Next Generation of Advanced Non-Small Cell Lung Cancer Therapy: Targeted and Immuno-Therapies

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Abstract
Lung cancer is one of the deadliest cancers in the world. Current clinical trials are focused on developing the next generation of therapies that target novel anti-cancer mechanisms. One approach is to prime the immune system, as the cancer has been known to suppress immune cells in the tumor microenvironment. Using immunotherapy, the immune system can be unleashed and suppress the cancer’s growth. Another pathway is targeting known oncogenic genes that are important for the cancer’s growth and survival. In lung cancer, the epidermal growth factor receptor and several other mutated proteins are targets of small-molecule inhibitors that have been shown to drastically improve patient survival and quality of life. Discussed in this review are broad highlights of the different immunotherapies and small molecule targeted therapies that have been studied in the latest clinical trials for lung cancer.

Key Words: Lung neoplasms; Non-Small-Cell Lung Carcinoma; immunotherapy; EGFR tyrosine kinase inhibitor; Molecular targeted therapy (Source: MeSH-NLM).

Introduction
Globally, cancer is increasingly one of the greatest health burdens, with an estimated 20% probability of being diagnosed with cancer before age 75 and a 10% chance of dying from it.1 According to GLOBOCAN in 2018, lung cancer had the highest incidence, with nearly 2 million cases and the highest mortality at almost 1.7 million deaths. In the United States, similar trends were observed where 234,930 lung cancer cases were diagnosed, accounting for 25% of cancer deaths.1

Lung cancer is histologically divided into small cell lung carcinoma (~15% of lung cancers) and non-small cell lung carcinoma (NSCLC) (85% of lung cancers).2 NSCLC is further subdivided into squamous, adenocarcinoma, and large cell carcinoma. These histopathological divisions help decide further investigations and management. Many of the development of the next generation of medical therapies has focused on stage IV, metastatic lung cancers and will be the focus of this review. Until recently, the first-line chemotherapy regimen for metastatic NSCLC is chemotherapy with two drugs, one of which is a platinum agent (known as platinum-doublet chemotherapy); where appropriate, maintenance chemotherapy with a single agent may take place after the end of 4-6 rounds of platinum-doublet chemotherapy.3 Few effective treatments are available after disease progression and mainly involve single-agent chemotherapy such as docetaxel.4

For treatment-naïve patients, identification of who benefits from immunotherapy is contingent on several main factors: lack of a driver mutation (e.g. EGFR or ALK as immunotherapies are likely less effective than targeted therapy in this population) and biomarker status.5 PD-L1/PD-1 is the most commonly used biomarker status for lung cancer as the approved therapies all target this immune blockade.6 The PD-L1/PD-1 axis is a mechanism by which cancer cells induce T cell anergy and exhaustion, and avoid anti-tumor immune cells. PD-L1/PD-1 antibodies block this interaction and allow the immune system to recognize and then suppress the cancer cells.7 The goal of this review is to provide a broad yet comprehensive overview of the different next-generation cancer therapies in NSCLC and provide a summary of the evidence rationalizing each therapy. The following section will focus on immune modulators that re-educate the immune system to attack the cancer cells based on phase III clinical trials data. The second section will discuss targeted therapies for lung cancers with driver mutations. Finally, the last section will propose an algorithm for treatment decision making based on the current evidence.

The adverse events and clinical trials described in this review use the Common Terminology for Adverse Events (CTCAE) terminology system which aims to unify the nomenclature in assessing the severity of each adverse event. Grade 1 represents mild adverse events and intervention is not needed to grade 4 where there are life-threatening consequences requiring immediate intervention.8,9 Grade 5 is reserved for cases where the adverse event led to death. An example of a grade 1 event in vomiting means it requires no intervention a grade 2 event is determined by the need for outpatient IV hydration, a grade 3 event requires hospitalization or tube-feeding and grade 4 carries life-threatening consequences. Table 1 has examples of different common adverse events reported in oncology clinical trials and their grading definitions.

Immunotherapy with Monotherapy
Nivolumab as second-line monotherapy for metastatic NSCLC
Nivolumab is a human IgG4 anti-PD-1 monoclonal antibody and has been approved for second-line therapy regardless of PD-L1 status. In the CheckMate 017 and CheckMate 057 trials, nivolumab was compared to docetaxel for patients with disease progression after first-line therapy for both squamous and non-squamous histology. Nivolumab lowered the risk of death compared to docetaxel in squamous (hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.44 to 0.79, P <0.001, minimum follow-up was 11 months) and non-squamous (HR 0.73, 95% CI 0.59 to 0.89, P = 0.002, minimum follow-up was 13.2 months) cell types.10,11 CheckMate 026 evaluated nivolumab monotherapy in the first line, which showed non-significant differences in overall and progression-free survival.12 However, the nivolumab group reported 18% grade 3-4 adverse events as opposed to 51% in the standard chemotherapy group, mainly with more fatigue and hematological...
Table 1. Common Terminology for Adverse Events (CTCAE) v5.0 examples.

| Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---------|---------|---------|---------|
| Rash    | Maculopapular | 10-30% BSA, limiting activities of daily living, or <30% BSA but no or mild symptoms of burning, pruritis, or tightness | >30% BSA with moderate to severe symptoms limiting self-care ADLs | Grade not available |

**Diarrhea**
- Increase of 4 stools per day over baseline, mild
- Increase of 1 stools per day over baseline, a moderate increase in ostomy output, limited instrumental ADL

**Neutropenia**
- <1.0-1.5 x 10^9/L
- <0.5-1.0 x 10^9/L
- <0.5 x 10^9/L

**Anemia**
- <10.0-10.5 mmol/L
- <9.0-9.5 mmol/L
- <9.0 mmol/L
- <8.0 mmol/L

**Hematocrit**
- <0.3-0.35
- <0.3-0.3

**Hemoglobin**
- <10.0-10.5 g/dL
- <9.0-9.5 g/dL
- <9.0 g/dL
- <8.0 g/dL

**Adverse events**
- Grade 1: least severe with no intervention needed
- Grade 2: mild to moderate, some intervention may be required
- Grade 3: severe, urgent intervention required
- Grade 4: life-threatening, urgent intervention required

All definitions were extracted directly from the Common Terminology for Adverse Events (CTCAE) v5.0, developed by the National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) published in November 2020.

The rationale is to target different T-cell activation pathways to induce a more robust tumor response. In CheckMate 227, another secondary goal was to compare nivolumab and ipilimumab treatment with nivolumab and chemotherapy for first-line metastatic NSCLC.

**Dual Immunotherapy**
Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another target of immunotherapy blockade, which combined with PD-L1 blockade, has demonstrated improvement in metastatic melanoma. The rationale is to target different T-cell activation pathways to induce a more robust tumor response. In CheckMate 227, another secondary goal was to compare nivolumab and ipilimumab treatment with nivolumab monotherapy in first-line metastatic NSCLC.

**Immunotherapy Combination Therapies**
Immunotherapy with chemotherapy for first-line metastatic NSCLC.

The latest clinical trials have expanded beyond the monotherapy realm to investigate more effective front-line therapies. One strategy is to combine chemotherapy and immunotherapy, and there is evidence to suggest they can work synergistically in melanoma trials. In the first-line setting, Keynote 189 compared standard platinum-based chemotherapy + pembrolizumab in non-squamous NSCLC. The immunotherapy with chemotherapy group demonstrated better overall survival (HR 0.49, 95% CI 0.38 to 0.64, P = 0.001) and the trend was preserved regardless of PD-L1 expression, where median follow-up was 10.5 months. Adverse events of grade 3 or higher were found in 57.2% for the combination group compared to 65.8% for the chemotherapy group. The main difference in grade 3 or higher events in the combination group was more febrile neutropenia. Keynote 407 (median follow-up of 7.8 months), which studied carboplatin + paclitaxel + pembrolizumab in squamous NSCLC, showed similar improvements for the combination group (HR 0.56, 95% CI 0.45 to 0.70, P = 0.001), with similar number of grade 3 or higher adverse events (59.8% vs. 68.7%) with more pneumonitis and autoimmune hepatitis in the combination group.

One of the CheckMate 227 secondary goals compared first-line platinum-doublet chemotherapy + nivolumab in the <1% PD-L1 patients, which showed OS benefit compared to chemotherapy alone (HR 0.78, 95% CI 0.60 to 1.02, P = 0.035, median follow-up was 29.3 months). IMpower 110 was a trial comparing first-line carboplatin and nab-paclitaxel + atezolizumab in squamous NSCLC, where there was improved progression-free survival (HR 0.715, 95% CI 0.60 to 0.848, P = 0.0001) but no differences in overall survival (P = 0.16). The IMpower 130 was a similar trial for non-squamous histological subtypes and reported at the European Society of Medical Oncology (ESMO) 2018 that atezolizumab + carboplatin and nab-paclitaxel had superior OS (HR 0.79, 95% CI 0.64 to 0.98, P = 0.033) and PFS (HR 0.64, 95% CI 0.54 to 0.77; P = 0.0001) compared to carboplatin and nab-paclitaxel alone.

**Dual Immunotherapy**
Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) is another target of immunotherapy blockade, which combined with PD-L1 blockade, has demonstrated improvement in metastatic melanoma. The rationale is to target different T-cell activation pathways to induce a more robust tumor response. In CheckMate 227, another secondary goal was to compare nivolumab and ipilimumab treatment with nivolumab monotherapy in PD-L1 ≥1%. This comparison showed trends towards benefit for the PD-L1 ≥1% population (HR 0.80, 95% CI 0.60-1.07) and PD-L1 0%-50% (HR 0.97, 95% CI 0.87-1.12), but there were more grade 3-4 adverse events in the dual immunotherapy group compared to the monotherapy group (55.8% vs. 19.4%). More specifically, it included more rash, pruritis, diarrhea and adverse events with suspected immunotherapies demonstrated more immune-related adverse events such as more severe skin reactions, pneumonitis and colitis. Keynote 42 was a follow-up trial that indicated that tumors with PD-L1 ≥1% treated with pembrolizumab showed superior overall survival (HR 0.81, 95% CI 0.71 to 0.93, P = 0.003) at a median follow-up of 12.8 months with a similar side effect profile demonstrated in the previous trials.

Sequential Durvalumab Monotherapy after Chemoradiation in Unresectable Stage III NSCLC
Durvalumab is an IgG1 kappa monoclonal antibody against PD-L1 that was investigated in the PACIFIC trial in stage III surgically unresectable NSCLC without disease progression after 2 cycles of platinum-based chemoradiation compared to placebo. Durvalumab-treated patients demonstrated superior overall survival (HR 0.68, 95% CI 0.47 to 0.977, P = 0.0025, median follow-up 25.2 months). For grade 3 or 4 adverse events due to any cause, 30.5% of the durvalumab treatment group reported these events compared to 26.1% in the placebo group. Most of the grade 3-4 event differences were due to increased pneumonia and radiation pneumonitis in the immunotherapy group. Durvalumab is unique as the only approved consolidation immunotherapy single agent for NSCLC.
immune etiology affecting the pulmonary, gastrointestinal, skin and endocrine systems.13

The MYSTIC trial investigated patients with PD-L1 > 25% with a durvalumab and tremelimumab (anti-CTLA-4) combination in the first-line setting. Unfortunately, the immunotherapy combo was unsuccessful in showing PFS or OS improvements over chemotherapy but had less grade 3-4 treatment adverse event profiles (22.1% in combination vs. 33.8% in chemotherapy).14 The NEPTUNE trial (durvalumab + tremelimumab vs. chemotherapy) includes ALK and EGFR patients, and is set to reveal results soon.15

### Immune-Related Adverse Events in Immunotherapies

Immunotherapies are not harmless despite a safer side effect profile compared to chemotherapy. Physicians caring for patients undergoing immunotherapies must be keenly aware of the unique and dangerous side effects compared to chemotherapy patients (Table 2). The unique danger in immune-oncology is an overstimulation of the immune system, which can induce an autoimmune condition. The most common immune-related adverse event (irAE) is dermatological rash/pruritis, with an estimated prevalence of 30% in nivolumab or pembrolizumab patients.16 Grade 1 toxicities do not necessarily necessitate stopping treatment and can be treated with topical steroids or symptomatic systemic treatment. Serious irAEs that require clinicians to be vigilant about are colitis, pneumonitis, endocrineopathies, neurological syndromes, and cardiovascular compromise (Table 2). For all toxicities, grade 1 events should be monitored for progression while grade 2 and above may necessitate withholding treatment or permanently discontinuing treatment and immunosuppressive treatment depending on the specific irAE.17 Specific irAE risk stratification and treatment strategies are summarized in the American Society of Clinical Oncology Clinical Practice Guidelines and the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group.18,29 Due to the potential for high morbidity and mortality associated with pneumonitis, colitis, neurological syndromes and cardiovascular toxicity, these warrant consideration of immediate discontinuation and referral to additional specialists. The mainstream of systemic treatment for grade 2 and above adverse events is corticosteroids, such as prednisone at 0.5-2 mg/kg/day depending on the grade of the toxicity, along with appropriate prophylaxis therapies.19 If refractory, immunomodulatory therapies could serve as the next step; for instance, infliximab has been reported in the use of refractory colitis.20,25

### Targeted Agents for NSCLC Patients Carrying Actionable Mutations

#### Epidermal Growth Factor Receptor

Epidermal Growth Factor Receptor (EGFR), a receptor tyrosine kinase responsible for cell proliferation and survival, is one of the most commonly identified driver mutations in NSCLC. The prevalence of EGFR alterations in NSCLC varies drastically based on geographical region, varying from 10% in North American and Western European cases to 30% in East Asian cases.24,25 Studies have reported a higher prevalence in females and non-smokers.24,26 From a histological perspective, it is most frequently seen in adenocarcinomas compared to any other NSCLC histologic subtype, with a rate of 30% compared to 2% of another diagnosis.27,28 The most common of these intracellular TK mutations include the L858R mutation in exon 21, or short in-frame deletions in exon 19, which both contribute 90% of the aberrations in this domain.

#### Gefitinib

Gefitinib is an EGFR inhibitor that competitively inhibits ATP. It is approved for first-line therapy of EGFR+ metastatic NSCLC. The IRESSA Pan-Asian Study (IPASS) was a seminal phase III trial demonstrating remarkable efficacy. In the EGFR+ subgroup, gefitinib was superior to carboplatin-paclitaxel, with an improvement in PFS (HR 0.48, 95% CI 0.36-0.64, P<0.001) and overall survival (HR 0.78, 95% CI, 0.50-1.20).27 Median follow-up in this study was 527 days. In the EGFR- subset, patients treated with the gefitinib showed a worse PFS (HR 2.85, 95% CI 2.05-3.98, P<0.001).27 From a toxicity perspective, in IPASS, gefitinib was associated with fewer grade 3-4 adverse events (28% vs 61%), and the most common toxicities for gefitinib included rash, diarrhea and mucositis, while neurotoxicities and hematologic toxicities were significantly lower compared to chemotherapy.27

#### Erlotinib

Erlotinib, like gefitinib, is an EGFR inhibitor and has a similar mechanism to gefitinib. It is approved for locally advanced or metastatic EGFR+ NSCLC. In the EURTAC trial, erlotinib was compared to cisplatin-docetaxel or gemcitabine in a first-line setting and found to have a significantly improved PFS (HR 0.16, 95% CI 0.10-0.26, P=0.001).28 The median follow-up in this study was 18.9 months in the erlotinib group. Other phase III trials using erlotinib in the first-line setting compared against platinum-based combination chemotherapy regimens, such as OPTIMAL and ENSURE, have shown similar results with erlotinib achieving a significant improvement in PFS.29 Erlotinib has also been studied as a combination therapy through the FASTACT trial where erlotinib intercalated with gemcitabine and platinum therapy versus chemotherapy with placebo was compared in patients with NSCLC. The erlotinib combination, in EGFR+ mutated NSCLC, showed a significant increase in PFS (HR 0.25, 95% CI 0.16-0.59, P=0.001).30 Erlotinib intercalated chemotherapy also showed significant improvements in overall survival (HR 0.48, 95% CI 0.27-0.84, P=0.009).31 Median follow-up in the erlotinib plus chemotherapy was 28.2 months. In the EURTAC trial, erlotinib had fewer grade 3-4 adverse events than chemotherapy (45% vs 65%). Rash and elevated amylase concentrations were the most frequent adverse events in the erlotinib group compared to neutropenia and anemia being the most frequent adverse events in the chemotherapy group.27

#### Afatinib

Afatinib is a second-generation EGFR tyrosine kinase inhibitor (TKI) and exhibits its effect by irreversibly binding to the kinase domain in all erBB family tyrosine kinases. LUX-LUNG-1 was a phase IIb/III trial that studied afatinib versus placebo in NSCLC patients who have previously received chemotherapy and have failed on a previous EGFR TKI. While there was no significant difference in OS, PFS was improved (HR 0.38, 95% CI 0.20-0.75, P = 0.029). Similar results were observed in a 2:1 phase III trial that followed for an estimated two years.32 In addition, in patients who previously developed resistance, PFS was significantly improved by

### Table 2. Potential Adverse Events for Immunotherapies for Oncology Treatment.

| Common Adverse Events | Uncommon Adverse Events | Indications to Stop Treatment |
|-----------------------|-------------------------|------------------------------|
| Maculopapular rash    | Renal involvement       | Pneumonitis                  |
| Pruritis              | Neurological syndromes  | Colitis                      |
| Fatigue               | Exocrine pancreas       | Neurological syndromes       |
| Drug-related reactions| Cardiovascular toxicity  | Potentially for cardiovascular toxicity |
| Diarrhea              | Hematological related   | Grade 2-4, reassessment for restarting treatment after symptom resolution |

Hepatitis                  | Ophthalmological inflammation |
Hypothyroidism             | Myositis                    |
Hypophysitis               | Pneumonitis                  |
Arthralgia                 | Colitis                      |

**Legend:** The table was adapted from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):1–28.
Review

Afatinib treatment, which supports its role as a treatment-following resistance development in first-line EGFR TKIs. Adverse events were similar between afatinib and chemotherapy, where the most frequently encountered events include rash, diarrhea and mucositis. In LUX-LUNG-8, afatinib showed improved PFS and OS compared to erlotinib.49

Osimertinib

Osimertinib is a third-generation EGFR TKI and, similar to afatinib, acts by binding irreversibly to the EGFR receptor. Intriguingly, this drug shows a pharmacological effect in patients with sensitizing mutations such as exon 19 deletion or exon 21 L858R as well as patients with the exon 21 L790M mutation, typically conferring resistance to EGFR TKIs. In the AURA3 trial, osimertinib was compared to platinum-pemetrexed in patients who had previously failed on first-line EGFR TKI. Osimertinib showed superior progression-free survival (HR 0.30, 95% CI 0.23-0.41, P<0.001) and greater grade 3-4 adverse events than chemotherapy (29% vs 47%). Median follow-up for all patients in this study was 8.3 months. The most common side effects within the osimertinib group were paronychia, rash and diarrhea compared to anemia and GI-related adverse events, which were the most common toxicities seen in the chemotherapy group.50 The FLAURA trial showed osimertinib provided a significant improvement in progression-free survival versus gefitinib or erlotinib in the first-line setting (HR 0.46, 95% CI, 0.37-0.57, P<0.001). Median follow-up for the osimertinib group was 15 months and 9.7 months in the standard EGFR-TKI group.46 The drug has recently been approved for first-line treatment of metastatic EGFR+ NSCLC.

NSCLC patients carrying Anaplastic Lymphoma Kinase translocations

Anaplastic Lymphoma Kinase (ALK) is a receptor tyrosine kinase normally found on chromosome 2. Under normal circumstances, it is expressed at low levels in the small intestines, neural tissue, male testes and has a role in neural development.46 It is found mutated and fuses with other protein genes in approximately 1-5% of NSCLC cases and, similarly to EGFR, is found in predominantly non-smokers and adenocarcinoma histology.47

Crizotinib

Crizotinib is a TKI that inhibits ALK. PROFILE-1007 was a phase III study comparing crizotinib to chemotherapy in ALK-positive NSCLC following failure on the first-line, platinum-based doublet chemotherapy. Crizotinib showed a significant PFS improvement to chemotherapy (HR 0.49, 95% CI 0.37-0.64, P<0.001).49 The median follow-up in the crizotinib group was 12.2 months. Crizotinib also showed a more tolerable toxicity profile compared to chemotherapy, where the most common adverse events were visual disorder, GI-related symptoms, and elevated aminotransferase levels. PROFILE 1014 studied crizotinib in chemotherapy-naive ALK-positive NSCLC and found PFS to be significantly improved in the crizotinib group compared to chemotherapy (HR 0.45; 95% CI 0.35-0.60, P<0.001, median follow-up of 17.4 months).46

Ceritinib

Ceritinib is a next-generation TKI approved for ALK mutated NSCLC. As a more potent inhibitor, ceritinib has displayed activity in certain cases that have developed resistance and progressive disease on crizotinib. The ASCEND-1 trial studied ceritinib in patients who were previously treated and progressed on crizotinib, and found that 96% responded (95% CI, 94-98%), and the median PFS was 6.9 months (95% CI, 5.6-8.7 months). Median follow-up was 11.1 months. The most common adverse events included GI-related symptoms, primarily grade 1 or 2 in severity, including elevated aminotransferase concentrations.50

Alectinib

Alectinib is another next-generation ALK-targeted TKI that has shown activity against crizotinib-resistant NSCLC. Of particular interest, this drug is not a P-Glycoprotein substrate and therefore, can achieve significantly improved intracranial concentrations for targeting CNS metastases. Alectinib was then compared to crizotinib in the first-line setting in two clinical trials, J-ALEX and ALEX, with improved PFS for alectinib and 12-month event-free survival rate, which was 68.4% vs. 48.7% (95% CI, 61-76% vs. 40-57%).51 Furthermore, CNS progression occurred in 12% of the alectinib group compared to 45% of the crizotinib group. Median follow-up in this study was 17.6 months in the crizotinib group and 18.6 months in the alectinib group. Overall, alectinib had more adverse events than crizotinib; however, when comparing based on severity, alectinib had marginally fewer grade 3-5 adverse events (41% vs 50%). The most common adverse events in the alectinib group include GI-related symptoms, elevated aminotransferase concentrations, peripheral edema and myalgia. Most impressively, the ALEX trial found a PFS of over 34 months compared to 12 months in patients treated with crizotinib, setting the stage for a change in first-line recommendations to alectinib soon.51

Brigatinib

Brigatinib is an additional next-generation ALK TKI that has shown activity in this NSCLC subtype. In the ALTA-1L phase III trial, brigatinib was compared to crizotinib in a front-line setting. Median follow-up in this trial was 11 months in the brigatinib group and 9.3 months in the crizotinib group. Brigatinib was found to be more efficacious for PFS (HR 0.49, 95% CI 0.39-0.74, P<0.001).52 In addition, brigatinib was found to show increased activity against CNS lesions with an observed response rate of 78% (95% CI, 52-94%) compared to 29% (95% CI, 11-52%) in the crizotinib group.53 The brigatinib group had a higher frequency of grade 3-5 adverse events, occurring in 61% of patients compared to 55% of the crizotinib group, the most common of which were elevated creatine kinase, elevated lipase levels and hypertension.54

Treatment Algorithm for Advanced NSCLC

The treatment of patients with metastatic or unresectable NSCLC is rapidly evolving and increasingly complex based on the most available data. The immunotherapy summary is adapted from the expert opinion provided by the Society for Immunotherapy of Cancer 2018 NSCLC consensus statement as well as the compilation of the targeted therapy trials highlighted above (Figure 1).55 With the diagnosis of advanced NSCLC, standard staging should first be conducted if not already completed. Following that, driver mutation analysis, histological subtype and PD-L1 expression are some of the most basic molecular profiling to decide on initial treatment decisions.

For patients with non-squamous histology and an actionable driver mutation, TKI therapy would be initiated first in almost all cases. For EGFR positive patients, alectinib, erlotinib, gefitinib and osimertinib may be used in first-line with osimertinib used in treatment-resistant cases. For ALK fusion tumors, ceritinib is considered first-line with ceritinib and alectinib following progression; however, this is likely to change soon given the superiority of alectinib in both efficacy and toxicity profiles in the first-line setting because of the ALEX trial results. Also, upcoming trial data of lorlatinib, a fifth ALK inhibitor, has some promise. For BRAF-mutated tumors, dabrafenib and trametinib can be considered. For patients who have failed targeted therapy, platinum doublet therapy should be considered as second-line therapy due to previous poor efficacy of immunotherapy in this subgroup.3 Third-line would include immunotherapy monotherapy, including atezolizumab, nivolumab or pembrolizumab. Patients with no identifiable, actionable driver mutation have the choice for pembrolizumab/immunotherapy alone or a combination for first-line therapy. While CheckMate 227 showed some initial promising data for dual-immunotherapy vs
monotherapy, it was not powered enough to detect a meaningful difference, and there were some initial concerns of immune-related adverse events. For patients with PD-L1 $\geq 50\%$, there is evidence for pembrolizumab with chemotherapy for both squamous (carboplatin + nab-paclitaxel or paclitaxel) and non-squamous cell histology (platinum + pemetrexed). For PD-L1 $< 50\%$ non-squamous cell, there is benefit from either pembrolizumab monotherapy or pembrolizumab + chemotherapy that is dependent on symptomology and how fast the cancer is progressing. For PD-L1 $< 50\%$ in squamous cells, there are similar choices but less strong evidence for combination therapy. Pending the peer-reviewed published results of IMpower 130, atezolizumab + carboplatin and nab-paclitaxel may be an alternative option for squamous cell carcinomas.

For patients who progress on immunotherapy, the second-line would include either pemetrexed (non-squamous) or docetaxel (squamous) based on standard second-line chemotherapy regiments. Furthermore, with patients with isolated sites of progression or “oligoprogression,” there is a consideration for local therapy, but the management is not within the scope of this review.

**Conclusion**

In summary, immunotherapies have transformed metastatic lung cancer care by providing more durable responses and more effective responses compared to traditional chemotherapy. There is no doubt about the clinical benefit of immunotherapies; however, the current question is identifying the patients who would benefit. Only 40-50\% of PD-L1 positive patients clinically benefit from immunotherapy, while 15\% of PD-L1 negative patients also benefit. This highlights the complexity of the mechanism of these immunomodulatory drugs that are not explained fully by PD-L1 expression. Tumor mutational burden, cytotoxic T cell infiltration, immune gene signatures and immune composite biomarkers are emerging biomarkers. For targeted therapies, the race between drug targets and resistance will continue, and novel strategies for identifying resistance and combination therapy will be the key to future success in controlling these oncogene-addicted cancers.

Given the substantial survival benefit with minimal side effect profile of targeted therapies, there should be a greater awareness in the medical education community to understand that even poor functional status patients with actionable mutations can benefit from these small molecule inhibitors. Furthermore, with the paradigm shift of immunotherapies in oncology where the goal is stimulation of the immune system, rather than immunosuppression as more classically taught with immune modulators, there should be greater education in learning about these mechanisms and immune-related adverse events.

One additional consideration for this new generation of therapies is the cost to the patient and the healthcare system. There are some studies that suggest that first-line pembrolizumab and consolidation durvalumab are cost-effective with a similar conclusion for EGFR+ and ALK translocation directed therapies in NSCLC. Future studies will help identify patients who can most benefit from these next-generation therapies and help minimize toxicities and undue financial burden.

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**Figure 1. Treatment Algorithm for Advanced NSCLC.**

Legend: The treatment of patients with advanced NSCLC is detailed here in the first-and second-line setting. Patients with no identifiable driver mutations follow along the treatment course on the left, while patients with EGFR/ALK/ROS1 molecular alterations follow the right side. Patients with NSCLCs that carry BRAF and NTRK molecular alterations were excluded from this algorithm as there is not enough evidence to suggest a straightforward treatment path and will be up to the discretion of the treating physician based on evidence discussed above. All treatment decisions should be tailored to a patient’s specific performance status, biomarkers, prior treatments and the physician’s clinical judgement. Parts of the figures were adapted from the Society of Immunotherapy, see reference 53, Herbst RS, Davies MJ, Neal JW, Sagnerky S, Gandhi L, Antonia SJ, et al. and The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of non-small cell lung cancer (NSCLC). J Immunother Cancer. 2018;6(3):1-15), while the targeted therapy part was adapted from the studies in this paper.
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