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STATE OF THE ART REVIEW

Update 2020: Management of Non-Small Cell Lung Cancer

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Abstract
The past decade has seen a revolution of new advances in the management of non-small cell lung cancer (NSCLC) with remarkable progresses in screening, diagnosis, and treatment. The advances in systemic treatment have been driven primarily by the development of molecularly targeted therapeutics, immune checkpoint inhibitors, and anti-angiogenic agents, all of which have transformed this field with significantly improved patient outcomes. This review will address updates in lung cancer screening, liquid biopsy, and immunotherapy in the front-line setting. We discuss recent advances and highlight the plethora of new approvals of molecular-targeted therapy for subgroups of NSCLC patients with sensitizing *EGFR, ALK, ROS1, RET, BRAF V600E*, *MET,* and *NTRK* alterations.

Keywords Lung cancer · Immune checkpoint inhibitors · Targeted therapy

Introduction

Lung cancer is the second most common cancer and the leading cause of cancer death in the USA. Approximately 247,270 new cases of lung cancer are estimated to occur in 2020, with 130,340 male cases and 116,930 female cases [1]. Prior studies have reported that lung cancer resulted in more deaths than breast cancer, prostate cancer, colorectal cancer, and leukemia combined in men ≥ 40 years old and women ≥ 60 years old. With the introduction of screening guidelines and decrease in tobacco use, the mortality rate for lung cancer has recently decreased by 48% in males and 23% in females. Despite this decrease in mortality rate, approximately 140,730 deaths are estimated to be secondary to lung cancer in 2020 [1].

The greatest risk factor for development of lung cancer is tobacco use. Secondhand smoking has also been shown to increase the risk of lung cancer by as much as 26% [2]. Other risk factors for lung cancer include asbestos exposure, family history of lung cancer, exposure to toxic substances including polycyclic aromatic hydrocarbons, heavy metals, and radon gas [2]. Long-term effects of electronic cigarettes are currently unknown, but mice exposed to electronic cigarettes were more prone to develop lung adenocarcinomas compared to mice exposed to control air [3].

Lung Cancer Screening

The National Lung Screening Trial (NLST) showed a 20% reduction in lung cancer mortality with three annual low-dose computed tomography (CT) screenings for patients with high risk for lung cancer at a median follow-up of 6.5 years. Based on these results, the US Preventive Services Task Force (USPSTF) recommends annual screening in patients between the ages of 55 to 80 years with a smoking history of 30 or more pack years, who currently smoke or quit smoking within the past 15 years. Recently, the NELSON (Nederlands–Leuvens Longkanker Screenings Onderzoek) trial showed that the 10-year lung cancer mortality was significantly lower when high-risk patients underwent screening compared to no screening (risk of dying lowered by 24% in men and 33% in women) [4]. These trials confirm that low-dose CT screening undoubtedly works in saving lives in a high-risk group with four rounds of screening over 5 years preventing 60 deaths from lung cancer among 6583 screened. These exciting findings are unfortunately not echoed in real-world practice. In a National Health Interview Survey between 2010 and

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2015, of the 6.8 million smokers eligible for lung cancer screening in 2015, only 3.9% of them actually received it [5]. This suggests that clinicians and smokers require increased education in the benefits of lung cancer screening for informed decision making.

Lung cancer patients infected with SARS-CoV-2 were recently tracked in the TERAVOLT (Thoracic cancERs international coVid 19 cOLlaboraTion) registry study [6]. Patients with advanced NSCLC were found to have a higher risk of complications and 33% succumbed to complications from COVID-19. A smoking history was found to be an important predictor of developing complications from COVID-19.

Clinical Presentation and Diagnostic Work-Up

To date, a majority of lung cancer cases are diagnosed in symptomatic individuals with the most common symptoms being cough, fatigue, dyspnea, chest pain, weight loss, and hemoptysis. Hemoptysis has the highest positive predictive value of 2.4%–7.5% but is a feature of only a fifth of lung cancers [7]. Diagnosis of lung cancer at the earliest stage is strongly associated with improved survival and therefore requires greater readiness by primary care physicians to investigate high risk patients, even when presenting with non-specific symptoms. To diagnose and stage lung cancer, imaging tests (such as CT scans) and tissue/pathologic reviews are required. There are multiple approaches for tissue evaluation, such as bronchoscopy with biopsy or fine needle aspiration (FNA), mediastinoscopy, and thoracentesis. Although the least invasive approach with the highest diagnostic yield is preferred, it is essential to have enough issue for PD-L1 testing and molecular analysis. For centrally located tumors and in patients with adenopathy, EBUS–TBNA has become first-line procedures but for more peripheral pulmonary lesions, image-guided transthoracic core needle biopsy may be preferred. Moreover, patients with a high suspicion of early resectable disease (stage I or II) may not require a biopsy before the surgical procedure.

Staging plays a key role in the selection of therapy based on clinical and pathological factors, which provides a consistency in describing patients in clinical studies and their prognosis. The International Association for the Study of Lung Cancer (IASLC) has developed the lung cancer stage classification based on statistical analysis of an international database of 100,000 patients. The recent 8th edition of this staging system has been modified to provide a more precise classification based on prognostic analysis of each tumor-node-metastasis (TNM) descriptors [8].

Liquid Biopsy

Liquid biopsy includes testing on a variety of cancer biomarkers, such as circulating tumor DNA (ctDNA), microRNA, and circulating tumor cells (CTCs). Minimally invasive, it can be collected from plasma, serum, urine, CSF, and other resources to determine actionable genomic alterations that may eventually guide therapy and help to assess response. In current clinical practice, tissue diagnosis is still considered the gold standard for initial diagnosis of NSCLC. Moreover, a negative result of liquid biopsy does not rule out the presence of an oncogenic alteration and tissue-based analysis should be further pursued when feasible. At the same time, ctDNA testing can benefit patients who are medically unfit for invasive procedures or when the initial tissue testing is not enough for molecular testing. The non-invasive versus invasive lung evaluation (NILE) study of 282 patients with previously untreated NSCLC showed that there was a 48% increase in the rate of biomarker detection with ctDNA testing compared to tissue analysis alone with a faster turnaround time [9].

The Guardant360 CDx assay is an FDA-approved liquid biopsy for detection of genomic alterations in patients with any solid tumors, and as a companion diagnostic test to identify *EGFR* mutations in patients with advanced NSCLC who could benefit from treatment with osimertinib. The FoundationOne Liquid CDx is another FDA-approved comprehensive pan-tumor liquid biopsy test. CtDNA testing has a high specificity (80%–95%) for *EGFR* driver mutations but sensitivity varies from 60% to 85% [10]. Results from the AURA3 study showed that early clearance of mutations in ctDNA was predictive of outcomes. Plasma samples collected at baseline, at 3 and 6 weeks following treatment with second-line treatment with osimertinib showed that median PFS was longer in patients with clearance of plasma EGFR at 6 weeks (11.1 months, 95% CI, 8.3–12.6) compared with patients who had detectable mutations (5.7 months, 95% CI 4.1–7.7). In the AURA2 study, patient's plasma was collected to test for *EGFR* T790M-resistant mutations with real-time PCR in addition to tissue [11]. There was a higher likelihood of a positive ctDNA in patients with extra-thoracic disease. In the FLAURA3 study, molecular alterations have been identified as a resistance mechanism to first-line osimertinib including *MET* amplification, *HER2* amplifications, *PIK3CA, RAS*, and *EGFR C797S* mutations [12]. ctDNA has also been successfully used for the detection of *ALK/ROS1* fusions, *BRAF V600E*, *RET* fusion, and *MET* exon 14 skipping mutations. In the BFAST study that screened 2200 patients' plasma, the prevalence of *ALK* fusions was consistent with tissue testing. For those patients who received alectinib based on

plasma test results, the response rate was 92% and 1-year duration of response was 78% [13]. Most recently, tumor mutation burden (TMB) has been analyzed through a blood-based assay in a subset of the POPLAR and OAK cases [14]. Blood TMB was found to be a predictive biomarker for PFS in patients receiving atezolizumab in NSCLC.

NSCLC Treatment Approaches

Depending on the stage, histology, genetic alterations, and patient's condition, the treatment approaches in NSCLC usually include surgery, radiotherapy, chemotherapy, immunotherapy, molecularly targeted therapy either alone or in combined modality. Surgical resection with curative intent is recommended for medically fit patients with early stages of NSCLC [Stage I, stage II, and stage IIIA (usually when the involvement of N2 lymph node disease is identified during surgical procedure)]. While adjuvant platinum-based chemotherapy is recommended for stages II-IIIA disease with an absolute decreased risk of death of 5.4% at 5 years, the relapse rates are high with a relatively high rate of toxicity [15]. Multidisciplinary discussion is recommended prior to treatment, especially for stage IIB and stage IIIA disease. Thus far, molecularly targeted therapies have not demonstrated an overall survival benefit in early-stage patients. Approximately 30% of patients with NSCLC will have locally advanced disease (T3-T4, N2-N3, stage IIIA-C). Most of the patients with stage III NSCLC are non-surgical candidates and the current standard of care is concurrent chemoradiotherapy followed by immunotherapy [8].

Targeted therapy has improved clinical outcomes in a significant proportion of NSCLC patients with advanced disease. Thus, molecular testing, preferably a broad panel-based approach, is recommended to identify these actionable genetic alterations. Tyrosine kinase inhibitors targeting the *EGFR, ALK, ROS1, RET, BRAF V600E, MET* Exon 14, and *NTRK* genetic alterations are now approved for the treatment of several subtypes of NSCLC patients (Table 1). If there are no targetable alterations, PD-L1 expression may assist in making the treatment decision for both squamous and non-squamous NSCLC.

Basics of Molecularly Targeted Therapy in Lung Cancer

In the advanced setting, molecular testing should be conducted at the time of diagnosis. Approximately 10%–30% of NSCLC tumors harbor activating mutations in the tyrosine kinase domain of the *EGFR* gene, with the incidence increasing up to 60% in Asians [16]. In patients with metastatic NSCLC harboring sensitizing *EGFR* mutations, the preferred front-line therapy is osimertinib, a third-generation *EGFR* TKI, based on the FLAURA study [17]. In this pivotal study, osimertinib was compared to the first-generation TKIs in patients with *EGFR*-mutated NSCLC and resulted in a superior median OS of 38.6 months for osimertinib versus 31.8 months for the comparator (HR 0.799, *p*-0.0462). Of note, there was also improved CNS control. Another recently approved option is the combination of the VEGF inhibitor, ramucirumab with erlotinib (a first-generation TKI) in the first-line setting in EGFR-mutated lung cancer (median PFS 19.4 months with the combination compared to 12.4 months, HR 0.59, 95% CI 0.46–0.76, $p < 0.0001$) [18]. Other FDA-approved options in the first-line setting include dacomitinib, afatinib, erlotinib, and gefitinib (Table 1). Multiple studies are currently studying the addition of chemotherapy to TKIs to improve survival in this patient population.

Approximately 5% of NSCLC tumors harbor ALK gene rearrangements. The phase 3 ALEX trial comparing alectinib (a second-generation ALK TKI) to crizotinib (a first-generation ALK TKI) showed a dramatic improvement in PFS (35 months vs. 11 months, HR 0.43), a remarkable control of CNS progression (HR 0.16, 95% CI 0.10–0.28), and lower toxicities [19]. Similarly, another option in the first-line setting for *ALK*-positive NSCLC is brigatinib. The recent ALTA 1L trial compared brigatinib to crizotinib and showed an improved median PFS (24 months vs. 11 months, HR 0.49, 95% CI 0.35–0.68, $p < 0.0001$) [20]. Other FDA-approved front-line options include crizotinib and ceritinib (Table 1). Upon progression, lorlatinib, other *ALK* TKIs and chemoimmunotherapy are options.

ROS1 rearrangement acts as an oncogenic driver in 1%–2% of NSCLC. There is a high degree of homology between the *ALK* and *ROS* tyrosine kinase domains. These *ROS1*-positive tumors are highly sensitive to the TKI ceritinib [21], crizotinib [22], and entrectinib [23]. Upon progression, lorlatinib is an option [24].

RET gene arrangements have been identified in 1%–2% of NSCLC. The recent LIBRETTO-001 trial showed that selpercatinib/LOXO-292 has efficacy in patients with *RET*-fusion-positive NSCLC [Overall response rate (ORR) 85%] with responses lasting 6 months or longer in patients who have never received systemic treatment [25]. Once they have progressed, cabozantinib has been shown to have efficacy (median PFS 5.5 months, median OS 9.9 months in 25 patients in a phase II trial) [26].

BRAF V600E mutations are found in 1%–3% of NSCLC and are candidates for the combination *BRAF* inhibitors, dabrafenib in combination with trametinib after progression on chemotherapy [Disease control rate (DCR) 79%, ORR of 63%] [27].

NTRK gene fusions are found in around 0.2% of NSCLC for which both entrectinib and larotrectinib are the treatment options as either front-line or subsequent lines [28].

Table 1 Current FDA-approved molecularly targeted therapies in the first-line setting

Drug	Major trial	Study population	Study intervention	Primary outcome	Toxicity	Reference
EGFR mutation positive						
Osimertinib	FLAURA	Advanced untreated NSCLC, *EGFR Ex19del/L8585R*, CNS metastases allowed	Osimertinib versus control (Gefitinib/Erlotinib)	OS 38.6 months in Osimertinib arm vs. 31.8 months in comparator (HR 0,80, 95% CI 0.64–1.00, $p=0.046$)	Rash/acne, diarrhea, dry skin	Ramalingam et al. [37]
Afatinib	LUX-Lung3, LUX-Lung 6	Advanced untreated *Ex19del/L858R*	Afatinib versus chemotherapy	Del19 positive only showed improvement in OS	Rash, acne, stomatitis, mucositis, neutropenia	Yang et al. [11]
Erlotinib	EURTAC	Advanced untreated *Ex19del/L858R*	Erlotinib versus chemotherapy	PFS 9.7 months vs. 5.2 months (HR 0.37, 95% CI 0.25–0.54, $p<0.0001$)	rash	Rosell et al. [15]
Dacomitinib	ARCHER 1050	Advanced untreated *Ex19del/L858R*	Dacomitinib versus Gefitinib	OS 34.1 months vs. 26.8 months (HR 0.760, 95% CI, 0.582–0.992, $p=0.044$)	Diarrhea, paronychia, dermatitis	Mok et al. [10]
Gefitinib		Advanced untreated patients; analyzed *EGFR* subgroup	Gefitinib versus Carboplatin/Paclitaxel	EGFR subgroup: PFS HR 0.48, 95% CI 0.36–0.64, $p<0.001$)	Rash, diarrhea	Mok T et al. [14]
Erlotinib + Ramucirumab	RELAY	Advanced untreated *Ex19del/L858R*	Erlotinib + Ramicriumab versus Erlotinib	PFS: 19.4 months vs. 12.4 months (HR 0.59, 95% CI 0.46–0.76, $p<0.0001$)	Hypertension, dermatitis acneiform	Nakagawa et al. [18]
ALK rearrangement positive						
Alectinib	ALEX	Advanced untreated *ALK*-positive NSCLC; CNS metastases included	Alectinib versus Crizotinib	PFS 68.4% in alectinib vs. 48.7% in crizotinib (HR 0.47; 95% CI 0.34–0.65)	Anemia, myalgia, increased bilirubin	Peters et. al. [37]
Brigatinib	ALTA-1L	Advanced untreated *ALK*-positive NSCLC; CNS metastases included	Brigatinib versus Crizotinib	PFS 67% vs. 43%, (HR 0.49, $p<0.001$	Diarrhea, nausea, increased CK levels, increased ALT	Camidge et al [20]
Ceritinib	ASCEND-4	Advanced untreated *ALK*-positive NSCLC; CNS metastases included	Ceritinib vs. platinum + Pemetrexed	PFS 16.6 months vs. 8.1 months (HR 0.55, 95% CI 0.42–0.73, $p<0.00001$)	Diarrhea, nausea, increased ALT	Soria et al. [12]
Crizotinib	PROFILE 1014	Advanced untreated *ALK*-positive non-squamous NSCLC	Crizotinib vs. platinum + pemetrexed	PFS 10.9 months vs. 7.0 months (HR 0.46, 95% CI 0.35–0.60, $p<0.001$)	Vision disorders, diarrhea, nausea, edema	Soloman et al. [22]
ROS1 rearrangement positive						
Crizotinib		Advanced NSCLC with *ROS1* rearrangement	Phase I trial; no comparator	Median PFS 19.2 months (95% CI 13.3 to NR)	Vision disorders, diarrhea, nausea, edema	Shaw et al. [22]

Table 1 (continued)

Drug	Major trial	Study population	Study intervention	Primary outcome	Toxicity	Reference
Ceritinib		Advanced NSCLC with *ROS1* rearrangement; included CNS metastases	Phase II trial; no comparator	Previously untreated: PFS 19.3 months (1–37), OS 24 months (5–43)	Diarrhea, nausea, anorexia	Lim et al. [21]
Entrectinib	ALK-372–001, STARTRK-1, STARTRK-2	Advanced NSCLC with *ROS1* rearrangement	Integrated analysis of three phase1/2 trials; no comparator	ORR 77% (64–88); Median DoR 24.6 months (11.4–34.8)	Weight gain, neutropenia	Drilon et al. [23]
BRAF V600E mutation positive						
Dabrafenib/Trametinib		Advanced NSCLC; pretreated with *BRAF* V600E mutations	Phase II; no comparator	ORR 63.2% (95% CI 49.3–75.6)	Pyrexia, anemia, confusion, decreased appetite	Planchard et al. [27]
MET Exon 14 Skipping mutation						
Crizotinib		Advanced NSCLC with *MET* exon 14 alterations	Phase II; no comparator	ORR 35% (21–45); median PFS 7.3 months (5.4–9.1)	Vision disorders, diarrhea, nausea, edema	Drilon et al. [23]
Capmatinib	GEOMETRY mono-1	Advanced NSCLC with *MET exon 14* alterations	Phase II; no comparator	ORR was 68% (95% CI: 48, 84) with a response duration of 12.6 months (95% CI: 5.5, 25.3)	peripheral edema, nausea, fatigue, vomiting	Wolf et al. [23]
NTRK Gene fusion positive						
Larotrectinib		Any *TRK*-positive cancers (3 Lung tumors)	Phase I/II; no comparator	ORR 75% (61–85)	Anemia, increased ALT	Drilon et al. [28]
Entrectinib	STARTRK-1; STARTRK-2	Advanced NSCLC; pretreated	Phase I; no comparator	ORR 78% (95% CI 65–89)	CHF, QT prolongation, CNS toxicities, fractures, hepatotoxicity, hyperuricemia	Doebele et al. [23]
RET Rearrangement positive						
Selpercatinib/LOXO-292	LIBRETTO-001	Any *RET* rearranged tumor (253 with NSCLC); includes CNS mets	Phase I; no comparator	Treatment naïve ($n=34$): ORR 85% (69–95), median DOR and PFS not reached	Hypertension, increased ALT	Drilon et al. [25]
Cabozantinib		Advanced NSCLC with *RET* rearrangements	Phase II; no comparator	ORR 29% (12–49)	Lipase elevation, increased ALT/ AST	Drilon et al. [25]
Vandetanib		Advanced NSCLC with *RET* rearrangements; pretreated	Phase II; no comparator	ORR 18%, Disease control rate 65%, PFS 4.5 months, OS 11.6 months	Rash, hypertension, increased QT	Lee et al. [21]

OS Overall survival, *PFS* Progression-free Survival, *DOR* Duration of response, *ORR* Objective response rate

Another notable oncogenic driver with FDA-approved targeted therapy is *MET* exon 14 skipping mutation, which can occur in 2%–4% of NSCLC. The GEOMETRY mono-1 trial showed that patients with metastatic NSCLC with confirmed MET exon 14 skipping mutation benefited from capmatinib in the first-line setting (ORR 68% with a response duration of 12.6 months) [29]. Other options upon progression are crizotinib or cabozantinib.

Principles of Immunotherapy (Either as Monotherapy or in Combination)

Immunotherapy has demonstrated a survival benefit in patients with locally advanced NSCLC. In the PACIFIC trial, a phase III randomized trial comparing durvalumab and placebo as consolidation therapy given every 2 weeks up to 1 year in unresectable stage III NSCLC, patients who received anti-PD-L1, durvalumab after chemoradiation had a remarkable improvement in overall survival (median OS not reached in the durvalumab arm compared to 29.1 months with placebo [HR 0.69 (95% CI 0.55–0.86)] [30, 31]

In patients with no targetable genetic alterations and no contraindications to PD-1/PD-L1 inhibitors, immunotherapy either as monotherapy or in combination has become the standard of care in the front-line setting for advanced squamous and non-squamous lung cancer (Table 2). The checkpoint inhibitors used in advanced NSCLC are the anti-PD-1 pembrolizumab and nivolumab; anti-PD-L1 inhibitors atezolizumab; and the anti-CTLA4 inhibitor, ipilimumab.

Pembrolizumab demonstrated efficacy in KEYNOTE-024, a phase III randomized trial comparing single agent pembrolizumab against platinum chemotherapy in untreated stage IV NSCLC patients. In this trial, patients with tumors expressing PD-L1 tumor proportion score (TPS) ≥ 50% demonstrated superior response rate of pembrolizumab monotherapy over chemotherapy, 44.8% vs. 27.8%, and superior overall survival, median OS 30.0 months (95% CI 18.3 months–not reached) vs. 14.2 months (95% CI 9.8 vs. 19.0 months) [32, 33]. The overall survival benefit of pembrolizumab monotherapy was also demonstrated in patients with PD-L1 TPS of ≥ 1% in KEYNOTE-042, a randomized phase III trial which demonstrated superior overall survival in untreated metastatic NSCLC patients receiving pembrolizumab compared to chemotherapy in patients with TPS ≥ 50%, TPS ≥ 20%, and TPS ≥ 1% [34]. In the exploratory analysis, overall survival of pembrolizumab was not statistically significant in patients with TPS 1%–49%, which suggested that survival benefit in TPS ≥ 1% group was primarily driven by improved survival in patients with TPS ≥ 50% [34]. Atezolizumab was also demonstrated to have superior overall survival benefit in metastatic treatment naïve NSCLC patients with PD-L1 tumor cells ≥ 50% or tumor infiltrating immune cells ≥ 10%, compared to chemotherapy by 7 months in the IMpower-110 study [35]. Superior overall survival was also observed in patients with PD-L1 tumor cells ≥ 5% or tumor infiltrating immune cells ≥ 5% [35]. A newly approved chemotherapy-free option for patients with PD-L1 ≥ 1% is the combination immunotherapy, ipilimumab and nivolumab as seen in CHECKMATE-227 [36]. When compared to chemotherapy, the median OS was 17.1 months vs. 14.9 months (HR 0.79, 95% CI 0.67–0.94, $p = 0.0066$).

Most recently, front-line doublet immunotherapy with nivolumab and ipilimumab demonstrated improved overall survival benefit compared to chemotherapy alone. In the PD-L1 ≥ 1% population, patients who received nivolumab and ipilimumab had median duration OS of 17.1 months (95% CI 15–20.1) compared to 14.9 months (95% CI 12.7–16.7) with chemotherapy alone [37]. Similar benefit in overall survival was observed in patients with PD-L1 < 1%, 17.2 months (95% CI 12.8–22.0) in doublet immunotherapy compared to 12.2 months (95% CI 9.2–14.3) in chemotherapy and nivolumab groups [37]. Grade 3 or 4 treatment-related adverse effects were comparable between the two groups, 32.8% in doublet immunotherapy compared to 36% in chemotherapy [37]. Although it was observed that patients with PD-L1 < 1% who received doublet immunotherapy had improved overall survival compared to patients who received combination chemoimmunotherapy with nivolumab, it is unknown whether doublet immunotherapy outperforms single agent nivolumab as the study was not powered to make such a comparison [37].

In patients with PD-L1 < 1%, there are several combination chemoimmunotherapy options based on KEYNOTE-189, KEYNOTE-407, CHECKMATE-9LA, and IMpower-150 [38–40].

In KEYNOTE-189, a phase 3 trial, patients with non-squamous NSCLC regardless of TPS were randomized to cisplatin or carboplatin plus pemetrexed with pembrolizumab or placebo followed by pemetrexed and pembrolizumab or placebo maintenance therapy [38]. Overall survival was superior in the chemoimmunotherapy group for all subgroups of TPS: TPS < 1% (HR 0.59, 95% CI 0.38–092), TPS 1–49% (HR 0.55, 95% CI 0.34–0.90), and TPS ≥ 50% (HR 0.42, CI 0.26–0.68) [38]. Similarly, improved overall survival of chemoimmunotherapy regardless of PD-L1 expression was demonstrated in patients with metastatic squamous NSCLC in KEYNOTE-407 [39]. Patients who received carboplatin and taxane-based therapy, either paclitaxel or nanoparticle albumin-bound (nab)–paclitaxel, in combination with pembrolizumab had improved overall survival, median OS 15.9 months (95% CI 13.2–not reached), compared to chemotherapy and placebo, median OS 11.3 months (95% CI 9.5–14.8) [39]. Patients with PD-L1 < 1% by TPS also had improved OS, HR 0.61 (95% CI 0.38–0.98) [39].

Table 2 Current FDA-approved immune checkpoint inhibitor regimens for metastatic non-small cell lung cancer in the first-line setting

Immune checkpoint inhibitor	FDA approval	Diagnostic approved test	Major study	Intervention/Comparator arm	Primary outcome: months (95% CI) or hazard ratio	Toxicities	Reference
Pembrolizumab	October 2016	PD-L1 ≥ 50%, by 22C3 by DAKO	Keynote-024	Pembrolizumab vs. Investigator's choice platinum-based chemotherapy	OS 26.3 vs. 14.2	Diarrhea/fatigue/pyrexia	Reck [33]
Atezolizumab	May 2020	PD-L1 TC ≥ 50% or IC ≥ 10% by SP142 by Ventana	IMpower-110	Atezolizumab vs. Investigator's choice Carboplatin or Cisplatin + Pemetrexed (non-squamous)/ Gemcitabine (squamous) followed by maintenance Pemetrexed (non-squamous) or best supportive care (squamous)	OS: 20.2 (16.5, not reached) vs. 13.1 (7.4–16.5)	Fatigue/asthenia	Spigel [35]
Pembrolizumab	April 2019	PD-L1 ≥ 1% by 22C3 by Agilent	Keynote-042	Pembrolizumab vs. investigator's choice platinum-based chemotherapy	OS: TPS ≥ 50%: 20 (15.4–24.9) vs. 12.2 (10.4–14.2) TPS ≥ 20%: 17.7 (15.3–22.1) vs. 13 (11.6–15.3) TPS ≥ 1%: 16.7 (13.9–19.7) vs. 12.1 (11.3–13.3)	Hypothyroidism, pneumonitis	Mok [34]
Nivolumab + Ipilimumab	May 2020	PD-L1 ≥ 1% by 28–8 antibody by DAKO	Checkmate-227	Nivolumab + ipilimumab vs. Nivolumab vs. doublet chemotherapy (PD-L1 ≥ 1%) Nivolumab + ipilimumab vs chemotherapy + Nivolumab vs. doublet chemotherapy (PD-L1 < 1%)	OS: 17.1 (15.2–19.9) vs. 13.9 (12.2–15.1)	Diarrhea, rash, fatigue	Peters [13]
Pembrolizumab + platinum + Pemetrexed	August 2018	PD-L1 by 22C3 by Agilent	Keynote-189	Pemetrexed-platinum + Pembrolizumab/ placebo followed by maintenance Pemetrexed + Pembrolizumab/ placebo	OS: not reached vs. 11.3 (8.7–15.1) PFS: 8.8 (7.6–9.2) vs. 4.9 (4.7–5.5)	Diarrhea, rash	Gadgeel [19]
Pembrolizumab + (Paclitaxel or Nab-paclitaxel) + Carboplatin	October 2018	PD-L1 by 22C3 by Agilent	Keynote-407	Carboplatin + (Paclitaxel or Nab-paclitaxel) + Pembrolizumab/ placebo	OS: 15.9 (13.2-not reached) vs. 11.3 (9.5–14.8) PFS: 6.4 (6.2–8.3) vs. 4.8 (4.3–5.7)	Alopecia, pruritus	Paz Ares [39]

Table 2 (continued)

Immune checkpoint inhibitor	FDA approval	Diagnostic approved test	Major study	Intervention/Comparator arm	Primary outcome: months (95% CI) or hazard ratio	Toxicities	Reference
Atezolizumab + Bevacizumab + platinum + Paclitaxel	December 2018	PD-L1 by SP142 by Ventana	IMpower-150	ACP vs. BCP vs. ABCP	PFS: 8.3 ABCP (7.7–9.8) vs. 6.8 BCP (6.0–7.1) OS: 19.2 ABCP (17.0–23.8) vs. 14.7 BCP (13.3–16.9)	rash, hepatitis, hypothyroidism, hyperthyroidism, pneumonitis, colitis	Reck [42]
Nivolumab + Ipilumumab + platinum doublet	May 2020	PD-L1 by 28–8 antibody by DAKO	Checkmate-9LA	Platinum doublet	OS: 14.1 (13.2–16.2) vs. 10.7 (9.5–12.5), HR 0.69	Fatigue, arthralgias, nausea, diarrhea, rash	Reck [40]

PFS Progression-free survival, *OS* overall survival, *ACP* aztezolizumab/carboplatin/paclitaxel, *BCP* bevacizumab/carboplatin/paclitaxel, *ABCP* tezolizumab/bevacizumab/carboplatin/paclitaxel

CHECKMATE-9LA randomized patients with advanced NSCLC that were treatment naïve to combination immunotherapy, nivolumab plus ipilimumab and two cycles of platinum-doublet chemotherapy versus platinum-doublet chemotherapy [40]. Regardless of PD-L1 expression, the median OS was 14.1 months in the combination versus 10.7 months with chemotherapy alone (HR 0.69, 0.55–0.87).

IMpower-150 also demonstrated improved survival of chemoimmunotherapy in treatment naïve patients with advanced non-squamous NSCLC. Patients who received combination atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP) had superior overall survival, median OS of 19.2 months, compared to bevacizumab, carboplatin, and paclitaxel alone (BCP), median OS of 14.7 months, HR 0.78 (95% CI 0.64–0.96) [41]. Exploratory analysis also demonstrated improved OS of ABCP in patients with *EGFR* mutations, especially with sensitizing mutations, HR 0.31 (95% CI 0.11–0.83), which suggests ABCP to be an option for patients with *EGFR* mutation who fail initial tyrosine kinase inhibitor therapy [42]. Patients with liver metastasis had superior OS with ABCP, where there was a 46% reduction in death compared to BCP (HR 0.54, 95% CI 0.33–0.88) [43]. The improved PFS of ABCP was observed in all PD-L1 groups, including patients with PD-L1 expression less than 1% of in the tumor cells and/or tumor infiltrating cells, HR 0.77 (95% CI 0.61–0.99), but the overall survival was not statistically significant among the PD-L1-negative group (HR 0.82, 95% CI 0.62–1.08) [41, 43].

Principles of Managing Immune-Related Adverse Effects

Management of immune-related adverse effects is an integral part of immunotherapy. Toxicities can involve any organ system and commonly involves the skin, gastrointestinal tract, lung, thyroid, and pituitary gland. It can occur even after discontinuation of immunotherapy; thus careful monitoring of symptoms remains vital [44].

There are several general guidelines for the management of immunotherapy-related adverse effects [44]. Grade 1 toxicities are monitored without holding the medication. With grade 2 toxicities, immunotherapy is generally held until toxicity improves to grade 0 or grade 1 and treatment with 0.5-1 mg/kg/day of prednisone is begun. With grade 3 toxicities, higher dose of prednisone, 1-2 mg/kg/day or IV methylprednisolone 1–2 mg/kg/day is begun after discontinuation of immunotherapy. If symptoms do not improve after 3–5 days, next line of therapy includes infliximab or vedolizumab. Once toxicity improves to grade 1, patients may be re-challenged. With grade 4 toxicity, however, it is generally recommended that immunotherapy is discontinued permanently unless it is an endocrine immune toxicity that can be controlled with hormone replacement. More detailed

information regarding specific adverse effect and recommended management has been described [45, 46].

Conclusion

Many revolutionary advances have recently been made in the management of NSCLC. First, in lung cancer screening, both National Lung Screening Trial and the NELSON trial have shown that low-dose CT screening can be effective in lowering lung cancer mortality rates. Second, immunotherapy is now at the forefront of treatment in oncogenic driver negative NSCLC. Immunotherapy continues to demonstrate a significant overall survival benefit in advanced NSCLC. As monotherapy, pembrolizumab or atezolizumab is superior to first-line chemotherapy in tumors with (high) positive PD-L1 expression. As combination approach, a number of chemo–immunotherapy combinations prove to be superior to chemotherapy, regardless of PD-L1 expression (keynote-189, keynote-407). Third, there have been a number of approvals of molecular-targeted therapy for subgroups of NSCLC patients with sensitizing *EGFR, ALK, ROS1, RET, BRAF V600E*, *MET*, or *NTRK* alterations.

Compliance with Ethical Standards

Conflict of interest Mariam Alexander and So Yeon Kim do not have any conflicts of interest to disclose. Haiying Cheng has received research funding from Genentech/Roche, Eisai, Spectrum, Regeneron, Bayer, and Vaccinex.

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