HHS Public Access

Author manuscript

Biochim Biophys Acta. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Biochim Biophys Acta. 2015 December ; 1856(2): 189–210. doi:10.1016/j.bbcan.2015.08.002.

Lung cancer: biology and treatment options

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Abstract

Lung cancer remains the leading cause of cancer mortality in men and women in the U.S. and worldwide. About 90% of lung cancer cases are caused by smoking and the use of tobacco products. However, other factors such as radon gas, asbestos, air pollution exposures, and chronic infections can contribute to lung carcinogenesis. In addition, multiple inherited and acquired mechanisms of susceptibility to lung cancer have been proposed. Lung cancer is divided into two broad histologic classes, which grow and spread differently: small-cell lung carcinomas (SCLC) and non-small cell lung carcinomas (NSCLC). Treatment options for lung cancer include surgery, radiation therapy, chemotherapy, and targeted therapy. Therapeutic-modalities recommendations depend on several factors, including the type and stage of cancer. Despite the improvements in diagnosis and therapy made during the past 25 years, the prognosis for patients with lung cancer is still unsatisfactory. The responses to current standard therapies are poor except for the most localized cancers. However, a better understanding of the biology pertinent to these challenging malignancies, might lead to the development of more efficacious and perhaps more specific drugs. The purpose of this review is to summarize the recent developments in lung cancer biology and its therapeutic strategies, and discuss the latest treatment advances including therapies currently under clinical investigation.

Keywords

Lung cancer; Non-Small Cell Lung; Small-Cell Lung Carcinomas; Mesothelioma; Therapies; Treatments; Surgery; targeted therapies; Immunotherapies

1. Introduction

Lung cancer, a highly invasive, rapidly metastasizing and prevalent cancer, is the top killer cancer in both men and women in the United States of America (USA). During 2014, an estimated 224,210 new cases and 159,260 deaths for lung cancer were predicted in the USA [1]. It causes more deaths per year than the next four leading causes of cancer (Colon/rectal,

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Competing interests:
None.

breast, pancreas, and prostate) death combined in the United States. Its incidence and mortality patterns are consistently associated with 20 or more years of smoking history. The individual susceptibility to tobacco-induced lung cancer may be dependent on competitive gene–enzyme interactions that affect activation or detoxification of procarcinogens and levels of DNA adduct formation as well as determined by the integrity of endogenous mechanisms for repairing lesions in DNA. Lung cancer is highly heterogeneous that can arise in many different sites in the bronchial tree, therefore presenting highly variable symptoms and signs depending on its anatomic location. 70% of patients diagnosed with lung cancer present with advanced stage disease (stage III or IV) (Figure.1).

Squamous cell lung cancers (SQCLC) represent about 25%–30% of all lung cancers and tend to arise in the main bronchi and advance to the carina (Table 1). Adenocarcinomas (AdenoCA) account for approximately 40% of all lung cancers and consist of tumors arising in peripheral bronchi. AdenoCAs advance by producing lobar atelectasis and pneumonitis. Bronchioloalveolar cancers (BAC), now reclassified into adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), arise in alveoli and spread through the interalveolar connections. AIS and MIA describe patients with very good disease-free survival after complete resection (5-year rate nears 100%) [2,3]. Small cell lung cancers (SCLC) derived from the hormonal cells of the lung, are the most dedifferentiated cancers and tend to be central mediastinal tumors. SCLCs comprise 10%–15% of all lung cancers, and are extremely aggressive disseminating rapidly into submucosal lymphatic vessels and regional lymph nodes, and almost always present without a bronchial invasion. Large cell anaplastic carcinomas (LCAC), also termed NSCLC not otherwise specified (NOS), are more proximal in location and locally tend to invade the mediastinum and its structures early. NSCLC-NOS comprises about 10% of all NSCLC. and behaves similarly to small cell cancers with a rapid fatal spread. Pancoast cancer arises in superior sulcus and advances by local invasion into juxta-opposed structures. All lung cancer types can become multifocal in the lobe they arise in (T3), or spread into the lung of origin (T4), or spread to the contralateral lung (M1) (Figure.1) [3]. The compression of mediastinal structures is associated invariably with advanced lymph node involvement, which can lead variously to esophageal compression and difficulty in swallowing, venous compression and congestion associated with collateral circulation, or tracheal compression. Signs of metastatic disease involving such remote sites as the liver, brain, or bone are seen before any knowledge of a primary lung lesion.

2. International Staging System for Lung Cancer

Cancer staging is a critical step in the diagnosis process, and its objectives are multifarious including 1) Helping the clinician to recommend a treatment plan; 2) Giving some indication of prognosis; 3) Aiding in the evaluation of the results of treatment; 4) Facilitating the exchange of information between treatment centers; 5) Contributing to the continuing investigation of human cancer. The international TNM-based staging system describes the anatomical extent of the disease (Table 3). The T category describes the size and extent of the primary tumor. The N category describes the extent of involvement of regional lymph nodes. The M category describes the presence or absence of distant metastatic spread. The addition of numbers to these categories describes the extent of the cancer. All possible

combinations of the T, N, and M categories are then used to create TNM subsets (Table 2). TNM subsets with similar prognoses are then combined into stage groupings. NSCLC stages range from one to four (I through IV). The lower the stage, the less the cancer has spread. SCLC is defined using two stages: Limited (confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes) and extensive (spread beyond the supraclavicular areas) [4].

The term stage, without further classification, relates to the pretreatment, clinical stage or cTNM [3,5–7]. cTNM is derived using the evidence available from clinical history and examination, blood tests, imaging, endoscopic examination, biopsy material, surgical examination, and any other test considered necessary prior to making a decision as to the appropriate treatment in any individual. If this decision leads to surgical treatment, then additional information becomes available at surgery and by pathological examination allowing a more accurate assessment of disease indicated by the pathological, postsurgical stage or pTNM. pTNM does not replace the cTNM, which should remain as a record in the patient's notes. If the patient undergoes preoperative "induction" therapy, usually with either or both chemotherapy and radiotherapy, then a reassessment is made after this treatment, prior to a final decision on surgical treatment [3,5–7]. The evidence available from this process is used to create the ycTNM, and after surgical treatment in these circumstances, the postsurgical pathological extent of disease is described as ypTNM. At various points in the patient's journey, events may allow or demand a reassessment of disease extent. An rTNM may be established if relapse occurs after a disease-free interval. An aTNM may be formulated if the disease is first discovered at an autopsy. In each case, previous assessments of TNM are retained in the patient records [3,5–7].

3. Lung cancer biology

Lung cancer cells have defects in the regulatory circuits that govern normal cell proliferation and homeostasis. The transformation from a normal to malignant lung cancer phenotype is thought to arise in a multistep fashion, through a series of genetic and epigenetic alterations, ultimately evolving into invasive cancer by clonal expansion [8,9]. Following the development of the primary cancer, continued accumulation of genetic and epigenetic abnormalities, acquired during clonal expansion, influences the processes of invasion, metastasis, and resistance to cancer therapy [8,9]. The identification and characterization of these molecular changes are of critical importance for improving disease prevention, early detection, and treatment. The knowledge of both a patient's tumor characteristics and genetics will significantly advance the personalized prognosis and ideal treatment selection for each patient.

3.1. Genomic alterations

Recently, the Cancer Genome Atlas Research Network reported the molecular profiling of 230 lung adenocarcinomas. High somatic mutation rates were seen from the whole-exome sequencing (mean 8.87 mutations per megabase of DNA). Eighteen genes were identified to be significantly mutated both in the abovementioned 230 AdenoCA cases as well as in 182 AdenoCA tumors previously analyzed in similar fashion. Genomic alterations include point mutations (missense and nonsense mutations, frameshift and slicing site alterations),

rearrangement (transversions and transitions) as well as somatic copy number alterations [10]. The alterations of kinase protein levels or activities have also been studied. Using RNA-seq analysis in 7000 tumors (20 solid cancer types), novel and recurrent kinase gene fusion events were identified. In lung adenocarcinomas (513 samples), fusion events were found in ROS1, RET, PRKCB, NTRK, MET and ALK genes and were found in PRKCB, PRKCA, PKN1, FGR, FGFR1, FGFR2 an FGFR3 genes in lung squamous cell carcinomas (492 samples) (Table 5) [11]. These findings may have significant clinical impact and new therapeutic approaches could be developed targeting these alterations. Another large systematic genomic study reclassified 12 tumor types into 11 subtypes based on the sequencing data from 3527 tumor cases (DNA copy number, DNA methylation, mRNA expression, microRNA expression, protein expression and somatic point mutation). Somatic mutations such as KEAP1 and STK11 are preferentially mutated in LUAD-enriched tumors group, containing most of the lung adenocarcinoma cases, while CDKN2A, NOTCH1, MLL2 and NFE2L2 were found mutated preferentially in squamous-like tumors group encompassing most of the lung squamous cell carcinoma cases. Squamous-like tumors also showed frequent MYC amplification and loss of CDKN2A, RB1 and TP53. The reclassification generated new prognostic information that could be used to guide therapeutic decision [12].

3.2. Molecular pathology of lung cancer

Several targetable genetic alterations have been identified in lung cancer [13] (Table 6), including 1) Activating mutations in a number of proto-oncogenes including KRAS, EGFR, BRAF, PI3K, MEK and HER2. Noteworthy, EGFR (Epidermal growth factor receptor) plays a critical role in regulating normal cell proliferation, apoptosis, and other cellular functions. Approximately 10% of NSCLC patients in the US and 35% in East Asia have tumor associated *EGFR* mutations [14–16]. 2) Structural rearrangements in ALK, ROS1 and possibly RET. 3) Amplification of proto-oncogenes such as MET in adenocarcinomas, FGFR1 and DDR2 in squamous cell lung carcinomas. 4) Oncogenic gene overexpression by microRNAs (miRNAs). 5) Inactivation of Tumor Suppressor Genes (TSG), including TP53, RB1, CDKN2A, FHIT, RASSF1A, and PTEN. 6) Enhanced telomerase activity, which contributes to cellular immortality by maintaining telomere length through de novo synthesis of telomeres and elongation of existing telomeres (100% of SCLCs and 80% to 85% of NSCLCs). The hTERT gene is amplified in 57% of NSCLCs.

Remarkably, scores of the aforementioned aberrations correlate with patient's smoking history as well as with racial and gender differences, which suggest a possible role of the host's genetic makeup as key determinants in lung carcinogenesis [8,9].

3.3. Clinical applications

Tremendous work has been conducted to translate the acquired information of these genetic anomalies into improvement of patient care in the clinic including early detection and treatment and prognosis prediction:

1. Discovery of biomarkers for early detection of primary and recurrent disease: Currently, the diagnosis of lung cancer is primarily based on symptoms and lung

cancer detection often occurs when curative intervention (i.e., surgery) is no longer possible. The five-year survival rate in early-stage, operable NSCLC is approximately 50%–70%, but drops to 2%–5% for patients whose cancers have spread distantly [17]. Numerous potential early lung cancer detection biomarkers, have been investigated. However, there are still no biomarkers for detection of lung cancer in clinical use due to the lack of either or both a robust sensitivity and specificity or a functional relevance of these biomarkers to lung carcinogenesis.

2. Development of novel therapies: EGFR- and ALK- targeted therapies are currently approved for lung cancer. Angiogenesis inhibitors (i.e., Bevacizumab) are also available for treatment of lung cancer. These targeted therapies are a promising effective way to personalize treatment of lung cancer. However, resistance to these treatments often develops and side effects can be an issue. Therefore, the clinical challenge is to determine for each patient the most effective combination therapy that may provide optimal treatment with minimum side effects.

   Platinum-based regimens are standard of care in advanced lung cancer. However, their clinical effectiveness is limited by cumulative haemato- and neuro-toxicities highlighting the need for alternative treatment strategies. ERCC1 functions as a key enzyme in nucleotide excision repair (NER). Low ERCC1 expression correlates with increased sensitivity to platinum-based therapy and high ERCC1 expression correlates with better overall prognosis in NSCLC [18,19]. Nearly 50% of NSCLC patients have low levels of ERCC1, and therefore could benefit from alternative therapies exploiting this tumor ERCC1 deficiency [19]. RRM1 is the regulatory subunit of ribonucleotide reductase essential for the deoxyribonucleotides (dNTP) synthesis.

   RRM1 is the main target for the antimetabolite drug gemcitabine, which is an underpinning cancer therapy in the treatment of many malignancies including lung cancer. Gemcitabine directly binds to RRM1 and irreversibly inactivates ribonucleotide reductase [20–28]. High RRM1 levels are associated with tumor resistance and low RRM1 levels with tumor sensitivity to gemcitabine treatment [21,23,25–28].

   Recent studies have suggested that low levels of the heparan sulfate 6-O-endosulfatase (SULF2) through methylation in NSCLC may be predictive of better survival and increase sensitivity to topoisomerase-1 inhibitors (TPI) [29]. SULF2 is overexpressed in many tumors including lung adenocarcinomas and lung squamous carcinomas to remove critical sulfation modifications from sulfated heparin sulfate proteoglycans (HSPGs) and thus release growth factors essential for tumor growth [30–32]. It was established that SULF2 methylation via induction of high expression of Ubiquitin-Like Modifier (ISG15) sensitizes lung cancer cells to TPIs via suppression of ubiquition and proteasomal degradation [29].

   A number of new potentially targetable alterations were identified in NSCLC including FGFR1 amplification and DDR1 mutation found in squamous cell lung carcinomas. These alterations might be important prognostic and predictive factors

for patient's response to treatments with FGFR inhibitors or DDR1 inhibitors (e.g., Dasatinib) [33,34].

3. Discovery of prognostic and predictive biomarkers: The prognostic and/or predictive value of an extensive panel of molecular markers has been tested in early and advanced stage lung cancer. In advanced NSCLC, positive EGFR mutation (10–15% of NSCLC) or ALK rearrangement (ALK-EML4 fusion) status (5–7% of NSCLC) was shown to be predictive for a significant clinical benefit from EGFR tyrosine kinase inhibitors (TKIs) [35,36], or ALK TKI (crizotinib) [37–40], respectively. ALK-EML4 fusion positivity in NSCLC seems to be a prognosticator of poor response to EGFR TKI therapy [41–44] as EGFR mutations and EML4-ALK fusions occur almost exclusively in adenocarcinomas. Nevertheless, EML4-ALK appears to be mutually exclusive to that of EGFR or KRAS mutations in NSCLC and is more common in never or former light smokers [45].

3.4. Tumor microenvironment

The tumor microenvironment and the complex interactions of its various cell types and their released signaling molecules are an emerging hallmark of cancer [46]. It consists of stromal cells, cancer-associated fibroblasts, stem cells and a comprehensive set of immune cells recruited into tumors. The tumor microenvironment is altered to suppress host immune responses, foster tumor growth, and help cancer cells evade immune surveillance [47]. The tumor-associated immune cells include tumor-associated macrophages (TAM), dendritic cell (DC) subsets, cytotoxic and regulatory T-cells (CTLs and Tregs), natural killer (NK) cells, and myeloid-derived suppressor cells (MDSC). The amounts of different immune cell subsets in the tumor microenvironment can vary considerably among patients and may be used as a predictor of treatment outcome and survival in certain cancers [48–50]. The altered tumor microenvironment is established by the cancer cells through the loss of MHC class I molecules, the loss of antigen variants, and the active secretion of several growth factors, such as vascular endothelial growth factor (VEGF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) [51]. The immune cells present in the tumor microenvironment are functionally impaired, and the newly infiltrating immune cells become alternatively activated, resulting in a perturbed phenotype [51]..

Myeloid cells including myeloid-derived suppressor cells (MDSC), macrophages, and dendritic cells (DC), can act as regulatory cells in the tumor microenvironment. MDSCs exert their pro-tumor effects through the inhibition of T-cell proliferation and activation by increasing levels of NO synthase and arginase-1 [52] [51,53,54], releasing IL-10 and overproducing reactive oxygen species (ROS) [55]. In the peripheral blood of advanced stage NSCLC patients, increased levels of MSDC were detected compared to healthy controls and were associated with lower levels of CD8+ T-cells [56].

Tumor-associated macrophages (TAM) show a higher frequency of the pro-tumor M2-phenotype, which accumulate in the tumor stroma and correlate with poor patient outcome and decreased OS [57]. These alternatively activated macrophages show impaired ability to present antigen and appropriate co-stimulation to T-cells [51]. In contrast, macrophages of the M1 phenotype accumulate intratumorally and show antitumor functions through

expression of HLA-DR, inducible nitric oxide synthase (iNOS) and TNF-α [58]. Furthermore, a high intratumoral density of CD68+ macrophages correlates with increased survival in NSCLC [59].

DCs are the most important antigen-presenting cells at the border of the innate and adaptive immune system. However, in the tumor microenvironment, DCs are often in an immature state that fail to prime T-cells efficiently due to low expression levels of co-stimulatory molecules such as CD80 and CD86 and a weak antigen presenting capacity [60,61]. Peripheral blood lymphocytes can also be used as a prognostic marker in NSCLC: 1) the total blood count of lymphocytes was shown to be associated with a lower hazard ratio for death [57,62]; 2) a neutrophil to lymphocyte ratio (NLR) >3.81 was identified in the same study as a predictor of survival in patients with Stage I NSCLC; 3)Treg cells were also detected at elevated levels in the peripheral blood of NSCLC patients compared to healthy controls [63,64].

In early-stage NSCLC, a tertiary lymphoid structure is detected in the tumor stroma that contains mature and follicular DC, CD4+ T-cells, and CD20+ B-cells. This tertiary lymphoid structure is defined as Tumor-induced Bronchus Associated Lymphoid Tissues (Ti-BALT) [48,65]. A small retrospective study demonstrated that the density of mature DC (DC-LAMP +) homing in the Ti-BALT correlates with disease-free survival, disease-specific survival, and OS in early-stage NSCLC patients [48].

Chronic inflammation can also play a significant role in the tumor environment through the release of reactive oxygen and nitrogen species, as well as TNF-α. Consequently, chronic inflammation can facilitate tumor growth via activation of NF-κB and the subsequent suppression of adaptive immune responses [48]. NSCLC tumors often show hypoxic areas, which leads to the release of pro-angiogenic factors such as VEGF, thereby increasing tumor angiogenesis [66,67].

3.5. Racial and ethnic diversity in lung cancer

There is considerable variation in cancer incidence as well as death rates among different racial and ethnic groups [68]. Although the cause of this racial and ethnic disparity in cancer risk and outcomes remains controversial [69], there is a growing consensus that the interaction of genetic and environmental factors including diet is at least partially responsible for the ethnic differences in cancer risk and outcome [70].

Regarding lung cancer, women have lower incidence and death rates than men. African-American men have the highest incidence and death rate in the United States, followed by White, American Indian or Alaskan Natives, Asian American or Pacific Islanders, and Hispanic/Latino men. In women, the highest rates are in white women, followed by American Indian or Alaskan Natives and African Americans, Asian American or Pacific Islanders, and Hispanic/Latino groups [68]. Moreover, clinical trials have shown that Asian ethnicity is an independent favorable prognostic factor for OS in NSCLC patients regardless of their smoking history. The frequency of the activated EGFR mutations is higher in East Asian patients as compared with Caucasian patients (30 vs. 7 %, respectively). Numerous studies showed that EGFR mutation-positive patients of Asian origin have better efficacy

outcomes with first-line EGFR tyrosine kinase inhibitors (TKI), especially patients with adenocarcinoma histology and never smokers [71]. In contrast, prevalence of K-ras mutations is lower in Asian patients (<10 vs. 18 %) [71]. Deciphering these racial disparities requires the identification of risk factors for lung cancer in multiracial, multiethnic groups such as genetic polymorphisms and gene-environment interactions. Moreover, inclusion of minority groups in lung cancer screening and clinical trials may be advantageous in reducing these disparities.

Environmental factors/geography as well as socioeconomic status may also affect lung cancer susceptibility, treatment outcome, and survival rates [72]. Access to treatment and adherence to treatment regimen [73] appear to be an enabling factor for racial disparities in lung cancer. It has been shown that White and African-American patients with early-stage NSCLC who were eligible and received surgical resection had comparable survival rates. In contrast, African-Americans who did not undergo surgery (due to un-insurance, limited access to health care, fear to diagnosis or beliefs) had the lowest survival rate [73]

4. Treatment of Non-Small-Cell Lung Cancer

In this section, the standard and emerging treatments for early stage, advanced, and recurrent NSCLC, as well as brain metastasis will be discussed (Table 7). The various drugs and corresponding targets mentioned in this section are summarized in (Table 8).

4.1. Treatment of early stage (stage I and Stage II) Non- Small-Cell Lung Cancer

The primary treatment for resectable and operable early stage disease (Stage I and II) is surgery [74] which provides the best option for long-term survival [75]. Five-year survival rates after surgical resection are 60%–80% for stage I NSCLC and 30%–50% for stage II NSCLC patients [76]. For patients refusing surgical resection or with unresectable tumors, primary radiotherapy can be used such as stereotactic body radiotherapy (SBRT) for high-risk patients or unresectable tumors [72]. However, post-surgery radiotherapy is not recommended for stage I and II patients [72]. To date, adjuvant platinum-based chemotherapy was shown to be beneficial for stage II NSCLC patients [77] and is the recommended treatment strategy for completely resected patients [72]. Conversely, a clear benefit has so far not been proven for adjuvant chemotherapy in stage I NSCLC patients [78].

4.2. Treatment of stage III Non- Small-Cell Lung Cancer

More than 70 % of NSCLC patients are diagnosed in advanced stages or metastatic disease [2] (stages III and IV). Stage III NSCLC is a heterogeneous disease, and varies from resectable tumors with microscopic metastases to lymph nodes to unresectable, bulky disease involving multiple nodal locations. The 5-year OS rate varies between 10% to 15% for stage IIIA-N2 disease and 2% to 5% for stage IIIA bulky disease with mediastinal involvement. In this heterogeneous population of stage III NSCLC patients, the treatment strategies, including radiotherapy, chemotherapy, and surgical resection are determined by the tumor location and whether it is resectable.

The standard treatment consists of surgery followed by chemotherapy for patients with resectable stage IIIA NSCLC. It has been shown that the adjuvant chemotherapy significantly prolonged OS rate in clinical studies [79–83] and that adjuvant radiation therapy can improve control of resected stage IIIA-N2 disease [84]. Meta-analyses of numerous clinical studies showed that neoadjuvant chemotherapy provides a modest 5% to 6% improvement in survival at five years [85].

For unresectable stage IIIA patients, standard treatment may include either a sequential or concurrent combination of chemotherapy and radiation therapy (chemoradiation), and external radiation therapy for patients who cannot be treated with combined therapy. Meta-analyses of multiple randomized clinical studies showed that platinum based chemoradiation therapy provides a significant 10% reduction in the risk of death when compared with radiation therapy alone [86–88]. Several clinical investigations showed that the radical surgery in Stage IIIA patients with bulky primary tumors may provide up to 50% increase in the 5-year survival rate as compared to patients with incomplete resection [89–91].

Stage IIIB NSCLC represents about 17.6 % of all lung cancers [92] with a 5-year survival rate of 3% to 7% [93]. The options and sequence of treatments for stage IIIB NSCLC are determined based on the site of tumor involvement and the patient's performance status (PS) (Table 4). Generally, patients with stage IIIB NSCLC do not benefit from surgery alone. The standard therapy for these patients consists of either a sequential combination of chemotherapy or external radiation therapy. As palliative treatment, Stage IIIB NSCLC may receive external radiation therapy alone to relieve pain and other symptoms to improve the quality of life.

4.3. Treatment of Stage IV Non-Small Cell Lung Cancer

Stage IV NSCLC accounts for 40% of the newly diagnosed NSCLC patients. The choice of treatment for stage IV NSCLC patients depends on many factors including, comorbidity, PS, histology, and molecular genetic features of the cancer [94]. Standard treatment options for stage IV NSCLC disease may include palliative external radiation therapy, combination chemotherapy, combination chemotherapy and targeted therapy, and any Laser therapy or internal endoscopic radiation therapy as needed. Similar to radiation therapy, surgery could also be used in some cases to alleviate disease-related symptoms.

4.3.1. Chemotherapy—For NSCLC, Chemotherapy is usually well tolerated by patients with PS 0 and 1 but rarely effective in patients with a PS 3 and 4 where palliative care is preferred. Use of chemotherapy is controversial in PS 2 NSCLC patients, which represent nearly 40% of advanced stage NSCLC patients. Chemotherapy is recommended only for PS 2 patients who are reasonably fit, and awake for more than 50 % of the day.

i. First-line Chemotherapy: The median OS is 4.5 months when no chemotherapy is given to advanced metastatic NSCLC or after failure of all treatments. Use of chemotherapy improves the 1-year OS rate from 10%–20% up to 30%–50% [74]. A combination of two cytotoxic drugs is the recommended first-line therapy for Stage IV NSCLC patients with a PS of 0 or 1. Platinum (Cisplatin or carboplatin)-based combination therapies yield better response and OS rates than the non-platinum combination therapies. First line platinum-

based chemotherapeutics may include doublets of cisplatin or carboplatin given in combination with taxanes (paclitaxel, docetaxel, or vinorelbine), antimetabolites (gemcitabine or pemetrexed), or vinca alkaloids (vinblastine) with comparable activity [95]. Use of single cytotoxic chemotherapy is preferred in stage IV patients with a PS of 2 due to their greater risk of toxicity and drug intolerance, comparing to patients with a PS 0 to 1.

ii. First-line combination chemotherapy with targeted therapy: Currently, the addition of bevacizumab, an antibody targeting VEGF, to first-line doublet combination chemotherapy, is supported for the treatment of stage IV NSCLC patients with exception (squamous carcinoma histology, brain metastasis, significant cardiovascular disease or a PS greater than 1) due to fatal bleeding concerns. The combination of bevacizumab with carboplatin and paclitaxel doublet appeared to be superior to the combination with cisplatin and gemcitabine.

4.3.2. EGFR tyrosine kinase inhibitors (first line)—The first of the approved targeted drugs for NSCLC patients are agents that specifically block the EGFR) such as tyrosine kinase inhibitor (TKI) Erlotinib (Tarceva) and gefitinib (Iressa). Mutations of EGFRs can lead to abnormal activation of this receptor triggering uncontrolled cell growth, which may account for several subsets of cancers including NSCLC.

Evidence from several randomized clinical trials demonstrated that use of single-agent gefitinib as a first-line therapy might be recommended for patients with activating EGFR mutations, particularly for patients who have contraindications to platinum therapy. Conversely, cytotoxic chemotherapy is preferred if EGFR mutation status is negative or unknown. Three large controlled and randomized trials showed that gefitinib or erlotinib are better than platinum combination chemotherapy as first-line treatment for stage IIIB or IV lung adenocarcinomas in nonsmokers or former light smokers in East Asia [35,36,96,97].. Data from these trials demonstrated that gefitinib or erlotinib improved PFS but not OS and have favorable toxicity profiles compared with combination chemotherapy of patients with chemotherapy-naïve and EGFR mutations adenocarcinoma. Similar benefits of erlotinib versus platinum-based chemotherapy as first-line were reported in one European large randomized clinical trial (PFS: 9.7 vs. 5.2 months, respectively) [98]. Neither erlotinib nor gefitinib is recommended for use in combination with cytotoxic chemotherapy as first-line therapy

4.3.3. Maintenance therapy following first-line chemotherapy—Maintenance therapy is the treatment continuation until disease progression of a cancer that has not advanced following the first-line therapy. The primary goal is to improve cancer-related symptoms, and, hopefully, improve survival time beyond that provided by the first-line therapy. It has lately gained great interest in the treatment of advanced NSCLC (stage IIIB and stage IV) [99]. To date, pemetrexed (Alimta), and erlotinib (Tarceva) are the two medications that have been approved by the FDA as maintenance therapy for advanced lung cancer. Evidence from two randomized controlled clinical trials showed a statistically significant improvement of PFS (4.1 to 4.3 months vs. 2.6 to 2.8 months), with the addition of pemetrexed as maintenance therapy following standard first-line platinum-based combination chemotherapy [100–103]. Remarkably, pemetrexed maintenance therapy

appears to be effective only in patients with adenocarcinoma and large cell carcinoma as well as in patients with EGFR mutations in their tumors, but not in patients with squamous cell lung carcinoma.

Data from a large randomized controlled clinical trial showed improved survival (both PFS and OS) with erlotinib maintenance treatment following platinum-based chemotherapy in NSCLC patients without progressive disease (PFS: 12.3 weeks vs. 11.1 weeks) [104]. Similar to pemetrexed, erlotinib maintenance therapy improved outcome primarily in non-squamous cell lung carcinoma NSCLC patients. Patients with activating EGFR mutations in their tumors showed greatest PFS benefit comparing to patients with wild type EGFR who also experienced improvement in their median PFS. This trial also demonstrated that KRAS mutation status was a significant, negative prognostic factor for maintenance erlotinib-induced PFS [105]. Moreover, never-smoking women with better PS seems to derive the utmost survival advantage from maintenance erlotinib therapy.

4.3.4. Second- and third-line therapies in the treatment of advanced NSCLC—

Docetaxel (Taxotere), pemetrexed, erlotinib, and gefitinib, are currently approved as second-line therapy for patients with advanced NSCLC who have failed first-line platinum-based therapy and have an acceptable PS.

Evidence from several randomized clinical trials and meta-analyses [106–108] showed that docetaxel in the second-line setting leads to better survival and quality of life (QoL) when compared to best supportive care [107] or to single agent ifosfamide or vinorelbine [109]. Pemetrexed yielded similar clinical response comparing to docetaxel (a median survival of about 8 months, one-year survival of 30%, and a response rate of 10%) [110] with better toxicity profile that may benefit older patients with a PS of 3 [111]. Pemetrexed also provided better outcome in lung adenocarcinoma patients, whereas docetaxel treatment was more effective in lung squamous cell carcinoma patients [112]. Erlotinib related response was more common in women with adenocarcinoma, never-smokers, or east-Asians, which is correlated with more frequent EGFR activating mutations [113]. To date, erlotinib is approved and may be recommended as second- or third-line therapy for patients with a PS of 0 to 3 who have not received prior erlotinib or gefitinib.

Because of the scarcity of data on cytotoxic chemotherapy as third-line therapy, there are no recommendations for or against using a cytotoxic chemotherapy in the third-line setting. However, Phase III clinical trials of docetaxel, erlotinib, gefitinib, and pemetrexed allowed patients to continue chemotherapy, as tolerated, until disease progression.

4.4. Standard Treatment Options for Recurrent NSCLC

Recurrent or relapsed NSCLC is a cancer that has progressed or returned following an initial treatment with surgery, radiation therapy, and/or chemotherapy. The cancer may return in the lung, brain, or other parts of the body. For NSCLC patients who have never been treated with chemotherapy, the treatment plan is similar to that of Stage IV NSCLC. For those patients who have already been treated with chemotherapy, standard treatment options may include: 1) External palliative radiation therapy, which achieves palliation of symptoms from a localized tumor mass [114], to relieve pain and other symptoms and improve the

quality of life; 2) Cytotoxic chemotherapy [107,110,115]; 3) EGFR inhibitors (TKIs) in patients with or without EGFR mutations.; 4) EML4-ALK inhibitor (Crizotinib) in patients with EML-ALK translocations.[116,117]; 5) Surgical resection of isolated cerebral metastases (for selected patients who have a very small amount of cancer that has spread to the brain) [118]; 6) Laser therapy or interstitial radiation therapy using an endoscope (for endobronchial lesions) [119]. 7) Stereotactic radiation surgery (for selected patients who cannot have surgery) [120,121].

4.4.1. Cytotoxic Chemotherapy for Recurrent NSCLC—Evidence from clinical studies showed that use of cytotoxic chemotherapy and targeted therapy may achieve objective responses, albeit with small improvement in survival for patients with recurrent NSCLC [122]. In some trials, platinum based chemotherapy has also been shown to achieve palliation of symptoms, which occurred more often than the objective response in patients with good PS [123,124]. Treatment options for NSCLC patients whose cancer has recurred after platinum-based chemotherapy may include either new cytotoxic chemotherapy such as docetaxel [107,114] and pemetrexed [110], or a targeted therapy such as erlotinib [113], gefitinib [115], and crizotinib for cancers with EML4-ALK translocations [116,117]. Patients with squamous lung carcinomas benefit more from docetaxel, whereas those with non-squamous NSCLC appeared to benefit more from pemetrexed [125].

4.4.2. EGFR Inhibitors for Recurrent NSCLC—A large randomized phase III trial comparing gefitinib to placebo in recurrent NSCLC patients suggested that gefitinib might be a valid treatment for recurrent NSCLC patients with improved survival compared to placebo in never-smokers (median survival 8.9 mo vs. 6.1 mo), and Asian patients (median survival 9.5 mo vs. 5.5 mo) [126], In two large randomized, placebo controlled trials, erlotinib has also been shown to improve survival and quality of life in patients with recurrent NSCLC after first-line or second-line chemotherapy compared to placebo [113,127]. Moreover, erlotinib treatment also induced a greater improvement in patients' symptoms, such as cough, pain, and difficulty in breathing, compared to placebo [113]. Conversely, erlotinib did not improve survival when compared to standard second-line chemotherapy with docetaxel or pemetrexed [128], in recurrent NSCLC patients after a first-line platinum combination therapy.

4.4.3. ALK/MET Inhibitors for Recurrent NSCLC—Translocations of EML4 and ALK occur on the short arm of chromosome 2, and the fusion of EML4 and ALK (normally a dormant gene) results in a constitutive activation of the ALK kinase. The EML4-ALK fusion oncogene has been identified in approximately 4% in the NSCLC population, and is generally found in individuals who do not typically respond to EGFR TKI therapy [40,45]. EGFR and EML4-ALK mutations appear to be mutually exclusive with exceptions. Tumors harboring the EML4-ALK fusion oncogene are sensitive to crizotinib, a selective, ATP-competitive ALK and MET/HGF dual TKI, which is FDA approved for the treatment of patients with locally advanced or metastatic ALK positive-NSCLC [117]. Crizotinib (XALKORI@, Pfizer) is currently approved in Switzerland for treatment of patients with previously treated ALK-positive advanced NSCLC, and in the USA for treatment of patients with locally advanced or metastatic, ALK-positive NSCLC.

Crizotinib therapy has shown improvement in survival of patients with advanced, ALK-positive NSCLC compared to standard therapies for advanced NSCLC [117] [129]. Similar to the kinase inhibitors already used in clinic, such as imatinib and EGFR inhibitors, resistance to crizotinib frequently develops in patients' tumors [130]. These tumors might either acquire additional ALK kinase domain mutations (i.e., L1196M, C1156Y mutations) that alter drug sensitivity [131], or other ALK alterations, including amplification, gain in copy number, and loss of ALK genomic rearrangement [132]. Furthermore, signaling through other kinases, such as EGFR, might compensate for ALK inhibition, thereby mediating resistance to ALK inhibitors [132]. Mutation in the KRAS gene was also shown to play a role in resistance to crizotinib and around 8 % of ALK-positive NSCLC patients were shown to harbor either a KRAS or EGFR mutation in addition [130].

4.5. Treatment of Second Primary Tumor

A second primary cancer is a separate cancer arising in a patient who had another cancer in the past. Second or higher order primary tumors account for about 6 to 10% of all cancer diagnoses, and are the fifth most commonly diagnosed cancer in Western countries. The risk of developing a second primary cancer may increase with the use of cancer therapies, such as chemotherapy and radiation therapy. However, it is crucially important to remember that this cancer therapy-related risk is minimal when compared to the benefits of treating the original primary cancer. Patients with lung cancer are at high risk of developing second primary lung cancers. However, it may be difficult to accurately determine whether the new tumor is a secondary primary cancer or a metastasis from the original cancer. Studies have shown that in the majority of lung cancer patients the new lesion is a second primary tumor. When the original primary tumor has been surgically removed, surgical resection of second primary tumors may achieve a 5-year survival rate of 60%, with a comparable expected operative morbidity and mortality to the primary surgery. Tumors 2 cm or smaller are associated with significant positive long-term prognostic factors for survival and freedom from recurrence following resection of a the second primary cancer [133–135]

4.6. Treatment of Brain Metastases

Brain metastases are a common problem in lung cancer patients and a significant cause of morbidity and mortality. Brain metastases are found in about 80% of SCLC and 30% NSCLC at two years from diagnosis [136,137]. Among the various histologies of NSCLC, the incidence of brain metastases in patients with adenocarcinoma and large cell carcinoma is greater than in patients with squamous cell carcinoma [138,139]. The median survival for untreated lung cancer patients with brain metastases is 4 to 7 weeks [140–142]. The treatment may be for relief of symptoms or therapeutic strategies. Treatment options for lung cancer patients with brain metastases may include Whole Brain Radiotherapy (WBRT), surgical resection, Stereotactic Radiosurgery (SRS), Systemic therapy and Radiosensitization, or a combination of these various treatment modalities.

a) Whole Brain Radiotherapy (WBRT)—WBRT is the standard of care for cerebral metastasis in lung cancer patients. Several randomized trails have assessed numerous WBRT dose and fractionation schedules but showed no significant difference in either survival times, or symptomatic response rates and duration. Nevertheless, the results of these

trials have suggested better palliative effects from the more prolonged schedules and the choice of dose fractionation schedule should be based on patients' prognosis [143]. Additionally, a systematic imaging study of dose response based on tumor size and histology, following WBRT (30 Gy in 10 fractions) [144], showed an improved response rate for smaller tumors without necrosis. The complete response rate was 37% for SCLC, 25% for squamous cell carcinoma, and 14% for non-breast adenocarcinoma.

b) Surgery—Resection of a single brain metastasis combined with WBRT is a standard treatment option of brain metastases [134,145]. A prospective randomized study [134], demonstrated superiority of surgical removal of the brain tumor followed by radiotherapy over needle biopsy and radiotherapy, with lower recurrence rates at the site of the original metastasis (20% vs. 52%,), and a significantly longer time to recurrence of the original brain metastasis (median >59 weeks vs. 21, $p < 0.0001$). Moreover, the median survival with surgery and adjuvant WBRT was much longer than with WBRT alone (40 weeks vs. 15 weeks, $p < 0.01$). Patient's functional independence (KPS score of ≥70) was also preserved much longer with combined surgery and WBRT than with radiation alone (median: 38 weeks vs. 8 weeks, $p < 0.005$).

In patients with multiple brain metastases, surgery is typically limited to the resection of the dominant, symptomatic lesion. Various studies have shown that surgery combined with adjuvant WBRT or stereotactic radiosurgery (SRS) has similar survival outcome in patients with multiple lesions compared with patients with single brain metastasis or a single lesion [146–148]. About 50% of patients treated with resection and postoperative radiation therapy develop recurrence in the brain [118]. Few patients with recurrent brain metastasis and good PS, but without progressive metastases outside of the brain, may be treated with surgery or stereotactic radiation surgery [118,120]. However, most patients with recurrent brain metastasis may be treated with additional radiation therapy, albeit with a limited palliative benefit [149].

c) Stereotactic Radiosurgery (SRS) with and without WBRT—Stereotactic radiosurgery (SRS) is a form of non-invasive radiation therapy that focuses high-power energy on a precisely defined small target (e.g. the center of the tumor). The suggested mechanisms of SRS-induced tumor killing are radiation-induced DNA damage, endothelial cell apoptosis, microvascular dysfunction, and induction of a T-cell response against the tumor [150–152]. Because of the generally small size and well-defined margin of brain metastases at presentation [153,154], SRS may be an effective alternative to surgery for up to four small brain metastases (up to 4 cm in size) [154].

Several studies showed that SRS might achieve better prognosis and prolonged survival in lung cancer patients with good PS, no systemic disease, and longer survival time from the diagnosis of primary disease [155–160]. The addition of SRS to WBRT could be beneficial for patients who are not eligible for surgery due to tumor location in the brain or other medical contradictions.. A large randomized controlled Phase III trial study, showed that the local recurrence at one year decreased significantly with the combination of WBRT and SRS (18 vs. 29%, $p = 0.01$) [161]. A planned sub-analysis, in patients with a single brain metastasis revealed an improved median survival (6.5 vs. 4.9 months; $p = 0.039$) and

improved quality of life with WBRT and SRS.[161–163]. The addition of adjuvant WBRT to SRS yielded a significant increase in the average time to deterioration in patients with one to four brain metastases (16.5 months vs. 7.6 months, p = 0.05) although no survival advantage was observed [164].

d) Systemic Therapy and Radiosensitization—In 30–70% of patients with a single brain metastasis, lung cancer is the primary disease [165]. Generally, most chemotherapeutic agents are unable to cross the blood brain barrier reach the CNS. However, the endothelium leakiness of the tumor vessels, which may disrupt the blood-brain barrier, is well documented in human cancer, particularly in case of macroscopic metastases or relapsed disease. In keeping, several small phase II studies demonstrated that chemotherapy alone yields response rates of brain metastases of 43%–100% and 0%–38% for metastases from SCLC and NSCLC, respectively [165]. However, combining chemotherapies (thalidomide, teniposide, topotecan, paclitaxel, and cisplatin) to WBRT did not demonstrate survival benefit although some showed enhanced response rates [166–175].

Radiosensitizing agents, such as motexafin gadolinium (Xcytrin) and efaproxyn (efaproxiral or RSR-13), may increase oxygen levels in the tumor and therefore enhance its sensitivity to radiation therapy. However, initial trials showed that the addition of radiosensitizers to WBRT may improve response rate and time to progression (TTP), but not survival. Overall, the evidence to date does not support the clinical use of chemotherapy or radiosensitizers in conjunction with WBRT in the treatment of brain metastases.

4.7. Role of Angiogenesis Inhibitors in NSCLC

Angiogenic pathways provide an important target in NSCLC treatment since they foster tumor growth through the development of new blood vessels. The complex process of angiogenesis is regulated by pro-angiogenic factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), as well as angiopoietins [176]. Currently, only the monoclonal antibody bevacizumab, targeting circulating VEGF, is approved for first-line treatment of advanced NSCLC in combination with platinum-base chemotherapy [176]. Several anti-angiogenic agents are under clinical investigation, including sorafenib and sunitinib.

A randomized phase III trial (ECOG 4599) assessing the efficacy of bevacizumab in combination with first-line platinum-based chemotherapy (carboplatin/paclitaxel) showed significantly improved response rates (35 % vs. 15 %, P<0.001), PFS (6.2 vs. 4.5 months, P<0,001), and overall survival (OS) (12.3 vs. 10.3 months, P=0.003) in the antibody group, compared to chemotherapy alone [177]. Further analysis revealed that baseline tumor cavitation is the most significant risk factor for the fatal side effect after bevacizumab therapy [178]. The trial also suggested that patients with adenocarcinoma histology might benefit more from the treatment with bevacizumab [179].

However, resistance to treatment with anti-VEGF agents is a challenge and occurs in all patients eventually. This resistance might, at least partially, be caused by up-regulation of compensatory angiogenic pathways, e.g. through PDGF or FGF signaling [176]. Multi-targeted anti-angiogenesis therapies therefore represent an interesting treatment strategy for

NSCLC patients. In keeping, the multiple tyrosine kinase inhibitor (TKI) sorafenib which targets VEGFR-2/3, PDGFR-β, c-Kit, Raf, and Flt-3, produced promising response rates in several phase I and II studies [176]. Although sorafenib showed activity as single agent in NSCLC patients, it did not show an added improvement when combined with the carboplatin, paclitaxel and EGFR TKI (erlotinib) [176]. Interestingly, Sorafenib treatment resulted in an increased disease control rates in NSCLC patients with K-Ras mutations [176]. Several phase II/III studies for sorafenib in NSCLC are still ongoing [176].

Another multiple TKI, sunitinib, targeting VEGFR-1/2/3, PDGFR-α/β, c-Kit, Flt-3, and RET, have also been evaluated in NSCLC patients [176]. Similar to sorafenib, sunitinib demonstrated singe-agent activity in pretreated NSCLC patients but did not show promising results when combined with paclitaxel/carboplatin alone, with bevacizumab or with erlotinib in two phase II trials [180,181]. Moreover, several other agents inhibiting VEGFR in combination with PDGFR are currently in clinical development, including cediranib, axitinib, motesanib, and linifinib [176].

Conversely, the angiogenesis inhibitors have not proven to increase the efficacy of standard platinum-based chemotherapy in advanced NSCLC possibly due to lower doses required to reduce toxicities [176]. In addition to dual-targeted therapies, several agents with activity against three angiogenic pathways (VEGFR, PDGFR, and FGFR) are currently under clinical investigation. An example of the aforementioned inhibitors is the small molecule inhibitor nintedanib which targets VEGFR-1/2/3, PDGFR-α/β, FGFR-1/2/3, as well as Flt-3 and Src family members [182]. Nintedanib achieved disease stabilization in 46 % of the patients, with a median PFS of 6.9 weeks and median OS of 21.9 weeks, in stage IIIB/IV advanced NSCLC patients [183]. Pazopanib is another interesting multi TKI, targeting VEGFR-1/2/3, PDGFR-α/β, and FGFR-1 and 3 [184]. In a phase II study treating naïve stage I/II resectable NSCLC patients, pazopanib showed significant activity as single agent. 86 % of the pazopanib treated patients had a reduction in tumor volume, with two patients achieving a reduction of over 50 %. Pazopanib is currently under investigation in advanced NSCLC [176].

4.8. Other Molecular Targeted Agents, under Clinical Evaluation for NSCLC Treatment

a) Talactoferrin—The glycoprotein lactoferrin was first described as an iron-binding protein in breast milk and shows immune-modulatory functions [185,186]. The human recombinant lactoferrin, talactoferrin, is given orally, and is able to recruit immature dendritic cells (DC) into the gut-associated lymphoid tissue, where cross-presentation of tumor antigens and subsequent DC maturation can occur [186]. Preclinical data also showed an increase in splenic NK cell activity and inhibition of NSCLC tumor growth with talactoferrin [187]. A double blind, placebo controlled phase II study using talactoferrin as monotherapy showed improved OS (median 6.1 vs, 3.7 months after a follow-up of 15.2 months). When combining with chemotherapy (carboplatin and paclitaxel) in treating advanced stage IIIB/IV NSCLC patients, talactoferrin also showed a promising trend for disease-control rates in the intention-to-treat and evaluable population [188].

b) Insulin-like Growth Factor Inhibitors—The insulin-like growth factor system (IGF system) comprises two receptors: Insulin-like growth factor 1 receptor (IGF-IR) and IGF-IIR with their respective ligands: Insulin-like growth factors 1 and 2 (IGF-1 and IGF-2) and six high-affinity IGF binding proteins (IGFBP) that function as carrier proteins for these ligands. IGF 1 and 2 are involved in the regulation of the development and growth of somatic tissues, as well as carbohydrate metabolism [189,190]. The IGF signaling pathway promotes cell growth by stimulating cell proliferation and differentiation. Additionally, IGF-IR, but not IGF-IIR, signaling inhibits apoptosis [191]. These ligands bind to the extracellular domain of the IGF receptor 1 (IGF-1R), which is expressed on many normal human cells [192,193], and overexpressed in many cancers, including lung cancer. Furthermore, increased IGF-1 levels, and decreased IGFBP-3/4 level correlate with a higher risk of lung cancer [190,194].

A number of inhibitors for the IGF signaling pathway have been developed, including monoclonal antibodies and small-molecule TKIs, which target the intracellular domain of the receptor [190]. Figitumumab, a monoclonal antibody against IGF-1R, showed significantly increased overall response rates compared to chemotherapy alone (54 % vs. 42 %, $P<0.0001$) in a phase II trial in previously untreated locally advanced or metastatic NSCLC patients, Squamous tumors showed a response rate of 78 % and PFS (12-week) of 89 % [195]. However, two phase III trials that used Figitumumab in combination with chemotherapy in non-adenocarcinoma NSCLC were closed due to severe lethal adverse events and unmet primary endpoint [190,196,197]. Two other monoclonal antibodies against IGF ligands, cixutumumab and dalotuzumab, as well as small molecule TKIs are currently under clinical investigation [190].

c) Histone Deacetylase Inhibitors—Histones are nuclear structural enzymes and, as part of the chromatin, are involved in nucleosomal DNA organization and gene regulation. Conformational changes in DNA structure are regulated by histone acetylation and deacetylation, a mechanism that is often affected in tumor cells [198]. Histone deactylases (HDACs) are involved in chromatin condensation and repression of gene expression and are frequently overexpressed in many cancers [190]. Contrary to genetic mutations, the epigenetic modifications induced by HDACs are reversible, and therefore, HDACs are an attractive target for cancer therapy [198]. Various HDAC inhibitors have been developed and shown to modulate the acetylation status of several important cellular proteins involved in tumor cell growth and proliferation, including p53, HSP90, STAT3, subunits of NFκ-B and α-tubulin [190,199,200]. Moreover, the HDAC inhibitors can also modify the cell cycle and lower the apoptotic threshold [190,199,200]. Many HDAC inhibitors showed anticancer activity in cell culture and animal models of carcinogenesis. Two of these HDAC inhibitors, suberoylanilide hydroxamic acid (SAHA, Vorinostat) and Romidepsin (Depsipeptide, FK228), have already been FDA approved for the treatment of cutaneous T-cell lymphoma (CTCL). The addition of vorinistat to chemotherapy was able to improve the response rate compared to the placebo addition to chemotherapy (34 vs. 12.5 %, $P=0.48$) in treating advanced stage IIIB/IV NSCLC patients [201,202]. However, a phase III trial of vorinostat in combination with carboplatin and paclitaxel was stopped due to increased adverse effects, and a lack of efficacy in the vorinostat group [203]. A number of other HDAC inhibitors

including entinostat, pivanex, cI-994, panobinostat, and romidepsin, are currently under clinical investigation for treatment of NSCLC [204].

d) Pro-Apopototic Agents—Apoptosis has long been known as a hallmark of cancer, and cancer cells exploit both upregulation of antiapoptotic as well as downregulation of pro-apoptotic mechanisms [46,205]. Novel pro-apoptotic drugs are currently being investigated for the treatment of NSCLC. To date, both Mapatumumab, a high-affinity monoclonal antibody against the death receptor DR4/TRAIL-R1, and a pro-apoptotic agent apomab did not show clinical benefit as monotherapy or in combining with chemotherapies (carboplatin and paclitaxel) in clinical trials [206,207] [208] [190,209]. A number of other new pro-apoptotic agents, such as Conatumumab (targeting DR1) and YM155 (targeting survivin), are currently under clinical investigation for the treatment of NSCLC and have shown synergistic effects in combination with chemotherapy [190,210,211].

4.9. Immunotherapy

a) Immune Checkpoint Inhibitors

1) CTLA4: Tumors ascribe certain immune-checkpoint pathways as a chief mechanism of immune resistance, particularly against T cells that are specific for tumor antigens. Several of these immune checkpoints are initiated by ligand–receptor interactions, and thus are amenable to inhibition by antibodies or modulated by recombinant forms of ligands or receptors [186]. Two monoclonal antibodies, ipilimumab and tremelimumab, have been used successfully in NSCLC against the cytotoxic T-lymphocyte-associated antigen (CTLA-4), an inhibitory T-cell co-receptor found on activated T-cells and regulatory T-cell subsets [186,212]. A multicenter double-blind phase II trial showed that the combination of ipilimumab and chemotherapy (carboplatin or paclitaxel) significantly improved the immune-related PFS in advanced stage IIB/IV NSCLC patients with squamous cell carcinoma (without prior chemotherapy) [186,213]. Tremelimumab has also been tested in a randomized, phase II trial as maintenance after first-line chemotherapy, compared to best supportive care. However, the results of this trial showed no improvement in PFS [214].

2) PD-1 and PD-L1: The immune-checkpoint receptor, programmed death-1 (PD-1), is a promising target, for stimulation of antitumor immune responses by the patient's own immune system. Unlike CTLA4, the main role of PD-1 is to control the activity of T cells in peripheral tissues at the time of an inflammatory response to infection and to limit autoimmunity [215–222]. This translates into a major immune resistance mechanism within the tumor microenvironment [223–225]. Another interesting immunotherapeutic option is the direct targeting of PD-1 ligands (PD-L1), B7-H1/PD-L1 and B7-DC/PD-L2. It has been shown that B7-H1/PD-L1 is selectively upregulated in many human cancers including lung cancer [223,226]. An encouraging phase I study showed clinical activity of PD-L1 blocking agents in NSCLC [223,226].

A dose-escalation study testing a monoclonal antibody against PD-1 (MDX-1106) in the treatment of refractory-metastatic solid tumors (melanoma, renal cell cancer, colon cancer, NSCLC), showed objective responses in five of 49 NSCLC patients [222]. This result highlights the potential activity of anti-PD-1 against a non-immunogenic tumor [226].

Another study assessed the safety and antitumor activity of the anti-PD-1 monoclonal antibody BMS-936558 or nivolumab in patients with advanced tumors (NSCLC, melanoma, prostate, renal cell, and colon cancer) [227]. Durable, objective responses (partial and complete) were observed in 18 % of NSCLC patients. Significantly, the objective responses to anti-PD-1 therapy and clinical benefit correlated with PD-L1 expression by tumor cells (P=0.025 and 0.005, respectively). Although the expression of PD-L1 by infiltrating immune cells did not significantly correlate with objective response (P=0.14), marked correlation with clinical benefit was reported (P=0.038). The toxic side effects were milder with PD-1 inhibition compared to CTLA-4 inhibition, thus underlining the importance of targeting immune checkpoint-pathways with better benefit-to-toxicity ratios [186,226].

Several clinical trials are currently investigating immune checkpoint inhibitors, such as anti-CTLA-4 (nivolumab) and anti-PD-1 (ipilimumab), as monotherapy or in combination with chemotherapy in NSCLC [228]. Recently, results from two phase III trials (CheckMate-017 and 057) showed an OS benefit with Nivolumab compared to docetaxel in both nonsquamous and squamous NSCLC. In the phase III CheckMate-017 trial [229], there was a 41% OS improvement with nivolumab compared to docetaxel in the squamous setting. In the phase III CheckMate-057 trial [230], the OS benefit with nivolumab was 27% in patients with nonsquamous NSCLC. Based on data from CheckMate-017 trial, Nivolumab is now approved by the FDA in squamous NSCLC.

Recent publications evaluated expression of PD-1 and PD-L1 in NSCLC. Patients with KRAS mutations were shown to express higher levels of PD-1 compared to patients with wild type KRAS, whereas increased levels of PD-L1 were detected in patients with EGFR mutations or ALK translocations [231]. Interestingly, the clinical profile of PD-1 expressing patients included male smokers with adenocarcinoma more frequently, whereas PD-L1 was more frequently expressed in female non-smokers with adenocarcinoma. Both PD-1 and PD-L1 were recently shown to be upregulated through activation of EGFR, thereby leading to immune evasion [232,233]. Furthermore, patients with EGFR mutations and increased expression of PD-L1 showed a higher response rate to treatment with the EGFR-TKIs gefitinib or erlotinib, compared to PD-L1 negative patients, which resulted in longer TTP (11.7 vs. 5.7 months, P<0.0001) and OS (21.9 vs. 12.5 months, P=0.09) [231]. Taken together, these recent studies suggest that combination of EGFR TKIs with PD-1 inhibitors might be beneficial in treatment of NSCLC [231,232].

Another study analyzed the mechanism of combining immunotherapy with immune checkpoint inhibition in a B16 tumor mouse model. A TLR agonist enhanced GM-vaccine (TEGVAX) was shown to induce anti-tumor immune responses *in vivo*, which was associated with IFN-y dependent upregulation of PD-L1 in the tumor microenvironment. Combined treatment with TEGVAX and PD-1 inhibition led to regression of established tumors, whereas PD-1 inhibition alone did not induce anti-tumor immune responses [234]. Other antibodies against PD-1, such as pembrolizumab (MK-3475), MPDL3280A, and MEDI4736 are currently being investigated and have shown promising results in Phase 1 clinical trials [235]. A recent study used whole-exome sequencing to investigate the genomic determinants of response in two independent cohorts of NSCLC treated with this therapy [236]. This study revealed that a higher nonsynonymous mutation burden in tumors

was associated with improved ORR, durable clinical benefit, and PFS. Pembrolizumab clinical efficacy also correlated with the molecular smoking signature, higher neoantigen burden, and DNA repair and replication pathway mutations (e.g., mutations in POLD1, POLE, MSH2, Rad51, Rad17, DNA-PK) [236]. Remarkably, pembrolizumab–induced neoantigen-specific T cell reactivity was also observed in the peripheral blood, thus, suggesting possible blood-based assays to monitor response during anti–PD-1 therapy.

b) Vaccine Therapy for NSCLC—Vaccination against pathogens is one of the most important developments in modern medicine and saves millions of lives each year. For advanced NSCLC patients, median OS is about one year, and only 3.5 % survive five years after diagnosis, despite the addition of new therapies to standard chemotherapy [186]. Therefore, vaccinations for solid tumors, either preventive (for tumors related to infections such as human papilloma virus-associated cervical cancer [237]) or therapeutic (breaking tolerance and achieving long lasting response in tumors such as ipilimumab (anti-CTLA-4) in advanced melanomas [226,238]), have long been seen as the ultimate treatment option for cancer patients.

As many other cancers, NSCLC belongs to the non-immunogenic tumors and therefore the identification of tumor specific immunogenic antigens for vaccine therapy presents a major challenge. The most promising results of vaccines for NSCLC patients have been observed in the adjuvant setting and in locally advanced NSCLC [190]. A Summary of the various vaccine therapy evaluated in NSCLC is shown in Table 9.

A. MUC1: Mucin-1 (MUC1) is a glycoprotein present on normal epithelial tissue and in various cancers, including NSCLC [66,239]. A mutated MUC1protein overexpressed in cancer cells shows aberrant glycosylation pattern that is antigenically different from wild-type protein expressed on normal epithelial cells [66]. L-BLP25 is a synthetic vaccine against the core peptide of MUC1 combining the peptide with cyclophosphamide as an adjuvant [186,240]. Recently updated data from a phase IIB randomized study treating stage IIIB/IV NSCLC patients with L-BLP25 showed significant improvement in the vaccine group comparing to the supportive group (3-year survival rates: 31 vs. 17 % [241]).

The efficacy of TG4010, a recombinant vaccinia virus that combines the human MUC1 and interleukin-2 coding sequences [66], in combination with cisplatin and vinorelbine or as monotherapy has been investigated in a randomized phase II study for advanced NSCLC patients [242,243]. A subgroup with a detectable CD8+ T-cell response was able to generate an immune response against MUC1 and had longer median survival [243]. Data from another phase II study comparing the vaccine plus chemotherapy with chemotherapy alone in advanced NSCLC patients with confirmed MUC1 expression showed that higher numbers of activated NK cells might suppress DC and effector T-cells and result in decreased median OS rates as well as increased adverse effects. [244] [243].

B. EGF: CimaVax EGF is a new vaccine that is being developed for NSCLC treatment. This vaccine is made up of a low dose cyclophosphamide and EGF. It works as an immunoadjuvant to reduce the inhibition of Tsuppressor cells and to stimulate the

production of anti-EGF antibodies that may inhibit EGF binding EGFR on cancer cells, and consequently decrease cancer cells growth [66,243,245,246].

A phase I study showed that the production of anti-EGF antibodies and serum EGF levels after use of the EGF-based vaccine, correlate with increased survival rates in NSCLC patients [247]. A randomized phase II trial comparing the CimaVax vaccine to best supportive care in stage IIIB/IV patients [248] showed minimal toxicity and good antigen responses in 51.4% of the patients although the median OS did not improve [66]. Longer median survival rates were seen in good antigen responders than in poor antigen responders (11.7 vs. 3.6 months) [243]. In addition, longer median OS rates were seen in patients with EGF levels below 168 pg/ml (13 vs. 5.6 months) and under 60 years (11.57 vs. 5.33 months, P=0.0124) [243]. The vaccine has been approved for clinical trial development in the US stage IIIB/IV patients [243].

C. Melanoma-associated antigen (MAGE): Melanoma-associated antigen A3 vaccine (MAGE-A3) uses a tumor specific antigen, which is expressed in 35 % of NSCLC, most frequently in squamous cell carcinomas [186]. It ranges from 16 % in stage IA to 48 % in stage IIIB and may be associated with poor prognosis [66,249,250]. The MAGE-A3 vaccine, initially developed for metastatic melanoma patients, showed a positive sign of activity after 28 months in a phase II adjuvant therapy study in early stage NSCLC [251]. Prior to treatment, the NSCLC tumors were analyzed by gene expression profiling to identify a gene signature that correlates with the clinical activity of the vaccine [252]. The identified signature of genes related to the immune system overlapped with the gene set detected in the melanoma trial. Reduction in the relative recurrence risk after treatment with the MAGE-A3 vaccine showed a 2-fold increase for tumors containing the gene signature (57%), compared to the non-selected population (25%). This result underlines the value of the stratification of patient subpopulations and suggests that gene profiling for a certain tumor microenvironment or immune cells might have a predictive value in cancer immunotherapy [66,251–253].

D. TGF beta: The allogeneic vaccine belagenpumatucel-L combines four irradiated lung cancer cell lines (two adenocarcinoma, 1 squamous cell and one large cell carcinoma) with an antisense plasmid against TGF-b (transforming growth factor beta) [186], a poor prognostic factor in NSCLC. TGF-b2 suppresses dendritic cells, NK cells, and activated cytotoxic T lymphocytes and thereby may help tumors to escape immunosurveillance [186]. The use of four tumor cell lines in the belagenpumatucel-L vaccine increases the number of tumor antigens and the suppression of TGF-b expression through the antisense plasmid removes a major source of immune suppression at the injection site [186]. Preclinical data showed that the inhibition of TGF-beta2 could help to break the tolerance and to increase the immunogenicity of tumor vaccines [66,254,255]. Patients who received a high dose of the vaccine showed a significantly improved OS compared to low dose group in a randomized, dose-variable phase II trial with 75 NSCLC patients (stages II-IV) [255] [186].

E. PRAME: Another important tumor antigen for vaccine therapy is PRAME (preferentially expressed antigen of melanoma), which has recently been shown to contribute to carcinogenesis in NSCLC [256]. As the name suggests, it was first detected in

a melanoma patient [67], and is expressed in a variety of tumors [66]. PRAME seems to function via the suppression of the retinoic acid receptor (RAR), a signaling pathway which regulates cell death and cell cycle [66,257].. Overexpression of PRAME might be used by tumor cells to escape suppressive RAR signaling, thereby fostering tumor-progression [66]. Clinical data suggests that poor clinical outcome of some patient subpopulations correlates with PRAME expression in neuroblastoma [258] and breast cancer [259–261].

A new PRAME vaccine combining the purified recombinant PRAME protein with an adjuvant (liposomal preparation with the AS15 adjuvant system) has been developed. A currently ongoing phase II study (PEARL study) is evaluating the efficacy of the PRAME vaccine in resected NSCLC. This study enrolled patients radically resected for NSCLC, stages IA (T1b), IB, II or IIIA, and whose tumors exhibit PRAME expression. The primary endpoint of the study is disease-free survival (DFS) [257,262].

5. Small-cell lung cancer

Small cell lung cancer (SCLC) accounts for approximately 15% of all lung carcinomas [4,263]. The highest risk-factor for development of SCLC is smoking, and the decrease in percentage of smokers and amount of cigarettes smoked per person in the US might explain the recent decrease in SCLC incidence rates [263]. 30% of SCLC patients are diagnosed with limited-stage disease (LS-SCLC), where the cancer is confined to the hemithorax, the mediastinum, or the supraclavicular lymph nodes. 70% of SCLC patients are diagnosed with extensive-stage disease (ES-SCLC), with tumors spreading beyond the supraclavicular areas [4,263]. Although SCLC is initially more responsive to chemotherapy and radiation therapy than all other lung cancer types, it is very difficult to cure, due to its aggressive growth and its wide dissemination at the time of diagnosis.

As for other lung cancers, the treatment options for SCLC patients are determined by histology, stage, and general health and comorbidities of the patient. For patients with LS-SCLC, standard treatment options include platinum based chemotherapy and radiation therapy, combination chemotherapy alone, surgery followed by chemotherapy or chemoradiation therapy, and prophylactic cranial irradiation [264]. For patients with ES-SCLC patients, current treatment recommendations include combination chemotherapy, radiation therapy and prophylactic cranial irradiation [264]. For recurrent SCLC, the treatment options are chemotherapy and palliative therapy. Although chemotherapy and radiotherapy can lead to strong initial responses in SCLC, disease recurrence is common. Notwithstanding the improvements in diagnosis and therapy made during the past two decades, the current prognosis for patients with SCLC remains substandard. Untreated SCLC is the most aggressive of all type of lung cancers, with a median survival from diagnosis of only 2 to 4 months. The 2 years DFS, following treatment of SCLC patients, remains a dismal 10% [265]. Moreover, the OS at 5 years of all population of SCLC patients is merely 5% to 10% [4,265–267], with a better prognosis for patients with LS-SCLC (5-year survivals of 14%) than for patients with ES-SCLC [4,266,268,269]. In patients who showed complete response to chemoradiation, prophylactic cranial radiation may avert brain metastases recurrence, and thus, increase patients' survival [270,271].

Although surgery or chemotherapy alone can improve survival in patients with LS-SCLC, a greater improvement in long-term survival has been shown with combination therapy [269,272]. Particularly combining chemotherapy with thoracic radiation therapy (TRT) increases OS by 5% compared to chemotherapy alone [4,273–276]. Although median survival of 6 to 12 months may be achieved in patients with ES-SCLC with the currently available therapy, long-term DFS is rare in these patients [4,275,276].

Targeted therapies in SCLC

a) VEGF inhibitors—Inhibition of circulating VEGF with bevacizumab has been studied in ES-SCLC. Chemotherapy naïve patients treated with cisplatin, irinotecan, and bevacizumab, showed an ORR of 75 %, a median OS of 11.6 months, and a median PFS of 7.0 months [277]. A study investigating cisplatin, etoposide, and bevacizumab in previously untreated ES-SCLC patients showed that a higher baseline level of vascular cell adhesion molecule (VCAM) was associated with a higher risk of progression or death, compared to lower levels of VCAM, but no other biomarkers could be correlated with treatment outcome [278].

Other VEGF inhibitors, including the multi-kinase inhibitors sorafenib, sunitinib, and cediranib, are currently under clinical investigations in SCLC. [279] [264]. Aflibercept (AVE0005) is a fully humanized protein that contains immunoglobulin domains from the two VEGF receptors VEGFR1/2, fused to the constant region of IgG1. These soluble receptors work as a VEGFR-trap and inhibit binding of VEGF to its common receptors. Aflibercept is currently investigated in combination with topotecan in previously treated ES-SCLC [264].

b) EGFR inhibitors—Mutation of the EGFR is less frequent in SCLC compared to NSCLC, and only around 4% of patients were shown to harbor the mutation [280]. In a phase II study, patients were stratified according to chemosensitive or chemo-refractory relapsed SCLC and treated with gefitinib. However, the abovementioned study could not demonstrate a gefitinib benefit for SCLC patients [281].

c) Bendamustine—This cytotoxic agent causes DNA breaks through its alkylating activity. Compared with other alkylating agents, bendamustine causes more extensive and durable DNA single- and double-strand breaks [264]. Combining bendamustine with carboplatin in treating ES-SCLC [282], the ORR was 72.7 %, with a median TTP of 5.2 months and median survival time of 8.3 months.. As a single agent in second- and third-line setting in patients with relapsed/refractory SCLC, Bendamustine is well tolerated and effective agent [283].

d) Immunotherapy—To date, only few studies have evaluated immunotherapy in the treatment of SCLC [243]. The BEC2/BCG vaccine combines a monoclonal antibody that mimics the glycosphingolipid GD3, which is selectively expressed in SCLC, with the adjuvant bacillus Calmette-Guerin [243]. The BEC2/BCG vaccine has been demonstrated to develop antibodies against GD3 in Melanoma patients. In an early clinical study, although only 30% of the SCLC patients (5/15, ES/LS-SCLC=8/7) developed measureable anti-GD3

antibodies, the median OS was 20.5 months (relapse-free survival was longer in patients who developed measurable anti-GD3 antibodies) [243,284,285]..

Another novel vaccine (INGN-225) targeting p53 protein was developed, and is currently under investigation for treatment of SCLC [243]. The INGN-225 vaccine is produced from patients' autologous peripheral blood mononuclear cells (PBMCs). The autologous PBMCs are cultured in the presence of IL-4 and granulocyte-macrophage colony-stimulating factor (GM-CSF) prior to incubation with a viral construct containing wild-type p53 (adenovirus Ad.p53). In a preclinical study, dendritic cells transfected with Ad.p53 were able to induce cytotoxic T lymphocytes following vaccination [243]. In a recent phase I/II study.14 of the 54 enrolled ES-SCLC patients demonstrated a positive immune response and showed increased median survival (12.6 vs. 8.2 months, P=0.131) [243,286]. Among those responsive patients, 78.6% responded to second-line chemotherapy treatment.

6. Palliative Care for Patients with Lung Cancer

A high percentage of lung cancer patients suffers from substantial symptom burden, including fatigue, loss of appetite and weight loss, as well as dyspnea, hemoptysis, and chest pain [287]. Better quality of life, lower depressive symptoms, higher median survival and fewer needs on aggressive end-of-life care were observed in patients receiving early palliative care combined with standard oncologic care compared to standard oncologic alone for metastatic NSCLC.[287]. Megestrol acetate (MA), an appetite stimulant, is one of the supporting treatments that have shown success in treating cancer-related anorexia (CRA) and improve quality of life. Combining MA with olanzapine (OLN) for the treatment of CRA in 80 patients with either advanced gastrointestinal cancer or advanced lung cancer patients (stages III and IV) resulted in a significant improvement of mean symptom scores as measured by the MD Anderson Symptom Inventory (MDASI) [287] suggesting that combination MA and OLN may be an effective palliative therapy for patients with CRA [288]..

7. Mesothelioma

Malignant Mesothelioma (MM) is an extremely aggressive tumor affecting about 3,000 new patients in the United States annually [289]. The incidence of the disease in the US is expected to rise steadily and peak with about 85,000 new MM cases over the course of the next 20 years [290,291]. MM arises from the surface serosal cells of the pleura and, less frequently, from the peritoneum. Exposure to asbestos is a wellestablished cause, with occupational exposure being documented in 70–80% of MM patients [292–294]. MM is sub-typed into three forms according to the histological morphology: epithelial, sarcomatoid, and biphasic. Diffuse MM comprises about 75% of mesotheliomas diagnosed [295].

Treatment of MM with surgery, chemotherapy, or radiation therapy is rarely curative. Clinical trials of single modality treatment with extrapleural pneumonectomy or pleurectomy, chemotherapy or radiation therapy, have not shown significant improvement in survival compared with supportive treatment. Median survival has ranged from 10 to17 months [296]. Sugarbaker et al. reported a 15% 5-year survival with multimodal therapy and

a 25% 5-year survival in patients who underwent complete surgical resection [297]. Recent trials of new-generation platinum- and pemetrexed based regimens have reported encouraging results. In particular, a phase II trial of pemetrexed plus cisplatin for MM reported a median survival of 12 months compared with nine months after treatment with cisplatin alone [298]. Despite these promising results, long-term survival with currently available treatment is rare. Therefore, novel meaningful therapies for MM are urgently needed. Recent advances have shown that tumors carrying activating mutations in some cellular proto-oncogenes are particularly sensitive to targeted therapies directed against the mutant proteins [14,16,299–307].

Role of immunotherapy in malignant mesothelioma

A number of immunotherapy strategies have been tested in mesothelioma patients, with varying degrees of success.

a) Mesothelin—Mesothelin is an immunogenic glycoprotein specifically overexpressed in malignant mesothelioma, NSCLC, ovarian, and pancreatic cancers [186]. CRS-207, is a genetically-engineered, double-deleted bactria Listeria monocytogenes strain expressing the human mesothelin [186]. Phagocytic cells, such as macrophages and dendritic cells, take up CRS-207, and mesothelin is subsequently expressed and processed through the MHC I presentation pathway. This process is predicted to activate T cells in order to attack mesothelin-positive mesothelioma cells. In preclinical studies, CRS-207 was shown to elicit anti-mesothelin cell-mediated immunity [186]. In a phase I dose-escalation study treating patients with advanced mesothelin expression and treatmentrefractory cancers, with CRS-207, mesothelin-specific T-cell responses were in one of five patients with mesothelioma, with 15 months or more survival after the first dose [186]. Patients who received sequential CRS-207 treatment with prior immunotherapy or subsequent local radiation therapy benefited the most. CRS-207 is currently investigated in combination with first-line chemotherapy in mesothelioma patients.

b) WT1 analogue peptide vaccine—The transcription factor Wilms' tumor suppressor gene 1 (WT1) is frequently overexpressed in mesothelioma and other solid and hematopoietic tumors [186]. Recently, a multivalent WT1 peptide analog vaccine was developed [186]. A CD-4+ T-cell proliferation to WT1-specific peptides was seen in six of nine patients, and a CD8+ T-cell response was detected in six of six HLA-A0201 patients in an early study investigating the WT1 peptide analog vaccine in MM and NSCLC patients. Stimulated T-cells also showed cytotoxicity against WT1 positive cells [308]. A subsequent randomized phase II study is currently investigating the adjuvant WT1 analog peptide vaccine in MM patients who have completed combined modality therapy [309].

c) Dendritic cell vaccine—Dendritic cells (DCs) are the most potent antigen-producing cells, capable of sensitizing T cells to both new and recall antigens. DC-based cancer immunotherapy is aimed at using these cells to prime specific antitumor immunity through the generation of effector cells that attack and kill tumors. Dendritic cells can be matured using a standard cytokine cocktail and pulsed with autologous tumor cell lysates, which presents a source of tumor antigens for immunotherapy [186].

A phase I study has shown that the DC vaccine was well tolerated in newly diagnosed MM patients, who experienced a partial response or stable disease after previous combination chemotherapy [310]. A significant humoral response to keyhole limpet hemocyanin, a marker for immune response, was detected in serum samples from all patients. Nine patients had successful lymphocyte activation according to increased levels of granzyme B expressing CD3 and CD8 T-cells. However, no correlation between the clinical responses and the humoral or cellular immune responses was observed [186].

Another small Phase I/II study evaluated the feasibility, safety, immunogenicity, and clinical efficacy of consolidation treatment with autologous DC transfected with mRNA encoding the malignant mesothelioma-associated WT1 antigen [311]. Ten patients with unresectable MM and non-progressive disease after platinum/pemetrexed-based chemotherapy underwent leukapheresis: Isolating CD14+ monocytes to produce mature DC, followed by electroporation of WT1 mRNA and biweekly intradermal vaccinations [311].. DC vaccination was well tolerated; no systemic toxicity was recorded. The 6-, 12- and 18-month survival rates were 100%, 90%, and 75%, respectively. *In vivo* evidence of vaccine-elicited immunity to the DC vaccine administered was obtained in nine of the ten enrolled patients. The OS data suggest that adjuvant DC-based immunotherapy may provide a clinical benefit for patients with MM [311].

8. The future of thoracic malignancies

Despite the intensive research and development of several new targeted agents and immunotherapies, survival rates for lung cancer and mesothelioma patients remain dismal. More studies are still needed to identify the underlying genetic alterations and predispositions affecting clinical outcome. Early detection and treatment of these cancers may help dramatically in the improvement of patients' survival. Over 60% of lung cancer patients are in fact diagnosed at late stages of the disease, where current treatment modalities are unlikely to be effective. The 5-year OS rate is less than 10 % in patients with advanced disease, and greater than 70 % in patients with stage 1 disease. Reliable biomarkers are greatly needed to predict sensitivity to each therapeutic modality in thoracic malignancies that could support optimal selection of treatment on individual patient basis as well as for early detection of lung cancer that could improve its prognosis.

Acknowledgments

Funding

This work was supported in part by The Doctors Cancer Foundation grant A118560, the American Cancer Society grant IRG-97-150-13, and The NIH/NCI U01 grant NIH Grants 5U01CA168878.

Abbreviations

SCLC	Small-Cell Lung Carcinomas
NSCLC	Non-Small Cell Lung Carcinomas
MM	Malignant Mesothelioma

AdenoCA	Adenocarcinomas
SQCLC	Squamous Cell Lung Cancers
LCAC	Large Cell Anaplastic Carcinomas
OS	Overall Survival
PFS	Progression-Free Survival
TTP	Time to Progression
ORR	Objective Response Rate

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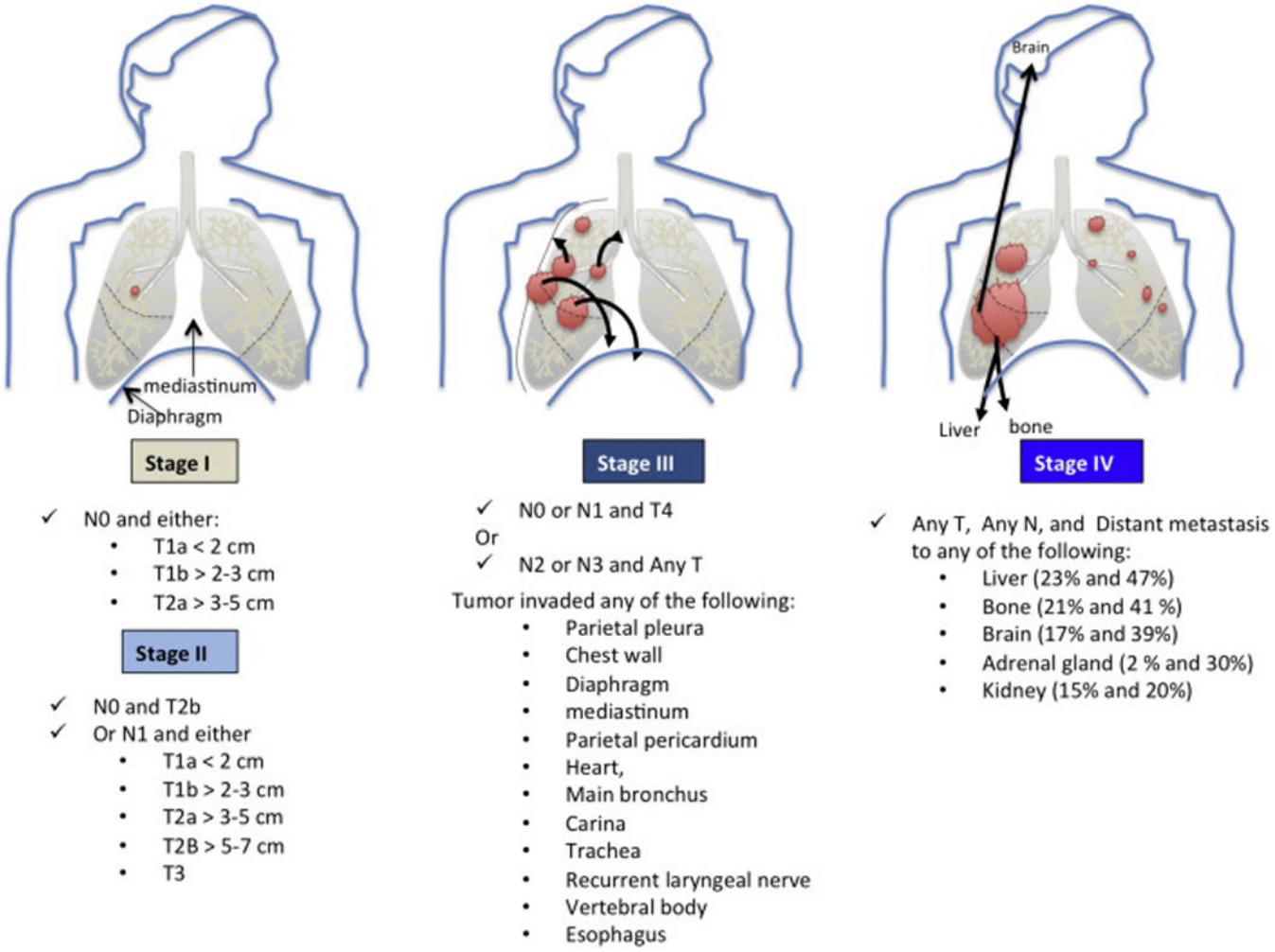

Figure 1.

Schematic illustration of the Non-Small Lung Cancer (NSCLC) staging. Of note, Squamous cell lung carcinomas arise in the epithelial cells of main and lobar Bronchi (not shown), whereas Adenocarcinomas originate in the peripheral lung tissue and arise in the epithelial cells of segmental bronchi. For stage IV NSCLC cancers, the incidence of distant metastasis to the extrathoracic organs is depicted. For each organ, the percentages represent the incidence of metastasis for squamous cell lung carcinomas and adenocarcinomas, respectively.

Table 1

Types of Lung Cancer.

Lung Cancer Type	% of All Lung Cancer	Anatomic Location
Squamous cell lung cancers (SQCLC)	25–30%	Arise in main bronchi and advance to the carina
Adenocarcinomas (AdenoCA)	40%	Arise in peripheral bronchi
Large cell anaplastic carcinomas (LCAC)	10%	Tumors lack the classic glandular or squamous morphology
Small cell lung cancers (SCLC)	10–15%	Derive from the hormonal Cells Disseminate into submucosal lymphatic vessels and regional lymph nodes almost without a bronchial invasion

Table 2

TNM stage grouping for NSCLC. TNM stand for the size and location of the **T**umor, the location of cancer in the lymph **N**odes and where the cancer has spread (**M**etastases).

T \ N	0	1	2	3
1a	IA	IIA	IIIA	IIIB
1b	IA	IIA	IIIA	IIIB
2a	IB	IIA	IIIA	IIIB
2b	IIA	IIB	IIIA	IIIB
3	IIB	IIB	IIIA	IIIB
4	IIIA	IIIA	IIIB	IIIB
M1a (Any T)	IV	IV	IV	IV
M1b (Any T)	IV	IV	IV	IV

T = Primary tumor: **T**1a (Tumor size ≤2 cm), **T**1b (>2–3 cm): **T**2a (>3–5 cm), **T**2b (>5–7 cm); **T**3 (>7 cm) and/or (Multiple tumor nodules in the same lobe); **T**4 (Multiple tumor nodules (of any size) in the same lung but a different lobe).
N0 = No regional lymph node metastasis; **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).
M = Distant metastasis: **M**1a (Malignant pleural or pericardial effusions and/or Separate tumor nodules in the contralateral lung); **M**2b (Distant metastasis in extrathoracic organs).

Table 3

TNM-based staging system.

Category	Description
T	Size and extent of the primary tumor
N	Extent of involvement of regional lymph nodes
M	Presence or absence of distant metastatic spread
Numbers (0–3)	Extent of the cancer
cTNM	Pretreatment, Clinical stage
pTNM	Postsurgical stage
ycTNM	Post-preoperative therapy stage
ypTNM	Postsurgical stage with preoperative therapy

Table 4

Eastern Cooperative Oncology Group (ECOG) Performance Status. The ECOG scale and criteria are used to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Table 5

Kinase fusion events identified in AdenoCA and SQCLC [12]

Lung Adenocarcinoma		
Gene name	Number of cases altered	Alteration
ALK	5/513	Known fusion
MET	1/513	New fusion
NTRK2	2/513	Known kinase-novel indication
PRKCB	1/513	New fusion
RET	2/513	Known fusion
ROS1	8/513	Known fusion
Lung Squamous Cell Carcinoma		
Gene name	**Number of cases altered**	**Alteration**
FGFR1	1/492	Known fusion
FGFR2	1/492	Known fusion
FGFR3	3/492	Known fusion
FGR	1/492	New fusion
PKN1	1/492	New fusion
PRKCA	2/492	Known kinase-novel indication
PRKCB	1/492	New fusion

Table 6

Oncogenes and tumor suppressor genes altered in NSCLC [14].

ONCOGENE	CANCER TYPE	Pathway
AKT1, AKT2, AKT3	AdenoCA (rare), SQCLC (20%, AKT3: 16%)	PI3K
ALK	AdenoCA (3–13%)	RTK
BRAF	AdenoCA (6%), SQCLC (4%)	RAF
CCNE1	AdenoCA (12%)	RB1/CDK
DDR2	SQCLC (3–8%)	RTK
EGFR	AdenoCA (40–50%), SQCLC (7%)	RTK
ERBB2	AdenoCA (7–14%)	RTK
ERBB3	SQCLC (2%)	RTK
FGFR1	AdenoCA (1–3%), SQCLC (22%), SCLC (6%)	RTK
HRAS	SQCLC (3%)	RAS
IGF1R	SCLC (95%)	RTK
KRAS	AdenoCA (30%), SQCLC (5%)	RAS
MDM2	AdenoCA (20%)	TP53
MET	AdenoCA (25%)	RTK
MLL	SCLC (10%)	Epigenetic regulation
MYC, MYCN, MYCL	AdenoCA (31%), SQCLC (rare), SCLC (16%)	Transcriptional regulators
NKX2.1/TTF1	AdenoCA (20%)	Developmental pathways
NRAS	AdenoCA (<1%), SQCLC (<1%)	RAS
NRF2	SQCLC (19%)	Oxidative stress response
PIK3CA	AdenoCA (rare), SQCLC (16%)	PI3K
RET	AdenoCA (1–2 %)	RTK
ROS	AdenoCA (1.5%)	RTK
SOX2	SQCLC (21%)	Developmental pathways
TP63	SQCLC (16%)	Developmental pathways
TUMOR SUPPRESSOR GENE	**CANCER TYPE**	**Pathway**
PTEN	AdenoCA (rare), SQCLC (8%)	PI3K
ARID1A	AdenoCA (8%)	Epigenetic Regulation
ASCL4	SQCLC (3%)	Developmental pathways
CDKNA2/p16INK 4	AdenoCA (>20%), SQCLC (72%)	RB1/CK
CEBBP	SCLC (9%)	Epigenetic Regulation
CUL3	SQCLC (7%)	Oxidative stress response
EP300	SCLC (9%)	Epigenetic Regulation
KEAP1	AdenoCA (11%), SQCLC (12%)	Oxidative stress response
LKB1	AdenoCA (15–30%), SQCLC (2%)	LKB1/AMPK
MLL2	SQCLC (19%)	Epigenetic Regulation
NF1	AdenoCA (8–10%), SQCLC (11%)	RAS
NOTCH	SQCLC (13%)	Developmental pathways

RASA1	SQCLC (4%)	RAS
RB1	AdenoCA (rare), SQCLC (7%), SCLC (100%)	RB1/CDK
SETD2	AdenoCA (5%)	Epigenetic Regulation
SMARCA4	AdenoCA (10%)	Epigenetic Regulation
TP53	AdenoCA (70%), SQCLC (80%), SCLC (70%)	TP53
TSC1, TSC2	SQCLC (6%)	PI3K

Table 7

Treatment options for NSCLC.

Stage	Treatment options
I, II-resectable	Surgery
I,II-unresectable	Radiotherapy
II-resectable	Surgery followed by chemotherapy (adjuvant)
IIIA-resectable	Surgery followed by chemotherapy
IIIA-resectable	Chemotherapy (neoadjuvant) followed by surgery
IIIA-unresectable	Sequential or combined chemoradiation
IIIA with bulky primary tumors	Radical surgery
IIIB	Chemotherapy or radiation
IIIB	Chemoradiation
IV with PS of 0 or 1	Chemotherapy (a combination of two cytotoxic drugs, platinum-based)
IV with PS of 0 or 1, with no squamous carcinoma histology, brain metastasis, significant cardiovascular disease	Bevacizumab (VEGF antibody) + first line doublet combination chemotherapy
IV with PS of 2	Chemotherapy (single cytotoxic drug)
NSCLC with EGFR mutations	EGFR targeted therapy (erlotinib and gefitinib)
III, IV (first-line platinum-based therapy failed with acceptable PS)	Docetaxel, pemetrexed, erlotinib and gefitinib
Recurrent NSCLC	External palliative radiation therapy, Cytotoxic chemotherapy, EGFR inhibitors (with or without EGFR mutations), EML4-ALK inhibitor (with EML-ALK translocations), Surgical resection (isolated cerebral metastases), Laser therapy or interstitial radiation therapy (endobronchial lesions), Stereotactic radiation surgery
Brain Metastases	Whole Brain Radiotherapy (WBRT), Surgery, Stereotactic Radiosurgery (SRS) with and without WBRT, Systemic Therapy and Radiosensitization

Table 8

Drugs and corresponding targets.

Drug	Target	Type
Aflibercept (AVE0005)	VEGF	Humanize VEGFR-trap
AMG 655/Conatumumab	TRAIL-R2	Monoclonal antibody
Apomab	DR5/TRAIL-R2/TNFRSF10B	Monoclonal antibody
Axitinib	PDGFR	Tyrosine kinase inhibitor
Bendamustine	DNA (SSB and DSB)	Alkylating agent
Bevacizumab	VEGF	Monoclonal antibody
Carboplatin	DNA	Small molecule inhibitor
Cediranib	PDGFR	Tyrosine kinase inhibitor
Cediranib	VEGF	Small molecule inhibitor
CI-994	Histone deactylases (HDACs)	Small molecule inhibitor
Cisplatin	DNA	Small molecule inhibitor
Cixutumumab	IGF-IR	Monoclonal antibody
Dalotuzumab	IGF-IR	Monoclonal antibody
Docetaxel	Tubulin	Small molecule inhibitor
Entinostat	Histone deactylases (HDACs)	Small molecule inhibitor
Erlotinib	EGFR	Tyrosine kinase inhibitor
Etoposide	Topoisomerase II	Small molecule inhibitor
Figitumumab	IGF-IR	Monoclonal antibody
Gefitinib	EGFR	Tyrosine kinase inhibitor
Ifosfamide	DNA	Alkylating agent
Iniparib	PARP-1	Small molecule inhibitor
Ipilimumab	CTLA-4	Monoclonal antibody
Irinotecan	Topoisomerase I	Small molecule inhibitor
Linifinib	PDGFR	Tyrosine kinase inhibitor
Mapatumumab	DR4/TRAIL-R1	Monoclonal antibody
Medl-4736	PD-L1	Monoclonal antibody
Motesanib	PDGFR	Tyrosine kinase inhibitor
MPDL-3280A	PD-L1	Monoclonal antibody
Nintedanib	VEGFR-1/2/3, PDGFR-α/β, FGFR-1/2/3, Flt-3, Src family	Multiple target Tyrosine kinase inhibitor
nivolumab	PD-1	Monoclonal antibody
Olaparib	PARP-1	Small molecule inhibitor
Paclitaxel	Tubulin	Small molecule inhibitor
Panobinostat	Histone deactylases (HDACs)	Small molecule inhibitor
Pazopanib	VEGFR-1/2/3, PDGFR-α/β, and FGFR-1 and 3	Multiple target Tyrosine kinase inhibitor
Pemetrexed	Thymidylate Synthase	Small molecule inhibitor
Pembrolizumab/MK-3475	PD-1	Monoclonal antibody
Pivanex	Histone deactylases (HDACs)	Small molecule inhibitor

Drug	Target	Type
Romidepsin (Depsipeptide, FK228)	Histone deactylases (HDACs)	Small molecule inhibitor
Sorafenib	VEGFR-2/3, PDGFR-β, c-Kit, Raf, and Flt-3	Multiple target Tyrosine kinase inhibitor
Sunitinib	VEGFR-1/2/3, PDGFR-α/β, c-Kit, Flt-3, and RET	Multiple target Tyrosine kinase inhibitor
Talactoferrin	Immune-modulatory function	Glycoprotein, recombinant
Topotecan	Topoisomerase I	Small molecule inhibitor
Tremelimumab	CTLA-4	Monoclonal antibody
Veliparib	PARP-1	Small molecule inhibitor
Vinblastine	Tubulin	Small molecule inhibitor
Vinorelbine	Tubulin	Small molecule inhibitor
Vorinostat	Histone deactylases (HDACs)	Small molecule inhibitor
YM155/Sepantronium bromide	Survivin	Small molecule inhibitor

Table 9

Types of vaccine therapy for NSCLC.

BEC2/BCG	**glycosphingolipid GD3 vaccine**	**Combines a monoclonal antibody that mimics the glycosphingolipid GD3 with the adjuvant bacillus Calmette-Guerin**
Belagenpumatucel-L	Allogeneic vaccine	Four irradiated lung cancer cell lines and an antisense plasmid against TGF-beta
CimaVax EGF	EGF vaccine	Cyclophosphamide and EGF
CRS-207	Mesothelin vaccine	Genetically-engineered Listeria monocytogenes
INGN-225	p53 vaccine	Produced from patients' autologous peripheral blood mononuclear cells (PBMCs)
L-BLP25/emepepimut-S	MUC-1 vaccine	Synthetic peptide derived from the mucin 1
MAGE-A3	Melanoma-associated antigen A3 vaccine	Tumor specific antigen Mage-A3
PRAME	PRAME vaccine	Recombinant PRAME protein combined with the AS15 Adjuvant System
TG4010	MVA-MUC1-IL2 vaccine	Modified vaccinia ankara encoding human MUC-1 antigen and interleukin-2