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Targeted and cytotoxic inhibitors used in the treatment of lung cancers

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ABSTRACT

Lung cancer is the leading cause of cancer deaths in the United States and the world. It is divided into two major types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). In the tumor-node-metastasis (TNM) cancer-staging classification system (Stages I/II/III/IV), the severity of neoplastic growth is characterized by the size of the tumor (T1 to T4), the extent of lymph node involvement (N0 to N3), and whether (M1) or not (M0) distant metastasis has occurred. Surgery is the treatment of choice for medically fit patients with Stage I/II NSCLC. Combination chemoradiotherapy and immune checkpoint inhibitor therapy are used across all NSCLC types. Oncogene-addicted tumors with sensitizing *EGFR* or *BRAF* mutations or activating *ALK*, *ROS1* or *NTRK* translocations are treated with their cognate orally active small molecule protein kinase blockers. On the order of 20 % of NSCLCs bear activating mutations in *EGFR* and are treated with osimertinib and other kinase antagonists. SCLC, which accounts for approximately 15 % of lung cancer cases, is a deadly high-grade neuroendocrine carcinoma with a poor prognosis. Limited-stage SCLC is confined to one hemi-thorax and one radiation port and extensive-stage disease signifies those cancers that do not meet the criteria for limited-stage disease. Local treatment options to control thoracic disease include radiotherapy and surgery. In patients with extensive-stage disease, a platinum agent (cisplatin or carboplatin) combined with etoposide and an anti-PDL1 inhibitor (atezolizumab or durvalumab) for four cycles followed by anti-PDL1 maintenance therapy is the recommended first-line regimen.

1. An overview of the incidence, diagnosis, and patient workup for lung cancer

1.1. Incidence

Lung cancer refers to malignancies that arise from the respiratory epithelium including the bronchi, bronchioles, and alveoli [1]. It is the leading cause of cancer deaths both in the United States and the world [2–4]. Siegel et al. estimated that about 234,000 new cases of lung cancer will be diagnosed in the United States in 2024 (116,000 men and 118,000 women) and 125,000 people will die of the disease (66,000 men and 59,000 women) [2]. Lung cancer deaths account for about one-fifth of all cancer-related deaths in the United States in 2024 [4] and about 18 % worldwide in 2020 [2]. The median age at the time of diagnosis of lung cancer in the United States is at 71 years. Cigarette smoking accounts for about 80 % all cases of lung cancer and is quantitatively the most important modifiable risk factor [3]. Despite the strong relationship to tobacco smoking, Rina et al. reported that fewer than one out of five heavy smokers develop lung cancer [5], whereas about 20 % of patients with lung cancer have never smoked. The incidence of lung cancer is currently falling owing to a decrease in the proportion of cigarette smokers in the general population. Cigarette smoke is the leading cause of lung cancer followed by radon gas and then environmental secondhand smoke. Radon (Rn^{222}) is a naturally occurring colorless, odorless decay product of underground uranium (U^{238}); it can penetrate the earth's crust and accumulate in buildings. It emits DNA damaging alpha particles. Other risk factors for lung cancer include exposure to chromium, asbestos, arsenic, vinyl chloride, and polycyclic aromatic hydrocarbons. This review focuses on carcinomas and does not consider uncommon lung neoplasms such as carcinoid tumors,

Abbreviations: CNS, central nervous system; CT, computed tomography; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration of the United States; HER2, human epidermal growth factor receptor-2; MAPK, mitogen activated protein kinase; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PD1, programed cell death protein 1; PDL1, programed cell death protein 1 ligand 1; PET, positron emission tomography; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKB, protein kinase B aka AKT; PKC, protein kinase C; PLC, phospholipase C; SCLC, small cell lung cancer; TPS, tumor proportion score; VATS, video-assisted thoracic surgery; VEGFR, vascular endothelial growth factor receptor.

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chondromas, fibromas, hamartomas, inflammatory myofibroblastic tumors, or lipomas.

1.2. Presenting symptoms

The signs and symptoms that prompt lung cancer patients to seek medical aid depend upon the size of the tumor and its specific location [1]. The most common chief complaints of patients at their initial clinic visit include coughing (75 %), weight loss (40 %), chest pain (20 %), and dyspnea or labored breathing (20 %). Other findings include hemoptysis (coughing up blood), dysphagia (difficulty swallowing owing to esophageal invasion), hoarseness (due to recurrent laryngeal nerve invasion), post-obstructive pneumonia, wheezing (owing to airway obstruction), and variable bone pain owing to metastatic lesions. Many patients are asymptomatic at the time of their initial clinical visit and the diagnosis is based upon an incidental chest X-ray, MRI, or CT scan performed for other reasons. Brain metastases (10 % in NSCLC and 20−30 % in SCLC) can present with headaches, nausea, vomiting, seizures, dizziness, or altered mental status [1]. Paraneoplastic syndromes occur in 10−20 % of lung cancer patients. The symptoms produced by these syndromes result from cytokines or hormones released by tumor cells or by an immune response against the tumor. Signs and symptoms include fever, hypercalcemia (fatigue, poor appetite, muscle weakness or twitching), and erythrocytosis (reddish face, hands, and feet, headaches, dizziness, hypertension, nose bleeds, or blurred vision).

1.3. Histopathology

The diagnosis of lung cancer is based upon the examination of a tissue or cytology specimen [1]. Fiberoptic or rigid bronchoscopy permit direct visualization of the airways and acquisition of clinical samples for laboratory testing. Transthoracic percutaneous needle aspiration and navigational bronchoscopy are useful in evaluating peripheral lung lesions and performing biopsies. Additionally, surgery may be required to obtain tissue samples through (i) open or (ii) video-assisted thoracoscopic surgery (VATS). Historically, lung cancer has been divided into two major types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). This identification is important in planning therapy. Adenocarcinomas (~50 %), squamous cell carcinomas (~30 %), and large cell carcinomas (~ 5–10 %) are the three main histological types of NSCLC [6]. More poorly differentiated histological subtypes that are not otherwise specified make up the remainder.

Adenocarcinomas are characterized histologically by gland formation and mucin production [1] (*aden* is Greek for gland). Such tumors express the thyroid transcription factor-1 (TTF-1) in the nucleus. They are usually solitary, slow growing, and found in the periphery of the lung (75 %). Squamous cell carcinomas arise from the epithelial layer of the bronchial wall. These neoplasms express p40 and p63, which are used for histological subtype identification. Squamous cell carcinomas arise in the central airways, often produce bronchial obstruction leading to obstructive pneumonitis or atelectasis (collapse of the lung), and they have less potential to metastasize when compared with adenocarcinomas. Large cell carcinomas are undifferentiated epithelial tumors that lack the cytologic features of the other forms of lung cancer and they typically possess large nuclei, prominent nucleoli, and a moderate amount of cytoplasm. Large cell carcinomas can develop anywhere in the lungs, but they occur most commonly around the outer edges. They are known for their rapid growth and ability to metastasize to the liver, bones, lymph nodes, and brain. Symptoms of large cell carcinomas are similar to those of other types of lung cancer and can include persistent coughing, dyspnea, chest pain, hemoptysis, and unintentional weight loss. Survival rates are lower for large cell carcinomas than for adenocarcinomas and squamous cell carcinomas. SCLCs demonstrate a high frequency of mitotic division and lack the architectural organization characteristic of adenocarcinomas or squamous cell carcinomas.

1.4. Gene alterations

Many lung cancers contain genomic alterations that can be targeted by low molecular weight drugs and various immunotherapies [5,7,8]. EGFR (epidermal growth factor receptor) is a transmembrane protein with protein-tyrosine kinase activity that participates in cell proliferation, survival, and differentiation. The EGFR family is among the most investigated receptor protein-tyrosine kinase groups owing to its general role in signal transduction and in oncogenesis. This family consists of four members that belong to the ErbB lineage of proteins (ErbB1/2/3/4) encoded by four genes including: (i) *EGFR/ERBB1/HER1*, (ii) *ERBB2/-HER2/NEU*, (iii) *ERBB3/HER3*, and (iv) *ERBB4/HER4*. Although there is a considerable crossover, the HER nomenclature is used more commonly in clinical papers and reports whereas the ERBB nomenclature is associated with the biological sciences. Schechter et al. discovered that a series of rat neuro/glioblastomas contain the Neu oncogene, which is related to the rat *Erbb2* gene of the EGFR family [9]. This discovery provided evidence for the possible role of the ErbB family of receptors in the pathogenesis of cancer and *NEU* is sometimes used in human gene nomenclature. The ErbB proteins function as homo and heterodimers [10–12]. Seven ligands bind to EGFR (EGF, transforming growth factor-α, amphiregulin, epigen, betacellulin, epiregulin, heparin-binding epidermal growth-like factor), none bind to ErbB2, two bind to ErbB3 (neuregulin1/2), and seven ligands bind to ErbB4 (betacellulin, epiregulin, heparin-binding epidermal growth-like factor, neuregulin1/2/3/4). Activating mutations in the *EGFR* gene were identified in NSCLC in 2004 [8]. On the order of 20 % of non-small cell lung cancers bear activating mutations in *EGFR* [12]. About 90 % of these patients have exon-19 deletions, exon-19 insertions, or the exon-21 L858R substitution [13]. About 5 % have exon-18 substitutions and fewer than 1 % have exon-20 substitutions. These mutations are associated with patients of East-Asian descent, females, never smokers, and the adenocarcinoma subtype.

The EML4 (echinoderm microtubule-associated protein-like 4)-ALK fusion protein and seven other ALK-fusion proteins (KIF5B, TFG, KLC1, PTPN3, HIP1, TPR, STRN) play a fundamental role in the development of about 5 % of non-small cell lung cancers [14–17]. Alk fusion-positive patients are former or never cigarette smokers and their tumors are usually adenocarcinomas, often with so-called signet ring morphology. Patients with ALK-positive NSCLC are generally younger than the typical lung cancer population. Such fusion proteins result from ALK 2p23 chromosomal translocations. The amino-terminal portions of the ALK fusion proteins result in dimerization and concomitant activation of the ALK protein kinase domain that plays a key role in the pathogenesis of lung cancers. Downstream signaling from the ALK fusion protein leads to the activation of the Ras/Raf/MEK/ERK cell proliferation module, the MEKK2/3-MEK5-ERK module, the JAK/STAT cell survival pathway, the CRKL-C3G-RAP1 signaling module, the PI3K/AKT/mTOR pathway, and the JUN pathway.

BRAF gene mutations occur in about 2–5 % of lung cancer cases [18]. B-Raf is a protein-serine/threonine kinase which is part of the Ras/-Raf/MEK/ERK signaling pathway that is involved in the regulation of cell growth, differentiation, and survival [19,20]. The Raf acronym corresponds to Rapidly accelerated fibrosarcoma, first described in mice. This signal transduction cascade is arguably the most important oncogenic pathway in human cancers [21]. Ras-GTP promotes the formation of active homodimers or heterodimers of A-Raf, B-Raf, and C-Raf by an intricate process [19,20]. These enzymes are protein-serine/threonine kinases that catalyze the phosphorylation and activation of MEK1 and MEK2 which, in turn, catalyze the phosphorylation and activation of ERK1 and ERK2 [22,23]. Most activating *BRAF* mutations involve the substitution of aspartate, glutamate, lysine, or arginine for valine 600 and they occur more commonly in adenocarcinomas [19,20].

ROS1 is a receptor protein-tyrosine kinase that participates in cell growth, differentiation, and survival [24,25]. It is activated

physiologically by NELL2 (neural epidermal growth factor-like 2), which consists of 816 amino acid residues with a signal sequence of 21 residues. ROS1 fusion proteins play a role in about 1–2 % of NSCLC cases, mostly in nonsmokers with adenocarcinoma. Such rearrangements are identified by either FISH (fluorescence *in situ* hybridization) or next-generation sequencing (NGS) procedures. Nearly all subtypes of adenocarcinomas have been described in *ROS1*-rearranged NSCLC including acinar, lepidic, papillary, solid, signet-ring, and mucinous cribriform patterns. Because of their ability to independently initiate tumorigenesis in lung cancer, *ROS1* rearrangements typically are mutually exclusive from other targetable driver alterations such as *KRAS* or *EGFR* mutations or *ALK r*earrangements. ROS1 fusion partners that have been reported in NSCLC include the following: CCKC6, CD74, EZR, FIG, LRIG3, SDC4, SLC34A2, and TMP. Multiple signaling pathways downstream of ROS1 have been implicated in mediating their oncogenic effect including the Ras-MAPK and PI3K/AKT/mTOR pathways.

RET is a transmembrane receptor protein-tyrosine kinase that is required for the normal development of the brain, the peripheral autonomic nervous system, the thyroid–calcitonin-producing C-cells, the thyroid gland, and the lung [26,27]. RET was discovered as a factor involved in the transformation of murine NIH 3T3 fibroblasts with sonicated human lymphoma DNA. The transforming sequence encompassed 34 kilobases and was made up of a rearrangement of two normal but unlinked DNA segments. Because this transforming sequence was the product of gene rearrangement during transfection, it was named RET for REarranged during Transfection. RET was identified as the receptor for the glial-cell derived neurotrophic factor (GDNF), artemin (ARTN), neurturin (NRTN), and persephin (PSPN). Aberrant activation of RET is the result of the formation of fusion proteins, which occurs in about 1–2 % of NSCLC cases. KIF5B-RET is the most common RET fusion protein identified in NSCLC. Other RET fusion partners include CCDC6, NCOA4, TRIM33, CUX1, and KIAA1468. The clinical features of patients with NSCLC harboring RET fusion proteins are younger (median age around 60 years), equal prevalence in both sexes, adenocarcinoma histopathology, poorly differentiated tumors, and no or low exposure to tobacco. Moreover, the incidence of brain metastases in RET-positive NSCLC patients is intermediate between ALK-positive and ROS1-positive patients.

MET is a receptor protein-tyrosine kinase whose activating ligand is hepatocyte growth factor/scatter factor (HGF/SF) [28–30]. Accordingly, MET is the hepatocyte growth factor receptor (HGFR). The term MET originally referred to the methyl group in the carcinogen (N-methyl-N′-nitroso-guanidine) used to generate the fusion protein in a human osteogenic sarcoma cell line. In addition to its role in promoting cell division and survival, MET also plays a role in the metastasis of cancer cells. MET may be thought of as an abbreviation for "metastasis" or an acronym for "mesenchymal-epithelial transition" factor. MET exon-14 skipping mutations are found in approximately 3 % of lung adenocarcinomas and slightly more than 2 % of lung squamous cell carcinomas [31]. These mutations retard receptor degradation and result in enhanced MET signaling. KIF5B-MET fusion proteins and MET overexpression also occur in NSCLC. The MET pathways (PI3K/AKT, Ras-MAPK, and STAT3) enhance tumor cell proliferation and survival, thereby supporting rapid tumor growth [30]. Additionally, MET signaling promotes the migration and invasive capabilities of tumor cells and facilitates local invasion and distant metastasis. Furthermore, the MET pathway stimulates angiogenesis, ensuring an adequate blood and nutrient supply to the tumor, thus fostering further growth and expansion.

The *NTRK1*, *NTRK2*, and *NTRK3* genes, which encode the TRKA, TRKB, and TRKC nerve growth factor receptor protein-tyrosine kinases, generate a variety of fusion proteins as the 3' end of the *NTRK* gene fuses with the 5' end of a fusion partner gene [5]. These gene-fusion proteins, which are aberrantly expressed and constitutively activated, participate in cell signaling by triggering the PI3K/AKT/mammalian target of the rapamycin (mTOR) pathway, the PLC/PKC pathway, and the Ras-MAPK pathway in about 1 % of all solid tumors and in 0.1–0.2 % of NSCLCs [32]. Most people with lung cancers harboring NTRK gene fusion proteins exhibit clinical characteristics similar to those possessing ALK, ROS1, or RET fusion proteins, specifically (i) a younger median age compared with nononcogene-addicted lung cancer patients, (ii) minimal or no prior history of cigarette smoking, and (iii) frequent CNS metastases. Immunohistochemistry (IHC), fluorescence *in situ* hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR), and next-generation sequencing (NGS) can be used to detect NTRK gene fusions.

K-Ras participates in many physiological signal transduction processes related to cell growth, division, and survival. K-Ras-2A/2B are small proteins (189/188 amino acid residues) that result from alternative splicing and they function as GTPases [33,34]. These proteins toggle between inactive and functional forms; the conversion of inactive Ras-GDP to active Ras-GTP is mediated by guanine nucleotide exchange factors (GEFs) that turn the switch on and the intrinsic Ras-GTPase activity stimulated by the GTPase activating proteins (GAPs) that turn the switch off. The Ras proteins are upstream components of the Ras/-Raf/MEK/ERK and the PI3K/AKT/mTOR signaling modules. *KRAS* mutations occur in about 35 % of lung cancers: 39 % in NSCLC and 5 % in SCLC [35]. The $KRAS^{G12C}$ mutation is by far the most commonly observed *KRAS* substitution followed by C12V and C12D substitutions. Approximately 40 % of adenocarcinomas harbor *KRAS* activating mutations regardless of smoking history [36]. Such mutations are more common in younger people and women. In contrast to other driver mutations, which are not associated with other gene alterations, *KRAS* mutations co-occur with those of other genes such as *STK11*, *TP53*, and *KEAP1*.

The *ERBB2* gene encodes HER2 (human epidermal growth factor receptor 2), a member of the EGFR family that includes ErbB1/2/3/4 [10–12]. There is no known ligand for ErbB2 and ErbB3 lacks protein kinase activity. It is thus paradoxical that the ErbB2/ErbB3 dimer is catalytically the most active EGFR family combination. *ERBB2* mutations occur in about 2 % of NSCLC cases and they are observed more frequently in adenocarcinomas when compared with other subtypes [5]. *ERBB2* alterations manifest themselves by gene amplification, point mutations, or overexpression. Amplification leads to overexpression of the Her2 protein on the cell surface thereby promoting uncontrolled cell proliferation and tumor cell survival. In contrast, point mutations in exon 20 lead to an increase in ErbB2 protein kinase catalytic activity. Activating mutations within the kinase domain of HER2, most notably insertions in exon 20 such as A775-G776 YVMAins are found in ~1.5 % of all NSCLC patients, which corresponds to an alteration near the protein kinase αC-regulatory helix [37]. *ERBB2* mutations are found predominantly in younger nonsmoking female patients and are associated with an unfavorable prognosis [38]. Patients with these mutations tend to present with more aggressive tumors and a less favorable response to therapy.

1.5. Immune biomarkers

In addition to the evaluation of actionable signal transduction mutations, it is important to assess lung cancer specimens for immune biomarkers [35]. The intricate interplay between tumor cells and the immune system indicates that tumor cells can evade destruction by the immune system through a bevy of complex mechanisms. Thus, it is routine to assess the levels of cytotoxic T-lymphocyte antigen-4 (CTLA-4) in lymphoid organs and PD1/PDL1 in peripheral tumor tissues owing to the importance of these components in the tumor escape mechanism. PD1 is an inhibitory immune transmembrane receptor of the CD28 family that modulates the activity of T cells in peripheral tissues [39]. It is expressed in T cells, many tumor infiltrating lymphocytes, natural killer cells, B cells, and monocytes. Under normal physiological conditions, the interaction of PD1 with its ligands (PDL1 or PDL2) prevents (i) excessive lymphocyte activation, (ii) excessive

inflammation, (iii) destructive autoimmunity, and (iv) maintains immune tolerance to self-antigens by negatively regulating the immune response. PDL1 is often overexpressed by various tumor cells including those of NSCLC. Consequently, tumor cells attenuate T-cell signaling to evade immune surveillance. Blocking PD1–PDL1/2 interaction can restore T-cell activation leading to an antitumor response.

1.6. Staging

The staging of SCLC and NSCLC in patients is used to designate disease severity, prognosis, and to plan treatment [1,40,41]. Chest computed tomography (CT imaging) and positron emission tomography (PET) imaging are two noninvasive procedures used for staging. The techniques for obtaining biopsies are invasive procedures that are used for staging. In the NSCLC tumor-node-metastasis (TNM) cancer-staging classification system, the severity of neoplastic growth is characterized by the size of the tumor mass (T1 to T4), the extent of lymph node involvement (N0 to N3), and whether (M1) or not (M0) distant metastasis has occurred. The larger the number in each of these parameters, the more advanced and/or disseminated the disease. For T1, the tumor is $\leq$3 cm in its greatest dimension; for T2, the cancer is between 3–5 cm, or it can involve the main airway or the inner lining of the chest cavity; for T3, the tumor is between 5–7 cm or it invades the chest wall, the phrenic nerve, or the parietal pericardium; for T4, the tumor is $\geq$7 cm or a tumor of any size that invades the mediastinum, heart, trachea, recurrent laryngeal nerve, esophagus, or vertebrae. For N0 disease, all nodes are tumor negative; for N1 disease, metastases are confined to nodes on the same side of the lung as the tumor; for N2 disease, metastases occur to nodes in the mediastinum; for N3 disease, metastases occur to nodes on the opposite side of the lung as the tumor. Taken together, the TNM characteristics of a lung cancer can be translated into a comprehensive staging scale ranging from I (localized) to IV (metastatic). The intermediate disease severity stages indicate local (Stage II) or regional (Stage III) tissue invasion.

2. Management of non-small cell lung cancer

2.1. Early-stage NSCLC (Stages I/II)

Stage I and Stage II diseases describe tumors that are contained within the lung and that can be completely resected with surgery; accordingly, surgery is the treatment of choice for medically fit patients with Stage I/II NSCLC (Table 1) [42]. A lobectomy, or removal of an entire lobe of the lung, achieves a better clinical outcome than the removal of a small wedge-shaped portion of the lung. Removal of an entire lung (pneumonectomy) can be required for hilar or proximal tumors at the lung origin. If a lobectomy is not possible because of co-morbidities or poor pulmonary function, sub-lobar resections may be acceptable in patients with peripheral tumors. Video-assisted thoracic surgery (VATS) is the approach of choice whenever feasible. This is a minimally invasive technique that allows surgeons to perform procedures in the chest without making large incisions or spreading the ribs. This technique involves the insertion of a thin tube with a camera at the end, called a thoracoscope, through a small incision in the chest. The surgeon uses the thoracoscope to guide various instruments through other small openings required to complete the procedure.

Perioperative NSCLC management was relatively simple decades ago involving conventional (classical) radiation therapy and chemotherapy [43,44]. Systemic therapy in NSCLC, however, has advanced significantly over the past 10–15 years with the development of targeted therapies for activating mutations in NSCLC and the use of immune checkpoint inhibitors (ICIs). Consequently, there have been significant developments incorporating neoadjuvant therapies (given before the primary treatment such as surgery to shrink the tumor), adjuvant therapies (given after the primary treatment to reduce the risk of the cancer returning), and a combination of these treatments. The post-surgery relapse rate is high and about 50 % of Stage I/II patients subsequently develop metastases. Postoperative adjuvant platinum-based chemotherapy for four cycles (cisplatin/vinorelbine) is indicated for patients (i) with nodal involvement or (ii) with node-negative tumors $\geq$ 4 cm in size. Postoperative radiotherapy is recommended after an incomplete tumor resection and can be considered in patients with lymph nodes in the mediastinum (N2).

Table 1
Synopsis of Stages I through IV NSCLC first-line therapies.

Stage	Treatment
I	Surgery Radiation therapy for nonsurgical candidates
II	Surgery + adjuvant platinum-based doublet chemotherapy (cisplatin/(vinorelbine or docetaxel or paclitaxel or etoposide or gemcitabine and for nonsquamous NSCLC, pemetrexed)) Radiation therapy for nonsurgical candidates
IIIA (N0)	Adjuvant chemotherapy (cisplatin with vinorelbine or etoposide or gemcitabine or docetaxel) and surgery
IIIA (N1)	Concurrent chemotherapy (cisplatin with vinorelbine) and radiation therapy (60 Gy in 30 fractions over six weeks) and surgery and atezolizumab or durvalumab or pembrolizumab
IIIA (N2)	Concurrent chemotherapy (cisplatin with vinorelbine) and radiation therapy (60 Gy in 30 fractions over six weeks) followed by atezolizumab or durvalumab or pembrolizumab
IIIB	Palliative radiation therapy
IV (no driver mutations)	Concurrent chemotherapy consisting of (i) cisplatin with paclitaxel or docetaxel or pemetrexed (for nonsquamous cell disease only) or gemcitabine or nab-paclitaxel or etoposide (for squamous cell disease) (ii) and immunotherapy (atezolizumab or durvalumab or pembrolizumab) Immune checkpoint inhibitor therapy (atezolizumab or durvalumab or pembrolizumab or nivolumab and ipilimumab)
IV (with driver mutations)	See Fig. 1

Radiotherapy is widely used in the management of more than half of all NSCLC patients [45]. For early-stage NSCLC, stereotactic body radiotherapy (SBRT) is usually reserved for patients who do not meet the criteria for surgical intervention or for those who decline surgery [46]. Up to 20 % of patients diagnosed with Stage I NSCLC do not meet the criteria for surgery [47]. These include people who display multiple co-morbidities, advanced age, low cardiopulmonary function, or a combination of the three. Retrospective studies, however, suggest that stereotactic body radiotherapy and surgical resection provide equivalent long-term outcomes for early stage NSCLC [48].

In patients who are medically unsuitable for surgery, early-stage treatment with stereotactic body radiotherapy is a recommended option [43,49]. Stereotactic radiotherapy uses multiple beams of radiation that meet at the tumor, delivering a high dose of radiation to the tumor while minimizing radiation to the surrounding tissue. X-rays produce small breaks in the DNA of cells and the cell dies and is removed by the body. Cancer cells are generally more sensitive to radiation damage than normal cells because they divide more frequently. Stereotactic body radiotherapy is an advanced procedure that uses precise positioning and imaging to target the tumor with ablative doses and limit the extent of normal tissue exposed to radiation. Stereotactic radiation therapy can be delivered using a cyber knife or gamma knife. The cyber knife robotic arm (i) with its attached linear accelerator producing X-rays and motion tracking technology allow for more treatment flexibility than (ii) the gamma knife, which uses cobalt-60 as a source of gamma rays. The former is used to treat tumors in the lung while the latter is used to treat brain metastases (not Stage I/II by definition). Gamma rays are a more energetic type of electromagnetic radiation than X-rays.

Stereotactic body radiation therapy is a noninvasive alternative to surgery and can be more effective than conventional radiation therapy because it is more precise and has fewer side effects [49]. Conventional radiotherapy for NSCLC is a type of external beam radiation therapy

(EBRT) that involves the use of two-dimensional beams to treat the tumor. This type of radiotherapy employs very large fields of radiation with an extensive margin surrounding the tumor. Radiation is delivered from a linear accelerator, usually from the front and back of the patient. Radiation treatments are typically given five days a week for five to seven weeks. The total radiation dosages are around 60–66 Gy (grays) where one Gy corresponds to the energy of one joule per kilogram.

Previous treatments of nonresectable Stage I NSCLC utilized conventional radiotherapy until more recent studies demonstrated that more modern radiotherapy modalities promote better outcomes. In a systematic review and meta-analysis, Li et al. reported that stereotactic body radiotherapy is superior to conventional radiotherapy in treating Stage I NSCLC [50]. Studies that examined overall survival found that 1-, 2-, 3-, 4-, and 5-year overall survival rates were higher in the stereotactic radiotherapy groups (86 %, 69 %, 55 %, 40 %, 29 %) than the respective conventional radiotherapy groups (78 %, 54 %, 40 %, 27 %, 27 %). Additionally, studies that evaluated lung cancer-specific survival (LCSS), local control rate (LCR), and progression-free survival (PFS) indicate that stereotactic body radiation is superior to conventional radiotherapy in all metrics. Trials that measured adverse events (AE) revealed a significant reduction in dyspnea, radiation pneumonitis, and esophagitis following stereotactic radiotherapy in comparison with conventional radiotherapy, with no significant differences in the incidence of other side effects. In summary, stereotactic body radiotherapy produces major therapeutic responses in treating NSCLC independent of modulating variables [51].

2.2. Locally advanced NSCLC (Stages IIIA/B)

Patients with Stage IIIA (N0/N1 disease) are candidates for surgery and should be offered adjuvant chemotherapy after a complete surgical resection [52]. In N0 disease, there is no cancer in any lymph nodes; in N1 disease, cancer cells are present within lymph nodes on the same side of the chest as the affected lung or in the hilum. People with Stage IIIA/B with N2 disease (cancer cells are present in the mediastinum) are generally treated with chemoradiotherapy delivered concomitantly (chemotherapy together with radiotherapy). Consolidation immunotherapy, or therapy given after the initial treatment, should be provided after concomitant chemoradiotherapy, with the PDL1 immune checkpoint inhibitor durvalumab for one year (Table 2); this treatment paradigm has been shown to improve overall survival. For elderly or less fit patients, sequential chemoradiotherapy represents a valid alternative. Selected fit patients with limited N2 involvement can be considered for multimodality treatment involving simultaneous chemoradiotherapy followed by surgery. Stage IIIB (either T3/T4 N2 M0 or T1/T2 N3 M0) patients are not candidates for surgery and are usually best managed with palliative intent as in Stage IV disease.

For locally-advanced Stage III NSCLC, radiotherapy was historically part of the standard treatment in combination with chemotherapy with or without surgical resection [53]. However, the control arm of the consequential PACIFIC clinical trial used a standard chemoradiation regimen plus placebo and compared it with the experimental group that received standard chemoradiation followed by immune checkpoint inhibition [54]. These patients had Stage III locally advanced unresectable NSCLC, and they received two or more cycles of platinum-based chemotherapy in combination with radiotherapy at a dose of 54–66 Gy. The experimental group received durvalumab, an anti-PDL1 monoclonal antibody, and this group had a longer progression-free survival. These results demonstrated the additive effect of a checkpoint inhibitor with chemotherapy and radiotherapy [55]. The KEYNOTE-001 trial demonstrated prolonged progression-free survival in patients with advanced NSCLC treated with pembrolizumab, an anti-PD1 monoclonal antibody, in comparison with the group treated with (i) chemotherapy, (ii) chemoradiation, or (iii) who were treatment-naive. A subsequent post hoc analysis of these patients demonstrated that those who received any form of radiotherapy before pembrolizumab had a longer disease-free survival when compared with patients who (i) received only chemotherapy or (ii) were treatment-naive [56]. Of interest, the outcomes in these trials were not dependent upon the level of PDL1 expression.

The PEMBRO-RT study offers a greater understanding of the mechanisms and benefits of antitumor effects of combination immunotherapy and radiation [57]. This study enrolled 76 patients with metastatic NSCLC to explore the outcomes associated with pembrolizumab following stereotactic body radiation at the primary tumor site (three doses of 8 Gy) versus pembrolizumab alone. The overall response rate at 12 weeks was 18 % in the control (pembrolizumab only) arm versus 36 % (radiotherapy plus pembrolizumab) in the experimental arm. Progression-free survival was 1.9 months in the control arm and 6.6 months in the experimental arm. A median overall survival of 7.6 months was observed in the control arm, compared with 15.9 months in the experimental arm. The improved overall response rate, progression-free survival, and overall survival in patients who received pembrolizumab after stereotactic radiotherapy provide evidence for the additive effects of immunotherapy and radiotherapy. This finding is supported by an MDACC trial involving 100 patients with metastatic NSCLC, which explored the clinical outcomes associated with pembrolizumab with or without concurrent radiotherapy (50 Gy in 4 fractions or traditionally fractionated radiotherapy 45 Gy in 15 fractions) regardless of tumor PDL1 expression [45]. The overall response rate found in the control arm was 25 % versus 22 % in the experimental arm. However, the median progression free survival of the control arm was 5.1 months compared to 9.1 months in the experimental arm. While the overall response rate in this trial is in disagreement with the results of the PEMBRO-RT trial, the progression free survival findings are similar. Both trials support treatment with the pembrolizumab and radiotherapy combination, but various discrepancies in clinical trial findings are common when the number of subjects is limited.

2.3. Metastatic NSCLC (Stage IV)

2.3.1. Overview of Stage IV NCSLC

NSCLC tumors are routinely evaluated for their molecular and immunological status, and they can be broadly separated into those with or without driver mutations, i.e., *EGFR* or *BRAF* mutations or activating *ALK*, *NTRK* or *ROS1* translocations [7]. Treatment decisions are based on the patient's age, co-morbidities, preference, and an evaluation of the ability to perform daily activities (performance status), with the objective of integrating concurrent palliative and supportive care. The Karnofsky Performance Scale (KPS) and the Eastern Cooperative Oncology Group (ECOG) performance scores are two widely used tools for measuring performance status [58]. Common co-morbidities include anemia, diabetes, hypertension, kidney disease, and chronic lung disease [59]. Advanced age should not preclude patients from systemic therapy if they have a good performance status, good organ function, and few co-morbidities. Stage IV patients with 1–3 synchronous metastases at the time of their diagnosis can experience long-term survival after systemic therapy and local consolidative therapy (stereotactic body radiotherapy, surgery).

2.3.2. First-line therapy for NSCLC without known driver mutations

If not contraindicated, all patients with Stage IV NSCLC without known driver mutations should be treated with an immune checkpoint inhibitor [59]. Contraindications include active brain metastases, autoimmune diseases requiring disease-modifying therapy, treatment with corticosteroids, or a poor performance status ($\geq$3). Patients with contraindications to immune checkpoint inhibitors should be treated with histology-specific chemotherapy. Thus, individuals with a non-squamous subtype NSCLC should be given platinum/pemetrexed, followed by maintenance pemetrexed, and patients with the squamous subtype NSCLC should be given non-pemetrexed–containing platinum-doublet chemotherapy (Tables 1 and 3) [1]. It should be noted

Table 2
FDA-approved monoclonal antibodies, their targets, and therapeutic indications for lung cancer[a,b].

Drug	Properties	Company	Trade name	Year approved	Targets	Therapeutic indications
Ado-trastuzumab emtansine	Humanized IgG1κ	Lonza	Kadcyla	2023	ErbB2	This antibody-drug conjugate consists of humanized trastuzumab covalently linked to cytotoxic DM1. The drug undergoes receptor-mediated internalization into cells and is catabolized in lysosomes where DM1-containing catabolites are released and bind tubulin to cause mitotic arrest and cell death.
Amivantamab-vmjw	Human IgG1κ	Janssen	Rybrevant	2021	EGF-MET	This antibody is bispecific EGFR- and MET-receptor directed and is approved in combination with carboplatin and pemetrexed for the first-line treatment of locally advanced or metastatic NSCLC with *EGFR* exon−20 insertion mutations. The FDA also granted its approval for locally advanced or metastatic NSCLC with *EGFR* exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.
Atezolizumab	Humanized IgG1κ	Roche	Tecentriq	2016	PDL1	This antibody is approved (i) as an adjuvant therapy following resection and platinum-based chemotherapy for patients with Stage II to IIIA NSCLC whose tumors have PDL1 expression on $\geq$ 1 % of tumor cells, (ii) as a first-line option in the treatment of patients with metastatic NSCLC whose tumors have high PDL1 expression (PDL1 stained $\geq$ 50 % of tumor cells [TC $\geq$ 50 %] or PDL1 stained tumor-infiltrating immune cells [IC] covering $\geq$ 10 % of the tumor area [IC $\geq$ 10 %]) with no *EGFR* or *ALK* genomic tumor aberrations, (iii) in combination with bevacizumab, paclitaxel, and carboplatin, for the first-line treatment of patients with metastatic nonsquamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations, (iv) in combination with paclitaxel protein-bound and carboplatin for the first-line treatment of patients with metastatic nonsquamous NSCLC with no *EGFR* or *ALK* genomic tumor aberrations, (v) in people with metastases who have disease progression during or following platinum-based chemotherapy; patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for NSCLC harboring these aberrations prior to receiving atezolizumab, and (vi) in combination with carboplatin and etoposide for the first-line treatment of adult patients with extensive-stage SCLC.
Bevacizumab	Humanized IgG1κ	Genentech	Avastin	2004	VEGF-A	Bevacizumab is used for the first-line treatment in combination with carboplatin and paclitaxel in patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC.
Cemiplimab-rwlc	Human IgG4κ	Regeneron	Libtayo	2018	PD1	This antibody is used (i) in combination with platinum-based chemotherapy for the first-line treatment of patients with locally advanced NSCLC without *EGFR*, *ALK* or *ROS1* gene aberrations and where tumors are metastatic and patients are not candidates for surgical resection or definitive chemoradiation, and (ii) as a single agent for the first-line treatment of patients who are not candidates for surgical resection or definitive chemoradiation but have locally advanced NSCLC whose tumors have high PDL1 expression [Tumor Proportion Score (TPS) $\geq$ 50 %] with no *EGFR, ALK* or *ROS1* gene aberrations.
Durvalumab	Human IgG1κ	AstraZeneca	Imfinzi	2017	PDL1	Durvalumab is used for the treatment of patients (i) with unresectable Stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy, (ii) in combination with tremelimumab-actl and platinum-based chemotherapy for the treatment of patients with metastatic NSCLC lacking *EGFR* or *ALK* genomic alterations, and (iii) with extensive-stage SCLC in combination with etoposide and either carboplatin or cisplatin as a first-line treatment.
Fam-trastuzumab deruxtecan-nxki	Humanized IgG1κ	AstraZeneca	Enhertu	2022	ErbB2	This antibody-drug conjugate consists of trastuzumab covalently linked to the topoisomerase I inhibitor deruxtecan. It is approved for the treatment of patients with metastatic (i) HER2-positive breast cancer who have received a prior anti-HER2-based regimen either (a) in the metastatic setting or (b) in the neoadjuvant or adjuvant setting and have developed disease recurrence during or within six months of completing therapy, (ii) HER2-low breast cancer who have received prior chemotherapy in the metastatic setting or developed disease recurrence during or within 6 months of completing adjuvant chemotherapy, (iii) or unresectable NSCLC whose tumors have activating *HER2* mutations and who have received a prior systemic therapy. Once bound to ErbB2, the antibody is internalized by the cell carrying the bound deruxtecan that interferes with the ability of the cell to replicate its DNA, leading to DNA damage and apoptosis.
Ipilimumab	Human IgG1κ	Bristol-Myers Squibb	Yervoy	2011	CTLA−4	Ipilimumab is used in combination with nivolumab for the first-line treatment of metastatic NSCLC expressing PDL1 ($\geq$1 %) with no *EGFR* or *ALK* genomic aberrations.
Necitumumab	Human IgG1κ	Eli Lilly	Portrazza	2015	EGFR	Necitumumab is used in combination with gemcitabine and cisplatin as a first-line treatment for metastatic squamous NSCLC.
Nivolumab	Human IgG4κ	Bristol-Myers Squibb	Opdivo	2014	PD1	Nivolumab is used for the treatment of NSCLC in patients (i) with resectable (tumors $\geq$4 cm and/or node positive) NSCLC in the neoadjuvant setting in combination with platinum-doublet chemotherapy, (ii) with metastatic NSCLC expressing PDL1 ($\geq$1 %) with no *EGFR* or *ALK* genomic tumor aberrations, (iii) with metastatic or recurrent NSCLC with no *EGFR* or *ALK* genomic tumor aberrations in combination with ipilimumab and 2 cycles of platinum-doublet chemotherapy as a first-line treatment, (iv) with

(*continued on next page*)

Table 2 (*continued*)

Drug	Properties	Company	Trade name	Year approved	Targets	Therapeutic indications
						metastatic NSCLC and progression on or after platinum-based chemotherapy, and (v) with *EGFR* or *ALK* genomic tumor aberrations with disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.
Pembrolizumab	Humanized IgG4κ	Merck	Keytruda	2014	PD1	Pembrolizumab is used (i) in combination with pemetrexed and platinum chemotherapy as a first-line treatment of patients with metastatic nonsquamous NSCLC lacking *EGFR* or *ALK* genomic aberrations, (ii) in combination with carboplatin and either paclitaxel or paclitaxel protein-bound as a first-line treatment of patients with metastatic squamous NSCLC, (iii) as a single agent for the first-line treatment of patients who are not candidates for surgical resection or definitive chemoradiation with Stage III NSCLC expressing PDL1 [Tumor Proportion Score (TPS) ≥1 %] and lacking *EGFR* or *ALK* genomic aberrations, (iv) as a single agent for the treatment of patients with metastatic NSCLC whose tumors express PDL1 (TPS ≥1 %) with disease progression on or after platinum-based chemotherapy; patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab, (v) for the treatment of patients with resectable (tumors ≥4 cm and/or node positive) NSCLC in combination with platinum-containing chemotherapy as a neoadjuvant treatment and then continued as a single agent as an adjuvant treatment after surgery, and (vi) as a single agent for the adjuvant treatment following resection and platinum-based chemotherapy for patients with Stage IB (T2a ≥4 cm), II, or IIIA NSCLC.
Ramucirumab	Human IgG1	Eli Lilly	Cyramza	2014	VEGFR2	Ramucirumab is used in combination with docetaxel for the treatment of metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving the antibody.
Tarlatamab-dlle	?	Amgen	Imdelltra	2024	DLL3 and CD3	This antibody is used in adults whose extensive-stage SCLC progressed during or after treatment with platinum-based chemotherapy.
Tremelimumab-actl	Human IgG2κ	AstraZeneca	Imjudo	2022	CTLA−4	This antibody is used as a first-line treatment in combination with durvalumab and platinum-based chemotherapy for the treatment of patients with metastatic NSCLC with no sensitizing *EGFR* or *ALK* genomic alterations.

[a] www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm

[b] Therapeutic antibody nomenclature conventions: - mab refers to a monoclonal antibody; - mumab refers to a human mab (e.g., ipilimumab), - zumab refers to a humanized mab (e.g., atezolizumab).

that pemetrexed is contraindicated in those with squamous NSCLC. Immune checkpoint inhibitors can be delivered either as a single-agent monotherapy or in combination with chemotherapy. The efficacy of immune checkpoint inhibitors often increases with the magnitude of tumor PDL1 expression, and it should be measured in all NSCLC tumor types to guide therapy and correlate with checkpoint inhibitor efficacy.

The anti-PD1 immune checkpoint inhibitor pembrolizumab is one of the preferred options for the treatment of Stage IV NSCLC (Table 2) [60]. Pembrolizumab can be delivered either as single-agent monotherapy or in combination with chemotherapy, the choice of which depends upon the stage and the disease histopathology. Pembrolizumab is indicated in combination with platinum-based chemotherapy in untreated people with advanced NSCLC regardless of their PDL1 expression status. The KEYNOTE-407 study, a phase 3 randomized clinical trial, demonstrated a prolonged median overall survival with pembrolizumab plus chemotherapy compared with chemotherapy alone [61]. Patients with a high (≥50 %) PDL1 expression benefitted the most from immune checkpoint inhibitor therapy with a higher overall response rate and longer overall survival. In individuals with nonsquamous Stage IV NSCLC, reports from the KEYNOTE-189 study indicated a one-year overall survival of 70 % in people receiving pembrolizumab plus chemotherapy (platinum/pemetrexed) versus 48 % for those receiving only chemotherapy, regardless of PDL1 expression [62]. The objective response rate was also greater in the combination group (48 % vs. 20 %). One recommended treatment of patients with Stage IV squamous NSCLC includes carboplatin/paclitaxel (Keynote-407 clinical trial), followed by maintenance pembrolizumab that can continue for up to two years [43].

The IMpower130 study, a phase 3 randomized clinical trial, compared atezolizumab with carboplatin/nab-paclitaxel (nanoparticle paclitaxel albumin-stabilized formulation) versus chemotherapy alone as a first-line treatment of individuals with metastatic nonsquamous Stage IV NSCLC [63]. Median overall survival was 18.6 months in the atezolizumab plus chemotherapy arm versus 13.9 months in the carboplatin/nab-paclitaxel arm. An alternative regimen for non-squamous NSCLC is treatment with atezolizumab, an anti-PDL1 immune checkpoint inhibitor (Table 2), delivered in combination with carboplatin/paclitaxel/bevacizumab (as in the IMpower150 phase 3 randomized clinical trial) [64]. It should be noted that bevacizumab, which targets VEGF, is contraindicated in squamous NSCLC. Atezolizumab is also prescribed in combination with platinum-based chemotherapy in untreated people with metastatic NSCLC, regardless of PDL1 expression. The IMpower150 study compared first-line therapy with the ABCP (atezolizumab, bevacizumab – an anti-angiogenic agent that binds to VEGF – carboplatin, paclitaxel) regimen for individuals with metastatic nonsquamous NSCLC versus bevacizumab with chemotherapy. Median overall survival was 19.2 months in the ABCP arm versus 14.7 months in the bevacizumab plus chemotherapy arm.

In terms of double-agent immune checkpoint inhibitor therapy, the CheckMate 9LA study, a phase 3 randomized trial, compared first-line nivolumab (anti-PD1)/ipilimumab (anti-CTLA-4) therapy and two cycles of platinum-doublet chemotherapy (Tables 1 and 3) versus four cycles of chemotherapy alone in individuals with metastatic squamous or nonsquamous NSCLC, regardless of PDL1 expression levels [65]. With a minimum follow-up of 57 months, patients continued to derive overall survival (OS) benefit with nivolumab plus ipilimumab with chemotherapy over chemotherapy alone (5-year overall survival rates, 18 % vs. 11 %), regardless of (i) PDL1 expression (PDL1 < 1 %, 22 % vs. 8 %; PDL1 ≥ 1 %, 18 % vs. 11 %), (ii) histology (squamous, 18 % vs. 7 %; nonsquamous, 19 % vs. 12 %), or (iii) the presence of baseline brain metastases (20 % vs. 6 %). The five-year duration of response rates was 19 % versus 8 % with nivolumab plus ipilimumab with chemotherapy versus chemotherapy alone, with consistent benefit across all subgroups.

Table 3
Cytotoxic drugs used in the treatment of lung cancer.

Drug	Trade name	Orally bioavailable	Mechanism of action
Carboplatin	Paraplatin	No	Carboplatin promotes the formation of DNA intra- and inter-strand cross-links and inhibits DNA replication and transcription.
Cisplatin	Platinol	No	Same as carboplatin.
Cyclophosphamide	Cytoxan	Yes	Same as carboplatin. Given orally and by injection in patients with SCLC.
Docetaxel	Taxotere	No	An antimitotic taxane that prevents microtubules from depolymerizing during mitosis, which ultimately leads to apoptosis.
Doxorubicin	Adriamycin	No	Doxorubicin blocks the action of the topoisomerase II-DNA complex which relieves supercoils and untangles DNA strands thereby blocking replication.
Gemcitabine	Gemzar	No	The drug is an cytidine analogue that inhibits (i) DNA synthesis, repair, and function, (ii) ribonucleotide reductase, (iii) thymidylate synthase, and (iv) RNA function.
Irinotecan	Camptosar	No	Irinotecan inhibits the topoisomerase I-DNA complex and prevents the re-ligation of single-strand breaks leading to apoptosis and cell death.
Lurbinectedin	Zepzelca	No	A DNA alkylating agent that binds to DNA guanines and impairs DNA repair pathways and transcription factor activity.
Paclitaxel	Taxol	No	An antimitotic taxane that stabilizes microtubules and impedes depolymerization during mitosis, which ultimately leads to apoptosis.
Nab-paclitaxel	Abraxane	No	The mechanism of paclitaxel albumin-stabilized nanoparticle formulation is the same as paclitaxel.
Pemetrexed	Alimta	No	An antifolate that inhibits (i) dihydrofolate reductase, (ii) thymidylate synthase, and (iii) purine synthesis *de novo*.
Temozolomide	Emozolomide	Yes	Same as lurbinectedin
Topotecan	Hycamtin	No	Same as irinotecan
Vincristine	Oncovin	No	The drug binds to the tubulin protein and prevents tubulin dimers from polymerizing to form microtubules, and it causes existing microtubules to depolymerize. This stops cells from separating their chromosomes during metaphase, which ultimately leads to apoptosis.
Vinorelbine	Navelbine	No	An antimitotic that stimulates microtubule depolymerization and mitotic spindle destruction leading to the arrest of mitosis, which ultimately leads to apoptosis. Used in the treatment of SCLC.

Ipilimumab is a fully human anti-CTLA-4 monoclonal IgG1κ antibody (Table 3) [39,66]. It binds to CTLA-4 and prevents its interactions with CD80/CD86, which inhibits T cell activation. Blocking the CTLA-4//CD80/86 interaction makes it possible to induce *de novo* T cell responses against tumors. Nivolumab is a human IgG4κ anti-PD1 monoclonal antibody. Pembrolizumab is a humanized anti-PD1 IgG4κ monoclonal antibody. Such antibodies inhibit PD1, a receptor that is expressed on activated cytotoxic T cells, and block their interaction with PDL1, a ligand that is located on the surface of tumor cells. The blockade of PD1/PDL1 interaction promotes antitumor immunity. This interaction can also be inhibited by (i) atezolizumab – a humanized Fc-modified IgG1κ anti-PDL1 monoclonal antibody – and (ii) durvalumab – a human anti-PDL1 IgG1κ monoclonal antibody. For a discussion of human and humanized monoclonal antibodies, their production, and their use in cancer therapy, see Ref. [67].

2.3.3. Second-line therapy for Stage IV NSCLC without known driver mutations

Following relapse or disease progression on first-line protocols, patients are usually given an immune checkpoint inhibitor as monotherapy. Options for second-line therapy include (i) anti-PD1 pembrolizumab for PDL1 positive (TPS $\geq$1 %) tumors (Keynote-010 clinical trial), (ii) anti-PD1 nivolumab (Checkmate-017 and −057 clinical trials) regardless of PDL1 expression, or (iii) anti-PDL1 atezolizumab for PDL1 high expression tumors (PD-L1 stained $\geq$ 50 % of tumor cells [TC $\geq$ 50 %] or PD-L1 stained tumor-infiltrating immune cells [IC] covering $\geq$ 10 % of the tumor area [IC $\geq$ 10 %]) (OAK clinical trial) [68–71]. Following relapse in the second-line setting, or if the patient remains unsuitable for checkpoint inhibitor therapy, there are additional treatment options. All subtypes or histologies are suitable for treatment with docetaxel and ramucirumab – the anti-VEGFR2 blocker (REVEL clinical trial) [72]. Nonsquamous NSCLC can be treated with pemetrexed monotherapy [43]. For a summary of the FDA-approved first-line and later-line uses of monoclonal antibodies alone and in combination with other agents, see Table 2.

2.3.4. NSCLC with known driver mutations

Oncogene-addicted tumors with sensitizing *EGFR* or *BRAF* mutations or activating *ALK*, *ROS1* or *NTRK* translocations are more common in those who lack a significant smoking history [43]. However, they can occur in current and former smokers. Such NSCLCs are often of the adenocarcinoma subtype. If a sensitizing variant is identified, sequential lines of kinase inhibitor therapy are given until ultimately none is effective, in which case chemotherapy is then prescribed. Multiple actionable gene alterations generally do not occur in the same tumor.

EGFR-mutant NSCLC is over-represented in never smokers or former light-smokers, in patients of East-Asian descent, and in women [43]. *EGFR* mutations occur in about 15 % of people with NSCLC [73]. There are several FDA-approved oral protein-tyrosine kinase inhibitors that target mutant *EGFR* and offer lasting disease control (Table 4). The choice of which agent to use depends on physician/patient selection [7]. Following the recommendations of Riely et al., treatment choices include: (i) first-generation erlotinib and gefitinib, (ii) second-generation afatinib and dacomitinib, and (iii) third-generation osimertinib (Fig. 1). The latter offers longer progression-free and overall survival, along with better intracranial activity, as compared to the first- and second-generation blockers. For patients relapsing on first-line

Table 4
FDA-approved small molecule protein kinase inhibitors, their primary targets, and therapeutic lung cancer indications[a].

Drug	Code	Company	Trade name	Year approved	Primary driver mutation targets[b]	Therapeutic indications
Afatinib	BIBW 2992	Boehringer Ingelheim	Tovok	2013	ErbB1/2/4	First-line NSCLC and second-line squamous NSCLC post platinum chemotherapy
Alectinib	CH5424802	Roche	Alecensa	2015	ALK	ALK-positive metastatic NSCLC
Binimetinib	MEK162	Array BioPharma	Mektovi	2018	MEK1/2	Mutant *BRAF V600E* NSCLC in combination with encorafenib
Brigatinib	AP 26113	Ariad Pharm	Alunbrig	2017	ALK	ALK-positive metastatic NSCLC
Capmatinib	INC−280	Novartis	Tabrecta	2020	MET (HGFR)	Metastatic NSCLC with a *MET* exon−14 skipping mutation
Ceritinib	LDK378	Novartis	Zykadia	2014	ALK	ALK-positive metastatic NSCLC resistant to crizotinib
Crizotinib	PF 2341066	Pfizer	Xalkori	2011	ALK, ROS1	ALK- or ROS1-postive metastatic NSCLC
Dabrafenib	GSK2118436	GSK	Tafinlar	2013	B-Raf	Metastatic NSCLC with a *BRAF V600E* mutation
Dacomitinib	PF−00299804	Pfizer	Visimpro	2018	EGFR	Metastatic NSCLC with an *EGFR* exon−19 deletion or an exon−21 L848R substitution
Encorafenib	LGX818	Array BioPharma	Braftovi	2018	B-Raf	Metastatic NSCLC with a *BRAF V600E* mutation in combination with binimetinib
Entrectinib	RXDX−101	Genentech	Rozlytrek	2019	TRKA/B/C, ROS1	NSCLC with an NTRK fusion protein, ROS1-positive metastatic NSCLC
Erlotinib	OSI−774	Genentech	Tarceva	2004	EGFR	Metastatic NSCLC with an *EGFR* exon−19 deletion or an exon−21 L848R substitution
Gefitinib	ZD1839	AstraZeneca	Iressa	2003	EGFR	Metastatic NSCLC with an *EGFR* exon−19 deletion or an exon−21 L848R substitution
Lazertinib	GNS1480	Janssen	Lazcluze	2024	EGFR	Locally advanced or metastatic NSCLC with an *EGFR* exon−19 deletion or an exon−21 L848R substitution in combination with amivantamab-vmjw
Larotrectinib	LOXO−101	Bayer	Vitrakvi	2018	TRKA/B/C	Metastatic NSCLC with an NTRK fusion protein
Lorlatinib	PF−06463922	Pfizer	Lorbrena	2018	ALK	ALK-positive metastatic NSCLC
Mobocertinib	TAK−788	Takeda Pharm.	Exkivity	2021	EGFR	Mobocertinib FDA approval for NSCLC with an *EGFR* exon−20 insertion was withdrawn in 2023
Osimertinib	AZD−9292	AstraZeneca	Tagrisso	2015	EGFR	This drug is FDA approved (i) for adjuvant therapy after tumor resection in patients with NSCLC whose tumors have an *EGFR* exon−19 deletion or an exon−21 L858R mutation, (ii) for the first-line treatment of patients with metastatic NSCLC whose tumors have an *EGFR* exon−19 deletion or an exon−21 L858R mutation, (iii) in combination with pemetrexed and platinum-based chemotherapy, for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have an *EGFR* exon−19 deletion or exon−21 L858R mutation, and (iv) for the treatment of patients with metastatic *EGFR* T790M mutation-positive NSCLC
Pralsetinib	Blu−667	Blueprint Medicines	Gavreto	2020	RET	RET-fusion positive metastatic NSCLC
Repotrectinib	TX−0005	Bayer	Augtyro	2023	ROS1	ROS1-positive locally advanced or metastatic NSCLC
Selpercatinib	CEGM9YBNG	Lilly	Retevmo	2020	RET	RET fusion-positive metastatic NSCLC
Tepotinib	EMD 1214063	EMD Serono Inc.	Tepmetko	2021	MET (HGFR)	*MET* exon−14 skipping mutant metastatic NSCLC
Trametinib	GSK1120212	GSK	Mekinist	2013	MEK1/2	Metastatic NSCLC with a *BRAF V600E* mutation in combination with dabrafenib
Trilaciclib	G1T28	G1 Therapeutics	Cosela	2021	CDK4/6	Myelosuppression prior to the treatment of extensive-stage SCLC with a platinum/etoposide- or topotecan-containing regimen

[a] Data from Ref. [74].
[b] Although many of these drugs are multikinase inhibitors, only the primary therapeutic targets are given here.

non-osimertinib options, circulating tumor DNA or the progressive tumor should be tested for the $EGFR^{T790M}$ mutation and, if positive, treated with (i) osimertinib, (ii) erlotinib/bevacizumab combination therapy, (iii) or gefitinib and chemotherapy. The structures and physicochemical properties of all FDA-approved small molecule protein kinase inhibitors can be found at www.brimr.org/PKI/PKIs.htm.

ALK translocations are observed in 3–5 % of adenocarcinomas, usually in never-smokers [73]. Alectinib, brigatinib, and ceritinib are second generation ALK inhibitors that are superior to first-generation crizotinib [7]. They have good intracranial activity and are recommended as first-line options [14,15]. Lorlatinib is approved for the second and third-line treatment of ALK-positive NSCLC. It is a derivative of crizotinib that was specifically designed to penetrate the blood-brain barrier to increase its effect on brain metastases frequently experienced by patients with lung cancers. An alternative treatment strategy is to begin first-line crizotinib and then use the next-generation ALK inhibitors or lorlatinib at disease progression. ALK mRNA is expressed in various adult human tissues such as the brain, colon, prostate, small intestine, and testis, but it is not found in the normal human heart, kidney, liver, lung, lymphoid cells, ovary, pancreas, placenta, skeletal muscle, spleen, or thymus. Limited ALK expression may be advantageous to the patient because it decreases the likelihood of toxicity in response to medicines targeting this enzyme.

ROS1 rearrangements occur in approximately 1 % of patients with NSCLC, usually in younger never-smokers with adenocarcinoma [75]. Crizotinib is currently the recommended first-line ROS1 blocker [7]. Entrectinib, lorlatinib, and reprotrectenib are FDA-approved for the treatment of ROS1-positive rearrangements and they are used to treat relapsed ROS1-positive NSCLC. Ceritinib is FDA-approved for the second-line treatment of ROS1-positve NSCLC following crizotinib failure. The $BRAF^{V600E}$ mutation occurs in 1–2 % of NSCLC adenocarcinomas, and patients should be treated with BRAF/MEK combination inhibitors: encorafenib/binimetinib or dabrafenib/trametinib (Table 4) [7,43]. NTRK1/2/3 fusion proteins are uncommon moieties that occur in 0.1–0.2 % of individuals with NSCLC. Riely et al. recommend either larotrectinib or entrectinib treatment for these patients [7].

Activating mutations of *KRAS* occur in many solid tumors and they are found in about 35 % of lung cancers [33,34]. The $KRAS^{G12C}$ substitution is the most common mutation in smokers who develop NSCLC because of G:C > T:A DNA transversions in response to bulky adducts generated by mutagens found in tobacco smoke. In contrast, $KRAS^{G12D}$ is the most common mutation found in NSCLC patients who are

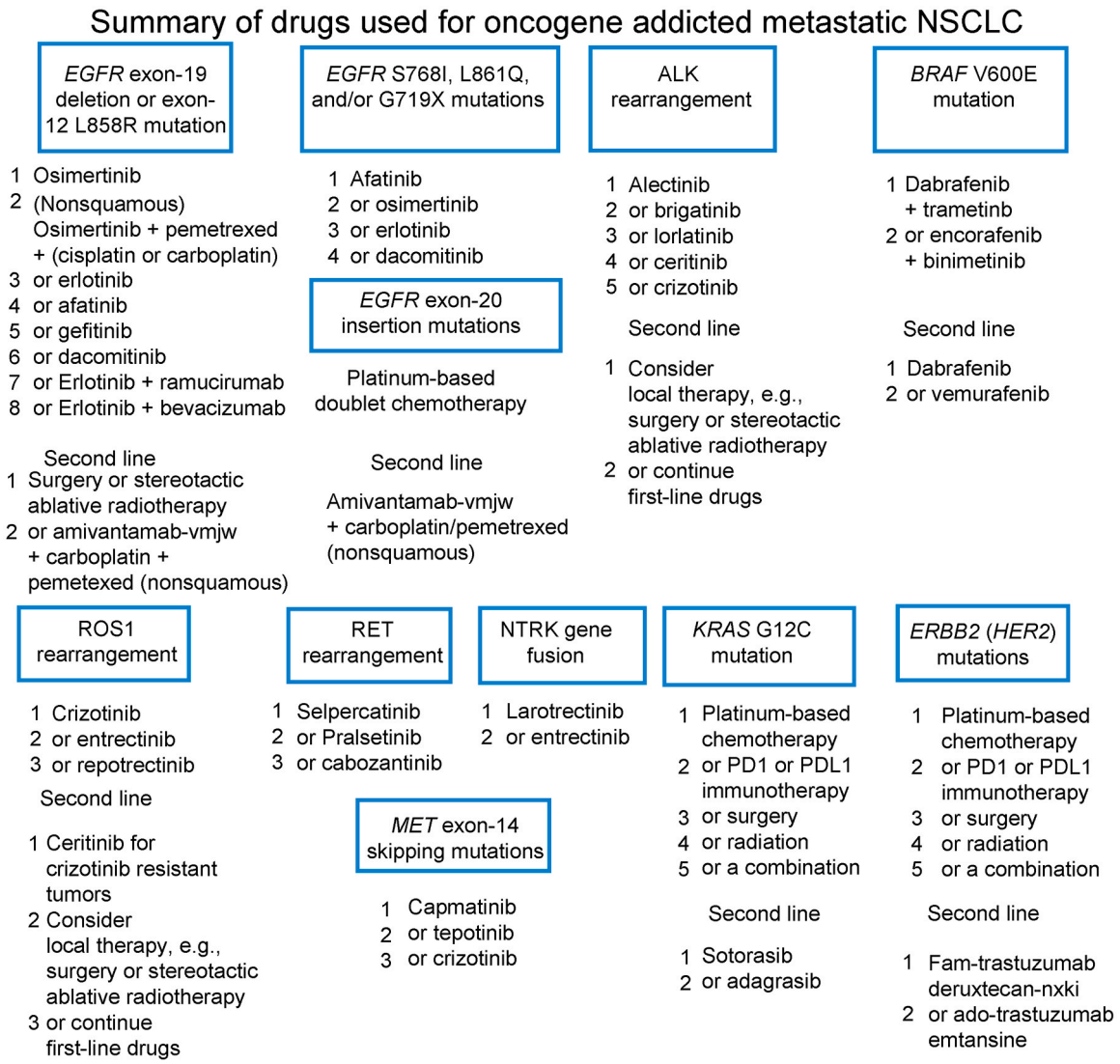

Fig. 1. Summary of drugs used in the treatment of driver mutation-positive NSCLC. Data from Ref. [7].

nonsmokers. At one time considered undruggable because of the smooth shallow surface of K-Ras, experiments demonstrated that the activated G12C-mutated K-Ras isozyme can be directly inhibited by targeting a newly identified switch II pocket. This finding led to the discovery of a novel class of selective covalent small-molecule inhibitors against the K-Ras^{G12C} isoform that includes adagrasib and sotorasib [33,34]. These agents are FDA-approved for the treatment of locally advanced or metastatic NSCLC patients who have received at least one prior systemic therapy. A locally advanced cancer extends beyond the organ in which it has started but has not spread to distant body parts while a metastatic cancer has spread to distant parts of the body. A lung cancer, for example, may spread to adjacent lymph nodes (locally advanced) and metastasize to the brain (a distant part of the body). Given the long protein half-life of K-Ras (≈ 22 h), covalent inactivation allows for a durable pharmacodynamic response.

ERBB2 (*HER2*) gene alterations occur in about 3 % of NSCLCs, consisting of insertions, point mutations, or overexpression [75]. This ErbB2 activation prompted the repurposing of antibody-drug conjugates (ADCs) from breast cancers to lung cancers that deliver cytotoxic payloads to ErbB2-expressing cells [34,75,76]. The FDA approved fam-trastuzumab deruxtecan-nxki in 2022 for NSCLC based on a response rate of >55 %, a duration of response >9 months, and progression free survival >8 months and manageable adverse events. Deruxtecan is a topoisomerase I blocker. Although ado-trastuzumab is not FDA-approved for the treatment of this disorder, it is recommended in the NCCN guidelines for second-line therapy [7]. In ado-trastuzumab, the antibody is linked to cytotoxic DM1 whose metabolites bind to tubulin and inhibit mitosis.

2.3.5. *Management of central nervous system (CNS) metastases*

Brain metastases are detected in about 21 % of patients with lung cancer at the time of diagnosis and are the sole metastatic site in about 35 % of patients with Stage IV disease [77]. The optimal first-line therapy for NSCLC depends on both tumor PDL1 expression and the presence or absence of a targetable genetic alteration in genes such as *EGFR* or *ALK*. In the absence of such a target, options include chemotherapy, immune checkpoint inhibition, or a combination of the two. Initial local therapy followed by systemic therapy is the current standard of care for the management of brain metastases; it may include whole-brain radiotherapy, stereotactic radiotherapy, or craniotomy for surgical resection followed by consolidative radiation. This strategy is effective in achieving local control, but it is unclear if this approach is best for every patient.

To be considered for initial checkpoint inhibitor-based therapy, the patient should meet the following criteria: the person should be free of neurological symptoms and the lesions should be small and not located

in a critical region of the CNS. If corticosteroids are indicated for the treatment of symptomatic brain metastases, the requirement should be low (prednisone 10 mg/day or less), and PDL1 expression should be high. The decision to proceed with first-line checkpoint therapy without local therapy in patients with brain metastases should be made in a multidisciplinary fashion and patients should undergo frequent surveillance imaging so that salvage local therapy can be provided as necessary. For patients with brain metastases who are unsuitable for stereotactic radiation, whole-brain radiotherapy is an option for those with a favorable prognosis. However, in summarizing the Quality of Life after Treatment for Brain Metastases (QUARTZ) clinical trial, Mulvena et al. found no survival advantage for whole-brain radiotherapy over best supportive care; accordingly, whole-brain radiotherapy is limited for use in selected cases [78].

3. Overview of small cell lung cancer

3.1. Clinical course of SCLC

Small cell lung cancer, which accounts for approximately 15 % of all lung cancer cases, is a deadly high-grade neuroendocrine carcinoma with a poor prognosis [79,80]. It is characterized by an extremely rapid growth rate, high probability of early metastasis, and poor prognosis. The primary etiological factor for SCLC is exposure to carcinogens present in cigarette smoke. Only 2 % of SCLC cases arise in never-smokers (defined as a lifetime smoking of fewer than 100 cigarettes) [81]. The prevalence of SCLC is somewhat greater in men than women owing to their larger percentage of cigarette smokers. Patients often have massive enlargement of the mediastinal lymph nodes that lead to symptoms such as coughing and dyspnea. Perhaps half of all SCLC patients have distant metastatic disease at the time of their initial diagnosis. The most common sites of metastasis include the contralateral lung, the brain, the adrenal glands, liver, and bone. Clinical findings associated with distant metastases include bone pain, weakness, weight loss, and neurological symptoms. SCLC has an unusually high mortality rate in comparison to other solid tumors.

Microscopically, SCLC cells are round to fusiform in shape, with minimal cytoplasm and nucleoli, and finely granular nuclear chromatin [79]. These cells typically grow in clusters and demonstrate a high frequency of mitotic division with an average of about 60 per mm^2. The use of immunohistochemistry is useful in ascertaining the diagnosis of SCLC and differentiating it from other lung cancers. Commonly used neuroendocrine markers for this disorder include chromogranin, synaptophysin, and CD56 (NCAM). Unlike NSCLC, oncogene addiction involving the mutation of driver genes such as *EGFR*, *ALK*, and other protein-tyrosine kinases is rare in SCLC. However, the concomitant inactivation of two tumor suppressors – *TP53* and *RB1* – is found in most SCLC tumors. Analyses indicate that amplification of the MYC family of genes (*MYC, MYCL,* and *MYCN*) also occur in a subset of SCLC tumors. *PIK3A* (activation) and *PTEN*, *NOTCH1*, and *CREBBP* (inactivating mutations) occur in 5–7 % of SCLC specimens.

It would be helpful to differentiate the genomic landscape of SCLC by determining subtypes that can predict outcomes with specific therapies. Gay et al. defined four distinct subtypes of SCLC based upon the production of specific transcription factors [82]. These include SCLC-A (high ASCLC1) and SCLC-N (high NEUROD1), which are both neuroendocrine factors, and SCLC-P (high POUF2F3), which is a non-neuroendocrine factor, and SCLC-I (low ASCLC1, NEUROD1, and POUF2F3), which is an inflamed gene signature. The SCLC-I subtype patient seems to benefit the most with the addition of immunotherapy to chemotherapy. Additional clinical trials are needed to determine whether these or other subtypes are predictive of benefit for rationally designed targeted therapies [83]. Unfortunately, there is no confirmed role for any predictive biomarker to guide the treatment of patients with SCLC and this is not for lack of trying.

Owing to the aggressive nature of SCLC, the diagnostic and staging workup should be performed as soon as possible after presentation and diagnosis [79]. The evaluation includes (i) imaging (contrast-enhanced CT or ^{18}F-fluordeoxyglucose PET of the chest, abdomen and pelvis, and brain MRI with contrast) to define the extent of the disease and (ii) blood chemistries to ensure safety before treatment with cytotoxic drugs. The diagnosis is confirmed by histopathological examination and cytology. The radiological findings in SCLC are similar to those of other lung cancers with a trend for tumors to be larger, centrally located, and more advanced at presentation. Metastatic spread is common and may include pleural or pericardial effusions.

There are two staging systems for SCLC in common use [79]. The Veterans Administration Lung Study Group (VALSG) defines (i) limited-stage (LS) disease for those tumors that are confined to one hemi-thorax and one radiation port in the absence of pleural or pericardial effusion and (ii) extensive-stage (ES) disease for those cancers that do not meet the criteria for limited-stage disease [84]. The International Association for the Study of Lung Cancer Lung Cancer Staging Project defines the tumor-node-metastasis classification based upon tumor size and extent, extent of the nodal dissemination, and the presence of metastasis [41]. The former classification system is commonly used at community hospitals while the latter classification is used at academic medical centers and centers involved in clinical trials. Stage for stage, the prognosis and outcome of SCLC is consistently poorer than that of NSCLC [79]. Brain metastases are common in SCLC with 10 % of patients presenting with CNS involvement at the time of diagnosis and an additional 50 % subsequently developing them. MRI is more sensitive than CT in detecting brain involvement.

3.2. Management of SCLC

The initial approach to SCLC treatment varies somewhat by stage – with the addition of immune checkpoint inhibitors in extensive-stage disease [85]. In nonmetastatic limited-stage SCLC, the objectives of therapy include the control of thoracic disease and minimizing the risk of metastases. It is possible to achieve five-year overall survival rates of 25–30 % by using combined modality treatments. Surgery and radiotherapy represent local treatment options to control thoracic disease. Systemic chemotherapy can increase the effectiveness of radiotherapy and lessen micrometastatic disease. The traditional chemotherapy regimen in patients with limited-stage disease is cisplatin/etoposide, which has been used for more than three decades. This doublet therapy can be delivered at its full recommended dosage in patients treated with concurrent radiotherapy or after surgical resection. In patients who are not suitable for cisplatin owing to hearing loss, renal impairment, peripheral neuropathy, poor performance status or advanced age, carboplatin–etoposide is a satisfactory alternative. The role of prophylactic cranial irradiation in patients with limited-stage disease following surgery and adjuvant chemotherapy or concurrent chemoradiation is under evaluation.

SCLC is very chemo-responsive and radio-responsive, but neither modality alone controls the disease [85]. Concurrent combined therapy is the standard treatment of limited-stage SCLC in patients with adequate performance status. Single-modality or sequential therapy may be appropriate for those who are debilitated or have serious co-morbidities. In patients with extensive-stage disease, a platinum agent (cisplatin or carboplatin) combined with etoposide and an anti-PDL1 inhibitor (atezolizumab or durvalumab) for four cycles followed by maintenance anti-PDL1 therapy is the recommended first-line regimen. Unlike NSCLC, where PDL1 serves as a reliable marker of the efficacy of immune checkpoint inhibitors, no correlation between the expression of this molecule in tumors and the efficacy of immunotherapy in SCLC has been established.

Most patients diagnosed with SCLC will relapse, including nearly all those who present with extensive-stage disease and greater than 75 % of those who receive optimal treatment of limited-stage disease [85]. Patients who experience a chemotherapy-free interval (CTFI) greater than

90 days are considered to have chemotherapy-sensitive disease while those with a CTFI interval of less than 90 days are classified as chemo-resistant. Survival for the chemo-sensitive patients averages six months and that for the chemo-resistant group is less. The goals for the treatment of patients with relapsed SCLC are palliative and include symptom management and optimization of quality of life.

An optimal therapeutic strategy for patients with relapsed SCLC following first-line chemoradiation and immune checkpoint therapy has not been determined [85]. Patients whose cancer relapses ≥6 months after initial therapy are often retreated with a first-line chemotherapy doublet (cisplatin/etoposide). Topotecan, lurbinectedin, and tarlatamab-dlle are FDA-approved therapeutic agents for relapsed SCLC. Tarlatamab-dlle is a bispecific T-cell engager that binds delta-like ligand 3 (DLL3) and CD3 [86]. It binds to DLL3 on the surface of tumor cells and CD3 on the surface of cytotoxic T lymphocytes (CTL), resulting in T-cell activation, release of inflammatory cytokines, and CTL-mediated cell death of DLL3-expressing tumor cells. Trilaciclib is a targeted CDK4/6 blocker that is FDA-approved for decreasing the incidence of chemotherapy-related myelosuppression in SCLC patients receiving chemotherapy [87]. Other agents that have regulatory approval that are used for SCLC off label include irinotecan, paclitaxel, temozolomide, and gemcitabine.

4. Concluding remarks

Owing to the frequency and importance of lung cancer in the United States and the world, clinical and basic science investigators have studied the biology and clinical course of this disorder for decades [25,45,79]. The selection of treatments is based upon patient demographics, clinical features, and the biomarker profile of tumor samples. Such data are used in the practice of personalized medicine. The treatment of patients with SCLC and NSCLC is increasingly complex as treatment modalities are many and continue to evolve. Of great importance is an accurate tumor and lymph node assessment because the prognosis and treatment decisions are dependent on the stage of the disease. Significant advances in the treatment of metastatic lung cancer with targeted therapies (NSCLC) and immune-checkpoint inhibitors (SCLC, NSCLC) have occurred over the last two decades.

The armamentarium of first-line systemic therapy for patients with unresectable NSCLC has expanded rapidly in recent years [35]. Molecularly targeted therapy and immune checkpoint inhibitor therapy have improved progression-free and overall survival with favorable toxicity profiles. Those patients with actionable gene alterations receive protein kinase inhibitors for first-line and follow-up therapy. These inhibitors are all bioavailable, a property that eases treatment (not requiring a visit to a hospital or clinic) and is appreciated by the patient. All immune therapies are given by injection as are most of the cytotoxic drugs. As can be seen in Tables 1–3, antibody-based therapy alone or in combination with cytotoxic drugs or with a second antibody are dependent upon the staging, the large number of cytotoxic drugs, the multitude of therapeutic antibodies, and the use or not of radiation therapy.

The estimated five-year survival of NSCLC diagnosed at all stages is about 28 % and that for SCLC is about 6 % (https://www.cancer.org/cancer/types/lung-cancer/detection-diagnosis-staging/survival-rates.html). A large number of planned and ongoing clinical trials with new drugs and drug combinations are exploring treatment effectiveness in the adjuvant and neoadjuvant settings. However, there are many questions regarding the optimal treatment sequence, drug combinations, and personalized therapies based on disease stage, biomarker expression, and other patient-specific factors. Addressing these questions will aid in reducing lung cancer-related deaths among patients with SCLC and NSCLC.

Declaration of Competing Interest

The author is unaware of any affiliations, memberships, or financial holdings that might be perceived as affecting the objectivity of this review.

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Data Availability

No data was used for the research described in the article.

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