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Precision Management of Advanced Non–Small Cell Lung Cancer

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Abstract

The rapid evolution of treatment for advanced lung cancer is a story of how scientists have struggled to move from nonselective cytotoxic chemotherapy to personalized precision medicine. In this century, extraordinary advances have been made in the management of advanced and metastatic non–small cell lung cancer, especially in the development of small molecules targeting specific tyrosine kinase receptors and immune checkpoint inhibitors. These developments have led to a significant improvement in survival for lung cancer patients with metastatic disease. Now, the core guidelines to treat non–small cell lung cancer are based on the identification of targetable driver mutations and immune checkpoints. Continued investigations of newly identified druggable genetic alterations, explorations of biomarkers of immune checkpoint inhibitors, development of next-generation immunotherapy, and optimization of combination therapy are necessary to provide better treatment outcomes for lung cancer patients in the future.

INTRODUCTION

VEGF: vascular endovascular growth factor

EGFR: epidermal growth factor receptor

PD-L1: programmed-death ligand 1

Lung cancer is the most common cancer and the leading cause of cancer-related death in the world, accounting for more than 1.7 million deaths every year (1). Approximately 80–85% of lung cancers are classified pathologically as non–small cell lung cancer (NSCLC), of which adenocarcinoma (ADC) and squamous cell carcinoma (SqCC) are the two major subtypes (2). Though cigarette smoking is the most important risk factor associated with lung cancer (3), the association is higher in lung SqCC and small cell lung cancer than in lung ADC. In the past four decades, ADC has emerged as the predominant histological subtype among NSCLC cases, especially in women and never-smokers (4). The tumorigenesis of ADC may be multifactorial; factors include cigarette smoking, second-hand smoke, environmental exposure, and inherited genetic susceptibility.

The evolution of advanced NSCLC management is a story in which scientists and clinical physicians have struggled to move from nonspecific regimens to personalized therapy tailored according to the specific characteristics of each patient's tumor and host factors. Platinum-based doublet chemotherapy had been the standard first-line treatment in advanced NSCLC patients with good performance status (5). Maintenance with pemetrexed showed additional survival benefits if the tumors had been at least stable after 4–6 cycles of platinum-based doublet therapy (6). Docetaxel is generally considered a standard second-line treatment when patients show progression after having been treated with platinum-based chemotherapy (7). Other advances in chemotherapies in the past two decades include the following:

1. Compared with gemcitabine, pemetrexed is more effective and less toxic in non-SqCC NSCLC, making a pemetrexed/platinum doublet a favorable first-line option in ADC (8).
2. Antiangiogenesis strategies, such as monoclonal antibody against vascular endovascular growth factor (VEGF) or its receptor (VEGFR), showed additional survival benefits in combination with first-line platinum-based doublet chemotherapy (bevacizumab) (9, 10) or second-line docetaxel (ramucirumab or nintedanib) (11, 12).
3. The antiepidermal growth factor receptor (EGFR) monoclonal antibody necitumumab, in combination with platinum-based chemotherapies, has exhibited superior efficacy and survival benefits compared to chemotherapy alone in advanced SqCC patients (13).

Thanks to a better understanding of tumor biology, genomic mutational landscapes, cancer immunology, and tumor microenvironments, the treatment paradigms for advanced NSCLC patients have evolved through two major routes: (*a*) molecular targeted therapies based on different driver oncogenes in cancer cells and (*b*) immune checkpoint inhibitors, such as monoclonal antibodies against programmed-death ligand 1 (PD-L1) and programmed-death 1 (PD-1), that reverse the immunosuppressive effects elicited by tumor cells (14).

These advances have brought about many treatments with novel therapeutic targets approved by the US Food and Drug Administration (FDA) for metastatic NSCLC patients, including 12 small-molecule-targeted therapies (gefitinib, erlotinib, afatinib, dacomitinib, osimertinib, crizotinib, ceritinib, alectinib, brigatinib, lorlatinib, dabrafenib, and trametinib) and three immune checkpoint inhibitors (nivolumab, pembrolizumab, and atezolizumab) (**Figure 1**). The initial diagnosis and treatment paradigm changed dramatically due to the need for molecular diagnosis of tumor tissue for driver oncogenes and checkpoint expression (PD-L1). Currently, cytotoxic chemotherapies, molecular targeted therapies, antiangiogenic agents, and immune checkpoint inhibitors all play important roles in the treatment of NSCLC.

To determine an appropriate regimen for suitable patients, many clinical trials have been conducted to establish anticancer efficacy and treatment sequence as well as their combination

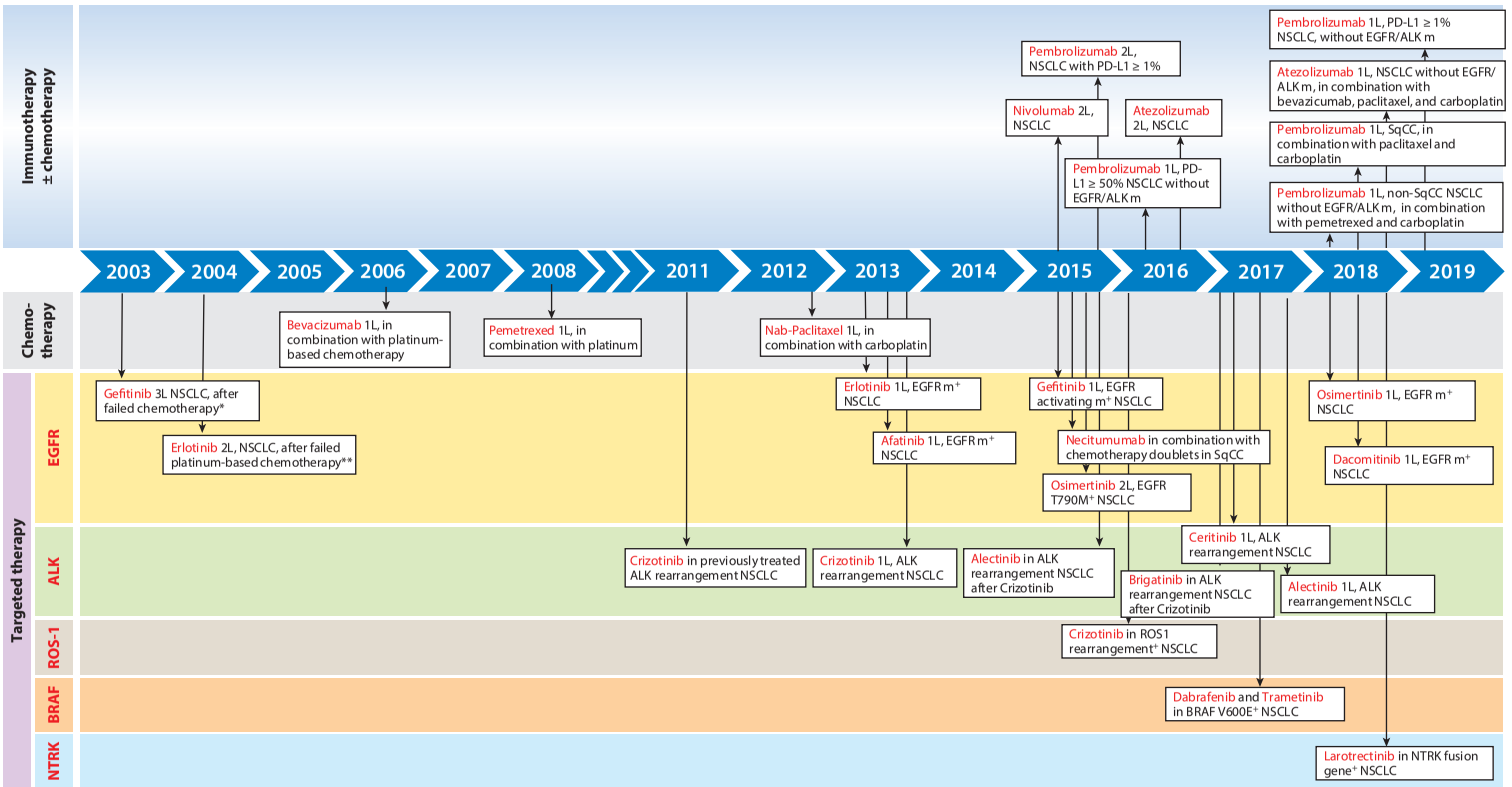

Figure 1

Timeline illustrating the US FDA-approved indications of NSCLC treatments since 2003. Abbreviations: 1L, first-line; 2L, second-line; 3L, third-line; ALK, anaplastic lymphoma kinase; BRAF, murine sarcoma viral oncogene homolog B; del19, deletion in exon 19; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; NSCLC, non–small cell lung cancer; NTRK, neurotropic tropomyosin receptor kinase; PD-L1, programmed-death ligand 1; ROS1, c-ros1 oncogene; SqCC, squamous cell carcinoma.

with selective biomarkers. In this review, we focus on updates to advanced and metastatic NSCLC management based on the clinical trials that established current treatment schema, with more focus on first-line treatments.

ALK: anaplastic lymphoma kinase

ROS1: c-ros1 oncogene

KRAS: Kristen rat sarcoma viral oncogene homolog

BRAF: murine sarcoma viral oncogene homolog B

NTRK: neurotropic tropomyosin receptor kinase

DRIVER MUTATION LANDSCAPE IN NON–SMALL CELL LUNG CANCER

The link between a specific oncogenic mutation and a relevant targeted therapy was the first breakthrough of NSCLC management in this century. Due to the great advances in genomic sequencing technology, several comprehensive large-scale genomic studies have found numerous genetic alterations in NSCLC (15–19). Most of the genetic alterations involve receptor tyrosine kinases, the oxidative response, mammalian target of rapamycin (mTOR) signaling, and cell cycle regulation. The potential actionable and clinically relevant targets, frequently identified in receptor tyrosine kinases, often involve an activating mutation that is probably implicated in very early tumor initiation. Thus, the tumor's growth is mainly dependent on the pathway in question, a dependence termed oncogene addiction. The clinical response is remarkable when the oncogene or its downstream signaling pathway is effectively blocked by potent specific small-molecule inhibitors. Most of the currently targetable oncogene mutations in receptor tyrosine kinases occur in lung ADC rather than SqCC (15–17, 19), such as sensitizing EGFR mutations and anaplastic lymphoma kinase (ALK) and c-ros1 oncogene (ROS1) rearrangements. The incidence of the driver mutations in lung ADC is different between Caucasians and East Asians. While Kristen rat sarcoma viral oncogene homolog (KRAS) mutation is most common in Caucasians, EGFR mutation is the leading driver oncogene in East Asians.

In contrast to lung ADC, dominant driver mutations in receptor tyrosine kinases have seldom been identified in SqCC (15, 20). In the genomic sequencing results from The Cancer Genome Atlas (15), the genetic alterations in lung SqCC are complex and mostly involved tumor suppression genes (*TP53*), cell cycle regulation genes (*CDKN2A/RB1*), and apoptotic signaling genes (*PI3K/AKT*). Only some copy-number variations in potentially druggable genes, including the genes encoding EGFR, fibroblast growth factor receptor 1 (FGFR1), or discoidin domain-containing receptor 2 (DDR2), are present in SqCC (20). The incidences of clinically relevant driver mutations in lung ADC (Caucasians and East Asians) and nondriver mutations in SqCC are illustrated in **Figure 2** based on several large, comprehensive genomic sequencing studies (15–17, 19, 20). Driver mutations in ADC are mutually exclusive in the majority of patients, making the decision to select molecularly targeted therapy simple.

MOLECULAR TARGETED THERAPY IN LUNG ADENOCARCINOMA

The development of genomic diagnosis and treatment paradigms for metastatic lung cancer is the most fascinating example of an application of precision medicine in cancer treatment. *EGFR* was the first discovered actionable oncogene (21), comprising approximately 15–25% of Western (16, 19) and 40–55% of East Asian lung ADC patients (17, 18). Patients with lung ADCs with sensitizing EGFR mutations derive great benefits from EGFR tyrosine kinase inhibitors (TKIs). In the past decade, more driver oncogenes were discovered, and the corresponding molecular targeted therapies were developed. Some of these targeted agents have been approved by the FDA, including ALK and ROS1 rearrangements, murine sarcoma viral oncogene homolog B (BRAF) V600E mutation, and neurotropic tropomyosin receptor kinase (NTRK) fusion genes. Several randomized phase III clinical trials compared traditional platinum-based chemotherapy to TKIs in biomarker-selected patients and demonstrated superior progression-free survival (PFS)

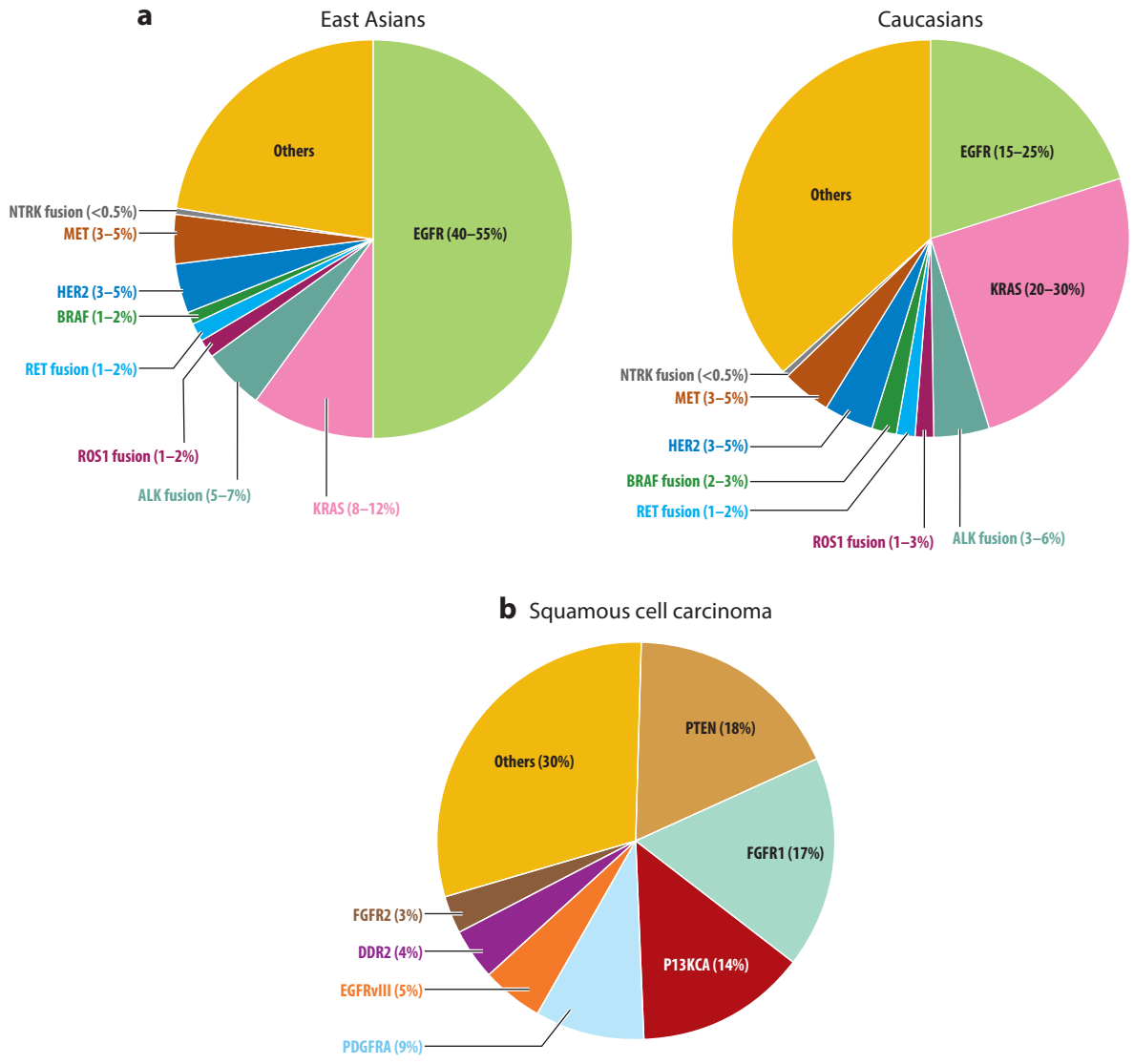

Figure 2

The prevalence of targetable or clinically relevant driver oncogenes in (*a*) lung adenocarcinoma among Caucasians and East Asians and (*b*) lung squamous cell carcinoma based on several large-scale genomic studies (15–20). Abbreviations: ALK, anaplastic lymphoma kinase; BRAF, murine sarcoma viral oncogene homolog B; DDR2, discoidin domain-containing receptor 2; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; KRAS, Kristen rat sarcoma viral oncogene homolog; NTRK, neurotropic tropomyosin receptor kinase; PDGFRA, platelet-derived growth factor receptor A; PI3KCA, phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha; PTEN, phosphatase and tensin analog; ROS1, c-ros1 oncogene.

Erratum >

in TKI-treated patients (EGFR TKI and ALK TKI). TKIs with promising anticancer efficacies on rare mutations (ROS1, BRAF, and NTRK mutations) gained accelerated FDA approval after single-arm studies because it is impractical to recruit sufficient patients for randomized clinical trials. Other emerging targets also attracted attention when early-phase clinical trials showed favorable responses, such as MET exon 14–skipping mutations, HER-2 mutations (ErbB-2),

and RET rearrangements. In 2018, the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology refined the recommendations of molecular testing: *EGFR*, *ALK*, *ROS1*, and *BRAF* should be tested in all patients with advanced nonsquamous disease irrespective of clinical characteristics, while *RET*, *HER2*, and *MET* molecular testing is not recommended as a routine stand-alone assay outside the context of a clinical trial. It is appropriate to include these genes as part of larger testing panels performed either initially or when routine *EGFR*, *ALK*, *ROS1*, and *BRAF* test results are negative (22). **Table 1** summarizes the results of pivotal clinical trials for first-line treatment of each actionable genetic alteration in metastatic lung ADC.

EGFR

EGFR is a member of the ErbB tyrosine kinase receptor family, which comprises EGFR (ErbB-1), HER-2 (ErbB-2), HER-3 (ErbB-3), and HER-4 (ErbB-4). As a transmembrane glycoprotein with a dimer structure, EGFR contains an extracellular ligand-binding domain and an intracellular tyrosine kinase domain, which phosphorylates several downstream pathways and induces cellular proliferation, angiogenesis, and survival when activated by ligand binding-induced dimerization. Activating EGFR mutations change the structure of the ATP-binding pocket of the tyrosine kinase domain, resulting in ligand-independent activation and oncogenic potential (23). Of note, these changes also alter the affinity of the ATP-binding pocket to ATP and offer an opportunity for the protein to be targeted by an EGFR TKI with higher affinity. The most common activating EGFR mutations sensitive to EGFR TKIs are deletions in exon 19 (del19) and a point mutation in exon 21 (a substitution of arginine for leucine at codon 858, L858R), comprising approximately 80–85% of all activating EGFR mutations (24).

Erlotinib (25) and gefitinib (21) were first-generation EGFR TKIs that had higher affinity to the ATP-binding pocket than ATP and could effectively block the signal transduction and hamper cancer cell growth. In several randomized phase III clinical trials, both gefitinib (26–29) and erlotinib (30, 31) exhibited superior objective response rate (ORR) and PFS compared with cytotoxic platinum-based chemotherapies in first-line treatment of lung ADC harboring activating EGFR mutations. The safety profiles of EGFR TKI therapies were also more favorable than those of chemotherapies. However, there was no significant difference in overall survival (OS) between the two treatment arms owing to the large proportion of patients in the chemotherapy arm who received EGFR TKIs as subsequent therapies (26, 32, 33).

Afatinib was a second-generation EGFR TKI with irreversible blocking activity (by covalent binding of afatinib to C797 of EGFR), and the inhibition activity spectrum extended to pan-HER family members (34). The two phase III clinical trials of afatinib, Lux-Lung 3 (35) and Lux-Lung 6 (36), demonstrated better ORR and PFS compared with platinum-based chemotherapies in treatment-naïve lung ADC patients with EGFR mutations, similar to the benefits of first-generation EGFR TKIs. In the subgroup of EGFR del19 patients, afatinib exhibited OS benefits over chemotherapy in two studies (37), which were not seen in any gefitinib or erlotinib study. In 2016, a phase IIb randomized controlled trial comparing gefitinib and afatinib in treatment-naïve lung ADC patients with activating EGFR mutations showed a modest PFS benefit in the afatinib arm [PFS in afatinib versus gefitinib: 11 versus 10.9 months; hazard ratio (HR) 0.73, 95% confidence interval (CI) 0.57–0.95, $p = 0.017$] (38). Though the OS did not differ significantly between the two arms, the study was not powered to detect OS superiority.

Another second-generation EGFR TKI, dacomitinib, demonstrated both PFS and OS benefits compared with gefitinib in the phase III clinical trial ARCHER 1050, which selected patients with two types of common EGFR mutation and no brain metastasis. However, patients in the

Table 1 Pivotal clinical trials of molecular targeted therapies leading to US FDA approval of first-line treatment

Study (references)	Phase	Design	ORR (%)	PFS (months)	OS (months)
EGFR					
IPASS (26, 29)	III	Gefitinib versus carboplatin plus paclitaxel	EGFR mutation: 72.1 versus 47.3	9.5 versus 6.3	21.6 versus 21.9
NEJ002 (27, 32)	III	Gefitinib versus carboplatin plus paclitaxel	73.7 versus 30.7	10.8 versus 5.4	27.7 versus 26.6
WJTOG 3405 (28)	III	Gefitinib versus cisplatin plus docetaxel	62.1 versus 32.2	9.2 versus 6.3	34.8 versus 37.3
EURTAC (30)	III	Erlotinib versus platinum-based doublets	58 versus 15	9.7 versus 5.2	22.9 versus 19.6
OPTIMAL (31)	III	Erlotinib versus carboplatin plus gemcitabine	83 versus 36	13.1 versus 4.6	22.8 versus 27.2
Lux-Lung 3 (35, 37)	III	Afatinib versus cisplatin plus pemetrexed	56 versus 23	11.1 versus 6.9	28.2 versus 28.2
Lux-Lung 6 (36, 37)	III	Afatinib versus cisplatin plus gemcitabine	66.9 versus 23	11 versus 5.6	23.1 versus 23.5
ARCHER 1050 (39)	III	Dacomitinib versus gefitinib	75 versus 72	14.7 versus 9.2	34.1 versus 26.8
FLAURA (51)	III	Osimertinib versus gefitinib or erlotinib	80 versus 76	18.9 versus 10.2	NR
ALK					
PROFILE 1014 (61)	III	Crizotinib versus cisplatin plus pemetrexed	74 versus 45	10.9 versus 7	45.8 to NR versus 32.2 to NR
ASCEND 4 (65)	III	Ceritinib versus cisplatin plus pemetrexed	72.5 versus 26.7	16.6 versus 8.1	NR versus 26.2
ALEX (66)	III	Alectinib versus crizotinib	82.9 versus 75.5	34.8 versus 11.1	NR
J-ALEX (67)	III	Alectinib versus crizotinib	85.4 versus 70.2	25.9 versus 10.2	NR
ROS1					
PROFILE 1001 (75)	I	Crizotinib in $ROS1^+$ NSCLC	72	19.3	51.4
BRAF					
BRF113928 (81)	II	Dabrafenib in pretreated NSCLC versus dabrafenib/trametinib in pretreated NSCLC versus dabrafenib/trametinib in treatment-naïve NSCLC	33 versus 63.2 versus 64	5.5 versus 8.6 versus 14.6	12.7 versus 18.2 versus 24.6
NTRK					
Drilon et al. (82)	I–II	55 cases of $NTRK^+$ tumors (lung cancer: 5)	75	NR (86% of patients with a response at 9.4 months)	NR

Abbreviations: ADC, adenocarcinoma; ALK, anaplastic lymphoma kinase; BRAF, murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; NSCLC, non–small cell lung cancer; NR, not reached; NTRK, neurotropic tropomyosin receptor kinase; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; ROS1, c-ros1 oncogene.

dacomitinib arm also experienced high rates of adverse events, leading to higher rates of dose reduction and drug discontinuation rates compared to first-generation EGFR TKIs (39).

Most if not all EGFR TKI–treated lung ADC patients will develop resistance. A point mutation in exon 20 (a substitution of methionine for threonine at codon 790, T790M) is the mechanism of acquired resistance in >50% of these patients (40). Other molecular alterations accounting for acquired resistance include HER2 amplification (41), MET amplification (42), PI3KCA mutation (43), BRAF mutation (44), epithelial–mesenchymal transition (45), and small cell transformation (46). The conformational change made by the T790M mutation results in a steric hindrance of the ATP-binding pocket and decreases the affinity of first- and second-generation EGFR TKIs.

Osimertinib, the third-generation EGFR TKI, was developed to overcome T790M resistance by establishing a covalent binding at the cytosine 797 residue (47). In addition to being effective on classical sensitizing mutations (EGFR del19 and L858R) and the acquired T790M mutation, osimertinib was designed to spare wild-type EGFR protein and thus harbor a more favorable profile of adverse events (47). Osimertinib showed high anticancer activity in patients with the T790M mutation after they had acquired resistance to EGFR TKIs in the phase I AURA trial (48). The randomized phase III AURA3 trial demonstrated that osimertinib had higher efficacy than platinum-based chemotherapy in advanced lung ADC patients who developed T790M resistance after first generation TKI treatment (49), establishing osimertinib as a standard second-line treatment in EGFR-mutated ADC with acquired T790M. Moreover, the phase I AURA trial demonstrated long PFS in TKI-naïve patients on osimertinib (50).

In the randomized phase III FLAURA trial, osimertinib showed superior PFS compared with first-generation EGFR TKIs (osimertinib versus gefitinib/erlotinib, 18.9 versus 10.2 months, HR 0.46, $p < 0.001$) in previously untreated NSCLC patients with common EGFR mutations. Though the OS data were not mature at this time, the HR was 0.63 (95% CI, 0.45–0.88, $p = 0.0068$, statistically not significant) (51). The mechanisms of resistance to first-line osimertinib are different from those in first- and second-generation EGFR TKIs. The analysis of cell-free plasma DNA from FLAURA patients of the osimertinib arm revealed that MET amplification (15%) was the most common resistance mechanism, followed by secondary EGFR mutation (C797X, 7%), PI3KCA mutation (7%), and HER2 amplification (2%) (52). To date, all the EGFR TKIs, including gefitinib, erlotinib, afatinib, dacomitinib, and osimertinib, are approved by the FDA as first-line therapies for advanced, EGFR-mutated lung ADC, and osimertinib provides the longest PFS among all EGFR TKI monotherapies. Otherwise, osimertinib can be used in at least half of the patients who acquire T790M after gefintinib/erlotinib/afatinib/dacominitib failure, and the salvage regimen for osimertinib is still chemotherapy.

Combination strategies were also applied in EGFR-mutant ADC, including EGFR TKI plus antiangiogenic agents or cytotoxic chemotherapies. Bevacizumab is a monoclonal anti-VEGF antibody that has been approved in the treatments of various neoplasms. In the phase III NEJ026 trial, bevacizumab in combination with erlotinib showed longer PFS (erlotinib plus bevacizumab versus erlotinib: 16.9 months versus 10.3 months, HR 0.605, $p = 0.01573$) than erlotinib alone in the first-line treatment of EGFR-mutant lung ADC (53). The combination of erlotinib and bevacizumab was approved by the European Commission and several countries as first-line therapy in lung ADC with sensitizing EGFR mutations. Though monotherapy with EGFR TKIs confers a high disease control rate in EGFR-mutant tumors, <10% of patients do not respond well and experience primary resistances, probably due to co-occurring genomic mutations or activated bypass signaling (54), thus justifying the use of chemotherapy in combination with EGFR TKIs. In the phase III NEJ009 trial comparing gefitinib plus carboplatin/pemetrexed and gefitinib alone in Japanese advanced NSCLC patients with sensitizing EGFR mutations, the combination therapy showed a significant PFS and OS benefit compared to gefitinib alone (55), although PFS2

(the duration from the start of treatment to disease progression after second-line treatment) was not significantly different between the two treatment arms. Whether chemotherapy plus EGFR TKI should become a standard of care is still debatable with regard to the safety profiles and the unknown superiority to osimertinib. The OS benefit should be examined in detail for subsequent treatment after first-line progression.

Uncommon EGFR mutations comprise <15% of EGFR mutations in lung ADC (19). Most of these mutations arise from exon 18 (e.g., G719X), exon 20 (e.g., S768I), and exon 21 (e.g., L861Q). Compared with common sensitizing EGFR mutations (del19 and L858R), lung ADC with uncommon mutations responded less well to first-generation EGFR TKIs (56). In a pooled analysis of Lux-Lung clinical trials, the second-generation EGFR TKI afatinib showed good efficacy for the uncommon mutations, with a median PFS of 10.7 months (57). The US FDA approved afatinib for the treatment of patients with the G719X, S768I, and L861Q EGFR mutations.

MAPK: mitogen-activated protein kinase

ALK

ALK rearrangement was first discovered in 1994 in a highly recurrent translocation (p23;q35) in anaplastic large cell lymphoma, resulting in a fusion with nucleophosmin (58). ALK translocations were later identified in a small proportion of NSCLC cases with a different translocation pattern (p21;p23) and distinct fusion partners, most often echinoderm microtubule-associated protein-like 4 (EML-4) (59). With a tyrosine kinase domain from the ALK protein, the fusion ALK genes also encode the N-terminal part of the partner, which contains a dimerization domain, leading to activation of ALK kinase and subsequent uncontrolled tumor growth.

Crizotinib is the first FDA-approved ALK inhibitor, which shows high activity against ALK, MET, and ROS1. In patients with ALK-rearranged lung ADC, crizotinib exhibited superior ORR and PFS compared with standard platinum-based chemotherapies (60, 61). Ceritinib (62), brigatinib (63), and alectinib (64) are second-generation ALK TKIs that showed superior efficacy compared to cytotoxic chemotherapy in crizotinib-treated ALK-positive patients. Similar to crizotinib, ceritinib was shown to be more effective than platinum-based chemotherapy in the first-line treatment of ALK-rearranged advanced lung ADC patients in the phase III ASCEND 4 trial (65), with a median PFS of 16.6 months and an ORR of 72.5%. Besides, two phase III clinical trials comparing alectinib and crizotinib in the first-line treatment of ALK-positive advanced lung ADC showed superior PFS and OS benefits in the alectinib arm. With alectinib treatment, the global ALEX trial (66) reported a median PFS of 34.8 months and an ORR of 82.0%; the J-ALEX trial in Japan (67) found a median PFS of 25.5 months and an ORR of 85.4%. The intracranial efficacy of alectinib is also promising (68). To date, alectinib, ceritinib, and crizotinib are approved by the FDA for first-line treatment of NSCLC in ALK-positive patients, and alectinib provided the longest PFS.

Similar to EGFR mutations, acquired resistance inevitably occurs after a treatment response to ALK TKIs. The mechanisms of ALK TKI resistance comprise either mutations within the ALK kinase domain or activation of bypass signaling pathways, including EGFR, c-Kit, insulin growth factor-1R (IGF-1R), or mitogen-activated protein kinase (MAPK) (69). A glycine-to-arginine substitution at codon 1202 (G1202R) is a common kinase domain mutation accounting for acquired resistance (70), which is sensitive only to lorlatinib, a third-generation ALK TKI with activity against ALK and ROS1. In a phase II clinical trial, lorlatinib showed promising efficacy in ALK-positive patients after failure of second-generation ALK TKIs, especially in tumors that developed a kinase domain mutation as the resistance mechanism (71). There are also studies regarding ceritinib or brigatinib (72) after the failure of alectinib. The optimal choice in ALK-positive ADC after the failure of a second-generation TKI is still debatable.

ROS1

MEK: MAPK/Erk kinase

The ROS1 gene encodes a family of insulin receptor tyrosine kinases. Rearrangement of ROS1 is present in only 1–2% of lung ADC patients and is more prevalent in younger adults (73). Similar to ALK, ROS1 is constitutively activated after rearrangement, and different fusion partners also drive ROS1 to localize in various subcellular compartments, resulting in downstream signal transduction and tumor survival (74). Most TKIs against ALK are also active on ROS1, including crizotinib, ceritinib, and lorlatinib. Both crizotinib (75) and ceritinib exhibited promising efficacy on treatment-naïve ROS1-positive lung ADC patients, with a median PFS of more than 19 months. Due to the low prevalence and limited case number precluding the possibility of a timely phase III clinical trial, crizotinib gained accelerated FDA approval in the treatment of ROS1-positive tumors.

A substitution of glycine to arginine in codon 2032 (G2032R) accounts for a common kinase domain mutation resulting in acquired resistance to crizotinib (76). Other bypass signaling mechanisms have also been reported to cause acquired resistance, including EGFR activation (77) and KRAS, HER2, and c-Kit mutations.

BRAF

BRAF mutations are present in 1–3% of NSCLC cases (78). A substitution of valine to glutamate at residue 600 (V600E) accounts for nearly 50% of these BRAF mutations, which lead to downstream activation of the MEK/MAPK signaling pathway. Unlike EGFR and ALK mutations, BRAF mutations are commonly found in patients who are smokers (79), and the tumor behavior is more invasive than that of BRAF wild-type tumors (78). Monotherapy of a BRAF inhibitor (vermurafenib or dabrafenib) yielded only a fair response in BRAF-mutant NSCLC patients (80). A combination of dabrafenib and the MEK inhibitor trametinib not only enhanced treatment efficacy, with an ORR of 64% and a median OS of 24.6 months (81), but also decreased the toxicities elicited through BRAF inhibition, especially skin neoplasms. The results facilitated the FDA approval that indicated a combination of dabrafenib and trametinib in advanced BRAF V600E mutant NSCLC irrespective of prior therapies.

Other Emerging Targeted Therapies

Targeted therapies acting on NTRK fusion proteins are the latest FDA-approved agents for specific driver oncogenes in NSCLC (82). NTRK genes encode the tropomyosin receptor kinases, TRKA, TRKB, and TRKC, which are involved in the normal development and maintenance of neural systems. NTRK gene rearrangement that drives tumor growth was found in various neoplasms including NSCLC, with an extremely low incidence of 0.1 to ~1% (83). NTRK fusions develop across age, gender, smoking status, and even histology in NSCLC. Larotrectinib is a selective pan-TRK inhibitor providing remarkable efficacy on NTRK fusion tumors in various neoplasms. A phase I–II trial enrolling 55 cases of multiple cancer types with NTRK fusions showed that larotrectinib had a pooled ORR of 75%, while the median PFS has not been reached (82). Four NSCLC cases were included in this cohort, and the results also drove the FDA approval across different cancers harboring NTRK fusions.

Other emerging targets include alterations in the genes for HER2, NF1, and MET, as well as RET fusion and EGFR exon 20 insertion, with some promising results from early-phase trials of targeted therapies. For example, a skipping mutation at exon 14 results in MET protein lacking the ubiquitin-binding site and therefore sustained MET activation and tumorigenesis (84). An exon 14 skipping mutation in MET was found in approximately 3% of NSCLC patients. In an

ongoing multicohort trial (PROFILE 1001), crizotinib achieved an ORR of 32% and a median PFS of 7.3 months in 65 advanced NSCLC patients with MET exon 14 mutations (85).

IMMUNE CHECKPOINT INHIBITORS

Immunotherapy acting on immune checkpoints was the most important breakthrough for cancer treatment in the past decade. The importance of immune checkpoint inhibitors (ICIs) was highlighted by the Nobel Prize awarded to Drs. Allison and Honjo in 2018 as well as FDA approval of numerous immune checkpoint inhibitors. In the tumor microenvironments, host immune systems are able to eradicate the cancer after recognizing the nonself-antigens presented by tumor cells or antigen-presenting cells (14). Through a mechanism of adaptive resistance, tumor cells can evade host immune surveillance by expressing immune checkpoints to disrupt the function of immune cells, mainly cytotoxic T cells, resulting in the exhaustion and apoptosis of effective immune cells (86). Reinvigoration of exhausted T cells to eliminate cancer cells can be achieved by monoclonal antibodies against either PD-1 or PD-L1 to block their interaction. Four anti-PD-1 or anti-PD-L1 monoclonal antibodies were approved by the US FDA for the management of advanced NSCLC, namely, nivolumab, pembrolizumab, atezolizumab, and durvalumab.

ICIs have almost fully replaced docetaxel as the second-line treatment of advanced NSCLC at progression after first-line platinum-based chemotherapy (87–90). As a second-line treatment, nivolumab showed a significantly longer OS than docetaxel, with median OS of 9.2 months (88) and 12.2 months (88) in lung SqCC and ADC, respectively. The OS benefit was more significant with higher tumor PD-L1 expression in lung ADC patients (88). Pembrolizumab (89) and atezolizumab (90) also exhibited a superior OS compared to docetaxel in phase III trials (KEYNOTE-010 for pembrolizumab, OAK for atezolizumab), and the pembrolizumab trial only enrolled NSCLC patients with tumor PD-L1 $\geq$ 1% (89).

Two observations were made in the second-line phase III trials, comparing ICI to docetaxel. First, though PD-L1 expression has been shown to be a predictive biomarker for ICI response in some studies, the predictive value was not comparable to the targeted therapies in patients with specific genomic driver mutations. The clinical trials' use of different antibodies for detection of PD-L1 expression in immunohistochemical tests adds another complication (Dako 28-8 for nivolumab, Dako 22C3 for pembrolizumab, SP142 for atezolizumab, and SP263 for durvalumab). Some harmonization studies among these antibodies showed good concordance rates between Dako 28-8, Dako 22C3, and SP263 (91), while SP142 was less sensitive to PD-L1 expression detection. Second, lung ADC with EGFR or ALK mutations had poor responses to ICI compared with wild-type tumors. The optimal role and timing for the use of ICI in patients with driver mutations are still the subject of investigation.

Pembrolizumab was tested as the first-line treatment in a population of patients with advanced NSCLC with PD-L1 expression $\geq$50% and wild-type EGFR/ALK. Compared with platinum-based chemotherapies, pembrolizumab monotherapy demonstrated a superior PFS and OS benefit, thus establishing its role as a standard of care in the first-line treatment of NSCLC with high PD-L1 expression (KEYNOTE-024) (92). The patient population appropriate for pembrolizumab was further expanded in a phase III clinical trial that compared pembrolizumab and platinum-based chemotherapy in treatment-naïve NSCLC patients with PD-L1 $\geq$ 1%. Though the OS results among patients with PD-L1 $\geq$ 50%, $\geq$ 20%, and $\geq$ 1% favored pembrolizumab, the superiority of ICI to chemotherapy was most driven by the subgroup of patients with PD-L1 $\geq$ 50% (93). In contrast, nivolumab failed to display superior OS or PFS compared to platinum-based chemotherapy in first-line treatment of NSCLC patients with PD-L1 $\geq$ 5% (CheckMate

026 trial), and there were no differences in the subgroup of PD-L1 ≥ 50% (94). Another biomarker of ICI, tumor mutation burden (TMB, calculated as the number of nonsynonymous mutations per mega base pair of whole exomes using next-generation sequencing), was evaluated in patients of the CheckMate 026 cohort. The results showed that patients with TMB in the upper tertile had a significant PFS benefit compared to the middle and lower tertiles, though the OS showed no significant differences (95).

CTLA-4: cytotoxic T lymphocyte antigen-4

To overcome the obstacle of low PD-L1 expression or non-PD-L1-driven immunosuppression in some tumors, a combination strategy with potential synergistic effects was considered. In the tumor microenvironments, cytotoxic chemotherapy may potentiate the response to ICI by killing cancer cells to increase antigen presentation, thereby reducing the immunosuppressive cytokines released by cancer cells and suppressing some immune cells that may hamper antitumor responses, including myeloid-derived suppressor cells and regulatory T cells. Three combination regimens approved by the FDA demonstrated superior ORR and PFS benefits compared with cytotoxic platinum-based chemotherapy in first-line treatment of NSCLC without EGFR/ALK mutations. These three are pembrolizumab in combination with pemetrexed/carboplatin in advanced lung ADC (96), pembrolizumab in combination with nab-paclitaxel (or paclitaxel) and carboplatin in advanced lung SqCC (97), and atezolizumab in combination with bevacizumab/paclitaxel/carboplatin in advanced nonsquamous NSCLC (98), irrespective of tumor PD-L1 expression. Another combination strategy is to block two axes of immune checkpoints simultaneously. The efficacy of nivolumab plus ipilimumab (an anti-CTLA-4 monoclonal antibody) is now being tested in a phase III clinical trial that has multiple arms with different combinations using either PD-L1 or TMB as stratification biomarkers. The preliminary data showed that in advanced NSCLC patients with high TMB (TMB ≥ 10 mutations/Mb from a target gene panel), ipilimumab plus nivolumab exhibited significantly better ORR and PFS than platinum-based chemotherapy (99). The major obstacle to ICI is the undetermined optimal biomarker, though either PD-L1 or TMB does enrich more responders in clinical practice. **Table 2** summarizes the results of pivotal clinical trials of immune checkpoint inhibitors.

Though a minority of patients had quite durable response after ICI treatments, primary and secondary resistance also occurred, with mechanisms distinct from those in molecular targeted therapies. Some genetic alterations resulted in immunosuppressive effects in the tumor microenvironment. For example, a loss-of-function mutation in serine/threonine kinase 11 (STK11), which is comutated in one-third of KRAS-positive NSCLC cases, can induce the accumulation of immunosuppressive neutrophils and decrease PD-L1 expression, conferring a mechanism of primary resistance to ICI (100). Otherwise, most of the responding patients still experienced acquired resistance, but the mechanisms are far different from those of molecular targeted therapies. The evolution of the neo-antigen landscape, a loss-of-function mutation of Janus kinase (JAK) or beta-2 macroglobulin (101), and the stability of epigenetic regulation in exhausted T cells have been proposed to account for resistance to ICI.

IMPACT OF PRECISION THERAPY ON SURVIVAL

In the early 2000s, most metastatic NSCLC patients could only be treated with nonselective cytotoxic chemotherapy, with a one-year survival rate of only approximately 30%. Now, in the era of precision medicine, the management of NSCLC is personalized; the treatment of each patient should be based on the targetable driver mutations identified or the expression of PD-L1 and TMB (**Figure 3**). Patients with druggable oncogenes treated with relevant TKI experienced longer survival compared to those without driver mutations or those who did not receive targeted

Table 2 Pivotal phase III clinical trials of immune checkpoint inhibitors leading to US FDA approval

Study (references)	Design	ORR (%)	PFS (months)	OS (months)
2L monotherapy				
CheckMate 017 (88)	Nivolumab (3 mg/kg) versus docetaxel in SqCC	20 versus 9	3.5 versus 2.8	9.2 versus 6
CheckMate 057 (87)	Nivolumab (3 mg/kg) versus docetaxel in non-SqCC NSCLC	19 versus 12	2.3 versus 4.2	12.2 versus 9.5
KEYNOTE-010 (89)	Pembrolizumab (2 mg/kg) versus pembrolizumab (10 mg/kg) versus docetaxel in NSCLC with PD-L1 ≥1%	18 versus 18 versus 9	3.9 versus 4 versus 4	10.4 versus 12.7 versus 8.5
OAK (90)	Atezolizumab (1,200 mg) versus docetaxel	14 versus 13	2.8 versus 4	13.8 versus 9.6
1L monotherapy				
KEYNOTE-024 (92)	Pembrolizumab (200 mg) versus platinum-based doublets in NSCLC with PD-L1 ≥ 50%	44.8 versus 27.8	10.3 versus 6	30 versus 14.2
KEYNOTE-042 (93)	Pembrolizumab (200 mg) versus platinum-based doublets in NSCLC with PD-L1 ≥ 1%	27 versus 27	5.4 versus 6.5	16.7 versus 12.1
1L combination therapy				
KEYNOTE-189 (96)	Pembrolizumab (200 mg) plus pemetrexed and carboplatin versus pemetrexed and carboplatin in NSCLC without EGFR/ALK mutation	47.6 versus 18.9	8.8 versus 4.9	NR versus 11.3
KEYNOTE-407 (97)	Pembrolizumab (200 mg) plus carboplatin and nab-paclitaxel/paclitaxel versus carboplatin versus nab-paclitaxel/paclitaxel in lung SqCC	57.9 versus 38.4	6.4 versus 4.8	15.9 versus 11.3
IMpower-150 (98)	Atezolizumab (1,200 mg) plus paclitaxel, carboplatin, and bevacizumab versus paclitaxel, carboplatin, and bevacizumab	63.5 versus 48	8.3 versus 6.8	19.2 versus 14.7

Abbreviations: 1L, first-line; 2L, second-line; ADC, adenocarcinoma; ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; NR, not reached; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; SqCC, squamous cell carcinoma.

Erratum >

therapy (18). Such outcomes necessitate that scientists and clinicians make even greater efforts to categorize the molecular and immunological subtypes of tumors.

CONCLUSION

Owing to advances in molecular targeted therapy and immunotherapy, the treatment of NSCLC has greatly changed during the past decade. Under most conditions, we can treat patients according to their specific driver mutations or immune profiles rather than offering a nonselective regimen. For molecular targeted therapy, the most important goals are to predict or overcome acquired resistance, to develop more potent inhibitors for some rare mutations, and to determine the best sequence of various targeted therapies in specific oncogene-driven tumors. For immunotherapy, there are still many unresolved issues, including whether an optimal biomarker does exist and how to balance the effectiveness, cost, and safety concerns between monotherapy and combination therapy. Now is an era in which medical advances emerge quickly and abundantly year by year, which makes conquering cancer an achievable goal rather than a dream.

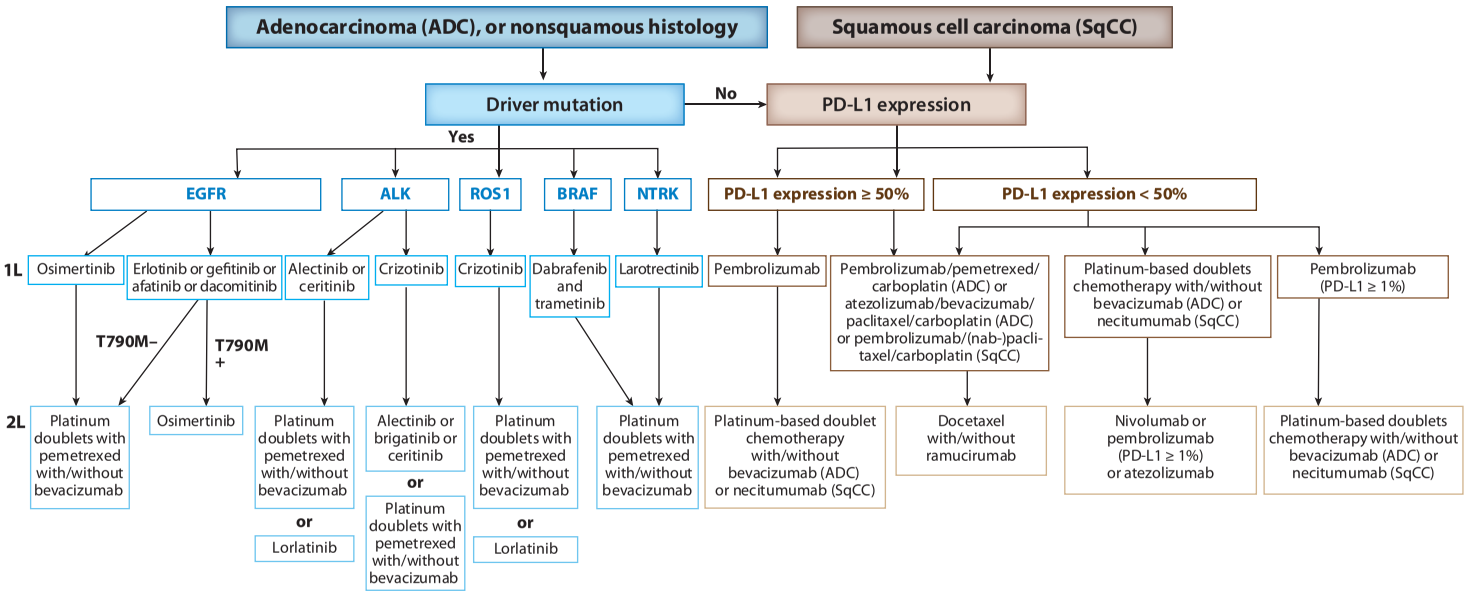

Figure 3

The treatment algorithm of metastatic NSCLC. Abbreviations: ADC, adenocarcinoma; ALK, anaplastic lymphoma kinase; BRAF, murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; NTRK, neurotropic tropomyosin receptor kinase; PD-L1, programmed-death ligand 1; ROS1, c-ros1 oncogene.

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LITERATURE CITED

1. Bray F, Ferlay J, Soerjomataram I, et al. 2018. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 68:394–424
2. Molina JR, Yang P, Cassivi SD, et al. 2008. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clin. Proc.* 83:584–94
3. Sun S, Schiller JH, Gazdar AF. 2007. Lung cancer in never smokers—a different disease. *Nat. Rev. Cancer* 7:778–90
4. Sun Y, Ren Y, Fang Z, et al. 2010. Lung adenocarcinoma from East Asian never-smokers is a disease largely defined by targetable oncogenic mutant kinases. *J. Clin. Oncol.* 28:4616–20
5. Rajeswaran A, Trojan A, Burnand B, Giannelli M. 2008. Efficacy and side effects of cisplatin- and carboplatin-based doublet chemotherapeutic regimens versus non-platinum-based doublet chemotherapeutic regimens as first line treatment of metastatic non-small cell lung carcinoma: a systematic review of randomized controlled trials. *Lung Cancer* 59:1–11
6. Ciuleanu T, Brodowicz T, Zielinski C, et al. 2009. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. *Lancet* 374:1432–40
7. Fossella FV, DeVore R, Kerr RN, et al. 2000. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. *J. Clin. Oncol.* 18:2354–62
8. Scagliotti GV, Parikh P, von Pawel J, et al. 2008. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. *J. Clin. Oncol.* 26:3543–51
9. Sandler A, Gray R, Perry MC, et al. 2006. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.* 355:2542–50
10. Reck M, von Pawel J, Zatloukal P, et al. 2009. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. *J. Clin. Oncol.* 27:1227–34
11. Garon EB, Ciuleanu TE, Arrieta O, et al. 2014. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. *Lancet* 384:665–73

12. Reck M, Kaiser R, Mellemgaard A, et al. 2014. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. *Lancet Oncol.* 15:143–55
13. Thatcher N, Hirsch FR, Luft AV, et al. 2015. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial. *Lancet Oncol.* 16:763–74
14. Pardoll DM. 2012. The blockade of immune checkpoints in cancer immunotherapy. *Nat. Rev. Cancer* 12:252–64
15. Cancer Genome Atlas Research Network. 2012. Comprehensive genomic characterization of squamous cell lung cancers. *Nature* 489:519–25
16. Cancer Genome Atlas Research Network. 2014. Comprehensive molecular profiling of lung adenocarcinoma. *Nature* 511:543–50
17. Liu L, Liu J, Shao D, et al. 2017. Comprehensive genomic profiling of lung cancer using a validated panel to explore therapeutic targets in East Asian patients. *Cancer Sci.* 108:2487–94
18. Seto T, Matsumoto S, Yoh K, et al. 2018. Contribution of nationwide genome screening in Japan (LC-SCRUM-Japan) to the development of precision medicine for non-small cell lung cancer. *J. Clin. Oncol.* 36:9085
19. Jordan EJ, Kim HR, Arcila ME, et al. 2017. Prospective comprehensive molecular characterization of lung adenocarcinomas for efficient patient matching to approved and emerging therapies. *Cancer Discov.* 7:596–609
20. Paik PK, Hasanovic A, Wang L, et al. 2012. Multiplex testing for driver mutations in squamous cell carcinomas of the lung. *J. Clin. Oncol.* 30:7505
21. Lynch TJ, Bell DW, Sordella R, et al. 2004. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl. J. Med.* 350:2129–39
22. Lindeman NI, Cagle PT, Aisner DL, et al. 2018. Updated molecular testing guideline for the selection of lung cancer patients for treatment with targeted tyrosine kinase inhibitors: guideline from the College of American Pathologists, the International Association for the Study of Lung Cancer, and the Association for Molecular Pathology. *J. Thorac. Oncol.* 13:323–58
23. Brewer MR, Yun CH, Lai D, et al. 2013. Mechanism for activation of mutated epidermal growth factor receptors in lung cancer. *PNAS* 110:E3595–604
24. Kobayashi Y, Mitsudomi T. 2016. Not all epidermal growth factor receptor mutations in lung cancer are created equal: perspectives for individualized treatment strategy. *Cancer Sci.* 107:1179–86
25. Pao W, Miller V, Zakowski M, et al. 2004. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *PNAS* 101:13306–11
26. Fukuoka M, Wu YL, Thongprasert S, et al. 2011. Biomarker analyses and final overall survival results from a phase III, randomized, open-label, first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J. Clin. Oncol.* 29:2866–74
27. Maemondo M, Inoue A, Kobayashi K, et al. 2010. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N. Engl. J. Med.* 362:2380–88
28. Mitsudomi T, Morita S, Yatabe Y, et al. 2010. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol.* 11:121–28
29. Mok TS, Wu YL, Thongprasert S, et al. 2009. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N. Engl. J. Med.* 361:947–57
30. Rosell R, Carcereny E, Gervais R, et al. 2012. 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.* 13:239–46
31. Zhou C, Wu YL, Chen G, et al. 2011. 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.* 12:735–42

32. Inoue A, Kobayashi K, Maemondo M, et al. 2013. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naive non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann. Oncol.* 24:54–59
33. Zhou C, Wu YL, Chen G, et al. 2015. Final overall survival results from a randomised, phase III study of erlotinib versus chemotherapy as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer (OPTIMAL, CTONG-0802). *Ann. Oncol.* 26:1877–83
34. Spicer J, Calvert H, Vidal L, et al. 2007. D7–02: Activity of BIBW2992, an oral irreversible dual EGFR/HER2 inhibitor, in non-small cell lung cancer (NSCLC) with mutated EGFR. *J. Thorac. Oncol.* 2:S410
35. Sequist LV, Yang JC, Yamamoto N, et al. 2013. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J. Clin. Oncol.* 31:3327–34
36. Wu YL, Zhou C, Hu CP, et al. 2014. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol.* 15:213–22
37. Yang JC, Wu YL, Schuler M, et al. 2015. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol.* 16:141–51
38. Park K, Tan EH, O'Byrne K, et al. 2016. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol.* 17:577–89
39. Wu YL, Cheng Y, Zhou X, et al. 2017. Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive non-small-cell lung cancer (ARCHER 1050): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 18:1454–66
40. Giaccone G. 2005. EGFR point mutation confers resistance to gefitinib in a patient with non-small-cell lung cancer. *Nat. Clin. Pract. Oncol.* 2:296–97
41. Takezawa K, Pirazzoli V, Arcila ME, et al. 2012. HER2 amplification: a potential mechanism of acquired resistance to EGFR inhibition in EGFR-mutant lung cancers that lack the second-site EGFRT790M mutation. *Cancer Discov.* 2:922–33
42. Engelman JA, Zejnullahu K, Mitsudomi T, et al. 2007. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 316:1039–43
43. Ludovini V, Bianconi F, Pistola L, et al. 2011. Phosphoinositide-3-kinase catalytic alpha and KRAS mutations are important predictors of resistance to therapy with epidermal growth factor receptor tyrosine kinase inhibitors in patients with advanced non-small cell lung cancer. *J. Thorac. Oncol.* 6:707–15
44. Ho CC, Liao WY, Lin CA, et al. 2017. Acquired BRAF V600E mutation as resistant mechanism after treatment with osimertinib. *J. Thorac. Oncol.* 12:567–72
45. Nurwidya F, Takahashi F, Murakami A, Takahashi K. 2012. Epithelial mesenchymal transition in drug resistance and metastasis of lung cancer. *Cancer Res. Treat.* 44:151–56
46. Niederst MJ, Sequist LV, Poirier JT, et al. 2015. RB loss in resistant EGFR mutant lung adenocarcinomas that transform to small-cell lung cancer. *Nat. Commun.* 6:6377
47. Cross DA, Ashton SE, Ghiorghiu S, et al. 2014. AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov.* 4:1046–61
48. Janne PA, Yang JC, Kim DW, et al. 2015. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N. Engl. J. Med.* 372:1689–99
49. Mok TS, Wu YL, Ahn MJ, et al. 2017. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N. Engl. J. Med.* 376:629–40
50. Ramalingam SS, Yang JC, Lee CK, et al. 2018. Osimertinib as first-line treatment of EGFR mutation-positive advanced non-small-cell lung cancer. *J. Clin. Oncol.* 36:841–49
51. Soria JC, Ohe Y, Vansteenkiste J, et al. 2018. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N. Engl. J. Med.* 378:113–25
52. Ramalingam SS, Cheng Y, Zhou C, et al. 2018. Mechanisms of acquired resistance to first-line osimertinib: preliminary data from the phase III FLAURA study. *Ann. Oncol.* 29(Suppl. 8):mdy424-063

53. Saito H, Fukuhara T, Furuya N, et al. 2019. Erlotinib plus bevacizumab versus erlotinib alone in patients with EGFR-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial. *Lancet Oncol.* 20:625–35
54. Blakely CM, Watkins TBK, Wu W, et al. 2017. Evolution and clinical impact of co-occurring genetic alterations in advanced-stage EGFR-mutant lung cancers. *Nat. Genet.* 49:1693–704
55. Nakamura A, Inoue A, Morita S, et al. 2018. Phase III study comparing gefitinib monotherapy (G) to combination therapy with gefitinib, carboplatin, and pemetrexed (GCP) for untreated patients (pts) with advanced non-small cell lung cancer (NSCLC) with EGFR mutations (NEJ009). *J. Clin. Oncol.* 36:9005
56. Chiu CH, Yang CT, Shih JY, et al. 2015. Epidermal growth factor receptor tyrosine kinase inhibitor treatment response in advanced lung adenocarcinomas with G719X/L861Q/S768I mutations. *J. Thorac. Oncol.* 10:793–99
57. Yang JC, Sequist LV, Geater SL, et al. 2015. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol.* 16:830–38
58. Morris SW, Kirstein MN, Valentine MB, et al. 1994. Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science* 263:1281–84
59. Soda M, Choi YL, Enomoto M, et al. 2007. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 448:561–66
60. Shaw AT, Kim DW, Nakagawa K, et al. 2013. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N. Engl. J. Med.* 368:2385–94
61. Solomon BJ, Mok T, Kim DW, et al. 2014. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N. Engl. J. Med.* 371:2167–77
62. Shaw AT, Kim TM, Crino L, et al. 2017. Ceritinib versus chemotherapy in patients with ALK-rearranged non-small-cell lung cancer previously given chemotherapy and crizotinib (ASCEND-5): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* 18:874–86
63. Kim DW, Tiseo M, Ahn MJ, et al. 2017. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J. Clin. Oncol.* 35:2490–98
64. Novello S, Mazieres J, Oh IJ, et al. 2018. Alectinib versus chemotherapy in crizotinib-pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: results from the phase III ALUR study. *Ann. Oncol.* 29:1409–16
65. Soria JC, Tan DSW, Chiari R, et al. 2017. First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomised, open-label, phase 3 study. *Lancet* 389:917–29
66. Peters S, Camidge DR, Shaw AT, et al. 2017. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N. Engl. J. Med.* 377:829–38
67. Hida T, Nokihara H, Kondo M, et al. 2017. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet* 390:29–39
68. Gadgeel S, Peters S, Mok T, et al. 2018. Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann. Oncol.* 29:2214–22
69. Toyokawa G, Seto T. 2015. Updated evidence on the mechanisms of resistance to ALK inhibitors and strategies to overcome such resistance: clinical and preclinical data. *Oncol. Res. Treat.* 38:291–98
70. Lin JJ, Zhu VW, Yoda S, et al. 2018. Impact of EML4-ALK variant on resistance mechanisms and clinical outcomes in ALK-positive lung cancer. *J. Clin. Oncol.* 36:1199–206
71. Shaw AT, Felip E, Bauer TM, et al. 2017. Lorlatinib in non-small-cell lung cancer with ALK or ROS1 rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial. *Lancet Oncol.* 18:1590–99
72. Lin JJ, Zhu VW, Schoenfeld AJ, et al. 2018. Brigatinib in patients with alectinib-refractory ALK-positive NSCLC. *J. Thorac. Oncol.* 13:1530–38
73. Bergethon K, Shaw AT, Ou SH, et al. 2012. ROS1 rearrangements define a unique molecular class of lung cancers. *J. Clin. Oncol.* 30:863–70

74. Neel DS, Allegakoen DV, Olivas V, et al. 2019. Differential subcellular localization regulates oncogenic signaling by ROS1 kinase fusion proteins. *Cancer Res*. 79:546–56
75. Shaw AT, Ou SH, Bang YJ, et al. 2014. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N. Engl. J. Med.* 371:1963–71
76. Awad MM, Katayama R, McTigue M, et al. 2013. Acquired resistance to crizotinib from a mutation in CD74-ROS1. *N. Engl. J. Med.* 368:2395–401
77. Vaishnavi A, Schubert L, Rix U, et al. 2017. EGFR mediates responses to small-molecule drugs targeting oncogenic fusion kinases. *Cancer Res*. 77:3551–63
78. Marchetti A, Felicioni L, Malatesta S, et al. 2011. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. *J. Clin. Oncol.* 29:3574–79
79. Cardarella S, Ogino A, Nishino M, et al. 2013. Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. *Clin. Cancer Res.* 19:4532–40
80. Planchard D, Kim TM, Mazieres J, et al. 2016. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 17:642–50
81. Planchard D, Smit EF, Groen HJM, et al. 2017. Dabrafenib plus trametinib in patients with previously untreated BRAF(V600E)-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 18:1307–16
82. Drilon A, Laetsch TW, Kummar S, et al. 2018. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N. Engl. J. Med.* 378:731–39
83. Okamura R, Boichard A, Kato S, et al. 2018. Analysis of *NTRK* alterations in pan-cancer adult and pediatric malignancies: implications for NTRK-targeted therapeutics. *JCO Precis. Oncol*. **https://doi.org/10.1200/PO.18.00183**
84. Kong-Beltran M, Seshagiri S, Zha J, et al. 2006. Somatic mutations lead to an oncogenic deletion of Met in lung cancer. *Cancer Res*. 66:283–89
85. Drilon A, Clark J, Weiss J, et al. 2018. Updated antitumor activity of crizotinib in patients with MET exon 14-altered advanced non-small cell lung cancer. *J. Thorac. Oncol.* 13:S348
86. Schreiber RD, Old LJ, Smyth MJ. 2011. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* 331:1565–70
87. Borghaei H, Paz-Ares L, Horn L, et al. 2015. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N. Engl. J. Med.* 373:1627–39
88. Brahmer J, Reckamp KL, Baas P, et al. 2015. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N. Engl. J. Med.* 373:123–35
89. Herbst RS, Baas P, Kim DW, et al. 2016. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 387:1540–50
90. Rittmeyer A, Barlesi F, Waterkamp D, et al. 2017. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 389:255–65
91. Tsao MS, Kerr KM, Kockx M, et al. 2018. PD-L1 immunohistochemistry comparability study in real-life clinical samples: results of blueprint phase 2 project. *J. Thorac. Oncol.* 13:1302–11
92. Reck M, Rodriguez-Abreu D, Robinson AG, et al. 2016. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N. Engl. J. Med.* 375:1823–33
93. Mok TSK, Wu YL, Kudaba I, et al. 2019. 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* 393:1819–30
94. Carbone DP, Reck M, Paz-Ares L, et al. 2017. First-line nivolumab in stage IV or recurrent non-small-cell lung cancer. *N. Engl. J. Med.* 376:2415–26
95. Peters S, Creelan B, Hellmann MD, et al. 2017. Impact of tumor mutation burden on the efficacy of first-line nivolumab in stage IV or recurrent non-small cell lung cancer: an exploratory analysis of CheckMate 026. *Cancer Res*. 77:CT082 (Abstr.)

96. Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. 2018. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N. Engl. J. Med.* 378:2078–92
97. Paz-Ares L, Luft A, Vicente D, et al. 2018. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N. Engl. J. Med.* 379:2040–51
98. Socinski MA, Jotte RM, Cappuzzo F, et al. 2018. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N. Engl. J. Med.* 378:2288–301
99. Hellmann MD, Ciuleanu TE, Pluzanski A, et al. 2018. Nivolumab plus ipilimumab in lung cancer with a high tumor mutational burden. *N. Engl. J. Med.* 378:2093–104
100. Skoulidis F, Goldberg ME, Greenawalt DM, et al. 2018. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. *Cancer Discov*. 8:822–35
101. Zaretsky JM, Garcia-Diaz A, Shin DS, et al. 2016. Mutations associated with acquired resistance to PD-1 blockade in melanoma. *N. Engl. J. Med.* 375:819–29