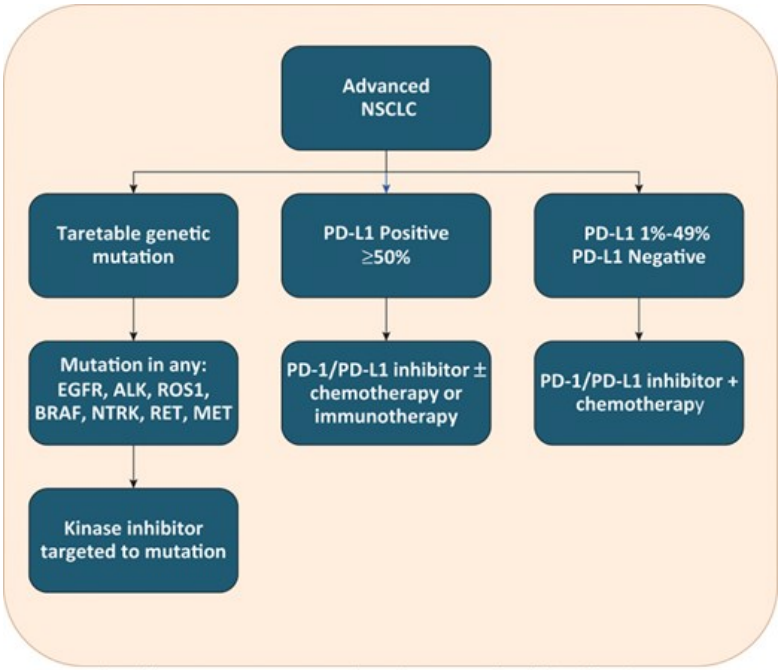
The treatment approach for NSCLC that has relapsed after initial treatment of localized disease is like the approach used for patients who have stage IV disease at diagnosis. The goal of initial therapy is to palliate symptoms, improve quality of life, and increase survival. Therapy for advanced-stage NSCLC depends on patient-specific factors and tumor characteristics.

The most important patient-specific factor is performance status, as described in Chapter 149, “Cancer: The Disease and Treatment.” Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 are most likely to derive benefit from intensive treatment. Patients with significant comorbidities should be considered for less intensive therapy (eg, single-agent therapy). Patients with poor ECOG performance status (3 or 4) do not respond well to chemotherapy and have a high likelihood of toxicity and should receive best supportive care and palliative radiation when necessary.[4,5]

Three pathways have been identified for advanced NSCLC: (1) targetable genetic mutation-driven, which is further divided based on the sensitizing mutation (eg, EGFR, ALK), (2) immune sensitive (PD-L1+), and (3) nonbiomarker-driven therapy treatment, which is further classified as squamous histology or nonsquamous histology due to drug toxicity and efficacy (Fig. 152-1). Unlike tumors of nonsquamous histology, tumors of squamous histology do not usually harbor targetable genetic mutations. Testing for these mutations in squamous tumors is encouraged, but optional. However, like other histologies of NSCLC, squamous histology tumors should have PD-L1 testing to determine sensitivity to first-line immunotherapy.[3,8,10]

FIGURE 152-1

Algorithm for initial treatment of advanced-stage NSCLC.



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

PD-L1 expression is tested with an immunohistochemistry assay; as it relates to treatment selection, a tumor is PD-L1+ if 1% or more of the viable tumor cells stain positive for PD-L1 expression (TPS ≥1%). Testing for targetable genetic mutations identifies tumors that harbor sensitizing mutations that respond to targeted therapies. Selected treatments for each group are listed in Table 152-4.

Targetable Genetic Mutation

7 Patients with advanced lung cancer with confirmed positive for targetable genetic driver mutation have several treatment options based on the specific mutation: EGFR, KRAS, ALK, ROS1, $BRAF^{V600E}$, METex14 skipping, NTRK, or RET-fusion. Genetic testing of tumors should be performed at the time of diagnosis in all patients, including those with localized disease.[3,5] Adverse drug reactions and monitoring parameters of select oral targeted therapies used in NSCLC are included in Table 152-6.

Tumors should be tested for mutations in the kinase domain of EGFR (exon 18–exon 24). Deletion mutations in exon 19 and point mutations in exon 21 comprise 90% of EGFR mutations. The only mutation associated with resistance to EGFR inhibitors is an insertion mutation in exon 20, which results in steric hindrance that prevents the drug from binding to the kinase. The prevalence of EGFR mutations varies depending on tumor histology, ethnicity, sex, and smoking history. The highest prevalence occurs in adenocarcinomas, patients of Asian descent, biological females, and nonsmokers. The overall prevalence is 32% of NSCLC patients worldwide.[35]

Patients with a tumor that harbors an activating mutation in the EGFR receptor should receive a first-line EGFR kinase inhibitor.[5] In prospective randomized trials, first-generation EGFR inhibitors (erlotinib and gefitinib) provide superior progression-free survival compared with chemotherapy. Erlotinib has been evaluated in combination with recombinant monoclonal antibodies targeting VEGF. Erlotinib in combination with bevacizumab or ramucirumab has demonstrated improved progression-free survival compared to erlotinib alone. However, this modest improved survival comes with more adverse drug reactions including hypertension and liver toxicities.[36,37] The second-generation inhibitor afatinib has also been shown to be better than chemotherapy as first-line therapy. Meta-analysis comparing EGFR inhibitors (erlotinib, gefitinib, and afatinib) suggests that these three agents have similar overall progression-free survival results (about 11 months) and response rates that are about two times higher than chemotherapy. The meta-analysis also showed that prognosis with exon 19 deletion is better than exon 21 L858R mutation.[38] Dacomitinib, another second-generation irreversible inhibitor, has been compared to gefitinib in this population. In a clinical trial, patients who were randomized to dacomitinib reported

improved progression-free survival (14.7 vs 9.2 months) and overall survival (34.1 vs 26.8 months) compared with gefitinib.[39]

Osimertinib, a third-generation EGFR tyrosine kinase inhibitor, shows the most impressive activity in EGFR-positive tumors. The FLAURA trial evaluated patients with EGFR-positive NSCLC to receive first-line osimertinib or prescriber's choice of gefitinib or erlotinib. Patients receiving osimertinib had significantly longer median progression-free survival (18.9 vs 10.2 months) and median overall survival also favored osimertinib (38.6 vs 31.8 months).[40] Two other endpoints in this trial that favored osimertinib were the improved CNS response rate and lower rate of CNS disease defining progression, which is consistent with the improved CNS penetration of osimertinib. This finding is important for NSCLC patients because more than half will develop CNS metastasis during their disease course.[41] Osimertinib is also better tolerated than the first-generation agents, which is consistent with the lower affinity for wild-type EGFR. These characteristics make osimertinib the preferred agent to target EGFR-mutation positive tumors.[3]

Subsequent therapy after progression during treatment with an EGFR inhibitor depends on initial treatment and further genetic evaluation. Many clinicians will repeat tumor genetic testing to identify other targetable mutations before starting new therapy. If patients received initial therapy with a first- or second-generation agent, testing for the acquired T790M mutation should be conducted. If the tumor tests positive for T790M, osimertinib is the drug of choice. If the patient received initial therapy with osimertinib, systemic therapy is recommended.

Patients with exon 20 insertions tend to be resistant to treatment with EGFR kinase inhibitors. New treatment options have emerged for these patients. Amivantamab is a bispecific antibody targeted to EGFR and MET. Overall response rate was 40% with a medium duration of response of 11.1 months in patients who progressed after platinum-based chemotherapy.[42] Mobocertinib is a kinase inhibitor administered orally that irreversibly binds and inhibits EGFR exon 20 insertion mutations at lower concentrations than wild type EGFR. This selective inhibition for mutant EGFR leads to a more favorable adverse drug reaction profile compared to other EGFR inhibitors.[43] It also is effective after platinum-based chemotherapy (overall response rate, 28% median duration of response, 17.5 months).[44]

In summary, patients with advanced NSCLC that harbors an EGFR mutation of exon 19 or L858R should be treated with first-line osimertinib. Upon progression, patients can be retested for an additional targetable mutation/amplification. Most patients will proceed to a platinum doublet with or without immunotherapy. Patients with exon 20 insertions who have progressed on platinum-based chemotherapy should be treated with amivantamab or mobocertinib.

KRAS point mutations are another type of frequently occurring oncogenic mutation, occurring in 25% of patients with adenocarcinomas.[3] This mutation is more commonly associated with cigarette smoking and carriers a poor prognosis.[45] Since the discovery of this therapeutic target, finding an effective treatment for patients with KRAS mutations has been elusive. Two KRAS inhibitors are indicated for the treatment of patients with KRAS G12C mutated advanced NSCLC who were previously treated with standard therapies. Sotorasib use resulted in an objective response was observed in 37.1% of patients and was durable (median duration of response, 11.1 months).[46] Adagrasib use in this population resulted in an objective response in 43% of patients with a median duration of response of 8.5 months.[47]

The presence of an ALK rearrangement represents another therapeutic target for patients with NSCLC. The ALK mutation is less common than EGFR mutations, occurring in 2% to 5% of lung cancer patients.[48] Several ALK inhibitors have been approved for use. First-generation ALK inhibitors crizotinib and ceritinib established ALK inhibition as superior to chemotherapy. Each has shown improvement in median progression-free survival compared to chemotherapy (crizotinib: 10.9 vs 7 months; ceritinib 16.6 vs 8.1 months).[49,50] Second-generation inhibitors alectinib and brigatinib have higher activity than their first-generation counterparts and have demonstrated a dramatic improvement in outcomes compared with crizotinib therapy (median progression-free survival: alectinib, 34.8 vs 10.9 months and brigatinib, 24 vs 11 months).[51,52] The third-generation inhibitor lorlatinib has built on the success of its predecessors with improved potency and improved penetration of the blood-brain barrier. The CROWN trial demonstrated superiority of lorlatinib over crizotinib in a head-to-head comparison (median progression-free survival, not yet reached, [exceeding 33 months] vs 9.3 months).[53] It is important to note that of the second- and third-generation ALK inhibitors, only alectinib has shown improved overall survival compared to crizotinib.[50] Based on this evidence, patients with ALK-positive advanced NSCLC should receive initial treatment with a second (alectinib or brigatinib) or third (lorlatinib)-generation ALK inhibitor.[3]

Patients who relapse while receiving initial ALK-targeted therapy may be treated with an advanced-generation ALK inhibitor. Patients who initially received crizotinib can receive second- or third-generation inhibitors, while patients initially treated with a second-generation inhibitor should be

offered lorlatinib. Lorlatinib is able to produce complete responses, even in patients with CNS disease.[54] Patients already receiving lorlatinib who have limited relapse can be treated with local therapy (such as radiation) and continuation of lorlatinib. Patients with widespread relapsed disease should be considered for the nonbiomarker-driven pathway.[3,5]

Mutation in ROS1 is a rare genetic driver of NSCLC occurring in 1% of patients. It has proven to be a highly active target for drug therapy. In patients with metastatic, ROS1-positive NSCLC, regardless of prior chemotherapy for metastatic disease, crizotinib has a 72% response rate, including a 6% complete response rate.[55] Certinib and entrecitinib produce similar responses (62% and 77%), but are better tolerated than crizotinib.[3] Additionally, entrecitinb has better CNS penetration than crizotinib. Similar to when used in patients with ALK mutations, lorlatinib produces response rate was 36%, including in patients with CNS disease.[54] Ceritinib, crizotinib, or entrecitinib are recommended first-line agents, with lorlatinib and entrecitinib as potential second-line therapy.

For the 1% to 2% of patients with metastatic adenocarcinoma who have the $BRAF^{V600E}$ mutation, the combined use of trametinib, a mitogen-activated extracellular signal-regulated kinase, or MEK, inhibitor, and dabrafenib, an inhibitor of some mutated BRAF kinases, has been shown to be beneficial. The combination of trametinib and dabrafenib produces response rate of 63% to 64%, including complete responses in 6% of patients and median progression-free survival times of 9.7 to 10.9 months, in patients with or without prior chemotherapy.[56,57] This combination of kinase inhibitors is approved for the treatment of patients with metastatic $BRAF^{V600E}$-positive lung cancer, regardless of prior chemotherapy.[3]

Larotrectinib is a novel agent that is approved for the treatment of adult and pediatric patients with a metastatic solid tumor that is positive for an NTRK gene fusion. About 0.2% of patients with NSCLC have this genetic driver of tumor growth. Larotrectinib's approval is based on a study of patients with a variety of solid tumors, including NSCLC.[58] Similarly, entrectinib may be used as a first-line treatment for patients with NTRK gene fusions, based on an accelerated approval of three ongoing phase 1 or 2 clinical trials of patients with advanced or metastatic NTRK fusion-positive solid tumors.[59]

Other less common mutations that occur in NSCLC that have specific targeted agents available include METex14 skipping mutation and RET fusions, both of which occur in about 1% to 2% of all NSCLC patients.[3] Capmatinib is a tyrosine kinase inhibitor that inhibits several MET mutations, including METex14 skipping mutation.[60] Tepotinib can also be used in patients with METex14 skipping mutations.[61] In patients with RET gene rearrangements, selective RET inhibitors, selpercatinib and pralsetinib can be used, resulting in positive response in patients who have progressed on chemotherapy and patients who are treatment naïve.[62,63]

After options targeting genetic mutations have been exhausted, other systemic therapies may be considered with most patients proceeding down the "nonbiomarker-driven" pathway.[3]

Chemotherapy for PD-L1+ and Nonbiomarker Tumors

Cytotoxic chemotherapy with a platinum-based doublet backbone is considered the standard of care for managing NSCLC without targetable genetic mutation. A variety of combinations have been evaluated, but the most used doublets consist of either cisplatin or carboplatin combined with paclitaxel (or nab-paclitaxel) or pemetrexed.[3,4] In general, carboplatin and paclitaxel have less toxicity for patients with squamous cell NSCLC.[64] For patients with nonsquamous NSCLC, a combination of a platinum agent with pemetrexed is widely considered the preferred chemotherapy regimen. This was seen in a pivotal phase III trial of NSCLC patients compared six cycles of cisplatin and either gemcitabine or pemetrexed. When overall survival was analyzed by histology, cisplatin and pemetrexed was superior to other platinum combinations in patients with nonsquamous NSCLC. Furthermore, cisplatin and pemetrexed had less neutropenia, anemia, and thrombocytopenia but more nausea compared to other regimens.[65]

Maintenance therapy is the ongoing use of one or more agents after a positive tumor response to four to six cycles of an initial chemotherapy regimen until disease progression.[3] Several studies show that continuation or switch maintenance therapy improves survival of NSCLC patients with nonsquamous histology.[4] In continuation maintenance therapy, patients receive ongoing treatment with at least one of the agents used in the initial chemotherapy regimen. Alternatively, switch maintenance therapy starts a new agent not included in the initial regimen. Pemetrexed is the most established maintenance chemotherapy option. A meta-analysis showed that pemetrexed, given as maintenance therapy, provided a consistent overall survival benefit in patients with nonsquamous NSCLC.[66] A retrospective study reported improved progression-free and overall survival in patients who continued bevacizumab after completing initial chemotherapy with bevacizumab. A meta-analysis of trials of combined pemetrexed and bevacizumab maintenance therapy showed improved progression-free survival. However, no difference in overall survival was observed and the combination

resulted in more toxicity.[67] Because of concerns about efficacy (pemetrexed) and safety (bevacizumab), maintenance with these agents is not recommended for patients with squamous NSCLC. Based on the benefit of maintenance therapy, trials of immunotherapy included maintenance therapy with the monoclonal antibody components of their regimens.

Novel agents such as checkpoint inhibitors and other targeted therapies are often being combined with platinum doublet chemotherapy. These regimens and their survival benefits are described later in this chapter.

PD-L1+ Tumors

Patients who have PD-L1+ tumors and no sensitizing mutations are eligible for a variety of first-line immunotherapies with checkpoint inhibitors. Food and Drug Administration approved checkpoint inhibitors for NSCLC include pembrolizumab, atezolizumab, nivolumab, and cemiplimab. These immune checkpoint inhibitors either bind to the PD1 receptor on T cells (pembrolizumab, nivolumab, cemiplimab) or the PD-1 ligand (PD-L1) on tumor cells (atezolizumab, durvalumab). Checkpoint inhibitors are associated with improved overall survival compared to patients receiving cytotoxic chemotherapy.[3] These agents may be used alone, in combination with chemotherapy, or a CTLA-4 inhibitor, ipilimumab. Certain patients may be contraindicated to treatment with checkpoint inhibitors. These include patients with a history of autoimmune diseases, on concomitant treatment with immunosuppressive agents, or those who harbor driver mutations. Presently, recommended treatments are guided by a patient's PD-L1 positivity status or TPS threshold. Patients are divided into three distinct categories: PD-L1 TPS ≥50%, TPS 1%-49%, and TPS <1%.

PD-L1 ≥50% Treatment Recommendations

Regardless of histology, single-agent checkpoint inhibitor is recommended as initial treatment in patients with metastatic NSCLC with PD-L1 expression levels of at least 50%, and who are negative for sensitizing oncogenic mutations. This recommendation came from a pivotal phase III trial that showed both improved median progression-free (10.3 vs 6 months) and overall survival (30 vs 14.2 months).[68,69] In addition to pembrolizumab, atezolizumab and cemiplimab have significantly prolonged overall survival and improved tolerability compared to platinum chemotherapy in the first-line setting for patients with metastatic PD-L1+ ≥50% NSCLC tumors.[3,70,71] All three agents are designated as preferred first-line therapies in this setting. The selection of which agent to use is often made by the ordering clinician.

Although patients with NSCLC who are PD-L1 of more than 50% benefit from immunotherapy monotherapy, a variety of other treatment strategies may be utilized to enhance clinical benefit or due to immunotherapy contraindications. Alternatives to immunotherapy monotherapy include chemoimmunotherapy, dual immunotherapy, or chemotherapy alone. These treatment modalities are described in more detail below.

PD-L1 1%-49% Treatment Recommendations

Combination therapy that consists of a checkpoint inhibitor and chemotherapy is recommended as the preferred first-line treatment in patients with metastatic NSCLC, regardless of PD-L1 expression levels and histology. For adenocarcinoma NSCLC, combination therapy with pembrolizumab plus chemotherapy is preferred because it improves overall 1-year survival rates (69.2% vs 49.4%).[72] Different treatment regimens are utilized for patients with a diagnosis of squamous NSCLC. For this histology, a combination of pembrolizumab plus carboplatin and either paclitaxel (or albumin-bound paclitaxel) is preferred as initial treatment regardless of PD-L1 expression levels because it improves overall survival (15.9 vs 11.3 months).[3,73] Refer to Table 152-4 for additional treatment options for patients with squamous NSCLC.

Since the approval of pembrolizumab in combination with chemotherapy, the management of both squamous and nonsquamous NSCLC has substantially changed. At the time of this writing, over seven first-line treatments are now being utilized. Therefore, management has shifted from a defined algorithm of platinum doublet chemotherapy into one where there are multiple competing first-line strategies. The advantages of this paradigm shift are that treatment regimens can be individualized to a patient's treatment goal, preferences, specific factors, and/or performance status. One possible treatment strategy is to use a chemotherapy-free regimen of nivolumab and the cytotoxic T-cell lymphocyte associated protein 4, or CTLA-4, inhibitor, ipilimumab, which improves outcomes compared with chemotherapy alone in patients with metastatic NSCLC with a PD-L1 expression level of 1% or higher.[74] Dual immunotherapy is therefore an option for patients who are contraindicated to chemotherapy (eg, renal impairment.)[3] Another alternative treatment strategy is the concept of limited chemotherapy. The advantage of using a limited-chemotherapy strategy is that effective disease control and improved overall survival can be achieved without suppressing any immunogenicity.[75] This was demonstrated in a

landmark phase III double-blind trial who received nivolumab/ipilimumab and two cycles of platinum-doublet chemotherapy followed by nivolumab/ipilimumab maintenance compared to four cycles of chemotherapy alone. Overall survival was improved with chemoimmunotherapy (nivolumab/ipilimumab) and two cycles of platinum-doublet chemotherapy followed by nivolumab/ipilimumab maintenance compared to four cycles of chemotherapy alone (15.8 months vs 11 months, respectively).[76] This treatment strategy may be ideal for a patient who requires a limited-chemotherapy option or is contraindicated to receiving ongoing chemotherapy maintenance.

Furthermore, single-agent immunotherapy with pembrolizumab may also be used. This recommendation was based from a randomized phase III trial comparing first-line pembrolizumab to chemotherapy in patients with NSCLC with a PD-L1 expression of 1% or more (TPS of ≥1%).[77] Patients with the highest level of PDL-1 expression (TPS ≥50%) had a median overall survival of 20 months versus 12 months in the chemotherapy arm, respectively. The survival benefit decreased as PD-L1 expression decreased, but survival was higher for the pembrolizumab in all groups. In certain circumstances, such as poor ECOG performance status or those who cannot tolerate or refuse platinum-based chemotherapy, single-agent checkpoint inhibitors may be used in patients who have expression levels of 1%-49%. Other first-line treatment strategies may be utilized and can be seen in Table 152-4.

Nonbiomarker Driven

Approximately, half of the NSCLC patient population have PD-L1 TPS scores <1% or are PD-L1 negative.[78,79] Due to the lack of randomized clinical trials for this patient population, there are no defined or optimal treatment strategies that have been identified now. Therefore, patients who are PD-L1 <1%, a performance status of 0-2, and negative for actionable oncogenes are treated similarly to patients with TPS scores of 1% to 49% with pembrolizumab in combination with chemotherapy being the preferred initial treatment.[3]

For patients with metastatic NSCLC who are not candidates for targeted therapies or have progressed despite targeted therapies and are candidates for further therapy, combination chemotherapy in the form of a platinum doublet is the preferred treatment option. Targeted therapies have also been incorporated to various platinum doublet regimens. The benefit of adding the VEGF inhibitor, bevacizumab to a platinum doublet chemotherapy regimen leads to longer median progression-free survival (6.2 vs 4.5 months) and overall survival times (12.3 vs 10.3).[80] Therefore, the addition of bevacizumab to chemotherapy is recommended for patients with advanced NSCLC. However, due to the bleeding risk associated with bevacizumab, eligible patients must have nonsquamous histology, no recent hemoptysis, no CNS metastasis, and are not receiving therapeutic anticoagulation.[3] Cisplatin and pemetrexed have not been directly compared with carboplatin, paclitaxel, and bevacizumab and both regimens are listed as treatment options in nonsquamous NSCLC.

The most recent treatment advancement is using chemoimmunotherapy which was described earlier in this chapter. However, for patients with driver mutations, the use of chemoimmunotherapy is controversial. Patients with driver mutations like EGFR and ALK do not have the same responsiveness to immunotherapy compared to patients without driver mutations.[81] Furthermore, second-line trials have also demonstrated that these subsets of patients do not derive an overall survival benefit with checkpoint blockade.[82,83] When checkpoint inhibitors are combined with anti-angiogenic agents (eg, VEGF inhibitors), it is possible to overcome the tumor resistance seen in EGFR and ALK positive tumors. This may be due to VEGF inhibitors augmenting chemoimmunotherapy by suppressing antigen presentation and potentiating PD-L1 blockade.[83] This mechanism of action hypothesis was confirmed in the IMpower150 study which evaluated the addition of atezolizumab to treatment with carboplatin, pemetrexed, and bevacizumab (ABCP) in patients with nonsquamous NSCLC.[84] ABCP resulted in significantly longer median progression-free survival for all patients (8.3 vs 6.8 months) as well as those with EGFR or ALK mutations (9.7 vs 6.1 months). ABCP remains the first chemoimmunotherapy regimen to show a benefit in patients with driver mutations. Clinical guidelines recommend the combination of checkpoint inhibitors with a VEGF inhibitor, and chemotherapy as first-line therapy for patients with nonbiomarker-driven NSCLC.[3]

Relapsed Disease

Inevitably, patients with metastatic NSCLC will experience disease progression. For patients without driver mutations or patients who have exhausted available targeted therapies, systemic chemotherapy or immunotherapy remain the treatment of choice.

Monotherapy with nivolumab, pembrolizumab, atezolizumab, docetaxel, or pemetrexed are the most commonly considered options for second-line therapy in patients with a good performance status who progress during or after first-line chemotherapy.[3–5] Nivolumab and pembrolizumab, and atezolizumab, are options in the second-line setting for patients who have not previously received immunotherapy. A meta-analysis of randomized

trials of PD-1 inhibitors found that these agents significantly improved survival outcomes as compared to single-agent chemotherapy.[85] This benefit was seen regardless of histology. Clinical benefit from PD-1 inhibitors is superior compared to docetaxel regardless of the level of PD-1 expression. However, patients with higher levels of PD-1 expression received an even greater benefit than those patients with low-level expression.

For patients who have failed initial treatment with immunotherapy, second-line treatment would be chemotherapy. Docetaxel was the first chemotherapy to receive Food and Drug Administration approval for the treatment of advanced NSCLC after failure of a platinum-based chemotherapy regimen. Docetaxel, at the 75 mg/m^2 dose, was superior to best supportive care in terms of time-to-disease progression (10.6 vs 6.7 weeks), median survival (7.5 vs 4.6 months), and 1-year survival (37% vs 11%).[86] The efficacy of docetaxel has been improved with the addition of ramucirumab. A large, randomized trial of docetaxel with or without ramucirumab reported longer progression-free survival (4.5 vs 3 months) and overall survival (10.5 vs 9.1 months) favoring the ramucirumab arm.[87] Response by histology was not analyzed, but ramucirumab appeared to be active in all histologies. Due to the relatively modest improvement in survival, clinicians must decide if the benefit outweighs the risks in adverse drug reactions and cost. Although ramucirumab binds to the VEGF receptor, it is important to note that safety concerns (serious and fatal bleeding) like those seen with bevacizumab and chemotherapy in squamous histology were not reported.

The second chemotherapy agent approved as second-line treatment is pemetrexed. When compared to docetaxel, there were no difference in efficacy outcomes but there were significantly fewer adverse drug reactions in patients receiving pemetrexed, including lower rates of hospitalizations due to toxicities.[88] Pemetrexed is a preferred chemotherapy option based on this study, but it is not appropriate as second-line therapy when it is used as maintenance therapy. It is also important to note that pemetrexed should not be used for patients with squamous NSCLC.

The comparative trials indicate that pemetrexed and docetaxel are equally effective, and docetaxel plus ramucirumab is superior to docetaxel alone. Similarly, nivolumab, pembrolizumab, and atezolizumab are superior to docetaxel alone.[89] All five monotherapies and ramucirumab-docetaxel are acceptable regimens, but checkpoint inhibitors are preferred in patients who are naïve to this modality due to an impressive durability of response.[3] It is not clear, if a platinum doublet should be used or a single cytotoxic agent. If a platinum doublet is selected, then the regimen would be selected based on histology (as described below for tumors that are PD-L1 negative and have no targetable genetic mutations). If single-agent chemotherapy is selected, pemetrexed is preferred for nonsquamous cell tumors and docetaxel with or without ramucirumab for squamous cell tumors (Table 152-5). However, since most patients with relapsed metastatic disease are heavily pretreated and are more likely to experience significant adverse drug reactions, single-agent chemotherapy tends to be preferred.

Third-line therapy (and beyond) is reasonable for patients who have a good performance status and can tolerate another agent. Monotherapy with an active agent would typically be used in this setting. For patients who received a PD-L1 guided therapy, docetaxel would be an option with or without ramucirumab. For those who received second-line docetaxel with or without ramucirumab, an immune checkpoint inhibitor would be an option. For patients who want treatment beyond third line, a single agent could be used.[3–5] The best agent(s) has not been determined in clinical trials. Therapeutic decisions are based on patient-specific factors including prior therapies and potential contraindications to specific agents. The most common treatment option is monotherapy with an agent known to have activity in clinical trials.

Older Patients and Poor-Performance Status

Single-agent chemotherapy is an alternative in older patients (>65 years old) or those with an ECOG performance status of 2 or greater. First-line, single-agent chemotherapy has objective response rates of 5% to 25% with no significant effect on overall survival. Rarely, complete responses occur and tend to have limited durations.[90] The most active cytotoxic chemotherapy agents are cisplatin, carboplatin, docetaxel, paclitaxel, etoposide, gemcitabine, ifosfamide, irinotecan, topotecan, mitomycin, vinblastine, vinorelbine, and pemetrexed.[3] Targeted therapies are also active as a single agent and should be considered in patients with a mutation-positive tumor.

Historically, patients with an ECOG performance status 2 were excluded from NSCLC trials because of excessive toxicity with minimal benefit from combination cytotoxic therapy. Updated ASCO guidelines state that available data support the use of single-agent and combination chemotherapy but are relatively weak and incorporate older patients or poor patients with a poor performance status. They emphasize the need to individualize this decision.[4,5] A recent meta-analysis shows that patients with performance status 2 benefit from treatment. The NCCN guidelines list both single agents and combinations for patients with a performance status of 2, and best supportive care for patients with a performance status of 3 or 4 unless they have a mutation or gene rearrangement where they can receive a tyrosine kinase inhibitor.[3]

Evaluation of Therapeutic Outcomes

For patients who have undergone surgical resection, a physical examination and chest radiography are recommended every 3 to 4 months for the first 2 years, then every 6 months for 3 years, and then annually. In addition, a low-dose spiral chest CT scan is recommended annually to monitor for evidence of local recurrence. Suspicious symptoms or physical findings (eg, bone pain, visual abnormalities, headache, or elevated liver function tests) should prompt an evaluation to rule out distant metastases.[3–5]

Tumor response to chemotherapy is generally evaluated at the end of the second or third cycle and at the end of every second cycle thereafter. Patients with stable disease, with an objective response, or with a measurable decrease in tumor size (complete or partial response) should continue until four to six cycles have been administered. Patients with nonsquamous histology tumors who respond (ie, nonprogressive disease) should be considered for maintenance therapy with pemetrexed. Following initial therapy for NSCLC, patients must be monitored for evidence of disease progression.[3–5] Second-line therapy and beyond is traditionally given until progression. The immune checkpoint inhibitors can display a different response pattern than traditional chemotherapy or targeted therapy. It can take some time for the immune system to become activated and then the tumor will initially be infiltrated with cytotoxic lymphocytes that can appear radiographically as progression prior to a response. The median time-to-response for immune checkpoint inhibitors is 10 to 12 weeks. Although the registry trials continue to assess response based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria, an immune response criterion has been proposed where progression needs to be documented on two consecutive assessments at least 4 weeks apart.[91]

Small Cell Lung Cancer

Small cell lung cancer is a rapidly dividing malignancy that spreads early in the disease course. Consequently, about 60% to 70% of patients present with extensive-stage disease. When patients with SCLC are not treated, the disease quickly becomes fatal. Fortunately, SCLCs are responsive to chemotherapy and radiation. Chemotherapy with or without radiotherapy is the treatment of choice for most patients. Even after a complete response to therapy, the cancer usually recurs within 6 to 8 months, and survival time following recurrence is typically short (about 4 months). With treatment, median survival rates for patients with limited and extensive disease are 14 to 20 and 9 to 11 months, respectively. Treatment planning starts with stage of disease (ie, limited vs extensive stage), but must also consider other factors, including performance status (treatment usually restricted to performance status 0 or 1), patient age, comorbid conditions (eg, renal failure), and patient desire to receive treatment.[2,16]

Limited Disease

When a single SCLC mass is found, local therapy with radiation or surgery is considered, although the use of surgery in SCLC is limited to solitary nodules, without evidence of metastasis to lymph nodes. One of the differences between SCLC and NSCLC is that radiation is preferred for treatment of local disease over surgery. Radiation is always combined with chemotherapy in limited-stage SCLC, and the regimen of choice is etoposide and cisplatin (ie, EP regimen). Carboplatin may be substituted for cisplatin to reduce nausea and vomiting, nephrotoxicity, or neurotoxicity, although increased thrombocytopenia may result.[92] Alternative regimens have failed to demonstrate improved outcomes compared to EP plus concurrent radiation and typically have more toxicity. Guidelines recommend that the EP regimen be used with concurrent radiotherapy.[2,16] Regimens used in the treatment of SCLC can be found in Table 152-7. Because patients with SCLC commonly have a recurrence in the CNS, trials have been performed to evaluate the benefit of prophylactic cranial irradiation (PCI). A pivotal study showed that PCI reduces the incidence of brain metastasis and increases 3-year survival from 15% to 21%.[93] Therefore, patients who achieve a complete response with treatment should be offered PCI.

TABLE 152-7

Chemotherapy Regimens Used in the Treatment of SCLC

	Regimen	Drugs and Doses
First Line	Etoposide/cisplatin (EP)	Cisplatin 75 mg/m^2 IV on day 1 Etoposide 100 mg/m^2 IV on days 1-3; repeat cycle every 3 weeks for 4-6 cycles or Cisplatin 60 mg/m^2 IV on day 1 Etoposide 120 mg/m^2 IV on days 1-3; repeat cycle every 3 weeks for 4-6 cycles
	Etoposide/carboplatin (EC)	Carboplatin AUC 5-6 IV on day 1 Etoposide 100 mg/m^2 IV on days 1-3; repeat cycle every 3 weeks for 4-6 cycles
	EC + atezolizumab[a]	Carboplatin AUC 5 IV on day 1 Etoposide 100 mg/m^2 IV on days 1-3 Atezolizumab 1,200 mg IV on day 1; repeat cycle every 3 weeks for 4 cycles followed by Atezolizumab 1,200 mg every 3 weeks or 1680 mg every 4 weeks as maintenance
	EP + durvalumab[a]	Carboplatin AUC 5-6 IV on day 1 Etoposide 80-100 mg/m^2 IV on days 1-3 Durvalumab 1,500 mg IV on day 1; repeat cycle every 3 weeks for 4 cycles followed by Durvalumab 1,500 mg every 4 weeks as maintenance
	EC + durvalumab[a]	Cisplatin 75-80 mg/m^2 IV on day 1 Etoposide 80-100 mg/m^2 IV on days 1-3 Durvalumab 1,500 mg IV on day 1; repeat cycle every 3 weeks for 4 cycles followed by Durvalumab 1,500 mg every 4 weeks as maintenance
Second Line	Topotecan	Topotecan 1.5 mg/m^2/day IV days 1-5; repeat every 3 weeks
	Lurbinectedin	Lurbinectedin 3.2 mg/m^2/day IV day 1; repeat every 3 weeks

[a]Extensive stage only.

Extensive Disease

Historically, platinum regimens have been the treatment of choice in extensive disease as studies have failed to show superiority to the EP regimen as first-line treatment. As in limited disease, carboplatin is an acceptable substitute for cisplatin in EP.

8 Programmed death inhibition with either atezolizumab or durvalumab when added to standard chemotherapy in patients with extensive stage SCLC has been shown to improve overall survival. The addition of atezolizumab to standard chemotherapy improved median progression free survival (2 vs 4.3 months) and overall survival (12.3 vs 10.3 months).[94] Durvalumab demonstrated similar benefit, improving median overall survival from 10.3 to 13 months.[95] The complete regimens used in the studies are shown in Table 152-7.

Concurrent radiotherapy is not used routinely in extensive disease. However, a randomized study of extensive-stage patients responding to chemotherapy comparing observation or PCI reported that PCI decreased the 1-year risk of brain metastasis (14.6% vs 40.4%), and prolonged 1-year survival (27.1% vs 13.3%).[96] A more recent Japanese study reported that PCI reduced the risk of brain metastases but did not improve overall survival. The results of these studies led to guideline revisions recommending PCI for patients with extensive disease responding to chemotherapy.[2,16]

Relapsed Disease

Patients with SCLC who relapse or progress after first-line chemotherapy have a median survival of 4 to 5 months. Unfortunately, recurrent disease is usually less sensitive to chemotherapy.

10 Treatment approach for patients who experience relapsed SCLC often depends on the length of time between completion of the initial chemotherapy regimen and relapse. If this interval is less than 3 months, the patient has refractory SCLC and is unlikely to respond to second-line therapy and should receive best supportive care or be enrolled in a clinical trial. For those with greater than a 3-month time interval between first-line chemotherapy and relapse, the expected response rate to treatment is about 20%, and second-line therapy should be considered.[2,16] Based on limited evidence, if the interval between completion of initial chemotherapy and relapse is 6 months or greater, retreating the patient with the initial chemotherapy regimen may be considered.[2] Topotecan (intravenous and oral) is approved as second-line therapy for SCLC and has been considered standard second-line treatment of SCLC based on a trial that randomized patients to intravenous topotecan or to cyclophosphamide, doxorubicin, and vincristine (CAV) regimen.[97] The response rates, time-to-disease progression, and overall survival were not different between groups. The proportion of patients experiencing symptom improvement was higher in the topotecan arm. There were fewer dose reductions for topotecan (1% vs 11%) due to improved adverse drug reaction rates except for more anemia and thrombocytopenia from topotecan. Oral topotecan is similar in terms of dosing, toxicity, and effectiveness compared to intravenous topotecan.[98]

Lurbinectedin, an alkylating drug that binds guanine residues in deoxyribonucleic acid (DNA) inhibiting oncogenic transcription and causing apoptosis, is another effective second-line agent in relapsed SCLC and an alternative to topotecan.[99] In a single arm trial, it produced an overall response rate of 35.2% lasting a median of 5.3 months. Common adverse drug reactions include myelosuppression, fatigue, and elevations in serum creatinine and liver function tests. Other agents recommended in national guidelines include single-agent PD-L1 inhibitor, irinotecan, gemcitabine, paclitaxel, docetaxel, oral etoposide, temozolomide, and vinorelbine; CAV regimen; and participation in a clinical trial.[2,16]

Evaluation of Therapeutic Outcomes

The effectiveness of first-line therapy is evaluated after two to three cycles of treatment. If the patient achieves a complete or partial response, therapy is continued for four to six cycles of therapy. If the patient has evidence of progressive disease, therapy is discontinued or changed to a non–cross-resistant regimen. In the case of SCLC, responding patients benefit from the addition of PCI following initial therapy. After recovery from first-line therapy, follow-up visits should occur every 3 months for years 1, 2, and 3, then every 4 to 6 months for years 4 and 5, and then annually for patients with either a partial or complete response.[2,3]

Complications and Supportive Care

Patients with lung cancer frequently have numerous concurrent medical problems. Such problems may be related to invasion of the primary tumor and its metastases, paraneoplastic syndromes (see “Clinical Presentation” earlier), chemotherapy and radiotherapy toxicity, or concomitant disease states (eg, cardiac disease, renal dysfunction, chronic obstructive pulmonary disease, asthma, or diabetes). Depression is also common and sometimes persistent in patients with SCLC and NSCLC and should be treated. Identification, diagnosis, and treatment of the whole patient may improve the patient’s overall quality of life and tolerance to cancer treatments.

The chemotherapy regimens used in the management of lung cancer are intensive and are associated with a wide variety of toxic effects. Nausea and vomiting may be severe. Cisplatin-containing regimens require the use of aggressive acute and delayed antiemetic regimens containing agents, such as serotonin antagonists, dexamethasone, and neurokinin-1 receptor antagonist, and olanzapine.[100] Patients experiencing protracted nausea and vomiting may require intravenous hydration and nutritional support. Myelosuppression is often the dose-limiting toxicity associated with chemotherapy. Granulocytopenia places patients at high risk for serious infections. Other toxic effects associated with these chemotherapy regimens include mucositis, anemia, nephrotoxicity, peripheral neuropathies, and ototoxicity. In multiple phase II clinical trials, trilaciclib, a cyclin-dependent kinase 4/6 inhibitor, has demonstrated efficacy in decreasing the incidence and severity of chemotherapy-induced myeylosuppression when administered prior to chemotherapy for extensive stage small cell lung cancer.[101] Its utility in other settings, or in comparison/combination with colony stimulating factors, has not been established.

About 30% to 65% of advanced-stage NSCLC patients will develop bone metastases, which may lead to significant bone pain, pathologic fractures, spinal cord compression, and hypercalcemia. A large meta-analysis determined denosumab, a RANK-ligand inhibitor and zoledronic acid (bisophosphonate) decrease the incidence of skeletal-related events such as fractures. Additionally, both agents have been shown to delay the onset of first event. The meta-analysis also found that denosumab has been shown to prolong overall survival compared to no treatment for bone metastases. Zoledronic acid was not determined to affect survival.[102]

Patients receiving radiation therapy may experience complications including severe esophagitis, fatigue, radiation pneumonitis, and cardiac toxicity. These toxicities are usually more common and severe when radiation is combined with chemotherapy. The patient's baseline performance status and the degree of pulmonary dysfunction (eg, chronic obstructive pulmonary disease from years of tobacco use) must be considered in decisions concerning radiation dosage and fractionation.

Patients who receive an immune checkpoint inhibitor can develop immune-related adverse events, which frequently include the gastrointestinal tract, skin, and pneumonitis. Holding therapy and intervening with steroids can blunt the progression of these toxicities. The other key point is that responses to immune checkpoint inhibitors can be delayed in onset.[103] A new response criterion has been developed for immunotherapies, which differs from RECIST criteria by requiring documentation of significant tumor grown on two occasions at least 4 weeks apart to be defined as progression.

Lung cancer patients frequently receive complex pharmacologic regimens that include chemotherapeutic agents, immune checkpoint inhibitors, antiemetics, antibiotics, analgesics, anticoagulants, bronchodilators, corticosteroids, anticonvulsants, and cardiovascular agents. Such regimens necessitate intensive therapeutic monitoring to avoid drug-related and radiotherapy-related toxic effects and to optimize therapeutic outcomes for individual patients.

CONCLUSION

Lung cancers remain the leading cause of cancer-related mortality in the United States. Early detection of lung cancer through appropriate screening methods, along with decreased use of tobacco products have helped lower lung cancer incidence and mortality. Advances in targeted therapies, such as inhibitors of the programmed death pathway and oral kinase inhibitors targeting specific mutations found in tumor cells, have had significant impact on the survival of patients with lung cancer.

ABBREVIATIONS

ALK	anaplastic lymphoma kinase
ASCO	American Society of Clinical Oncology
AUC	area under the curve
BRAF	B-rapidly accelerated fibrosarcoma

CAV	cyclophosphamide, doxorubicin, and vincristine
CBC	complete blood count
CMP	comprehensive medical panel
CNS	central nervous system
CPK	creatine phosphokinase
CT	computed tomography
DNA	deoxyribonucleic acid
EC	etoposide and carboplatin
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EP	etoposide and cisplatin
ETS	environmental tobacco smoke
HER2	human epidermal growth factor
IP	irinotecan and cisplatin
KRAS	Kirsten rat sarcoma viral oncogene homologue
LDCT	low-dose computed tomography
MET	mesenchymal epithelial transition factor
MIA	minimally invasive adenocarcinoma
NCCN	National Comprehensive Cancer Network
NSCLC	non-small cell lung cancer
NTRK	neurotrophic receptor kinase
PCI	prophylactic cranial irradiation
PD-1	programmed death-1
PD-L1	programmed death ligand-1
PET	positron emission tomography

RECIST	response evaluation criteria in solid tumors
RET	rearranged during transfection
ROS1	receptor tyrosine kinase 1
SCLC	small cell lung cancer
TKI	tyrosine kinase inhibitor
TNM	tumor, node, and metastasis
TPS	tumor proportion score

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SELF-ASSESSMENT QUESTIONS

1. A 59-year-old individual with recently diagnosed limited-stage small cell lung cancer comes to the clinic for treatment. Which of the following would be the most appropriate treatment?

   A. Cisplatin plus vinorelbine

   B. Surgery followed by adjuvant cisplatin plus etoposide

   C. Carboplatin, paclitaxel, and bevacizumab

   D. Cisplatin, and etoposide along with concurrent thoracic radiation therapy

2. Which of the following is the leading cause of cancer-related mortality in the United States?

A. Breast cancer

B. Prostate cancer

C. Lung cancer

D. Pancreatic cancer

3. A 68-year-old individual who quit smoking 18 years ago comes to the clinic asking, “Should I undergo screening for lung cancer?” Past medical history is significant for hypertension and chronic obstructive pulmonary disease. Social history is significant for a 31-pack year history of smoking and drinks a beer or two a day. What is the appropriate lung cancer screening recommendation for this patient?

A. Lung cancer screening is not appropriate for this patient

B. Annual chest x-ray

C. Annual sputum cytology

D. Annual helical CT scan

4. Which of the following is a leading risk factor for the development of lung cancer?

A. Chronic obstructive pulmonary disease

B. Asthma

C. Cigarette smoking

D. Carbon monoxide inhalation

5. Which subtype of lung cancer is the most commonly diagnosed?

A. Non-small cell lung cancer

B. Small cell lung cancer

C. Mesothelioma

D. Large cell carcinoma

6. Which of the following patients with lung cancer should be a treatment goal of cure?

A. A patient with newly diagnosed stage II adenocarcinoma who is able to undergo surgery

B. A patient with extensive stage small cell lung cancer

C. A patient with newly diagnosed stage IV lung cancer that is positive for the NTRK mutation

D. A patient with squamous cell carcinoma of the lung that has relapsed after initial treatment that included surgery followed by combination chemotherapy

Use the following scenario to answer Questions 7-9

TQ is a 63-year-old individual with a new diagnosis of metastatic large cell carcinoma of the lung. Complete pathologic review revealed the following profile: ALK negative, EGFR negative, $BRAF^{V600E}$ negative, PD-L1 negative. The oncologist has recommended starting chemotherapy with carboplatin/pemetrexed.

7. Which of the following monoclonal antibodies could be added to TQ's chemotherapy regimen to help improve efficacy?

   A. Necitumumab

   B. Cetuximab

   C. Nivolumab

   D. Pembrolizumab

8. TQ continued prior treatment for 14 months with stable disease. Unfortunately, the lung cancer has now progressed and TQ is to begin a new lung cancer treatment. Which of the following would be most appropriate for now?

   A. Cisplatin/gemcitabine

   B. Docetaxel/ramucirumab

   C. Carboplatin/paclitaxel

   D. Paclitaxel/erlotinib

9. An 82-year-old individual with recently diagnosed adenocarcinoma of the lung is found to have stage IV disease (liver metastases). PD-L1 TPS is 17%. Targetable genetic mutations were not identified. At home, the patient is bedridden due to severe chronic obstructive pulmonary disease that requires home oxygen. Social history is significant for a 60-pack year history. Which of the following approaches would be most appropriate for this patient?

   A. Best supportive care

   B. Osimertinib

   C. Carboplatin, pemetrexed, and pembrolizumab

   D. Pembrolizumab

10. What is the best treatment option for a 49-year-old individual who is chemotherapy naïve and was recently diagnosed with extensive-stage small cell lung cancer?

    A. Carboplatin, pemetrexed, plus pembrolizumab

    B. Cisplatin plus gemcitabine

    C. Carboplatin plus paclitaxel

    D. Cisplatin, etoposide, plus durvalumab

Use the following scenario to answer Questions 11-13

SP is a 62-year-old individual with a recent diagnosis of stage IIB NSCLC, adenocarcinoma histology. Complete pathological evaluation showed ALK positive, EGFR negative, ROS1 negative, $BRAF^{V600E}$ negative, and PD-L1 negative. A prior medical history includes hypertension, type 2 diabetes, peripheral neuropathy, and gastroesophageal reflux disease. SP underwent surgery and is ready to receive chemotherapy.

11. Which of the following therapies is most appropriate for SP now?

    A. Cisplatin and vinorelbine

    B. Carboplatin, pemetrexed, and bevacizumab

C. Alectinib

D. Pembrolizumab

12. Which of the problems in the patient's prior medical history is most likely to be worsened if the patient were to receive platinum-based chemotherapy?

A. Hypertension

B. Type 2 diabetes

C. Peripheral neuropathy

D. Gastroesophageal reflux disease

13. Two years after completing chemotherapy, SP presents to the primary care physician with new-onset cough with hemoptysis. The evaluation revealed the patient's lung cancer has relapsed, now with multiple tumors in the lung of origin as well as several suspicious tumors in the liver. The pathologic evaluation reveals the same genetic features as the original tumor. Which of the following is the most appropriate treatment for SP now?

A. Docetaxel and ramucirumab

B. Atezolizumab

C. Alectinib

D. Osimertinib

14. Which of the following patients with small cell lung cancer should receive prophylactic cranial irradiation?

A. Patients with limited-stage SCLC who achieve a complete response to their initial therapy.

B. Patients with extensive-stage SCLC who do not respond to their initial therapy.

C. All patients with limited-stage SCLC.

D. All patients with extensive-stage SCLC.

15. A 64-year-old individual with a performance status of 1 returns to clinic with relapsed small cell lung cancer (SCLC), new bone, and liver metastases. The previous chemotherapy of carboplatin and etoposide was completed 9 months ago, followed by a course of cranial irradiation. The patient has been in good health and reports no other medical problems and request further treatment if it is reasonable. Based on this information, which of the following treatments would be appropriate?

A. Topotecan

B. Carboplatin and etoposide

C. Pembrolizumab

D. Lurbinectidin

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** For limited-stage SCLC, the preferred chemotherapy regimen is cisplatin with etoposide. Thoracic radiation should be administered concurrently with chemotherapy to improve the likelihood of a complete response (see the "Limited Disease" section).

2. **C.** Lung cancer is the leading cause of cancer-related mortality for both men and women in the United States (see the "Introduction and Epidemiology" section).

3. **A.** The NLST showed that in patients aged 55 to 74 years with at least a 30-pack year smoking history, annual low-dose helical CT scan decreases lung cancer–related mortality by 20% compared to annual chest x-ray. The patients in this study had to be current smokers or active smokers within the last 15 years. Since the individual quit smoking 18 years ago, they do not meet the criteria (see the "Screening and Prevention" section).

4. **C.** Cigarette smoking is the leading risk factor for the development of lung cancer (see the "Etiology" section).

5. **A.** Non-small cell lung cancer is the most commonly diagnosed form of lung cancer. Within this subcategory, adenocarcinoma is the most commonly diagnosed (see the "Histologic Classification" section).

6. **A.** Early-stage lung cancer, such as stage II resectable adenocarcinoma should be treated with curative intent. Advanced lung cancers, including stage IV NSCLC and extensive stage NSCLC, along with cancers that have relapsed, should be treated with the intent of prolonging survival and improving quality of life (see the Desired Outcomes" section).

7. **D.** Pembrolizumab has been shown to improve the efficacy of combination chemotherapy in the treatment of metastatic, nonsquamous NSCLC, regardless of PD-L1 expression. It has specifically been studied in combination with carboplatin and pemetrexed (see the "Nonbiomarker Driven" section).

8. **B.** Recurrent/relapsed NSCLC that is negative for all biomarkers (EGFR, ALK, $BRAF^{V600E}$) is most often treated with single-agent chemotherapy, such as docetaxel. Clinical trial evidence has shown that the addition of ramucirumab to docetaxel in this setting improved median overall survival. Ramucirumab may be used in all types of NSCLC (see the"Relapsed Disease section).

9. **A.** The patient has a performance status of 4 due to severe COPD. Treatment of NSCLC in patients with a poor performance status (PS) has not been shown to improve survival. The Eastern Cooperative Oncology Group (ECOG) PS delineation ranges from fully active to confinement to bed. Generally, patients with a status of 4 are typically not offered treatment, rather are managed with best supportive care (see the "PD-L1+ Tumors" section).

10. **D.** For extensive-stage SCLC to maximize survival, one should utilize cisplatin plus etoposide regimen. The addition of atezolizumab or durvalumab improves outcomes over chemotherapy alone (see the "Extensive Disease" section).

11. **A.** The patient is due to start adjuvant chemotherapy for the treatment of early-stage nonsquamous NSCLC. The combination of cisplatin and vinorelbine is one of the combination regimens recommended in this setting. (see the "Local Disease" section).

12. **C.** Cisplatin and carboplatin are both associated with neuropathy. In patients with preexisting neuropathy, platinum-based therapy can worsen their symptoms (see the "Complications and Supportive Care" section.)

13. **C.** The patient is positive for ALK. Since the initial regimen was used in the adjuvant setting for the treatment of early-stage lung cancer, chemotherapy was initially used. Now, in the relapsed setting, targeted therapy is preferred when possible. Since the patient is positive for ALK, therapy targeting this kinase can be used. Alectinib has demonstrated superior progression-free survival when compared to crizotinib, the first-generation ALK inhibitor (see the"Targetable Genetic Mutation" section).

14. **A.** Whether limited or extensive stage, patients with SCLC who achieve a complete response to their chemotherapy regimen should receive prophylactic cranial irradiation (PCI). In this situation, PCI decreases the incidence of brain metastases and improves overall survival (see the "Limited Disease" section).

15. **B.** The patient experienced relapse 9 months after completing the initial chemotherapy. Clinical practice guidelines recommend retreatment with the original regimen in patients with SCLC who achieve complete remission of 6 months or longer. Retreatment with carboplatin and etoposide is appropriate ("Relapsed Disease" section).