Paradigm shift in the management of metastatic Non-small Cell Lung Cancer

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Abstract

Background: Lung cancer is one of the leading causes of cancer mortality in the US. The use of precision medicine in the past 10 years has significantly changed the therapeutic landscape of lung cancer. Management of advanced non-small cell lung cancer (NSCLC) has transitioned from a chemotherapeutic approach to targeted treatments and immunotherapeutic agents. Several tyrosine kinase inhibitors (TKIs) have been approved for patients with targeted mutations while patients who do not have driver mutations; immunotherapy has been recently approved as frontline therapy, which has resulted in marked improvement in overall survival and added a new tool in our armamentarium. Aims: The purpose of this review is to highlight recent advancements in diagnostic approach and management strategies in patients with metastatic NSCLC. Materials and methods: Published studies included in Medline (via PubMed) and National Comprehensive Cancer Network Guidelines were reviewed for data gathering. Conclusion: The use of next generation sequencing has significantly changed our understanding of molecular oncogenic mechanisms of lung cancer. These advancements have created a paradigm shift in the treatment strategies of metastatic lung cancer from primarily chemotherapeutic approach to increasing use of targeted therapies and immune check point inhibitors (ICI) leading to better survival rates and lesser toxicity.

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Abstract

Background:

Lung cancer is one of the leading causes of cancer mortality in the US**.** The use of precision medicine in the past 10 years has significantly changed the therapeutic landscape of lung cancer. Management of advanced non-small cell lung cancer (NSCLC) has transitioned from a chemotherapeutic approach to targeted treatments and immunotherapeutic agents. Several tyrosine kinase inhibitors (TKIs) have been approved for patients with targeted mutations while patients who do not have driver mutations; immunotherapy has been recently approved as frontline therapy,which has resulted in marked improvement in overall survival and added a new tool in our armamentarium.

*Aims***:**

The purpose of this review is to highlight recent advancements in diagnostic approach and management strategies in patients with metastatic NSCLC.

*Materials and methods***:**

A literature search was conducted on Medline (via PubMed) andNational Comprehensive Cancer Network Guidelines using the keywords "precision diagnosis," "advanced non-small cell lung cancer," "target therapies," "immunotherapy."

Conclusion:

The use of next generation sequencing has significantly changed our understanding of molecular oncogenic mechanisms of lung cancer. These advancements have created a paradigm shift in the treatment strategies of metastatic lung cancer from primarily chemotherapeutic approach to increasing use of targeted therapies and immunecheckpointinhibitors (ICI) leading to better survival rates and lesser toxicity.

Data gathering method

Published studies regarding the use of biological therapies in advanced non-small cell lung cancer were reviewed using Medline (via PubMed) and National Comprehensive Cancer Network Guidelines for data gathering.

Take-home' message for the clinician

Lung cancer continues to be the leading cause of cancer deaths. The molecular landscape of lung canceris rapidly evolving leading to a paradigm shift in the management ofadvanced non-small cell lung cancer. The new therapeutic regimens are primarily designed to use target therapies, mainly tyrosine kinase inhibitorsin patients with targeted mutations and immunotherapies (with or without chemotherapy) in patients without driver mutations. Both novel treatments have lesser toxicities and better safety profile compared to chemotherapeutic agents.

Introduction

Lung cancer is one of the most frequent and deadly cancers worldwide. In the United States, approximately 230,000 patients are diagnosed with lung cancer and it is known to cause over 135,000 deaths annually [1]. Tobacco smoking is known to be the most common etiology for lung cancer accounting for approximately 80% of the lung cancer cases in the United States and other countries where smoking is common [2].However, 20% of lung cancer cases occur in patients who have never smoked, most commonly in women from East Asia, and has been associated with environmental exposures such as second-hand smoking, pollution and occupational carcinogens [3-5]. In 2010, data from the National Lung Screening Trial (NLST)showed that

screening with low-dose helical CT scans in highrisk patients as compared with chest radiography resulted in significant reduction in the rates of both death from lung cancer (20%) and death from any cause (6.7%) [6-8].

The understanding of the biology and oncogenic mechanisms in lung cancer has greatly expanded in the last 20 years. This has led to the development of new biomarker-targeted therapies andimmune checkpoint inhibitors, with or without cytotoxic therapy regimens,for use in patients without targetable mutations.In an exploratory analysis conducted by Lung cancer mutation consortium, nearly 64% of 1007 patients with advanced lung adenocarcinoma were found to have targetable oncogenic drivers. Patients with driver mutations who received targeted therapies were found to have longer overall survival (OS) as compared to those with targetable mutation who did not receive targeted treatments or those without driver mutations (median survival, 3.5 years vs. 2.4 years and 2.1 years, respectively). [9] In the future, ongoing efforts to improve precision diagnosis by determining additional novel molecular markers and targeted therapies will continue to broaden the patient spectrum with advanced NSCLC patients who can benefit from these treatments and further improve clinical outcomes.

Since histologic features allow subtyping and molecular analysis of lung cancers and determine the major treatment options, a pathological diagnosis is essential.

There are various histological subtypes of NSCLC with adenocarcinoma (60%) being the most common type followed by squamous cell carcinoma (15%). NSCLC favoring adenocarcinoma is characterized by IHC staining positive for thyroid transcription factor 1 and cytokeratin 7 and negative for small cell cancer markers. NSCLC favoring squamous cell carcinoma is characterized by tumor markers negative for adenocarcinoma and positive for p63, cytokeratin 5, or cytokeratin 6. The tumor is classified as NSCLC, not otherwise specified (NOS) if all the above markers are negative. [10].

In this review, we provide an overview of the recent advances made in understanding the disease biology, mechanisms of tumor progression and multimodal treatment of metastatic NSCLC.

Molecular characteristics of lung cancer

Lung cancer is a molecularly heterogeneous disease, and several forms of genomic instability can drive its development.A recent report on whole exomegenomic sequencing of 100 NSCLC tumor samples revealed that besides clonal driver mutations, other processes such as chromosomal instability, genome duplications and subclonal mutations cause genetic heterogeneity, all of which have an influence on prognosis [11]. Understanding the biology and molecular characteristics of this disease have been crucial for the development of modern treatment strategies in patients with lung cancer.

The molecular analysis of lung cancers has shown thatEGFR and KRAS and the tumor suppressor genes TP53, KEAP1, STK11 and NF1 are the most commonly mutated genes in lung adenocarcinoma, while in squamous cell lung cancer are tumor suppressor gene TP53, which is present in more than 90% of tumors, and CDKN2A are the most commonly mutated genes[12]. Actionable mutations in receptor tyrosine kinases are rarely observed in squamous cell lung cancers (SCLC) even though EGFR amplification may be found in them [13]. Mutations in KRAS and EGFR genes when detected are usually present in the founder clones, indicating their roles in tumor initiation and can be targets for therapeutic intervention, while mutations in tumor protein TP53 are commonly observed with advancing grade, suggesting a role during tumor progression [14].KRAS and EGFR are mutually exclusive but when they coexist, KRAS mutation can confer resistance to EGFR inhibitors [14].

The genomic profile of smokers is markedly distinct from that of non-smokers [12,15]. Non-smokers have predominant transversionof cytosine to thymine, harbor tumors that have a lower than average mutation load, and have a higher prevalence ofoncogenic drivers such as EGFR mutations, anaplastic lymphoma kinase (ALK) rearrangements , ROS proto-oncogene receptor tyrosine kinase 1 (ROS1) , BRAF V600 E mutations, and neurotrophic receptor tyrosine kinase (NTRK) gene fusions;tumors from smokers contain higher mutation frequency, predominantly cytosine to adenine nucleotide transversions, and non-actionable

mutations such as KRAS and TP53 [9,12,15].

An oncogenic driver identified relatively recently in NSCLC is human epidermal growth factor receptor (HER2, also known as ERBB2),a member of the EGFR receptor tyrosine kinase family,which has been added to the growing list of actionable targets [16,17].Early studies observed HER2 overexpression in approximately 1% to 2% of lung cancer cases, whereas results from more current studies show a range of approximately 6% to 30%[18].Data from tumor models and patients expressing HER2 mutations suggest that they tend to be insensitive to EGFR tyrosine kinase inhibitors (TKIs), suggesting the need for specific HER2-directed therapies for these patients. Many clinical trials are being conducted to identify effective and safe targeted treatment for metastatic HER2-mutated NSCLC patients [19].

Due to increasing knowledge of tumor heterogeneity, molecular testing is now performed at the time of metastatic non-small cell lung cancer diagnosis to identify gene mutations or rearrangements for which there are targeted therapies. The molecular targets of non-small cell lung cancer described above are shown in Figure 1.

The use of immune checkpoint inhibitors has become the standard of care for patients with advanced NSCLC. The only predictive biomarker currently available to guide treatment with immunotherapy is programmed death- ligand 1(PD-L1) protein. [19] Studies have shown that PD-L1 tumor proportion score (TPS) measured by immunohistochemical assay is a better predictor of response to immunotherapy as compared to programmed cell death 1 (PD-1). Therefore it is recommended that all patients with advanced NSCLC should get testing for PD-L1 TPS.[20] A PD-L1 TPS score >50% is required for first line treatment with pembrolizumab while patients who have progressed on previous treatment can receive immunotherapy for PD-L1 negative tumors. [21] In patients with PD-L1 negative tumors, the selection of treatment may be based on tumor mutational burden, disease volume and performance status.[21] The research now is focused on finding a new predictive biomarker for immunotherapy so that it can guide optimal treatment benefit in patients.

Therapeutic strategiesfor advanced NSCLC

Targeted Therapy

The management of lung cancer has been transformed by the advent of next generation sequencing leading to identification of therapeutic targets resulting in better clinical outcomes compared to patients with absence of molecular targets. [9] Therefore molecular testing for treatable oncogenic alterations should be implemented as an essential part of diagnostic testing before deciding treatment plan for a patient with newly diagnosed NSCLC.[22,23]

EGFR- mutant advanced NSCLC

The incidence of somatic EGFR mutation in advanced NSCLC is approximately 20% in Caucasian patients, but higher incidence rates of about 48% have been found among patients of East Asian ethnicity [24]. The incidence of mutation also correlates with histologic type of NSCLC, sex and age of patient and smoking history. [25]EGFR belongs to a receptor kinase family that also includes human HER2(ERBB3) and HER3 (ERBB4) [26]. The most commonly seen mutations are EGFR exon 19 deletion or missense point mutation on exon 21 (EGFR L858R),associated with increased sensitivity to EGFR tyrosine kinase inhibitors (TKI) [26].First-generation EGFR TKIs, including gefitinib and erlotinib, resulted inhigher objective response rates (ORRs) and progression-free survival (PFS) compared to cytotoxic therapy in previously untreated patients with EGFR mutations [27-31]. In a meta-analysis of randomized trials of the EGFR tyrosine kinase inhibitors gefitinib, erlotinib and afatinib, significant improvement was seen in ORR and PFS, as compared with first-line chemotherapy (PFS 9.6-13.1 months versus4.6-6.9 months; (HR)for progression or death, 0.37; 95% confidence interval (CI), 0.32 to 0.41; $p<0.001$) [32].

In contrast to the first-generation EGFR TKIs gefitinib and erlotinib, which are reversible competitive ATP inhibitors targeting only EGFR, second-generation inhibitors including afatinib and dacomitinib are irreversible inhibitors that also target HER2 and HER4. Second-generation TKIsafatinib and dacomitinib-demonstrated improved PFS when compared to first generation TKI gefitinib[33, 34]. Despite impressive

initial responses to both first- and second-generation EGFR TKIs, most patients experience disease progression after 9-12 months of treatment, indicating the frequent emergence of resistance to these agents.

Many mechanisms of resistance have been known by which first and second generation TKIs become ineffective in patients taking it. The most common is a second mutation in exon 20, with a threonine-to-methionine substitution on codon 790 (T790M). [35] This eventually causes resistance either due to tyrosine kinase domain having increased affinity for ATP or from steric hindrance. [35] Other mechanisms of acquired resistance include SCLC transformation, mutations in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit-alpha (PIK3CA) , MET or BRAF and amplifications in HER 2. [36] Nearly 60% of patients develop resistance after first- or second-generation EGFR TKI due to T790M mutation and third generation EGFR TKI can specifically overcome it. [36]Therefore, it becomes important to repeat next generation sequencing at the time of disease progression. [36] Osimertinib, a third generation irreversible EGFR TKI targeting T790M mutation, binds covalently to cysteine on codon 797, overcoming the resistance. [37, 38]Osimertinib has now been FDA approved as upfront treatment for advanced NSCLC patients with exon 19 deletion or L858R sensitizing mutation replacing first and second generation TKIs. [39]This is based on efficacy and safety data results of the FLAURA trial. In this double-blind phase III randomized control study, 556 treatment naive EGFR mutation-positive advanced NSCLC patients were assigned to either receive osimertinib or standard EGFR-TKI (gefitinib or erlotinib) in 1:1 ratio. Osimertinib was found to have superior efficacy with median PFS 18.9 months vs 10.2 months ; $p<0.001$ and median OS 38.6 vs 31.8 months;$p= 0.046$ compared with erlotinib and gefitinib. Some other favorable outcomes with osimertinib were lower rates and grades of side-effects, fewer cases of central nervous system progression and improved post-progression outcomes.[40]

Unfortunately, patients eventually progress on osimertinib as well indicating resistance to the drug. One of the mechanisms suggested is acquisition of C797S mutation which along with L858R sensitizing mutation leads to resistance to third generation EGFR TKIs. [41] Patients with mutation in T790M, C797S and sensitizing mutations are called triple mutants and it causes resistance to all three generations of EGFR TKIs.[42] In order to overcome resistance caused by triple mutation, various strategies are being tried. Cetuximab, an anti-EGFR monoclonal antibody, is being used along with allosteric inhibitor EAI045 in patients with L858-R sensitizing mutation and an ALK inhibitor, brigatinib, known to have activity against EGFR mutations, in tumors with exon 19 deletion. [43,44]

Combinatorial approaches in the treatment of metastatic lung adenocarcinoma have shown promise. The combination of ramucirumab plus erlotinibwas approved by FDA for upfront treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletion or exon 21 (L858R) substitution mutation, based on a phase III multinational, randomized, double-blind, placebo-controlled trial, the RELAY trial[45]. A 1:1 randomization of 449 patients was done to receive oral erlotinib (150 mg/day) plus either intravenous ramucirumab (10 mg/kg) or matching placebo once every 2 weeks. Ramucirumab plus erlotinib group showed significantly longer PFS compared to erlotinib plus placebo (19.4 months; 95% CI, 15.4–21.6 versus 12.4 months;95% CI,11.0–13.5, respectively) with a HR of 0.59 (95% CI 0.46–0.76; $p<0.0001$) [45].

Future directions in the treatment of patients with EGFR mutated advanced NSCLC

Clinical trials using combinatorial approaches that have shown positive results are described below.

In an ongoing phase I/II study in patients withmetastatic EGFR-mutated (L858R or del19) NSCLC, 27 patients were given osimertinib plus gefitinib for treatment naïve patients[46]. The maximum tolerated dose was 80 mg osimertinib plus 250 mg gefitinib orally daily. 81.5% patients were able to complete[?] six cycles combination therapy (1 was discontinued for progressive disease, 4 for side-effects) with ORR of 85.2% (95% CI, 67.5%-94.1%).Nearly 82.4% of treated patients were found to have undetectable plasma EGFR at 2 weeks of treatment. The median progression- free survival was not reached (NR) at 14.8 months follow up [46].

In the phase II portion of a single-center phase I/II trial, the combination of first-line osimertinib plus bevacizumabresulted in a significantly improved 1-year PFS of76%as compared to historical rate of 51%[47].

In NEJ026, a phase III trial comparing bevacizumab plus erlotinib to monotherapy with erlotinibfor EGFR-mutated NSCLC, the combination regimen was associated with significantly superior PFS compared to single agent erlotinib[48]. At the time of interim analysis (12.4 months), patients in the erlotinib plus bevacizumab group had significantly better median PFS of 16.9 months (95% CI, 14.2-21.0) compared with 13.3 months (95% CI, 11.1-15.3) for patients in the erlotinib group (HR 0.605; 95% CI, 0.417-0.877; p=0.016)[48].Updated results of this trial presented at ASCO 2020 showed median OS with bevacizumab plus erlotinibof 50.7 months (95% CI, 37.3-NR) compared to 46.2 months (95% CI, 38.2-NR) with erlotinib alone (HR, 1.00; 95% CI, 0.68-1.48). Bevacizumab plus erlotinib were also found to have higher median survival time between enrollment and progression of disease with second line treatment (28.6 months compared to 24.3 months) with erlotinib alone

[49].

ALK Translocations

Nearly 5% of NSCLC patients are found to have overexpression of ALK protein caused by translocations of ALK. The first target drug that was associated with improved ORR and median PFS in these patients was crizotinib, which is an inhibitor of dual receptor tyrosine kinases including ALK and MET. In two randomized phase III trials involving patients with NSCLC and ALK alterations, crizotinib had superior efficacy as compared with chemotherapy in previously treated patients (median PFS, 7.7 vs. 3.0 months) [50], as well as in previously untreated patients in the PROFILE 1014 trial (median PFS, 10.9 vs. 7.0 months) [51]. ALK-TKIs became the standard of care as initial therapy based on the above phase III trials. This also highlighted the importance of doing next generation sequencing in all patients at the time of diagnosis of metastatic NSCLC. In the four-year follow up of the final OS analysis of PROFILE 1014 trial in 2018, median OS for crizotinibwas NR (95% CI, 45.8 months - NR) versus 47.5 months with chemotherapy (95% CI, 32.2-NR) [52] showing superior efficacy of crizotinib over chemotherapy.

Soon it became evident that patients with ALK translocations treated with crizotinib became resistant to the treatment and further analysis showed several complex escape mechanisms and secondary mutations as mechanisms of resistance [53]. This led to clinical trials with newer second generation ALK-TKIs (alectinib, ceritinib and brigatinib) that were more potent and effective in overcoming resistance to crizotinib as evidenced by radiographic responses among patients with ALK mutations who progressed on crizotinib[54-56].Response rates of 38%-56% have been reported with a median PFS of 5.7-8.0 months when second-generation ALK tyrosine kinase inhibitors such as ceritinib or alectinib were given to patients with ALK translocations after the failure of crizotinib therapy. Furthermore, these drugs show efficacy in patients with brain metastases (brain response rate, 33-57%), which is of clinical importance for this group of patients.

In untreated patients with ALK alterations, ceritinib proved superior to chemotherapy in the ASCEND-4 trial (median PFS, 16.6 vs. 8.1 months; HR for progression or death, 0.55; 95% CI, 0.42-0.73; p<0.001) [57]. Alectinibwas superior to crizotinib in the Japanese J-ALEX trial (PFSNR vs. 10.2 months; HR for progression or death, 0.34; 95% CI, 0.17-0.70; p<0.001) [58] and in the ALEX trial (PFSNR vs. 11.1 months; HR for progression or death, 0.47; 95% CI, 0.34-0.65; p<0.001) [59]. Another randomized study showed increased ORR and median PFS for alectinib compared to crizotinib in patients with previously untreated ALK-positive NSCLC, establishing alectinib as a first-line treatment option. Significantly higher median PFS was reported with alectinib compared to crizotinib (34.8 months versus 10.9 months, respectively) in an updated data on the ALEX trialin 2019 [60]. Alectinibwas found to have much better toxicity profile compared tocrizotinibdespite longer treatment duration with alectinib[60].In ALTA-1L study brigatinibshowed improved efficacy compared tocrizotinib (N = 275; 12-month Kaplan-Meier PFS rate, 67% versus 43%; $P < .001$), with fewer episodes of progressive disease in the CNS [61]. Updated data after more than 2 years of follow-up fromALTA-1L showed that the risk of disease progression or death was reduced by brigatinib by 76% (HR, 0.24; 95% CI, 0.12–0.45), in newly diagnosed patients who had CNS involvement at the time of enrollment. Brigatinibwas also associated with 57% reduction in the risk of disease progression or death in all patients [61].Alectinib was FDA approved on Nov 6, 2017 and brigatinibon May 22, as initial therapy for patients with ALK-positive NSCLC.

The emergence of drug resistance was unfortunately seen with second generation TKIs, alectinib and brigatinib as well despite a prolonged median disease-free period of 2 years. This led to further trials looking into third generation ALK inhibitor, loratinib for treatment of ALK-positive NSCLC patients who had progressed on two prior ALK-TKI. Loratinib finally got FDA approval on 2nd November 2018 for second- or third-line treatment of ALK-positive metastatic NSCLC based on a multiple-cohort phase 2 trial.[62]

This has led to median survival of nearly 5 years among patients with ALK-positive NSCLC treated with crizotinib followed by a second or third generation TKI.

ROS1-Rearranged NSCLC

Chromosomal rearrangements of the gene encoding ROS1 have been found in approximately 1% of patients with NSCLC [63]. Due to considerable homology between the kinase domains of ROS1 and ALK, drugs used to treat ALK-positive tumors including crizotinib[63], ceritinib [64] and lorlatinib [65] have also shown marked activity in ROS1-positive tumors. Crizotinib was found to have a response rate of 72% and median PFS of 19 months in 50 patients with NSCLC and ROS1 rearrangement [63]. Repotrectinib (TPX-0005) may be an effective therapeutic option for patients with NTRK1–3, ROS1 or ALK-rearranged advanced NSCLC who have progressed on earlier-generation TKIs as it is known to overcome resistance due to acquired mutations involving NTRK 1-3, ROS1 and ALK [66].Cabozantinib has also demonstrated anti-ROS1 activity in the second-line setting, including activity against G2032R.Most agents demonstrated good tolerability, with safety and efficacy data that are being confirmed in ongoing clinical trials, except cabozantinib which isassociated with higher toxicity, and it is therefore limited as a therapeutic agent for some patients.

BRAF-Mutant NSCLC

BRAF mutations have been identified in 2% of patients with NSCLC, half of whom have a BRAF V600E mutation. In these patients, the response rate was 63.2%, and median PFS was 9.7 months after treatment with a combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib[68].A response rate of 42% and median PFS of 7.3 months were reported after treatment with vemurafenib, another BRAF inhibitor [69].These data strongly recommend using targeted therapy to treating patients with BRAF-mutant lung cancer for better clinical outcomes .

MET exon 14-skipping mutations

Somatic mutations that affect MET exon 14, which contains the Y1003 residue required for ubiquitin-mediated degradation, lead to increased MET stability and prolonged signaling from hepatocyte growth factor stimulation [70]. On May 6, 2020, an accelerated approval to capmatinibwas granted by FDA for adult patients with metastatic NSCLC withMET exon 14-skipping mutations. This approval was based on the GEOMETRY mono-1trial, a multicenter, nonrandomized, open-label, multicohort study in which 97 patients with metastatic NSCLC with confirmed MET exon 14-skipping mutationswere treated with capmatinib[71]. The ORR was much higher, 68% among the 28 treatment-naive patients, with a response duration of 12.6 months (95% CI, 5.5–25.3) compared to ORR of 41% among the 69 previously treated patients, with a response duration of 9.7 months (95% CI, 5.5–13.0) [71].

The single-arm, international phase II VISION trial presented at ASCO 2020 has also shown tepotinib to have activity in patients withMET exon 14-skipping mutations. After nine months follow-up, the primary efficacy population of 99 patients had a 46.5% ORR, with duration of response of 11.1 months [72].

Rearrangements in RET

RET gene rearrangements can cause tumorigenesis in approximately 1 to 2% of patients with NSCLC [73]. Multiple RET targeting TKIs that have shown clinical efficacy in patients with RET rearrangements are available in the market. Cabozantinib and Vendatinib have shown modest clinical efficacy with ORR of 28% and 18% and PFS of 5.5 months and 4.5 months respectively. [74, 75]

In another multicenter, multi-cohort clinical trial LIBRETTO-001, efficacy of selpercatinib was evaluated in patients with RET fusion positive NSCLC.In this study, 105 adult patients previously treated with platinum

chemotherapy were treated with selpercatinibshowed ORR of 64% with 81% having responses lasting 6 months or longer. Selpercatinib was also given to 39 patients who never received systemic treatment before and was found to show ORR of 85% with 58% patients having responses lasting 6 months or greater. [76] Based on this trial, FDA granted accelerated approval to selpercatinib in metastatic RET fusion-positive NSCLC on May 8, 2020.

Fusions of the neurotrophic tyrosine receptor kinase (NTRK) genes 1, 2 and 3

NTRK fusions occur in many tumor types and are known to occur in less than 1% of NSCLC. The oral TRK inhibitor FDA approved in first line or subsequent setting for NSCLC patients harboring fusions in NTRK genes is Larotrectinib.

The efficacy of Larotrectinib was tested in phase I/II clinical trial that enrolled 55 patients with NTRK gene rearrangements regardless of cancer type. The ORR was 75% (95% CI, 61 to 85). At 1 year, PFS was 55% with 71% having ongoing responses. This led to the FDA approval of larotrectinib for NTRK-altered cancers as "tumor -agnostic" indication based on actionable genomic insights [77].

Mutations in HER2

Approximately 2% of patients with NSCLC are found to harbor HER 2 exon- 20- insertion mutation that is detected using PCR or NGS. HER 2- targeted antibody drug conjugate, ado-trastuzumab emtansine has shown modest clinical efficacy in these patients. [78]

In a phase II clinical trial, 18 patients with HER 2 mutated NSCLC were treated with ado-trastuzumab emtansine after a median of 2 prior line of systemic therapy. These patients were found to have ORR of 44%, median PFS of 5 months and median duration of response was 4 months, suggesting that we can offer this treatment off label in patients HER2-positive NSCLC refractory to other standard available therapies. [78]

In an ongoing, multicenter phase II study DESTINY-Lung01, 42 patients with non-squamous cell lung cancerwith HER2-activating mutation were administered trastuzumab deruxtecan. The ORR among these 42 patients was 62 percent with estimated median PFS of 14 months. [79]

Given that these two drugs are FDA approved for other HER2- positive malignancies, we can offer this treatment off label in patients with HER2-positive NSCLC refractory to other standard available therapies.

Immunotherapy in Advanced NSCLC

The targeted therapies described above have significantly changed the outlook for those patients with identifiable mutations. However, nearly 70% of patients with advanced NSCLC do not have driver genetic mutations, and immune checkpoint inhibitors are the mainstay of treatment for these patients [80]. These inhibitors target either programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1).PD-1 is a transmembrane protein that is expressed on T cells, B cells and Natural Killer cells and inhibits PD-L1 when it binds [81]. As PD-L1 is expressed on many tumor cells, the interaction of PD-1 and PD-L1 can be exploited in cancer treatment [80]. The PD-1 inhibitors pembrolizumab and nivolumab[80]and the PD-L1 inhibitors atezolizumab, avelumab, and durvalumab[80] can be used alone or in combination with chemotherapy based on individual patient factors, and have been shown to improve OS in patients with advanced NSCLC.

In patients with NSCLC who have not received chemotherapy, treatment decisions are based on the amount of PD-L1 expression. If PD-L1 expression is high (50% or greater), pembrolizumab can be used as monotherapy if patients do not have rapidly progressing disease.This is based on the KEYNOTE-024 trial of 305 patients with high PD-L1 expression who were assigned pembrolizumab monotherapy versus platinum-doublet therapy [82]. The results of this study showed prolonged PFS (10.3 versus 6 months) and higher ORR (45% versus 28%) in the pembrolizumab group compared to chemotherapy [82]. The pembrolizumab group also had a lower number of severe adverse events [82]. An update on KEYNOTE-024 presented 3 years later showed a median OS with pembrolizumab of 30.0 months (95% CI, 18.3-NR) versus 14.2 months (95% CI, 9.8-19.0)

with chemotherapy (HR, 0.63; 95% CI, 0.47-0.86) [83].No studies have been performed to directly compare pembrolizumab monotherapy versus chemotherapy plus pembrolizumab in patients without rapidly progressing disease. For patients with high PD-L1 expression and rapidly progressing disease, pembrolizumab with chemotherapy is recommended based on a meta-analysis of five studies with either pemborlizumab monotherapy or pemborlizumab in combination with chemotherapy[84]. Again, no randomized controlled trials have directly studied pembrolizumab monotherapy versus pembrolizumabplus chemotherapy in this patient group.

If PD-L1 expression is less than 50% and patients are treatment-naive, pembrolizumab with chemotherapy is the first line treatment option for both squamous and nonsquamous NSCLC. There have been two large randomized control trials comparing chemotherapy with and without pembrolizumab in patients with nonsquamous NSCLC, the KEYNOTE-021 and KEYNOTE-189 trials[85,86].KEYNOTE-021 randomized 123 patients to chemotherapy with and without pembrolizumab. The group with pembrolizumab had higher ORR (55% versus 29%) and PFS (13 versus 6 months) [85].KEYNOTE-189 studied 616 patients with nonsquamous NSCLC. These patients either received chemotherapy alone or with pembrolizumab, and patients receiving chemotherapy alone hadpembrolizumab added with disease progression. Pembrolizumabtreatment resulted in an improved PFS of 8.8 versus 4.9 months. There was also improved 12-month OS in the pembrolizumabpluschemotherapy versus chemotherapy alone (69% versus 49%)[86]. A similar study was performed in patients with squamous NSCLC, KEYNOTE-407, where 559 patients were randomized to either chemotherapy with pembrolizumab or chemotherapy with placebo. The addition of pembrolizumabagainresulted in improved OS and PFS[87].

The anti-PD-L1 antibodyatezolizumab may provide an alternative therapy to pembrolizumab and chemotherapy, and has been investigated in combination with chemotherapy in patients with nonsquamous NSCLC. The IMpower 150 trial assigned 1202 patients with advanced NSCLC to three groups: chemotherapy with atezolizumab, chemotherapy with atezolizumab plus bevacizumab, or chemotherapy with bevacizumab. Those receiving chemotherapy with atezolizumab plus bevacizumab had better PFS and OS (19.2 versus 14.7 months in the chemotherapy/bevacizumab group)[88]. The IMpower 130 and IMpower 132 trials also demonstrated improved OS and PFS with the addition of atezolizumab to chemotherapy in patients with nonsquamous NSCL. [89,90]. The addition of atezolizumab has also been studied in squamous NSCLC but did not demonstrate any OS benefit, so is not recommended for these patients [91].

Immunoglobulin G4 monoclonal antagonist antibodies such as nivolumabcan also play a role in the treatment of NSCLC. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a negative regulator of T cell activation and is implicated in immune surveillance of cancer [92].Ipilimumab is a monoclonal antibody directed against CTLA-4 that can be used in combination with nivolumab as an alternative to pembrolizumab and chemotherapy in patients with low PD-L1 expression [92].Nivolumab was studied as monotherapy in the CheckMate 026 trial of 541 patients with advanced, untreated PD-L1 positive tumors but did not result in prolonged PFS or OS[93],while the combination of nivolumab and ipilimumab used in the CheckMate 227 trial has shown improved OS compared to chemotherapy (17.1 versus 13.9 months) [94].The combination of nivolumab plus ipilimumab has also been shown to be beneficial in patients with high PD-L1 expression, though pembrolizumab remains the preferred treatment.

In another study presented at ASCO 2020, data from CheckMate9LA, a phase III trial evaluating nivolumab plus low-dose ipilimumab combined with chemotherapy showed superior OS compared to chemotherapy alone in the first line NSCLC treatment. Nivolumab plus ipilimumab combined with 2 cycles of platinum-doublet chemotherapy demonstrated superior OS versus chemotherapy alone (HR, 0.69; 96.71% CI, 0.55-0.87; p=0.0006), regardless of PD-L1 expression or tumor histology [95].

Although immunotherapy has been shown to impart a statistically significant survival benefit and drastically changed the current treatment of NSCLC, the survival difference is generally months over that achieved with conventional therapy. Therefore, it is imperative to discuss all of the risks and benefits of immunotherapy with a patient in order to best suit that individual's goals of care. Table 4 lists the ongoing clinical trials of immunotherapy in advanced NSCLC. Completion of these trials will potentially result in better treatment

options for the future.

Conclusion

In summary, precision medicine has helped with better understanding of the biology and oncogenic mechanisms of lung cancer. This has led to a new foundation of rationally designed therapeutic regimens including targeted and immunotherapy, thus expanding the therapeutic landscape of lung cancer. These regimens have high efficacy and manageable toxicity profiles, which in turn has led to improved survival. With these new advancements, we are touching new horizons in lung cancer treatment and in near future it is expected that chemotherapy will not be commonly used and lung cancer patients will have longer and better quality of life.

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Conflict of Interest

None

Author Contributions

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Data Availability

The authors declare that data supporting the findings of this study are available within

the article.

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