IJMS INTERNATIONAL JOURNAL of MEDICAL STUDENTS

Review

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

Sze Wah Samuel Chan,[1] Elliot Smith.[1*]

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 234,030 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.[3,4] Few effective treatments are available after disease progression and mainly involve single-agent chemotherapy such as docetaxel.[3]

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

[1] Medical Student, Faculty of Medicine, University of Toronto, Canada.
*Both authors are co-first authors

Correspondence:
Sze Wah Samuel Chan
Address: 1 King's College Cir, Toronto, ON M5S 1A8, Canada
Email: schan93@gmail.com

Editor: Mihnea-Alexandru Găman
Student Editors: Madeleine Jemima Cox
Submission: Nov 29, 2019
Acceptance: Dec 26, 2019
Publication: Apr 30, 2020
Process: Peer-reviewed

adverse events such as neutropenia, thrombocytopenia, and anemia in the chemotherapy group.[12]

Atezolizumab monotherapy as second-line therapy for metastatic NSCLC

Atezolizumab is a humanized monoclonal IgG1 PD-L1 antagonist. The OAK trial demonstrated in second-line therapy that atezolizumab improved overall survival (OS) (HR 0.73, 95% CI 0.62 to 0.87, P = 0.0003) compared to docetaxel with a median follow-up of 21 months.[13] Similar to nivolumab, the difference was significant regardless of PD-L1 tumor expression. Fewer grade 3-4 adverse events were observed with immunotherapy (15% vs. 43%), where chemotherapy had more hematological adverse events such as anemia, neutropenia, and febrile neutropenia.[13]

Table 1. Common Terminology for Adverse Events (CTCAE) v5.0 examples.

Grade 1	Grade 2	Grade 3	Grade 4
Rash – Maculo-papular			
<10% Body surface area (BSA)	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			
<4 stools per day over baseline, mile increase in ostomy output	Increase of 4-6 stools per day over baseline, a moderate increase in ostomy output, limits instrumental ADL	Increase of >7 stools per day over baseline, hospitalization is indicated, severe increase in ostomy output, limiting self-care ADLs	Life-threatening, urgent intervention required
Neutropenia			
<LLN including 1500/m^3, 1.5 x 10^9 / L	<1500 – 1000/mm^3, <1.5 – 1.0 x 10^9 / L	<1000 – 500/mm^3, <1.0 – 0.5 x 10^9 / L	<500/mm^3, <0.5 x 10^9 / L
Anemia			
Hemoglobin < LLN, including <10.0 g/dL, <6.2 mmol/L, <100 g/L	Hemoglobin <10.0-8.0 g/dL, <6.2-4.9 mmol/L, <100-80 g/L	Hemoglobin <8.0 g/dL, <4.9 mmol/L, <80 g/L; transfusion is indicated	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 2017, https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm). Each adverse event is graded according to severity, where grade 1 is the least severe with no intervention to grade 4, which requires urgent intervention and grade 5 is reserved for deaths related to the adverse event. Self-care activities of daily living (ADL), according to CTCAE, refer to bathing, dressing, undressing, feeding self, using the toilet, taking medication and not bedridden. Instrumental ADLs refer to preparing meals, shopping for groceries or clothing, using the telephone or managing money.

Pembrolizumab as monotherapy in first- or second-line metastatic NSCLC

Pembrolizumab, a humanized monoclonal IgG4 PD-1 receptor antagonist, was first tested in 2016 where the Keynote 10 trial compared pembrolizumab vs. docetaxel in the second-line, which showed superior overall survival (HR 0.61, 95% CI 0.49 to 0.75, P <0·0001, median follow-up was 13.1 months) driven mainly by patients with PD-L1 immunohistochemical staining of at least 50% (OS HR 0.50, 95% CI 0.36-0.70,P <0.0001) for which it was mainly powered to detect.[14] In the same year, Keynote 24, with a median follow-up of 11.2 months, confirmed the benefit in the . 50% PD-L1 setting now in the first-line setting. Pembrolizumab treatment induced longer overall survival (HR 0.60, 95% CI 0.41 to 0.89, P = 0.005) compared to platinum-based doublet therapy.[15] Furthermore, grade 3-5 adverse events were less in the immunotherapy group (26.6% vs. 53.3%), which were similar to nivolumab and atezolizumab, where the chemotherapy group had more hematological suppression. One key point from the trial was that immunotherapies demonstrated more immune-related adverse events such as more severe skin reactions, pneumonitis and colitis.[15] 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=0·0018) at a median follow-up of 12.8 months with a similar side effect profile demonstrated in the previous trials.[16]

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 chemoradiotherapy compared to placebo. Durvalumab-treated patients demonstrated superior overall survival (HR 0.68, 99.73% CI 0.47 to 0.997, 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.[17,18] Durvalumab is unique as the only approved consolidation immunotherapy single agent for 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.[19,20] 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.[21] Adverse events of grade 3 or higher were found in 67.2% 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.[21] 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 (69.8% vs. 68.2%) with more pneumonitis and autoimmune hepatitis in the combination group.[22]

One of the CheckMate 227 secondary goals compared first-line platinum-doublet chemotherapy ± nivolumab in the <1% PD-L1 population, which showed improved OS compared to chemotherapy alone (HR 0.78, 95% CI 0.60 to 1.02, P = 0.035, minimum follow-up was 29.3 months).[23] IMpower 131 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, 0.603 to 0.848; P = 0.0001) but no differences in overall survival (P = 0.16).[24,25] The IMpower130 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.[26]

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.[27] 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 0.90, 95% CI 0.76-1.07) and PD-L1 .50% (HR 0.87, 95% CI 0.68-1.12), but there were more grade 3-4 events in the dual immunotherapy group compared to the monotherapy group (35.5% vs. 19.4%). More specifically it included more rash, pruritis, diarrhea and adverse events with suspected

immune etiology affecting the pulmonary, gastrointestinal, skin and endocrine systems.[23]

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).[28] The NEPTUNE trial (durvalumab + tremelimumab vs. chemotherapy) includes ALK and EGFR patients, and is set to reveal results soon.[29]

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.[30] 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, endocrinopathies, 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.[31] 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.[30,31] 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 mainstay 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.[31] If refractory, immunomodulatory therapies could serve as the next step; for instance, infliximab has been reported in the use of refractory colitis.[31–33]

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 involvement	Neurological syndromes
Infusion-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, reference 31: Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):1–28.

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 aberrations in NSCLC varies drastically based on geographical distribution, varying from 10% in North American and Western European cases to 30% in East Asian cases.[34,35] Studies have reported a higher prevalence in females and non-smokers.[34,36] From a histologic 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.[35,36] 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).[37] 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).[37] From a toxicity perspective, in IPASS, gefitinib was associated with fewer grade 3-4 adverse events (28.7% vs 61.0%).[37] The most common toxicities for gefitinib included rash, diarrhea and mucositis, while neurotoxicities and hematologic toxicities were significantly lower compared to chemotherapy.[37]

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<0.0001).[38] 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.[39,40] 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 0.16-0.39, P<0.0001).[41] Erlotinib intercalated chemotherapy also showed significant improvements in overall survival (HR 0·48, 95% CI 0.27–0.84, P = 0·0092).[41] 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 aminotransferase 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.[38]

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 0.31–0.48, P<0·0001) with afatinib, and these patients were followed for an estimated two years.[42] In addition, in patients who previously developed resistance, PFS was significantly improved by

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.[43]

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 T790M 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 fewer grade 3-4 adverse events than chemotherapy (23% 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.[44] 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.[45] 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 partner 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).[48] 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-naïve 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).[49]

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 56% responded (95% CI, 49-65%), 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 0.33-0.74, 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.[52] 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.[52]

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).[53]

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, afatinib, erlotinib, gefitinib and osimertinib may be used in first-line with osimertinib used in treatment-resistant cases. For ALK-fusion tumors, crizotinib 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 preliminary evidence of efficacy in patients who have failed multiple other ALK inhibitors; however, phase III trial data is not yet available.[54]

For tumors carrying ROS1 fusions, there is evidence that crizotinib and lorlatinib are effective; entrectinib is another drug that is showing promise.[55,56] 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 subpopulation.[53] 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 < 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.

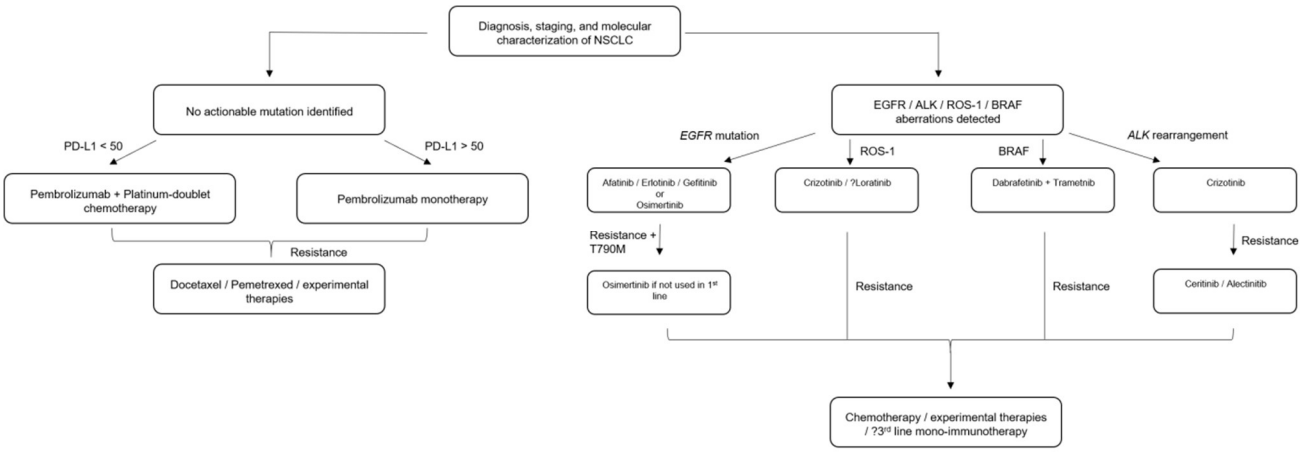
Conclusion

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.[57] 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 compositive biomarkers are emerging biomarkers.[58] 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.[59–65] Future studies will help identify patients who can most benefit from these next-generation therapies and help minimize toxicities and undue financial burden.

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/BRAF/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, Sagorsky 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(1):1–15), while the targeted therapy part was adapted from the studies in this paper.

References

1. Ferlay J. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. 2018;1–13.
2. Inamura K. Lung Cancer : Understanding its Molecular Pathology and the 2015 WHO Classification. 2017;7(August):1–7.
3. Brule S. Second Line and Maintenance Therapy for Advanced Non-Small Cell Lung Cancer without Driver Mutation: An Evolving Paradigm. Int J Cancer Clin Res. 2016 Jun 30;3(3):055.
4. Zarogoulidis K, Zarogoulidis P, Darwiche K, Boutsikou E, Machairiotis N, Tsakiridis K, et al. Treatment of non-small cell lung cancer (NSCLC). J Thorac Dis. 2013;5(SUPPL.4):2–9.
5. Miura Y, Sunaga N. Role of immunotherapy for oncogene-driven non-small cell lung cancer. Cancers (Basel). 2018;10(8):245.
6. Gong J, Chehrazi-Raffle A, Reddi S, Salgia R. Development of PD-1 and PD-L1 inhibitors as a form of cancer immunotherapy: a comprehensive review of registration trials and future considerations. J Immunother Cancer. 2018 Dec 23;6(1):8.
7. He J, Hu Y, Hu M, Li B. Development of PD-1/PD-L1 Pathway in Tumor Immune Microenvironment and Treatment for Non-Small Cell Lung Cancer. Sci Rep. 2015 Oct 17;5(1):13110.
8. Trotti A, Colevas AD, Setser A, Basch E. Patient-Reported Outcomes and the Evolution of Adverse Event Reporting in Oncology. J Clin Oncol. 2007 Nov 10;25(32):5121–7.
9. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE). 2017 [cited 2019 Dec 17]. Available from: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
10. Brahmer J, Reckamp KL, Baas P, Crinò L, Eberhardt WEE, Poddubskaya E, et al. Nivolumab versus Docetaxel in Advanced Squamous-Cell Non–Small-Cell Lung Cancer. N Engl J Med. 2015 Jul 9;373(2):123–35.
11. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Non-squamous Non-small Cell Lung Cancer. 2015 Oct 22;373(17):1627-1639.
12. Carbone DP, Reck M, Paz-Ares L, Creelan B, Horn L, Steins M, et al. First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer. N Engl J Med. 2017 Jun 22;376(25):2415–26.
13. Rittmeyer A, Barlesi F, Waterkamp D, Park K, Ciardiello F, von Pawel J, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet. 2017 Jan 21;389(10066):255–65.
14. Herbst RS, Baas P, Kim D-W, Felip E, Pérez-Gracia JL, Han J-Y, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet. 2016 Apr 9;387(10027):1540–50.
15. Reck M, Rodríguez-Abreu D, Robinson AG, Hui R, Csőszi T, Fülöp A, et al. Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer. N Engl J Med. 2016 Nov 10;375(19):1823–33.
16. Mok TSK, Wu Y-L, Kudaba I, Kowalski DM, Cho BC, Turna HZ, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. Lancet. 2019 May 4;393(10183):1819–30.
17. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Overall Survival with Durvalumab after Chemoradiotherapy in Stage III NSCLC. N Engl J Med. 2018;NEJMoa1809697.
18. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. N Engl J Med. 2017 Nov 16;377(20):1919–29.
19. Bracci L, Schiavoni G, Sistigu A, Belardelli F. Immune-based mechanisms of cytotoxic chemotherapy: implications for the design of novel and rationale-based combined treatments against cancer. Cell Death Differ. 2014 Jan 21;21(1):15–25.
20. Ogawara D, Soda H, Iwasaki K, Suyama T, Taniguchi H, Fukuda Y, et al. Remarkable response of nivolumab-refractory lung cancer to salvage chemotherapy. Thorac Cancer. 2018 Jan;9(1):175–80.
21. Gandhi L, Rodríguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer. N Engl J Med. 2018 May 31;378(22):2078–92.
22. Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer. N Engl J Med. 2018 Nov 22;379(21):2040–51.
23. Hellmann MD, Paz-Ares L, Bernabe Caro R, Zurawski B, Kim S-W, Carcereny Costa E, et al. Nivolumab plus Ipilimumab in Advanced Non–Small-Cell Lung Cancer. N Engl J Med. 2019 Nov 21;381(21):2020–31.
24. Cappuzzo F, Jotte R, Vynnychenko I, Stroyakovskiy D, Rodriguez DA, Hussein M, et al. IMpower131: Final OS Results of Carboplatin + Nab-Paclitaxel ± Atezolizumab in Advanced Squamous NSCLC. In: IASLC 2019 World Conference on Lung Cancer hosted by the International Association for the Study of Lung Cancer. Barcelona; 2019.
25. Jotte RM, Cappuzzo F, Vynnychenko I, Stroyakovskiy D, Rodriguez Abreu D, Hussein MA, et al. IMpower131: Primary PFS and safety analysis of a randomized phase III study of atezolizumab + carboplatin + paclitaxel or nab-paclitaxel vs carboplatin + nab-paclitaxel as 1L therapy in advanced squamous NSCLC. J Clin Oncol. 2018 Jun 20;36(18_suppl):LBA9000–LBA9000.
26. Cappuzzo F, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, et al. IMpower130: Progression-free survival (PFS) and safety analysis from a randomised phase III study of carboplatin + nab-paclitaxel (CnP) with or without atezolizumab (atezo) as first-line (1L) therapy in advanced non-squamous NSCLC. Ann Oncol. 2018 Oct; 29(suppl_8): mdy424.065.
27. Chae YK, Arya A, Iams W, Cruz MR, Chandra S, Choi J, et al. Current landscape and future of dual anti-CTLA4 and PD-1/PD-L1 blockade immunotherapy in cancer; lessons learned from clinical trials with melanoma and non-small cell lung cancer (NSCLC). J Immunother Cancer. 2018 Dec 16;6(1):39.
28. Rizvi NA, Chul Cho B, Reinmuth N, Lee KH, Ahn M-J, Luft A, et al. Durvalumab with or without tremelimumab vs platinum-based chemotherapy as first-line treatment for metastatic non-small cell lung cancer: MYSTIC. Ann Oncol. 2018;29(suppl_10):x39-x43.
29. Mok T, Schmid P, Arén O, Arrieta O, Gottfried M, Jazieh AR, et al. 192TiP: NEPTUNE: A global, phase 3 study of durvalumab (MEDI4736) plus tremelimumab combination therapy versus standard of care (SoC) platinum-based chemotherapy in the first-line treatment of patients (pts) with advanced or metastatic NSCLC. J Thorac Oncol. 2016 Apr 1;11(4):S140–1.
30. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2018 Jun 10;36(17):1714–68.
31. Puzanov I, Diab A, Abdallah K, Bingham CO, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: Consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer. 2017;5(1):1–28.
32. Merrill SP, Reynolds P, Kalra A, Biehl J, Vandivier RW, Mueller SW. Early administration of infliximab for severe ipilimumab-related diarrhea in a critically ill patient. Ann Pharmacother. 2014 Jun 20;48(6):806–10.
33. Pagès C, Gornet JM, Monsel G, Allez M, Bertheau P, Bagot M, et al. Ipilimumab-induced acute severe colitis treated by infliximab. Melanoma Res. 2013 Jun;23(3):227–30.
34. Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer. 2006 Jan 15;118(2):257-62.
35. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst. 2005 Mar 2;97(5):339-46.
36. Tokumo M, Toyooka S, Kiura K, Shigematsu H, Tomii K, Aoe M, et al. The relationship between epidermal growth factor receptor mutations and clinicopathologic features in non-small cell lung cancers. Clin Cancer Res. 2005 Feb 1;11(3):1167-73.
37. Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010 Jun 24;362(25):2380-8.
38. Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol. 2012 Mar;13(3):239–46.
39. Zhou C, Wu Y-L, Chen G, Feng J, Liu X-Q, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2011 Aug;12(8):735–42.
40. Wu YL, Zhou C, Liam CK, Wu G, Liu X, Zhong Z, et al. First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: Analyses from the phase III, randomized, open-label, ENSURE study. Ann Oncol. 2015 Sep;26(9):1883-9.
41. Wu Y-L, Lee JS, Thongprasert S, Yu C-J, Zhang L, Ladrera G, et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. Lancet Oncol. 2013 Jul;14(8):777–86.
42. Miller VA, Hirsh V, Cadranel J, Chen Y-M, Park K, Kim S-W, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol. 2012 May;13(5):528–38.
43. Soria J-C, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, et al. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of

the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2015 Aug;16(8):897–907.

44. Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017 Feb 16;376(7):629-640.
45. Soria J-C, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer. N Engl J Med. 2017 Nov;378(2):113–25.
46. Le T, Gerber DE. ALK alterations and inhibition in lung cancer. Semin Cancer Biol. 2016/09/13. 2017 Feb;42:81–8.
47. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H, et al. Global Survey of Phosphotyrosine Signaling Identifies Oncogenic Kinases in Lung Cancer. Cell. 2007 Dec 14;131(6):1190-203.
48. Shaw AT, Kim DW, Nakagawa K, Seto T, Crinó L, Ahn MJ, et al. Crizotinib versus Chemotherapy in Advanced ALK -Positive Lung Cancer. N Engl J Med. 2013 Jun 20;368(25):2385-94.
49. Solomon BJ, Reisman A, Mok T, Wilner KD, Paolini J, Blackhall F, et al. First-Line Crizotinib versus Chemotherapy in ALK -Positive Lung Cancer . N Engl J Med. 2014 Dec 4;371(23):2167-77.
50. Kim DW, Mehra R, Tan DSW, Felip E, Chow LQM, Camidge DR, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol. 2016 Apr;17(4):452-463. doi: 10.1016/S1470-2045(15)00614-2.
51. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim D-W, et al. Alectinib versus Crizotinib in Untreated ALK -Positive Non–Small-Cell Lung Cancer. N Engl J Med. 2017 Aug 31;377(9):829-838.
52. Camidge DR, Kim HR, Ahn M-J, Yang JC-H, Han J-Y, Lee J-S, et al. Brigatinib versus Crizotinib in ALK -Positive Non–Small-Cell Lung Cancer. N Engl J Med. 2018 Nov 22;379(21):2027-2039.
53. Herbst RS, Davies MJ, Neal JW, Sagorsky S, Gandhi L, Antonia SJ, et al. 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(1):1–15.
54. Shaw AT, Solomon BJ, Besse B, Bauer TM, Lin C-C, Soo RA, et al. ALK Resistance Mutations and Efficacy of Lorlatinib in Advanced Anaplastic Lymphoma Kinase-Positive Non-Small-Cell Lung Cancer. J Clin Oncol. 2019 Jun 1;37(16):1370–9.
55. Shaw AT, Solomon BJ, Chiari R, Riely GJ, Besse B, Soo RA, et al. Lorlatinib in advanced ROS1-positive non-small-cell lung cancer: a multicentre, open-label, single-arm, phase 1-2 trial. Lancet Oncol. 2019 Dec;20(12):1691-1701
56. Drilon A, Sankhala KK, Liu S V., Cho BC, Blakely C, Chee CE, et al. Abstract CT060: STARTRK-2: A global phase 2, open-label, basket study of entrectinib in patients with locally advanced or metastatic solid tumors harboring TRK, ROS1, or ALK gene fusions. In: Clinical Trials. American Association for Cancer Research; 2017. p. CT060–CT060.
57. Grizzi G, Caccese M, Gkountakos A, Carbognin L, Tortora G, Bria E, et al. Expert Review of Molecular Diagnostics Putative predictors of efficacy for immune checkpoint inhibitors in non-small-cell lung cancer : facing the complexity of the immune system. Expert Rev Mol Diagn. 2017;17(12):1055–69.
58. Voong KR, Feliciano J, Becker D, Levy B. Beyond PD-L1 testing-emerging biomarkers for immunotherapy in non-small cell lung cancer. Ann Transl Med. 2017 Sep ;5(18):376.
59. Huang M, Pietanza MC, Samkari A, Pellissier J, Burke T, Chandwani S, et al. Q-TWiST Analysis to Assess Benefit–Risk of Pembrolizumab in Patients with PD-L1–Positive Advanced or Metastatic Non-small Cell Lung Cancer. Pharmacoeconomics. 2019 Jan 4;37(1):105–16.
60. Huang M, Lou Y, Pellissier J, Burke T, Liu FX, Xu R, et al. Cost Effectiveness of Pembrolizumab vs. Standard-of-Care Chemotherapy as First-Line Treatment for Metastatic NSCLC that Expresses High Levels of PD-L1 in the United States. Pharmacoeconomics. 2017 Aug 15;35(8):831–44.
61. Criss SD, Mooradian MJ, Sheehan DF, Zubiri L, Lumish MA, Gainor JF, et al. Cost-effectiveness and Budgetary Consequence Analysis of Durvalumab Consolidation Therapy vs No Consolidation Therapy After Chemoradiotherapy in Stage III Non–Small Cell Lung Cancer in the Context of the US Health Care System. JAMA Oncol. 2019 Mar 1;5(3):358.
62. Lange A, Prenzler A, Frank M, Golpon H, Welte T, von der Schulenburg J-M. A systematic review of the cost-effectiveness of targeted therapies for metastatic non-small cell lung cancer (NSCLC). BMC Pulm Med. 2014 Dec 4;14(1):192.
63. Ting J, Tien Ho P, Xiang P, Sugay A, Abdel-Sattar M, Wilson L. Cost-Effectiveness and Value of Information of Erlotinib, Afatinib, and Cisplatin-Pemetrexed for First-Line Treatment of Advanced EGFR Mutation-Positive Non-Small-Cell Lung Cancer in the United States. Value Heal. 2015 Sep;18(6):774–82.
64. Lu S, Yu Y, Fu S, Ren H. Cost-effectiveness of ALK testing and first-line crizotinib therapy for non-small-cell lung cancer in China. Gangopadhyay N, editor. PLoS One. 2018 Oct 23;13(10):e0205827.
65. Wang S, Peng L, Li J, Zeng X, Ouyang L, Tan C, et al. A Trial-Based Cost-Effectiveness Analysis of Erlotinib Alone versus Platinum-Based Doublet Chemotherapy as First-Line Therapy for Eastern Asian Nonsquamous Non-Small-Cell Lung Cancer. PLoS One. 2013;8 (3) (no(e55917).

Acknowledgments

The authors would like to acknowledge Dr. Geoffrey Liu for his mentorship, critical review of the manuscript for accuracy and expert guidance.

Conflict of Interest Statement & Funding

The Authors have no funding, financial relationships or conflicts of interest to disclose.

Author Contributions

SWSC and ES were involved in the conceptualization, investigation of data and writing of the manuscript.

Cite as:

Chan, S, Smith, E. Next Generation of Advanced Non-Small Cell Lung Cancer Therapy: Targeted and Immuno-Therapies. Int J Med Students. 2020 Jan-Apr;8(1):26-32.

ISSN 2076-6327

This journal is published by the University Library System, University of Pittsburgh **as part of the** Digital Publishing Program **and is co-sponsored by the** University of Pittsburgh Press.