


2020 Innovation-Based Optimism for Lung Cancer Outcomes

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ABSTRACT

Lung cancer is the leading cause of cancer death in both males and females in the U.S. and worldwide. Owing to advances in prevention, screening/early detection, and therapy, lung cancer mortality rates are decreasing and survival rates are increasing. These innovations are based on scientific discoveries in imaging, diagnostics, genomics, molecular

therapy, and immunotherapy. Outcomes have improved in all histologies and stages. This review provides information on the clinical implications of these innovations that are practical for the practicing physicians, especially oncologists of all specialties who diagnose and treat patients with lung cancer. *The Oncologist* 2021;26:e454–e472

Implications for Practice: Lung cancer survival rates have improved because of new prevention, screening, and therapy methods. This work provides a review of current standards for each of these areas, including targeted and immunotherapies. Treatment recommendations are provided for all stages of lung cancer.

INTRODUCTION

Lung cancer has been the leading cause of cancer death in the U.S. and worldwide for many decades [1]. Most patients present with stage IV, metastatic disease that cannot be cured by past and current therapies. And most patients are current or former smokers, which was responsible for causing their disease [2–4]. These facts led to considerable pessimism and guilt among patients and physicians in the past. Fortunately, science is beginning to triumph over this past pessimism and the outlook is much brighter for patients as incidence and mortality rates fall [5]. In addition, attitudes are changing among physicians, scientists, patients, and advocates. In this article, we will review changes in science, pathology, prevention, early detection, and therapy.

ETIOLOGY, PATHOGENESIS, AND PREVENTION

Early studies identified the fact the carcinogens in the airway caused most lung cancers. Tobacco smoke from active cigarette smoking was identified as the primary cause of lung cancer especially from the studies of Peto and Doll and documented in the U.S. Surgeon General's reports [3, 4, 6]. Later, passive smoke exposure was also shown to cause lung cancer, and this recognition changed attitudes and laws that

regulated smoke exposure in public spaces as well as cigarette advertising, taxes, and laws [6, 7]. During World War II, uranium mining became frequent, and Saccomanno and others showed that the uranium decays to radon, a colorless and odorless gas emitting alpha particles that radiate the bronchial epithelium, leading to dysplasia and malignancy [8]. Subsequently, there have been declines in cigarette smoking and radon exposure that have led to declines in lung cancer incidence. However, smoking remains the leading preventable cause of lung cancer, especially in underdeveloped nations where smoking has not declined or increased. In developed countries, declines in cigarette smoking have led to marked declines in the incidence and mortality of lung cancer [1, 9] (Fig. 1).

In addition to causing pathologic changes in the bronchial epithelium, tobacco carcinogens produce molecular changes that become clonal at early times. The tumor suppressor gene, *p53*, was among the first to be characterized as an early event in lung cancer pathogenesis and remains the most frequently mutated gene in lung cancer [10]. Clonal *p53* mutations can be detected in premalignant lesions and are among the most frequent clonal truncal alterations. Loss of other tumor suppressor genes is also frequent, and the

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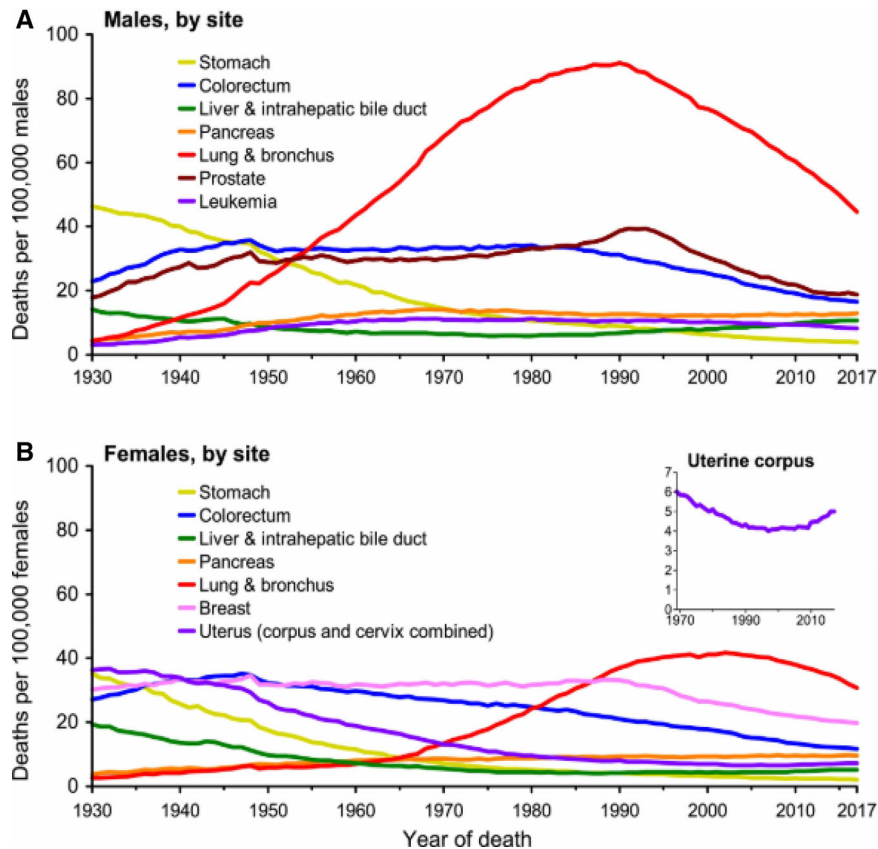


Figure 1. Lung cancer mortality rates in males and females in the U.S. by year [1]. Deaths per 100,000 males (**A**) and females (**B**) in the U.S. Although lung cancer has the highest mortality rates in both males and females, mortality rates are declining in both sexes.

combined loss of *p53* and *Rb* is almost universal in small cell lung cancers, while genetic alterations define subsets of small cell cancers and large cell neuroendocrine cancers [11, 12]. These alterations may also identify new therapeutic strategies [13, 14]. Mutations in dominant oncogenes were recognized in many lung cancer specimens and patient-derived cell lines. Mutations in *myc* family genes was reported in many small cell lung cancers, whereas *KRAS* proto-oncogene mutations were frequently reported in lung adenocarcinomas [11, 14, 15]. The types of *KRAS* mutations were shown to differ in smoking-related and non-smoking-related adenocarcinomas. Studies of non-small cell lung cancer (NSCLC) cell lines identified overexpression and amplification of human epidermal growth receptor (*HER*) family genes in many cancers, leading to development of inhibitors of these pathways and ultimately predictive biomarkers [16, 17]. More recently, whole genome studies, through the cancer genome project and other large efforts, have identified many recurring mutations in lung cancer that have become targets for therapy [18–21].

PREVENTION, SCREENING, AND EARLY DETECTION

After cigarette smoking was established as the major cause of lung cancer, the major goal worldwide was to reduce consumption of cigarettes and other tobacco products. Although this goal has been elusive, progress has been made, especially in developed countries, through a number of means

including increased tax rates, counter advertising, educational promotions, laws restricting public smoking, and others [6]. These prevention efforts have had a major effect on reducing lung cancer incidence and mortality as illustrated in the U.S. (Figs. 1, 2). Prevention efforts in reducing radon exposure, therapeutic cancer radiation exposure, and others have had some effect, although air pollution efforts have largely failed to date. As industry attempts to addict new youth through vaping and other strategies, new prevention efforts remain a priority.

Early detection efforts focused on sputum cytology and chest x-rays. Unfortunately, routine use of these modalities failed to improve lung cancer detection and survival rates [22–24]. Spiral chest computed tomography (CT) scans were shown to be considerably more sensitive for detecting small nodules [25], and the National Cancer Institute (NCI)-sponsored National Lung Screening Trial randomizing high-risk individuals to annual chest x-ray or CT screening demonstrated that the CT scanning detected more small lesions and led to a 20% reduction in lung cancer mortality [26]. This reduction in lung cancer mortality was confirmed in the large Netherlands–Leuven Longkanker Screenings Onderzoek (NELSON) trial in Europe, which also showed an even larger decrease in lung cancer mortality among females [27]. Multiple guidelines now recommend annual CT screening for high-risk individuals between the ages of 55 and 80 who have smoked for more than 30 pack-years and quit smoking less than 10 years previously [28–30]. The United

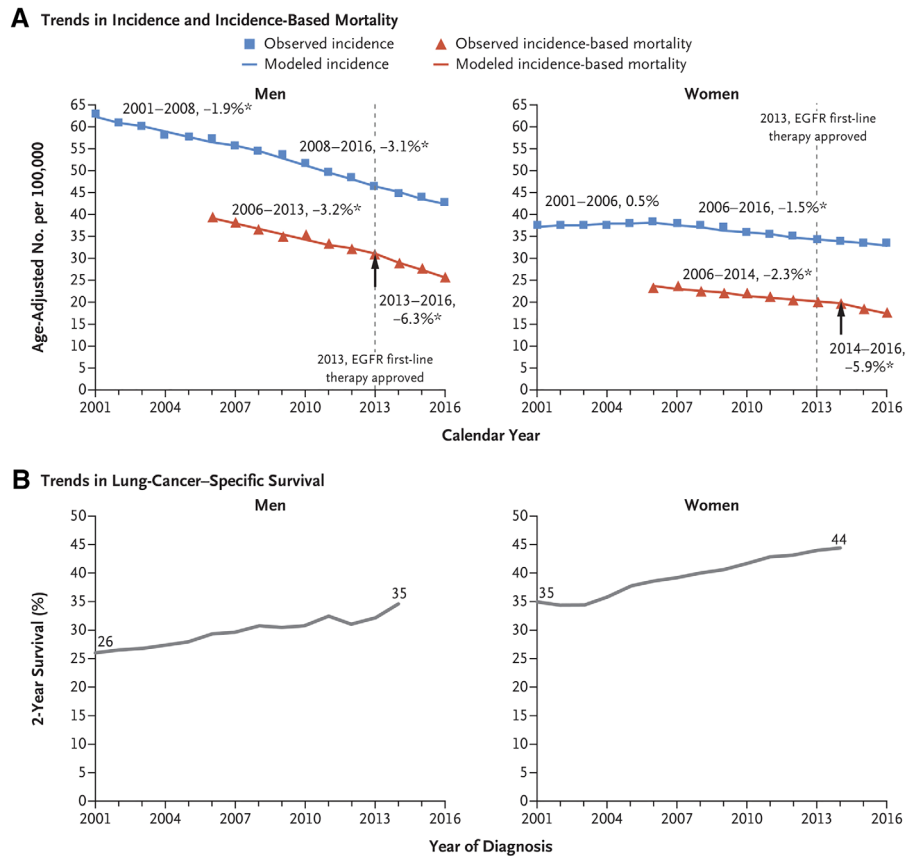


Figure 2. Trends in incidence and incidence-based mortality (**A**) and lung cancer-specific survival (**B**) in men and women in the U.S. [5].

Abbreviation: EGFR, epidermal growth factor receptor.

States Preventive Services Task Force is currently considering revising their screening recommendations by lowering the pack-year threshold for screening to 20 pack-years and reducing the lower limit of the screening age to 50 years old [31]. Many nodules that are detected on chest CT scans are not malignant, and there are CT properties that can identify risk associated with the nodules to determine if biopsies, resection, or continued follow-up scans are the best option. There are several computer-assisted programs using clinical features and CT features to identify risk [32, 33].

Annual chest CT scans are best for detection of peripheral tumors including adenocarcinomas. Mortality from small cell lung cancer was not reduced in the screening studies, and central squamous tumors were less frequently detected. Although not used for routine screening, sputum cytology and bronchoscopy with cytology and biopsy still have a role in early detection [34, 35]. Carcinoma in situ and high-risk dysplasia require serial follow-up. Several systemic approaches including iloprost and immune checkpoint inhibitors may be able to reverse high-risk lesions [36]. Three-dimensional bronchial progenitor cell cultures and genomic analyses may help with future early detection efforts [37, 38].

More recent efforts evaluating molecular changes in circulating tumor DNA, exosomes, and other blood elements have detected tumor-specific alterations in many patients, but their sensitivity is not sufficient for routine early detection protocols at present.

PATHOLOGY AND MOLECULAR PATHOLOGY

Lung cancers are classified according to the International Association for the Study of Lung Cancer (IASLC) pathologic system as adenocarcinomas (with varying subtypes), squamous carcinomas, large cell carcinomas with or without neuroendocrine features, and small cell carcinomas [39–41]. There also mixed tumors such as adenosquamous carcinomas and other rare tumors such as carcinoids. A variety of immunohistochemical markers may be used to help identify the specific histology in difficult cases. Among these are immunohistochemical testing of transcription termination factor 1 (*TTF1*) for adenocarcinomas, p40 and p63 for squamous carcinomas, and neuroendocrine markers for small cell and large cell carcinomas [42, 43].

The discovery that some lung adenocarcinomas have mutations in the epidermal growth factor receptor (*EGFR*) gene in 2004 and that there was a correlation between the presence of these mutations and sensitivity to *EGFR* tyrosine kinase inhibitors (TKIs) created the molecular targeted therapy era and the need to characterize the molecular alterations in individual lung cancers [44–47]. Subsequent studies including the Cancer Genome Atlas studies and others identified a number of recurring oncogene changes caused by mutation, gene fusion, amplification, and copy number changes. Many of these alterations were shown to be drivers of lung cancer growth and could serve as predictive biomarkers for specific TKI therapy [48–50]. Among the

alterations that serve as drivers as of 2020 are *KRAS*, *EGFR*, human epidermal growth receptor 2 (*HER2*), *B-Raf* proto-oncogene, serine/threonine kinase (*BRAF*), and *MET* proto-oncogene (*MET*), receptor tyrosine kinase mutations, *ALK* receptor tyrosine kinase (*ALK*), *ROS* proto-oncogene 1, receptor tyrosine kinase (*ROS1*), ret proto-oncogene (*RET*), and neuregulin 1 (*NRG1*) fusions. The therapeutic implications of these alterations are discussed below.

Pathologists and oncologists must decide whether to look for these alterations in tissue biopsies, blood, or other fluids. In 2020, it is clear that testing for multiple alterations simultaneously is the only practical and efficient way to do this. Next-generation sequencing (NGS) testing of DNA and RNA is the preferred method for tissue testing owing to the multiple types of mutations, fusions, and amplifications [47–50]. There are many commercial and local platforms that are Clinical Laboratory Improvement Amendments approved and test for all alterations for which there is a specific therapy. There also many guidelines that indicate the need for these tests at diagnosis and at the time of progression for those with a driver alteration. At present, guidelines indicate the need for these tests in all advanced lung adenocarcinomas and in other histologies with light or no smoking histories [48–50]. Many institutions now routinely test for these alterations in earlier-stage patients as well. As randomized trials of molecular and immunotherapy approaches are completed in earlier stages, it is likely that this panel testing will become mandatory in earlier stages as well. For clinicians, it is imperative that these tests be conducted as soon as a diagnosis is made so as not to delay therapeutic decisions.

STAGING

The IASLC, Union for International Cancer Control, and American Joint Committee on Cancer staging classifications are updated every 8 years, and we are currently in the eighth edition, which should be used to stage all patients at diagnosis [51]. The details of this tumor node metastasis classification are shown in Figure 3. The clinical stage is based on the results of CT and CT positron emission tomography (PET) scans as well as brain magnetic resonance imaging (MRI) scans that are indicated in all patients at diagnosis. Patients with enlarged and/or PET-positive hilar and mediastinal lymph nodes should have an endobronchial ultrasound procedure with node biopsies or mediastinoscopy prior to resection to complete the staging. Stage IV is now divided into stage IVA and IVB based on whether there is pleural-only disease or metastatic disease in a single site. The 5-year survival rates for stage IA1 (T1A, N0, M0) exceed 90%, and those for stage IA2 and IA3 exceed 80%. These patients are currently excluded from adjuvant and neoadjuvant trials. However, it is possible that immunotherapies could be studied in stage IA2 and IA3.

Treatment of Early-Stage Disease (I–IIIA)

Patients with early-stage disease will most often undergo a surgical resection, so a determination of resectability is usually undertaken consisting of evaluations of pulmonary and cardiac function. Patients with stage I disease (T1a, T1b, T1c, N0, M0) usually undergo resection alone. Resection is most

often lobectomy, but wedge resection, segmentectomy, bilobectomy, and pneumonectomy may be performed depending on size and location. The procedures are most often done by video-assisted thoracoscopic surgery or robotic resection, but conversion to an open thoracotomy occurs in about 10% of cases [52, 53]. Dissection of multiple lymph node stations is always performed.

Cases that are not eligible for surgical resection are most often treated with stereotactic body irradiation (SBRT) [54, 55]. Most recurrences after surgical resection or primary irradiation occur in distant sites, so systemic therapy is usually delivered before (neoadjuvant), after (adjuvant), or before and after (neo and adjuvant) the primary surgery or radiation therapy.

Neoadjuvant Therapy

Neoadjuvant platinum doublet-based chemotherapy was proven to improve survival in patients with resectable stage II and IIIA NSCLC [56]. For patients with an adenocarcinoma histology, the doublet is most often cisplatin combined with pemetrexed or paclitaxel, but vinorelbine and gemcitabine may also be used. For squamous histology, cisplatin is most often combined with paclitaxel, gemcitabine, or vinorelbine. The number of preoperative cycles has varied from two to four. A meta-analysis of neoadjuvant randomized trials showed an overall survival (OS) improvement of 5% at 5 years with a survival hazard ratio (HR) of 0.82 [56]. For patients with NSCLC with a single-station N2 involvement (stage IIIA), a few studies showed a survival advantage for adding nodal irradiation to the preoperative chemotherapy [57]. After neoadjuvant chemotherapy, at the time of surgery, the pathologic complete response rate was very low (<5%) whereas the major pathologic response rate (<10% viable tumor cells in the resection specimen) was 20% [58].

More recently, checkpoint immunotherapeutic antibodies alone or with chemotherapy have been studied in the neoadjuvant setting [58]. Table 1 summarizes results of trials where a single-agent checkpoint inhibitor produced a major pathologic response (MPR) rate of 27% with pathologic complete response (CR) rates averaging 9% [59–63]. Pathologic response rates have been higher in the single-arm trials using combined chemotherapy with checkpoint inhibitor antibodies [64–67]. Although patient numbers are small, MPR rates in these trials averaged 61% and pathologic CR rates averaged 27%. Long-term survival has not been reported in any of these trials but is expected to be higher than that achieved with chemotherapy alone. For that reason, there are multiple randomized phase III trials ongoing that compare neoadjuvant chemotherapy alone with combined chemoimmunotherapy (Table 2) [68]. After surgery, all of these neoadjuvant chemoimmunotherapy trials discontinue the chemotherapy but continue the immunotherapy for various periods, which is usually 1 year. Patients with driver molecular alterations are generally excluded from these trials because the response rates to immunotherapy are often lower in these patients. Recently, neoadjuvant studies of various molecular TKIs have been instituted, but there are few results to date.

A recent cardiovascular prevention trial with an anti-interleukin-1 β antibody, canakinumab, found a marked decrease in

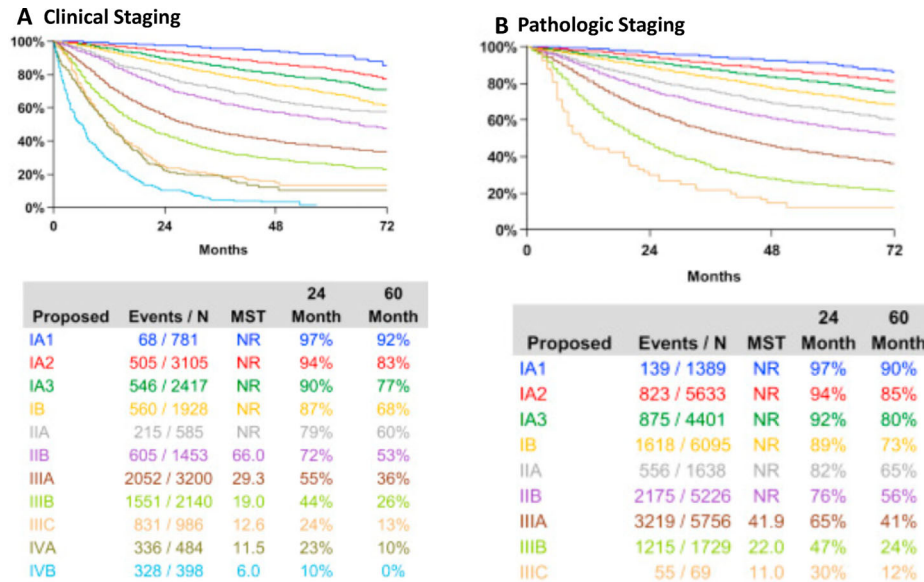


Figure 3. Stage groupings and survival in the eighth edition TNM staging classification [51]. Abbreviations: MST, median survival time; N, number; NR, not reached.

the incidence of lung cancer in subjects randomized to canakinumab [69, 70]. This trial raises many questions including whether this is a tumor microenvironment effect or a direct effect on malignant cells [70]. Based on these results and questions, there is an ongoing phase II randomized neoadjuvant trial comparing single-agent pembrolizumab, single-agent canakinumab, and the combination (Table 2).

The IASLC and Food and Drug Administration held a joint conference on neoadjuvant therapy that concluded that there are insufficient data at present to conclude that pathologic response rate correlates with overall survival or cure rates. However, it is hoped that a meta-analysis of these ongoing randomized trials could establish pathologic response as a proven surrogate endpoint [71]. A key aspect of this effort will be uniform pathologic assessments. The IASLC has published recommendations for scoring pathologic response and is undertaking a comparative review [72].

Adjuvant Therapy After Surgical Resection

For patients with resected stage II and IIIA NSCLC, postoperative platinum doublet-based chemotherapy was shown to improve 5-year survival rates by about 5%, which was associated with a hazard ratio of 0.82 in a meta-analysis of these trials [73, 74]. No OS benefit was seen in patients with tumors <3 cm without nodal involvement. These trials used several different cisplatin-based combinations. The recent Eastern Cooperative Oncology Group (ECOG) 1505 randomized trial allowed four different drugs to be added to cisplatin with randomization to the addition of bevacizumab or placebo. Overall, bevacizumab did not improve outcomes [75]. Although not a primary endpoint, there were no differences in outcomes between platinum doublets. An important aspect of this trial was the excellent survival in all arms, which exceeded 50% at 5 years. These survival results were better than the outcomes previously reported in the meta-

analyses. This is likely due at least in part to better staging through the routine use of PET and brain MRI scans.

Most adjuvant chemotherapy trials planned on four cycles of chemotherapy, but subsequent analyses did not find a difference in survival between those receiving three or four cycles. There was no benefit of postoperative radiation therapy, with the possible exception of N2 disease, where some benefit was observed in most meta-analyses of postoperative radiation trials [76, 77]. However, the recently presented randomized phase III LUNG ART trial suggested no improvement in disease-free survival (DFS) or OS for postoperative radiation in patients with pathologically identified N2 disease [78].

Based on data showing superiority of combined chemo/immunotherapy over chemotherapy alone in stage IV disease, large, randomized studies with the addition of immunotherapy to chemotherapy in the postoperative setting are being conducted. Table 2 shows these ongoing trials, although the results of these trials have not been reported yet [68]. The NCI's Adjuvant Nivolumab in Resected Lung Cancers (ANVIL) trial compares nivolumab with chemotherapy, whereas most other trials compare chemoimmunotherapy with chemotherapy alone. These trials have largely excluded patients with actionable molecular alterations.

Adjuvant trials in patients with *EGFR* mutations using various *EGFR* TKIs have been reported while others are ongoing. The early phase II, nonrandomized SELECT trial had a DFS endpoint based on historical controls treated with chemotherapy [79]. The study reported a 90% DFS at 2 years, which exceeded the historical benchmark. The EVAN trial was a randomized phase II study that compared 2 years of erlotinib with vinorelbine/cisplatin (VP) chemotherapy in patients with surgically resected stage IIIA NSCLC with *EGFR* mutation [80]. The ADJUVANT trial was a randomized phase III study that compared 2 years of adjuvant gefitinib with VP chemotherapy in patients with surgically resected stage II to IIIA (N1–N2)

Table 1. Results of neoadjuvant immunotherapy and combined chemotherapy/immunotherapy trials in resectable non-small cell lung cancer

| Rx | n | mPR, n (%) | pCR, n (%) | Ref |
|-------------------------------------|-----|------------|-------------|-----|
| Nivolumab | 21 | 9 (43) | 3 | 60 |
| Nivolumab or nivolumab + ipilimumab | 44 | 11/41 (25) | 8 (18) | 61 |
| Atezolizumab | 82 | 15 (18) | 4 (5) | 62 |
| Sintilimab | 22 | 10 (45) | 4 (18) | 63 |
| Pembrolizumab | 10 | 4 (40) | 0 | 64 |
| Total I/O alone | 179 | 49 (27) | 19/176 (11) | |
| Nivolumab + CT | 30 | 24 (80) | 13 (60) | 65 |
| Atezolizumab + CT | 30 | 17 (57) | 10 (33) | 66 |
| Nivolumab + CT | 13 | 11 (85) | 5 (38) | 67 |
| Durvalumab + CT | 67 | 33 (60) | 10 (18) | 68 |
| Total I/O + CT | 140 | 85 (61) | 38 (27) | |

Abbreviations: CT, chemotherapy; I/O, immunotherapeutic; mPR, major pathologic response; n, number; NR, not reported; pCR, pathologic complete response; Ref, reference; Rx, treatment.

Table 2. Ongoing clinical trials with neoadjuvant and adjuvant immune checkpoint inhibitors with or without chemotherapy adopted from neoadjuvant and adjuvant trials

| Trial | NCT # | Therapy | Stages | n | Phase | Primary endpoint |
|--------------------|----------|--|-----------------|-------|-------|---|
| Neoadjuvant | | | | | | |
| CANOPY N | 03968419 | Canakinumab or pembrolizumab (200 mg) or canakinumab + pembrolizumab × 2 cycles → S | IB–IIIA | 110 | II | MPR |
| KEYNOTE 617 | 03425643 | CT + pembrolizumab (200 mg) / placebo × 4 cycles → S → pembrolizumab / placebo × 13 cycles | IIB–IIIA | 786 | III | EFS, OS |
| CheckMate 816 | 02998528 | CT + nivolumab (360 mg) × 3 cycles → S vs. CT × 3 cycles → S | IB–IIIA | 350 | III | EFS, MPR |
| IMpower 030 | 03456063 | CT + atezolizumab (1200 mg) / placebo × 4 cycles → S → atezolizumab / placebo × 16 cycles | II–IIIB (cT3N2) | 374 | III | MPR |
| AEGEAN | 03800134 | CT + durvalumab (1,500 mg) / placebo Q3W × 4 cycles → S → durvalumab / placebo Q4W × 12 cycles | IIA–IIIB | 300 | III | MPR |
| Adjuvant | | | | | | |
| PEARLS | 02504372 | Pembrolizumab vs. placebo | IB–IIIA | 1,080 | III | DFS |
| BR31 | 02273375 | Durvalumab vs. placebo | IB–IIIA | 1,360 | III | DFS in PD-L1+ and all |
| ANVIL | 02595944 | Nivolumab vs. observation | IB–IIIA | 903 | III | DFS and OS |
| Impower 010 | 02486718 | Atezolizumab vs. observation | IB–IIIA | 1,280 | III | DFS in II–IIIA, DFS in PD-L1+, DFS in ITT |
| CANOPY-A | 03447769 | Canakinumab vs. observation | IB–IIIA | 1,500 | III | DFS |

Abbreviations: CT, chemotherapy; DFS, disease-free survival; EFS, event free survival; ITT, intention to treat; MPR, major pathologic response; n, number; OS, overall survival; PD-L1, programmed death-ligand 1; Q3W, every 3 weeks; Q4W, every 4 weeks; S, surgery.

NSCLC with *EGFR* mutation [81]. Both trials demonstrated significantly longer DFS in favor of adjuvant *EGFR*-TKI monotherapy compared with VP chemotherapy. However, the DFS curves came together at 3 years and there were no OS differences.

The RADIANT randomized phase III trial studied the role of adjuvant erlotinib after surgery and chemotherapy in patients with and without *EGFR* mutations [82]. Patients were randomized to erlotinib or placebo for 2 years. There was a significant prolongation of DFS in the patients with

EGFR mutations who received erlotinib. However, OS did not differ between therapies in the total population or in the *EGFR* mutant patients. Patients who relapsed were treated with erlotinib with high response rates. As expected, just over half of the patients in both arms had not recurred, and clearly, patients cured by surgery and chemotherapy will have toxicity but no benefit from the added TKI. Unfortunately, it is currently not possible to know who is cured and who is not.

The randomized phase III trial termed CTONG 114 randomized *EGFR* mutant patients following surgical resection to receive gefitinib or chemotherapy [83]. As in the RADIANT trial, there was improved DFS in the TKI group; however, there was no difference in OS. The likely explanation for these results is that just as complete responses are uncommon in advanced disease, there is sufficient cell kill to prolong recurrence but insufficient cell kill to lead to cure.

Most recently, early results of the ADAURA trial were presented and published [84, 85]. In this trial, postsurgical patients with *EGFR* mutations were randomized to receive “standard therapy” plus either placebo or osimertinib for 3 years after standard therapy. “Standard therapy” could include adjuvant chemotherapy, but radiation was not allowed even in stage III disease. There was a highly statistically significant prolongation of DFS. OS was not different, although the trial had very short follow-up. The DFS in the control group was shorter than that observed in prior chemotherapy trials such as ECOG 1505, perhaps because many patients in control group did not receive chemotherapy. Long-term survival results of this trial are eagerly awaited.

There are several other ongoing randomized trials whose results have not been reported including the NCI cooperative group ALCHEMIST trial that included subgroups with *EGFR* mutation who were randomized to erlotinib or placebo and those with *ALK* mutations who were randomized to crizotinib or placebo after surgery and standard chemotherapy [86]. There are other ongoing randomized trials evaluating other *EGFR* TKIs in the adjuvant setting.

Combined Modality Therapy for Unresectable Stage III Disease

Many years ago, randomized trials demonstrated that concurrent platinum doublet chemotherapy and chest radiotherapy provided longer survival than either modality delivered alone or sequentially [87]. Several different platinum doublet combinations appeared to give equivalent results, and additional chemotherapy after completion of the radiation did not improve outcomes [88].

More recent studies evaluated the optimal dose of chest radiation, comparing 60 Gy with 74 Gy. Patients receiving the 60 Gy schedule had superior outcomes compared with the higher dose [89]. This was attributed, at least in part, to increased cardiac toxicity of the higher dose. Other trials using higher radiation doses with newer techniques or using proton beam therapy are ongoing [90].

The results of trials in patients with stage IV disease showing benefit for checkpoint inhibitor immunotherapy led to the randomized PACIFIC trial that compared concurrent chemoradiation therapy followed by up to 1 year of placebo or durvalumab immunotherapy [91]. Patients who

did not progress after the initial chemoradiation and who did not have pneumonitis were randomized. The trial demonstrated a highly statistically significant improvement in progression-free survival (PFS) and OS in patients randomized to maintenance durvalumab. The study included patients with any programmed death-ligand 1 (PD-L1) levels. At the protocol-defined cutoffs, there was some benefit in all patients, but a post hoc evaluation did not find benefit in patients with no PD-L1 expression. At present, this regimen can be considered as a standard, although ongoing trials are evaluating the earlier start of the immunotherapy before or concurrent with the chemoradiotherapy.

There is mounting evidence that SBRT to oligometastatic sites can improve survival when used after initial response to TKIs for those with molecular drivers and after response to chemioimmunotherapy for those without molecular drivers [92, 93]. There are several ongoing trials to address this question.

Therapy of Stage IV NSCLC

Chemotherapy

Chemotherapy has been the backbone of therapy for patients with stage IV lung cancer for many decades [94]. Many years ago, meta-analyses of randomized trials of platinum-based doublet chemotherapy showed that the doublets improved survival compared with single-agent chemotherapy, including elderly patients and patients with performance status 2 [95, 96]. Later cooperative group trials showed equivalent results with several different platinum doublets with either cisplatin or carboplatin combined with vinorelbine, paclitaxel, docetaxel, or gemcitabine [97–99]. Still other trials showed that pemetrexed-based platinum doublets also produced equivalent survival with less toxicity in those with nonsquamous carcinomas [100]. Shortly after platinum doublets became standard, the *EGFR* and the vascular endothelial growth factor (VEGF) receptor became new targets for agents to add to platinum doublets. Anti-*EGFR* monoclonal antibodies such as cetuximab and necitumumab produced low response rates and little or no overall benefit when added to chemotherapy in the absence of biomarker selection. And although there was some evidence that biomarkers such as gene amplification could select patients most likely to benefit, use of these agents was largely abandoned [101–105].

Results with anti-VEGF agents were more promising. The anti-VEGF antibody bevacizumab showed promise, but early studies demonstrated bleeding toxicities in patients with central squamous cancers. Thus, subsequent bevacizumab trials were limited to nonsquamous histology. Randomized trials in these nonsquamous populations demonstrated that the addition of bevacizumab to a taxane/platinum doublet improved survival [106]. Trials in the nonsquamous population showed that pemetrexed/platinum combinations produced similar outcomes as taxane-based combinations and that there was survival benefit for maintenance pemetrexed [107]. This observation raised the question of whether maintenance pemetrexed, bevacizumab, or both would be optimal after a pemetrexed/carboplatin bevacizumab induction. Several comparative randomized trials showed no additional benefit of maintenance with combined pemetrexed and bevacizumab

over either alone [108–111]. Recent guidelines define optimal histology-based platinum doublets with maintenance in advanced lung cancer [112].

Because of the considerable toxicity of doublet chemotherapy, it is generally limited to patients with performance status of 0–1. Analyses of U.S. Surveillance, Epidemiology, and End Results data suggest that as many as 40% of patients with newly diagnosed lung cancer are never referred to an oncologist and receive no therapy, presumably because of poor performance status and comorbid disease [113]. As our supportive care measures have improved and as new therapies described below have fewer toxicities, it will be increasingly important to educate primary care physicians and change attitudes so that all patients have access to the best therapies.

Although platinum doublet chemotherapy remains a major part of first-line therapy in most patients, an increasing number may receive TKIs or immunotherapies alone in the first line. When these patients progress, a platinum doublet remains the major therapeutic choice if the performance status is adequate. When patients progress on a platinum doublet chemotherapy and immunotherapy or a TKI when indicated, second- and third-line single-agent chemotherapy remains the major treatment option.

Molecular Therapy

Early in the 21st century, there was increasing evidence that alterations in the *HER* family of receptors played a role in the pathogenesis of lung and other cancers. Thus, pharmaceutical companies developed TKIs for these receptors and their intracellular adenosine triphosphate (ATP) binding pockets. Early TKIs such as gefitinib and erlotinib produced low response rates (10% or so) in unselected patients, but these responses were often dramatic and long lasting [114]. Early studies suggested that high receptor expression or *EGFR* gene amplification were marginally useful predictive biomarkers [115]. A phase III trial comparing erlotinib with chemotherapy in the second- or third-line setting demonstrated erlotinib was superior to chemotherapy in overall response rate (ORR) and OS, but the ORR was only 9% [116]. The best predictive marker in this trial was not established [117]. Then, in 2004, three groups identified the fact that activating mutations in the *EGFR* gene predicted TKI benefit and that these *EGFR* TKIs preferentially bound to the mutated *EGFR* ATP binding pocket [44–46]. This finding revolutionized lung cancer therapy. These results led to a number of trials randomizing *EGFR* mutant patients to receive an *EGFR* TKI or chemotherapy (Table 3).

Recognizing the critical role of *EGFR* mutations in *EGFR* TKI sensitivity, the IPASS study randomized patients to receive first-line carboplatin/paclitaxel chemotherapy or the first-generation *EGFR* TKI gefitinib [118]. Those patients with activating *EGFR* mutations treated with gefitinib had higher response rates, longer PFS, reduced toxicity, and superior quality of life compared with those receiving first-line chemotherapy. The OS, however, was equivalent in part because second-line TKI therapy was also effective. The other randomized trials comparing gefitinib, erlotinib, afatinib, and icotinib with chemotherapy showed similar results, with the TKI producing higher response rates, longer PFS, and reduced toxicity

compared with chemotherapy, leading to guidelines recommending first-line TKI for *EGFR* mutant patients [118–121, 123, 125–127, 129] (Table 3).

As was seen with the *EGFR* TKIs, several randomized trials showed that *ALK* TKIs were superior to platinum doublet chemotherapy in patients with *ALK* fusions [131–133]. Soon, other activating genetic mutations including *BRAF*, *HER2*, and *MET* and genetic activating fusions including *ALK*, *ROS1*, neurotrophic receptor tyrosine kinase (*NTRK*) and *RET* fusions were identified. Specific TKIs were developed and produced similar high response rates, long PFS, and low toxicity rates in patients with these alterations. A group called the Lung Cancer Mutation Consortium showed that molecular studies could easily identify these patients and that those treated with gene-specific TKIs lived longer than those that did not receive a gene-specific TKI [130].

First-generation TKIs had poor central nervous system (CNS) penetration, and progression in the CNS was frequent. This observation led to the development of second- and third-generation TKIs with better CNS penetration. First-line randomized trials comparing these newer agents with platinum doublet therapy also demonstrated superiority for the TKI [131–133]. Other randomized trials compared first-line use of second- or third-generation TKIs with first generation TKIs. These trials demonstrated superiority of the newer agents in PFS, in reduced CNS metastases and sometimes in OS [134–140]. Like the studies showing that *EGFR* TKIs produced higher response rates, longer PFS, and decreased toxicity compared with platinum doublet chemotherapy, randomized trials showed that *ALK* TKIs were superior to platinum chemotherapy [131–133].

The frequency of activating genetic alterations in advanced NSCLC is illustrated in Figure 4 [50]. The frequency of these alterations is higher in adenocarcinomas and in light or never-smokers, and patients with these characteristics should always be tested prior to institution of therapy. However, patients with other histologies, especially light or never-smokers, should also be tested. There are some unique characteristics of patients with each molecular abnormality, but these are not sufficiently specific to treat without molecular characterization [15, 141–144]. Secondary mutations may be present as well. The most frequent of these is a mutation in *p53* that may associate with a slightly worse prognosis [144]. Therapy should, in general, not start until the results of these tests are known [145]. However, patients who require repeat biopsy or are too ill to wait may receive first-line chemotherapy and switch to a TKI if actionable alterations are subsequently found. However, sequential therapy can increase toxicity if it includes immunotherapy and a TKI [146].

Recently, several NGS panels conducted on blood samples have been approved, and these results are generally available in shorter time frames (5–14 days) [147–149]. Although these tests are not as sensitive as tissue tests, they are highly specific, so TKI therapy can be instituted when positive results are received.

Because first-line therapy with a TKI is standard and the best option, routine NGS testing for multiple genetic alterations is now recommended in multiple guidelines with first-line use of a TKI when actionable alterations are found [48,

Table 3. Phase III randomized trials of first-line EGFR TKI versus platinum doublet chemotherapy in patients with EGFR mutant non-small cell lung cancer

| First author | Study | TKI | # Pts | ORR % | Median PFS (mo) | Median OS (mo) |
|-----------------------------------|--------------|-----------|-------|----------|-----------------|----------------|
| Mok [118] | IPASS | Gefitinib | 261 | 71 vs 47 | 9.8 vs 6.4 | 21.6 vs. 21.9 |
| Maemondo [119] Inoue [120] | NEJGSG002 | Gefitinib | 228 | 73 vs 31 | 10.8 vs 5.4 | 27.7 vs 26.6 |
| Mitsudomi [121] Yoshioka [122] | WJTOG3405 | Gefitinib | 177 | 62 vs 32 | 9.2 vs 6.3 | 34.9 vs 37.3 |
| Zhou [123] Zhou [124] | Optimal | Erlotinib | 154 | 83 vs 36 | 13.1 vs 4.6 | 22.6 vs. 28.8 |
| Han [125] | First Signal | Gefitinib | 309 | 55 vs 46 | 5.8 vs 6.4 | 22.3 vs 22.9 |
| Rosell [126] | EURTAC | Erlotinib | 154 | 58 vs 15 | 9.7 vs 5.2 | 19.3 vs. 19.5 |
| Sequist [127] Yang [128] | LUX-Lung 3 | Afatinib | 345 | 56 vs 23 | 11.1 vs 6.9 | 28.2 vs 28.2 |
| Wu [129] | LUX-Lung 6 | Afatinib | 364 | 67 vs 23 | 11.0 vs 5.6 | 23.6 vs 23.5 |

Abbreviations: EGFR, epidermal growth factor receptor; EURTAC, European randomized trial of tarceva versus chemotherapy; First Signal, first-line single-agent iressa versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung; IPASS, Iressa Pan-Asia study; LUX-Lung 3, phase III trial of afatinib vs. pemetrexed/cisplatin in locally advanced or metastatic patients; LUX-Lung 6, equivalent to LUX-Lung 3 but with gemcitabine/cisplatin chemotherapy; NEJGSG002, North East Japan Gefitinib Study Group 002 trial; Optimal, erlotinib versus standard chemotherapy in the first-line treatment of patients with advanced *EGFR* mutation–positive non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; WJTOG, West Japan Thoracic Oncology Group.

150, 151]. Optimal NGS testing is conducted on tissue DNA and RNA because of the large number and types of alterations. A list of the molecular alterations associated with approved TKIs and other molecular alterations for which other TKIs are under investigation is shown in Table 4. Approved TKIs for *EGFR*, *BRAF*, and *MET* mutations and *ALK*, *ROS1*, *RET*, and *TRK* fusions are best given in the first line [134–139, 152–162].

The most frequent molecular alteration is a *KRAS* mutation. At present, specific TKIs are only available for *KRAS* G12C mutations, and these are investigational only [163, 164]. Other *KRAS*-specific drugs as well as drug combinations are under investigation. In patients with *KRAS* mutations, secondary mutations including *p53* mutations, serine/threonine kinase 11 mutations, *KEAP 1* mutations, and others may influence the response to different therapies [165]. At present, these secondary mutations do not alter therapy selection. Studies of combinations of these *KRAS* G12C inhibitors with SHP2 inhibitors, MEK inhibitors checkpoint inhibitors, CDK4/6 inhibitors and other agents are also in progress. There are several investigational TKIs that are under study for atypical *EGFR* and *HER2* insertional mutations, but none are approved for these mutations to date [166].

Two antibody drug conjugates have been studied in patients with NSCLC with *HER2* mutations: trastuzumab emtansine [167] and trastuzumab deruxtecan [168]. The latter produced an objective response rate of 63% with a median PFS of 14 months. These results are the best reported to date for *HER2* mutations in lung cancer, and additional trials are ongoing. There are several agents under study for *NRG1* fusions including both TKIs and monoclonal antibodies, but none are approved [169]. It is likely that other activating and recurring mutations may be found in the future, but these are likely to be quite rare in frequency.

In spite of the effectiveness of specific TKI therapy, these drugs rarely induce complete remissions and do not cure stage IV disease. Although several logs of cell kill may occur, the vast majority of cells are not killed by the treatments

and undergo a senescent phase where they neither grow nor die. Ultimately, they develop resistance to the TKI and progression occurs. The etiology of the progression has been studied in detail, and there are many similarities across different TKIs. Secondary mutations in the affected oncogene that create changes in the structure of the ATP binding pocket and decrease the affinity of TKI binding are a frequent cause of resistance [170–174]. The first example of this type of resistance was the T790M *EGFR* mutation that occurred in many patients treated with the first-generation *EGFR* TKIs gefitinib and erlotinib [171–173]. A third-generation *EGFR* TKI, osimertinib, is able to bind to the tumor cells with this secondary mutation and produce ORR >50% with median PFS around 10 months with superior outcomes compared with chemotherapy [171]. Patients treated with osimertinib in the second line frequently develop another resistance mutation, *C797S* preventing osimertinib binding [172, 173]. To date, no TKI has been approved that can bind to this *C797S* solvent front mutation. In a similar manner, resistance mutations occur with other oncogenes and new TKIs may bind to these resistance mutations and produce high response rates [170, 174–176]. A good example of this is the G1202R *ALK* resistance mutation that occurs in many patients treated with crizotinib or alectinib. Lorlatinib has excellent binding to this resistance mutation, produces high response rates in patients with G1202 *ALK* resistance mutations, and is approved for use in the setting [139].

Another frequent cause of resistance is the emergence of clones driven by other genetic driver alterations. For example, patients with *EGFR* mutations treated with osimertinib may develop mutations in *BRAF*, *KRAS* or *MET*, or *MET* amplification [175]. There are well-described cases where treatment with the appropriate second TKI (and osimertinib) produce responses in these instances. Patients with other oncogene drivers may also progress with new genetic alterations sensitive to inhibitors of the new alteration [174–177]. Histologic transformation to small cell lung cancer is another resistance mechanism [178]. Most often the transformed

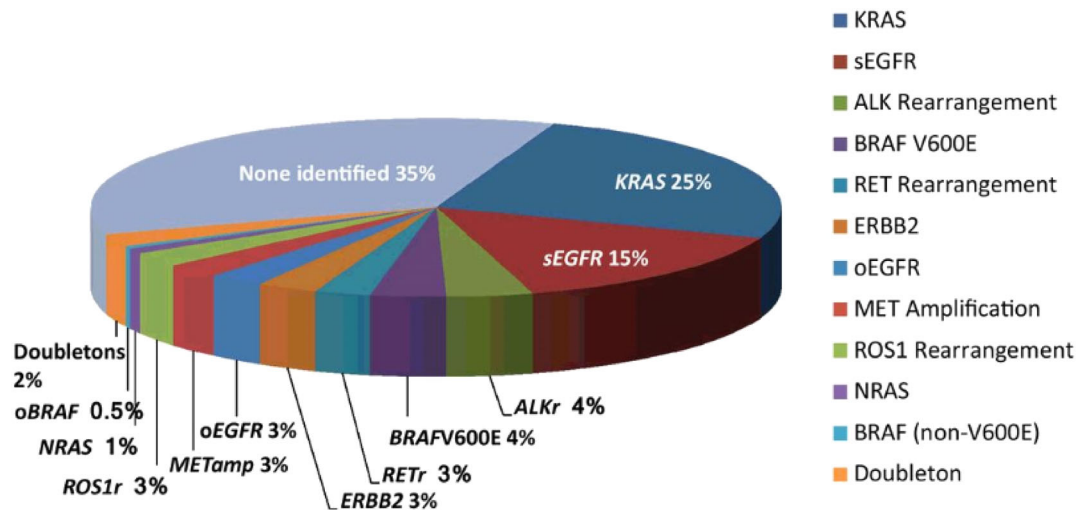


Figure 4. Frequency of various genetic alterations in advanced non-small cell lung cancer [50]. Abbreviation: EGFR, epidermal growth factor receptor.

cells have p53 and Rb mutations and respond to the etoposide/carboplatin combination [179].

It is well known that patients with activating genetic alterations have a high propensity for brain metastases. These metastases may occur in about 25% of patients at diagnosis, with as many as another 25% developing new metastases in each subsequent year [136–139, 180, 181]. Most of the first-generation TKIs such as erlotinib and gefitinib for *EGFR* mutations and crizotinib for *ALK* fusions do not cross the blood–brain barrier in high enough concentrations to inhibit these CNS metastases. Second- and third-generation TKIs such as the EGFR TKI osimertinib or the ALK TKIs alectinib, brigatinib, or lorlatinib are better able to cross the blood–brain barrier. These agents frequently treat patients with brain metastases and prevent the development of brain metastases in those without brain metastases [136–139]. These newer agents are thus usually preferred to be given first owing to a combination of longer PFS and prevention of brain metastases. Many of the newer TKIs for other genetic alterations such as lorlatinib or repotrectinib for *ROS1* fusions [157, 158], seliperatinib or pralsetinib for *RET* fusions [159, 160], entrectinib for *ROS1* and *NTRK* fusions [161], larotrectinib for *NTRK* fusions [156], and capmatinib [154] or tepotinib [155] for *MET* alterations cross the blood–brain barrier and can be used to treat and prevent brain metastases. These TKIs with or without stereotactic brain radiation serve as an alternatives to whole brain radiotherapy in patients with driver alterations who develop brain metastases [182].

It is unlikely that single-agent TKIs will remain the primary first-line therapy indefinitely, as CRs are rare and resistance is inevitable. What is needed are rational combinations that can prevent or treat the inevitable senescence that accompanies early treatment with any TKI. Early combination studies focused on the addition of VEGF receptor inhibitors or combination chemotherapy to EGFR TKI therapy. The addition of bevacizumab or ramucirumab to first-generation EGFR TKIs showed PFS benefit, but any advantage in OS benefit was less certain [183,

184]. It is also not clear that these results would be superior to those produced by osimertinib alone, so new randomized trials comparing osimertinib with the combination of osimertinib and bevacizumab or ramucirumab are ongoing. Similarly, chemotherapy added to first-generation EGFR TKIs showed PFS and sometimes OS benefit for the combination [185, 186]. Newer studies of the combination of third-generation agents and chemotherapy are ongoing.

Although rational combinations are urgently needed, it is not known whether the mechanisms preventing cell death from TKIs are similar or different across different genetic alterations. Thus, it is not clear whether new rational combinations will be the same or different across different driver alterations. One way to determine whether these mechanisms are the same or different is to conduct neoadjuvant trials that collect tissues at diagnosis and just prior to surgery after treatment for 6–8 weeks. RNA sequencing and other analyses of the tissue changes may allow for identification of alterations associated with senescence. Several groups are attempting to conduct such trials on patients with several different genetic alterations and several companies are conducting neoadjuvant trials with specific TKIs to answer this question [187].

Immunotherapy

The development of immunologic therapies has been a priority for many years. Early studies focused on soluble factors such as thymosin and interferons with little success [188]. More recent vaccine studies of Bacillus Calmette—Guérin and then other vaccines failed to show improved survival [188, 189]. After certain checkpoint inhibitors were shown to produce responses in experimental animals and melanomas, the Cytotoxic T-lymphocyte antigen 4 inhibitor ipilimumab was studied in both small cell and non-small cell lung cancers [189, 190]. Unfortunately, single-agent ipilimumab failed to improve survival alone or combined with platinum doublet chemotherapy.

Table 4. TKIs approved and under investigation for various genetic driver alterations in non-small cell lung cancer in 2020

| Oncogene driver | Approved agents | Investigational agents |
|--|---|---|
| EGFR | Gefitinib, erlotinib ^a , afatinib, dacomitinib ^b , osimertinib ^c | EA1045, JND3229 |
| EGFR exon 20 insertion Uncommon EGFR mutations, e.g., G719X, L861X, S7681V | Afatinib | Mobocertinib, TAS6417, BDTX-189, DS2087B, CLN081, osimertinib ^d |
| ALK | Crizotinib ^a , certitinib, alectinib, brigatinib, lorlatinib ^b | Ensartinib ^b |
| ROS1 | Crizotinib ^a , certinib ^b , entrectinib ^c | Repotrectinib, lorlatinib ^d , taletrectinib |
| RET | Selpercatinib ^b , pralsetinib ^b | Brigatinib ^d , ensartinib ^b |
| NTRK | Larotrectinib ^b , entrectinib ^b | Taletrectinib |
| MET | Capmatinib | Crizotinib ^d , tepotinib, savolitinib |
| BRAF V600E | Dabrafenib plus trametinib | Encorafenib |
| KRAS G12C | None | AMG 510, MRTX 849 |
| HER2 exon 20 insertions | None | Trastuzumab emtansine ^d trastuzumab deruxtecan ^d mobocertinib, TAS6417, BDTX-189, DS2087B, DZD9008, osimertinib ^d |
| NRG1 fusions | None | tarloxotinib, HER3 antibodies |

^aFirst-generation TKI with poor CNS penetration.

^bSecond-generation TKI with good CNS penetration.

^cThird-generation TKI with good CNS penetration, leads to resistance mutations like C797s.

^dApproved for other indications.

^eVandetanib, cabozantinib, and lenvatinib are multi-TKIs approved in other indications.

Abbreviations: CNS, central nervous system; EGFR, epidermal growth factor receptor; HER, human epidermal growth receptor; TKI, tyrosine kinase inhibitor.

Checkpoint Inhibitors in Second- and/or Third-Line Therapy

Exciting results in melanoma with programmed death receptor 1 (PD-1) checkpoint inhibitors such as nivolumab and pembrolizumab led to trials in lung cancer that initially evaluated their effectiveness in the second-line-or-later setting [193]. Various biomarkers were also evaluated for their predictive value, most often evaluation of the target PD-L1 protein expression. These early studies of PD-1 and PD-L1 monoclonal antibodies showed activity leading to randomized studies in the second- and/or third-line setting comparing these antibodies with chemotherapy. In these trials, pembrolizumab, nivolumab, durvalumab, and atezolizumab were all shown to be superior to chemotherapy in ORR, PFS, and OS [193–203].

Predictive Biomarkers

The early pembrolizumab trials used the anti-PD-L1 22C3 antibody as a biomarker and reported that higher expression levels correlated with higher response rates [194]. The investigators in these studies set cutoff levels of PD-L1 expression of 0, 1%–49%, and ≥50%, demonstrating higher response rates with higher expression levels. Long-term follow-up of these trials also showed that survival was related to the fraction of cells expressing the PD-L1 protein, which was called the tumor proportion score (TPS). Patients with high TPS scores (≥50) had longer OS than patients with lower scores, and for the highest levels, 5-year OS rates were around 30% after treatment in the first, second, or later lines of therapy [194].

These early immunotherapy studies used a variety of anti-PD-L1 antibodies and different cutoff values, but there was a relationship between PD-L1 expression and outcome

in all of these studies. The Blueprint study compared the performance and interagreement of these antibodies [204, 205]. There was a good agreement between assayed tumor PD-L1 expression for three of the antibodies (22C3, 28-8, S263), although one antibody (SP142) had a lower sensitivity. In the studies using SP142, both tumor cells and inflammatory cells were scored for expression and then were grouped with high tumor (TC) or inflammatory cell (IC) scores of 0, 1, 2, or 3. Higher scores correlated with higher ORR and longer PFS and OS [198–200]. Because subsequent randomized trials first established PD-L1 biomarker cutoffs with the 22C3 antibody, it has been the most frequently used predictive antibody and is approved for this use. However, subsequent comparative analyses demonstrated that there was good concordance between the 22C3 and SP263 assays and that both correlated with response to checkpoint inhibitors [206]. Objective responses are concentrated in, but not exclusive to, patients with high TPS, and not all patients with high TPS experience a response to immunotherapy. Thus, an ongoing effort is working to identify better predictive immunology biomarkers. Nevertheless, the clinical trials described below show the value of therapy selection based on TPS score. Routine assessment of TPS score is therefore recommended in all patients with metastatic NSCLC according to most clinical guidelines [112].

One potential biomarker for immunotherapy response lies within the tumor genome and the number of mutations it possesses. In theory, more mutations would result in a tumor expressing neoantigens that may be more readily recognized and eliminated by effector T cells in patients receiving immunotherapy. Several groups began to estimate neoantigen burden through tumor mutation burden (TMB)

using whole genome or whole exome sequencing [207]. Several studies evaluating TMB using whole exome sequencing demonstrated a correlation between the number of mutations and outcome from checkpoint inhibitors. Subsequent studies using smaller numbers of genes sequenced in tissue and blood showed some but inconsistent correlations with varying cutoffs [208]. Some of these studies indicated that the markers might be more prognostic than predictive [209]. To date, the role of TMB as a biomarker for immunotherapy response has not been established. This in part may be due to the heterogeneity in platforms used to quantify TMB and the variable cutoffs used to define TMB-low versus -high patients. Additionally, many of the mutations analyzed are not translated into proteins, and not all mutations result in neoantigens that ultimately activate the patient's T-cell repertoires [210]. Ongoing studies are working to refine TMB and potential neoantigen expression, but none are ready for routine use.

Furthermore, preclinical and early translational studies suggest that immune infiltration within the tumor microenvironment and systemic immunity may also influence patient responsiveness to immunotherapy [211]. Other areas of investigation include changes in levels of circulating tumor DNA and the role of the microbiome as biomarkers for response to immunotherapy. How these potential markers compare with PD-L1 or may be incorporated into current clinical care are unknown and remain investigational.

First-Line Immune Therapy for Patients with High PD-L1 (TPS \geq 50%)

Single-Agent Checkpoint Inhibitor Versus Chemotherapy

Once the value of pembrolizumab in the refractory setting was established and there was a known relationship with TPS score, two large randomized trials were conducted comparing pembrolizumab monotherapy with platinum doublet chemotherapy in patients with a high TPS score (\geq 50% in KEYNOTE-024) [212] or any TPS score (\geq 1% in KEYNOTE-042) [210]. Both trials included patients with NSCLC of any histology with a performance status of 0 or 1. Both trials met their primary endpoint of improved OS with pembrolizumab monotherapy. In KEYNOTE-042, OS was superior in prespecified analyses of patients with a TPS score of \geq 50% and all evaluable patients enrolled. In an unplanned analysis of patients with a TPS score of 1%–49%, no difference in overall survival was observed between the two arms, suggesting that the patients with TPS \geq 50% were driving the improved survival observed in the entire study population.

A phase III trial comparing nivolumab with chemotherapy in the first line failed to show an advantage for nivolumab in patients with a PD-L1 score $>$ 5%. Subsequent studies produced different results (see below) [214]. For nivolumab and nivolumab plus ipilimumab, the CheckMate 227 trial included patients with a PD-L1 score of 1% or higher with a subset analysis reporting on those with a PD-L1 score \geq 50% [215]. In these high-PD-L1-positive patients, both immunotherapy arms produced a survival superior to chemotherapy alone, with the nivolumab plus ipilimumab combination producing significantly longer OS than chemotherapy although the trial was not powered to compare the two immunotherapy arms.

For atezolizumab, the IMpower110 study randomized patients with any histology to receive atezolizumab alone or chemotherapy with carboplatin and nab-paclitaxel [216]. In patients with the highest PD-L1 expression (IC3/TC3 by SP142 assessment), atezolizumab alone produced a significant improvement in OS with a median of 20.2 months versus 13.1 months for chemotherapy (HR, 0.595).

For durvalumab, in the MYSTIC trial among 488 patients with 25% or more of tumor cells expressing PD-L1, median OS was 16.3 months (95% confidence interval [CI], 12.2–20.8) with durvalumab versus 12.9 months (95% CI, 10.5–15.0) with chemotherapy (HR, 0.76; 97.54% CI, 0.56–1.02; $p = .04$ [nonsignificant]) [217].

More recently, the results of a trial adding an anti-T Cell Immunoreceptor with Ig and ITIM Domains antibody to atezolizumab were presented showing a better ORR and PFS with the combination compared with atezolizumab alone in patients with high PD-L1 (\geq 50%) [218]. These results led to an ongoing phase III trial.

In summary, patients with PD-L1 TPS \geq 50% could be treated with single-agent pembrolizumab, single-agent atezolizumab, nivolumab plus ipilimumab, or a combination of either pembrolizumab or atezolizumab with chemotherapy, with the most data on pembrolizumab alone.

Checkpoint Inhibitor plus Chemotherapy Versus Chemotherapy in High PD-L1

A number of first-line randomized trials comparing a checkpoint inhibitor plus chemotherapy with the same chemotherapy alone were conducted in patients with any PD-L1 expression including those with the highest expression. Some trials included patients with only nonsquamous histology (KEYNOTE-189 [219], IMpower150 [220], and IMpower130 [218]) or only squamous carcinoma (KEYNOTE-407 [222] and IMpower131 [223]), whereas other trials included patients of any NSCLC histology (CheckMate 227 and CheckMate 9LA) [213, 224].

Two randomized phase III trials compared pembrolizumab combined with platinum doublet chemotherapy versus platinum doublet chemotherapy alone in patients with any TPS score who had nonsquamous histology (KEYNOTE-189) or squamous histology (KEYNOTE-407) [219, 222]. The chemotherapy doublet in KEYNOTE-189 was pemetrexed combined with cis- or carboplatin, and in KEYNOTE-407, the chemotherapy was carboplatin combined with paclitaxel or nab-paclitaxel. In both trials, patients with a TPS score \geq 50% experienced a statistically significant prolongation of both PFS and OS when treated with combined chemoimmunotherapy. In cross-trial comparisons, the combined chemoimmunotherapy trials demonstrated a higher ORR compared with pembrolizumab monotherapy responses in KEYNOTE-024 and 042 at the cost of higher toxicity with similar PFS and OS.

In the IMpower150 and 130 trials in nonsquamous carcinomas and in the IMpower131 trial in squamous carcinomas, the combination of atezolizumab plus chemotherapy was superior to chemotherapy alone in patients with TC3/IC3, although the hazard ratios were not as favorable as in the KEYNOTE trials. Similarly, in CheckMate 9LA, two cycles of chemotherapy plus nivolumab and ipilimumab was

superior to chemotherapy alone. In CheckMate 227, nivolumab plus ipilimumab was superior to chemotherapy alone in the high PD-L1 group.

In summary, for high PD-L1, several immunotherapies alone are superior to a platinum doublet chemotherapy for PFS and OS with less toxicity. Although the combination of chemotherapy and immunotherapy has higher ORR than immunotherapy alone, it has more toxicity and similar PFS and OS. Thus, many clinicians prefer the chemoimmunotherapy combination for patients with rapidly progressing cancers who need a rapid response and single-agent pembrolizumab atezolizumab or nivolumab plus ipilimumab for those with less aggressive tumors.

First-Line Immune Therapy for Patients with Negative or Intermediate PD-L1 (TPS <50%)

As noted above, the KEYNOTE-189 and 407 studies compared the combination of pembrolizumab and chemotherapy with chemotherapy alone in patients with any PD-L1 expression. The results favored the combined therapy in all TPS categories, including TPS 0. These trials established the combination of pembrolizumab with platinum doublet as the standard first-line therapy for patients of any histology and a TPS score of 0%–49%. Other phase III randomized trials evaluated different checkpoint inhibitor antibodies and systemic therapy combinations but with less success. For atezolizumab, the IMpower150 trial randomized patients with nonsquamous carcinoma to receive chemotherapy with paclitaxel plus carboplatin and bevacizumab, the same chemotherapy plus atezolizumab and bevacizumab, or the same chemotherapy–atezolizumab therapy without bevacizumab. The best results were in the four-drug regimen arm, although this arm was the most toxic for patients. In cross-trial comparisons, the hazard ratios for OS were not as striking as in the KEYNOTE trials discussed above. Similarly, the IMpower130 trial, which compared atezolizumab plus nab-paclitaxel/carboplatin with the same chemotherapy alone, showed advantage for the combination with less impressive hazard ratios for OS when compared with KEYNOTE 189. For patients with squamous carcinomas, IMpower131 compared nab-paclitaxel/carboplatin with the same chemotherapy combined with atezolizumab or with the combination of atezolizumab with paclitaxel/carboplatin. There was no survival advantage to the addition of atezolizumab in patients with a PD-L1 score of 0 to TC/IC 2.

The data for the use of nivolumab or the combination of nivolumab and ipilimumab with or without a chemotherapy doublet are a little more nuanced. The CheckMate 227 trial had three arms for patients of any histology with TPS <1% and three arms for patients of any histology with TPS ≥1%. In patients with TPS <1%, both the combinations of nivolumab with ipilimumab or nivolumab with chemotherapy were superior in OS to chemotherapy alone, with the best survival in the nivolumab plus ipilimumab arm. In patients with TPS ≥1%, the combination of nivolumab plus ipilimumab and nivolumab plus chemotherapy were superior to chemotherapy alone. The Checkmate 9LA study compared four cycles of platinum doublet chemotherapy with two cycles of the same chemotherapy plus both nivolumab and ipilimumab. The combination of chemotherapy plus

dual immune checkpoint blockade was superior to chemotherapy alone.

In conclusion, there are multiple options for first-line therapy in stage IV NSCLC without targetable driver alterations. For patients with the highest levels of PD-L1 expression, both a single-agent checkpoint inhibitor such as pembrolizumab and combination chemoimmunotherapy produce long survival. Combinations of a checkpoint inhibitor and chemotherapy produce higher ORR but no increase in OS. Thus, the combination may be best suited to patients needing a rapid response. Patients with intermediate, low, and no PD-L1 expression are most often treated with a combination of a checkpoint inhibitor and a platinum doublet with or without bevacizumab.

CONCLUSION

Within the last few years, the decades-long efforts in clinical trials, translational research, and basic science laboratories have resulted in new therapeutic approaches that have transformed the treatment options available to patients with lung cancer and reshaped our expectations for patient outcomes. For patients with targetable oncogene drivers and patients with high levels of PD-L1 expression, the expectation of benefit from first-line therapy and survival is measured in years. Although these advances are unprecedented, multiple opportunities exist to improve outcomes from prevention of lung cancer to improved therapies in metastatic disease.

The fundamental tenet of prevention is finding new ways to reduce tobacco use in all forms, including vaping. Furthermore, we need to capitalize on current efforts and develop new strategies to reduce the number of patients who present with advanced or metastatic NSCLC. More work is needed on new approaches for reversing premalignant airway lesions including high-risk nodules. For early detection, we must continue to work with patients and primary care providers to increase the fraction of patients who are screened for lung cancer according to guidelines. In conjunction with lung cancer screening, we also need to refine radiographic algorithms that better identify which small lung nodules will become malignant. The potential role for blood tests that detect circulating tumor DNA is critical in developing improved screening.

For patients with early stage, establishing surrogate markers such as pathologic response by correlating this readout with DFS and OS is necessary to more rapidly obtain approval of new therapies. We need to establish early studies of novel approaches in these patients, not just in patients with stage IV disease.

For all patients with stage IV disease, continued studies are needed to establish whether local consolidative therapy with radiation or surgery for residual disease or oligometastatic sites can improve survival in both patients with molecular drivers and those receiving immunotherapy with or without chemotherapy.

In patients with metastatic NSCLC and targetable molecular alterations, the foremost need is development of rational combinations that can produce greater log kill and thereby prevent or delay the development of resistance. Neoadjuvant studies may be the quickest and most rational way to discover and test such combinations. Additionally, investigations must establish whether adjuvant or neoadjuvant use

of targeted therapy improves OS for early-stage patients with molecular drivers.

For patients without molecular drivers, improving biomarkers to identify which patients will and will not respond to checkpoint inhibitor immunotherapy is a major unmet clinical need. For those patients who do not respond to clinically available immunotherapy, new immunotherapeutic approaches are needed as alternatives or to augment efficacy with current checkpoint inhibitors.

The marked advances in lung cancer outcomes can be attributed to consistent pursuit of science and clinical trials. If we continue these pursuits, the future is bright for patients with lung cancer.

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DISCLOSURES

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