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TOPIC HIGHLIGHT

WJCO 5th Anniversary Special Issues (1): Lung cancer

Review of the current targeted therapies for non-small-cell lung cancer

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Abstract

The last decade has witnessed the development of oncogene-directed targeted therapies that have significantly changed the treatment of non-small-cell lung cancer (NSCLC). In this paper we review the data demonstrating efficacy of gefitinib, erlotinib, and afatinib, which target the epidermal growth factor receptor (EGFR), and crizotinib which targets anaplastic lymphoma kinase (ALK). We discuss the challenge of acquired resistance to these small-molecular tyrosine kinase inhibitors and review promising agents which may overcome resistance, including the EGFR T790M-targeted agents CO-1686 and AZD9291, and the ALK-targeted agents ceritinib (LDK378), AP26113, alectinib (CH/RO5424802), and others. Emerging therapies directed against other driver oncogenes in NSCLC including *ROS1*, *HER2*, and *BRAF* are covered as well. The identification of specific molecular targets in a significant fraction of NSCLC has led to the personalized deployment of many effective targeted therapies, with more to come.

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Key words: Lung cancer; Non-small cell lung cancer; Targeted therapies; Epidermal growth factor receptor; Epidermal growth factor receptor; Anaplastic lymphoma kinase; Anaplastic lymphoma kinase; Acquired resistance

Core tip: The development of oncogene-directed targeted therapies has significantly changed the treatment of non-small-cell lung cancer. We review the data demonstrating efficacy of small-molecule tyrosine kinase inhibitors against epidermal growth factor receptor, anaplastic lymphoma kinase, ROS1, and other oncogenes. We also discuss the challenge of acquired resistance to these therapies and review promising agents which may overcome resistance.

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INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths around the world with approximately 1.3 million deaths per year and a poor prognosis for those with advanced stage disease treated with traditional chemotherapy agents[1,2]. However, the last decade has witnessed the discovery of molecular changes that drive lung cancer in a substantial minority of patients and development of many targeted therapies that have significantly changed treatment in this setting. In this paper we review the data leading to approval of targeted therapies against the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK), discussing the challenges of overcoming acquired resistance to these small-molecular tyrosine kinase

inhibitors (TKIs). We also review several other promising targeted therapies currently in development.

FIRST-GENERATION EGFR TKIS

The first available targeted therapies for advanced NSCLC were gefitinib and erlotinib, both of which are small-molecule TKIs against EGFR, also known as HER1 or ErbB-1. The dimerization of EGFR activates its tyrosine kinase, which in turn activates intracellular signal transduction pathways involved in many cellular processes. Early work on EGFR in lung cancer has shown that EGFR overexpression is commonly seen in NSCLC[3,4], motivating the development of EGFR TKIs.

Phase Ⅱ studies of gefitinib and erlotinib in the second- or third-line setting for advanced NSCLC in unselected patients were promising, showing a partial radiographic response rate of about 12% with symptomatic improvements[5-7]. The first clinical trial to show an improved overall survival (OS) was the Canadian phase Ⅲ BR.21 trial, which randomized patients with stage ⅢB or IV NSCLC, neither clinically nor molecularly selected for *EGFR* mutations, who had received one or two chemotherapy regimens, to either erlotinib or placebo. Patients receiving erlotinib had a median OS of 6.7 mo, compared with 4.7 mo for those on placebo[8]. Interestingly, a similar phase Ⅲ study, the Iressa Survival Evaluation in Lung Cancer (ISEL) trial, comparing gefitinib to placebo in the second- or third-line setting failed to demonstrate an improved OS. However, subgroups of never smokers and Asians did have statistically significant survival advantage on gefitinib compared to placebo[9]. That erlotinib apparently had greater efficacy than erlotinib might be due to the fact that erlotinib was dosed at its maximum tolerated dose (MTD)[8] while gefitinib was dosed at one-third of its MTD[9].

However, data from these clinical trials and others suggested that EGFR immunohistochemical staining intensity was not predictive of therapeutic benefit[5]. Subsequently, somatic activating *EGFR* mutations, most commonly including exon 19 deletions and exon 21 L858R missense mutations, were discovered to be a dominant predictor of responsiveness to EGFR TKIs[10-15]. It is estimated that these activating *EGFR* mutations are present in tumors from about 50% of Asian patients with NSCLC and 15% of Western patients[16-19]. The cause for this difference in the prevalence rates of *EGFR* mutations among various ethnic groups remains unknown, yet *EGFR* mutations are also observed most frequently in women, patients with no or minimal history of smoking, and tumors of adenocarcinoma histology[16,17,20].

More recent first line studies in advanced NSCLC attempted to enrich patients with activating *EGFR* mutations to compare EGFR TKI therapy with conventional chemotherapy. The pivotal Iressa Pan-Asia Study (IPASS) randomized over 1200 untreated patients who were never smokers or former light smokers to either gefitinib or the combination of carboplatin and paclitaxel. The progression-free survival (PFS) at 12 mo was 25% for gefitinib and 7% for chemotherapy. For patients with activating *EGFR* mutations, gefitinib was associated with a hazard ratio for progression of 0.48 ($P < 0.001$) compared to chemotherapy, while for patients who were negative for *EGFR* mutations, gefitinib was associated with shorter PFS with a hazard ratio for progression of 2.985 ($P < 0.001$). OS was similar between the two groups, presumably due to crossover[18,19]. Similar results have been observed in other trials involving gefitinib conducted in Asia. The First-SIGNAL trial from the South Korea comparing gefitinib to cisplatin and gemcitabine in the first-line setting for advanced pulmonary adenocarcinoma in never smokers demonstrated a PFS benefit for gefitinib but also no OS difference. This study also had significant crossover. For the subgroup of patients with *EGFR*-mutant adenocarcinoma, gefitinib was associated with a higher overall response rate (ORR) (84.6% *vs* 37.5%; $P = 0.002$) and a trend toward longer PFS (HR = 0.544; 95%CI: 0.269-1.100; $P = 0.086$) compared to chemotherapy. For those patients with tumors harboring wild-type EGFR, the reverse was found: chemotherapy showed a trend toward higher ORR and longer PFS[21]. Together, the IPASS and First-SIGNAL studies demonstrated that activating *EGFR* mutations are predictors of benefit with gefitinib and that wild-type *EGFR* patients do poorly with first-line gefitinib compared to platinum-based chemotherapy.

Instead of selecting patients by smoking status, subsequent studies included only patients with activating *EGFR* mutations. In randomized controlled trials, Japanese researchers confirmed the PFS superiority of gefitinib to chemotherapy as first-line treatment for patients with advanced *EGFR*-mutant NSCLC. In the West Japan Thoracic Oncology Group trial 3405, patients on the gefitinib arm had a median PFS of 9.6 mo, compared to 6.6 mo for those on cisplatin plus docetaxel[22,23]. In a North-East Japan Study Group trial, gefitinib was associated with a PFS of 10.8 mo *vs* 5.4 mo for carboplatin-paclitaxel[24]. In both Japanese trials, the differences in OS were not statistically significant[23,24].

Similar to gefitinib, erlotinib has also demonstrated PFS advantages compared to chemotherapy in patients with *EGFR*-mutant NSCLC in the first-line setting. The Chinese OPTIMAL trial showed a PFS of 13.1 mo for erlotinib *vs* 4.6 mo for carboplatin and gemcitabine[25]. The EURTAC trial demonstrated that EGFR TKIs were also effective for European patients with *EGFR*-mutant NSCLC in the first-line setting. In this study, patients receiving erlotinib had a PFS of 9.7 mo, compared to 5.2 mo for those receiving a platinum-based chemotherapy regimen[26]. OS was not statistically different between the erlotinib and chemotherapy arms in either the OPTIMAL or EURTAC trial[26,27].

More recent efforts have focused on newer-generation EGFR TKIs. Afatinib is an irreversible ErbB family inhibitor that, in preclinical models, has been shown to have activity against activating *EGFR* mutations as well

as the *EGFR* T790M mutation that confers resistance to erlotinib and gefitinib[28]. The initial randomized studies of afatinib addressed its efficacy in the EGFR-TKI resistance setting. In LUX-Lung 1, patients with *EGFR*-mutant NSCLC who had received a first-generation EGFR TKI and chemotherapy were randomized to either afatinib or placebo. PFS was 3.3 mo for afatinib, compared to 1.1 mo for placebo ($P < 0.0001$)[29]. The drug was then studied as a first-line treatment for *EGFR*-mutant NSCLC. The global LUX-Lung 3 phase Ⅲ study randomized 345 patients to either afatinib or cisplatin-pemetrexed. The median PFS was 11.1 mo for afatinib and 6.9 mo for chemotherapy (HR = 0.58; 95%CI: 0.43-0.78; $P = 0.001$)[30]. Similarly, the LUX-Lung 6 phase Ⅲ study randomized 364 Chinese patients with *EGFR*-mutant NSCLC to either afatinib or cisplatin-gemcitabine in a 2 to 1 ratio. The median PFS of patients on the afatinib arm was 11.0 mo *vs* 5.6 mo for chemotherapy, HR = 0.28, $P < 0.0001$[31]. In July 2013, nine years after the initial approval of erlotinib for treatment of advanced NSCLC (second or third line, regardless of *EGFR* mutation status) and only two months after the approval of erlotinib for first-line treatment of advanced EGFR-mutant NSCLC, the United States Food and Drug Administration (FDA) approved afatinib, for the first-line treatment of advanced NSCLC with activating exon 19 deletions and L858R *EGFR* mutations. A pooled subgroup analysis from trials of afatinib in TKI-naïve patients demonstrated good activity with a PFS of 10.7 mo in patients with other *EGFR* mutations that are classically sensitive to erlotinib, like L861Q and G719X[32]. However, tumors initially harboring historically TKI-resistant alterations including T790M and exon 20 insertions appear markedly less sensitive, with PFS of under 3 mo in both groups. The ongoing clinical trial LUX-Lung 7 is comparing afatinib against gefitinib in the first-line setting for *EGFR*-mutant NSCLC to help determine relative efficacy of the two TKIs (ClinicalTrials.gov identifier: NCT01466660).

OVERCOMING RESISTANCE TO EGFR TYROSINE KINASE INHIBITORS

The discovery of EGFR TKIs has thus revolutionized treatment of NSCLC with activating *EGFR* mutations, with erlotinib, gefitinib, and afatinib approved for use in various countries. While a small minority of patients have disease control for years on these drugs, on average these TKIs have a median response duration seldom exceeding one year due to acquired resistance. The mechanisms of resistance vary, with the *EGFR* T790M point mutation in exon 20 being the most common cause of acquired resistance, accounting for about 50% of cases. The T790M "gatekeeper" mutation was initially thought to simply exclude binding of EGFR-TKI drugs by steric hindrance, but more importantly it appears to restore the EGFR affinity for ATP, thus decreasing the binding of the ATP-competitive TKIs[33-35]. There is increasing evidence that a low level of the T790M mutation exists before treatment in many patients with EGFR-mutant NSCLC and predicts a worse PFS on erlotinib compared to those without pre-treatment T790M[36]. Another clearly described cause of acquired resistance to TKI is the amplification of the mesenchymal epithelial transition (MET) proto-oncogene, which activates an AKT-mediated signaling pathway, bypassing EGFR[37,38]. Several other *EGFR* mutations have also been implicated in conferring resistance to EGFR TKIs: D761Y[39], T854A[40], and L747S[41], in addition to activating *BRAF* mutations[42] and *HER2* amplification[43]. Interestingly, some TKI-resistant tumors undergo histologic changes, including transformation from non-small-cell to small cell or epithelial-mesenchymal transition, leading to resistance through less direct mechanisms[44].

Since half of acquired resistance is dependent on the T790M missense mutation, newer EGFR TKIs are in development to overcome resistance. The second-generation inhibitors afatinib and dacomitinib irreversibly inhibit both wild-type and mutant EGFR proteins, and to a lesser extent, T790M EGFR. In clinical trials designed to test activity in patients with acquired resistance, however, these drugs have not routinely induced reliable, robust responses. In the LUX-Lung 4 single-arm phase Ⅱ study from Japan, patients were enrolled with *EGFR*-mutant NSCLC that had progressed on gefitinib/erlotinib and chemotherapy. Treatment with afatinib was associated with a modest response rate of 8.2%, and median PFS of 4.4 mo with median OS of 19.0 mo[45]. Similarly, the larger placebo controlled trial of LUX-Lung 1 trial of afatinib after failure of chemotherapy and erlotinib or gefitinib evaluated 390 patients on afatinib and 195 patients on placebo. Compared with the afatinib group, the placebo group had an identical OS (10.8 mo *vs* 12.0 mo; HR 1.08; 95%CI: 0.86-1.35; $P = 0.74$). However, median PFS was statistically better in the afatinib group (3.3 mo *vs* 1.1 mo; HR 0.38; 95%CI: 0.31-0.48; $P < 0.0001$), yet the response rate was still unimpressive in this group (7%)[29]. Dacomitinib (PF-00299804) is another irreversible TKI active against EGFR, HER2, and HER4. In a preliminary report of a phase Ⅱ studying patients with NSCLC after failure of chemotherapy and erlotinib, responses were seen in 3 of 62 evaluable patients (5%)[46]. To confirm the activity in this population, a large phase Ⅲ study, the Canadian BR.26 trial, randomized 720 patients to dacomitinib or placebo for progressive disease after treatment with chemotherapy and an EGFR TKI (ClinicalTrials.gov identifier NCT01000025). According to a recent press release, however, this trial failed to meet its primary objective of prolonging overall survival *vs* placebo, with results to be reported in upcoming meetings[47]. Another phase Ⅲ study comparing dacomitinib *vs* gefitinib in treatment-naive patients with *EGFR*-mutant NSCLC is still ongoing (ClinicalTrials.gov identifier NCT01774721). With other second-generation EGFR inhibitors including neratinib[48] and XL647 (which also inhibits VEGFR)[49], similarly low response rates were reported in trials of acquired resistance.

The strategy of combination therapy incorporating second-generation inhibitors has also been employed with

mixed success. Cetuximab, a monoclonal antibody against EGFR, adds little activity when added to erlotinib in the setting of acquired resistance[50]. However, the combination of afatinib and cetuximab is surprisingly effective for acquired resistance. In a phase I b study, patients with acquired EGFR inhibitor resistance were given 40 mg daily of afatinib plus 500 mg/m^2 of cetuximab every other week. Of 61 reported patients at the recommended dose, 35% had confirmed response and 95% had stable disease or better, including patients with tumors with and without T790M mutations. Side effects including rash, diarrhea, and mucositis were significant[51]. Follow-up trials of these agents for patients with *EGFR*-mutant NSCLC are currently in development. The strategy of combined EGFR and MET inhibition has also been employed in phase I / II trials. In a dose-finding trial of erlotinib plus the MET and VEGFR inhibitor cabozantinib (XL-184), 53 patients were evaluable and had a response rate of 8%. Interestingly, the two patients with confirmed *MET* copy number gain had disease shrinkage[52]. Preliminary results from a phase I study using dacomitinib plus crizotinib (a MET and ALK inhibitor) noted a response rate of 5% in 20 patients who had previously had response or prolonged stable disease on an EGFR TKI[53]. Further study of the infrequent *MET* amplification cohort will be of interest using this combination.

Although the second-generation agents do not appear to effectively combat acquired resistance, a novel class of third-generation EGFR inhibitors has been recently identified that much more potently inhibits mutant EGFR with T790M than wild type EGFR. The first such described molecules demonstrated impressive preclinical effectiveness in a mouse model of T790M-dependent acquired EGFR resistance[54]. Since that time, two compounds with similar affinity for mutant, including T790M, EGFR protein, but minimal binding of wild-type EGFR, have early phase I results reported: CO-1686 and AZD9291. In a preliminary report of the CO-1686 clinical trial, 56 patients with *EGFR* activating mutations and failure of prior EGFR TKI therapy have been enrolled to a dose escalation trial. Of the 9 patients with tumors testing positive for T790M who were treated at the highest dose, 6 responded, 2 had stable disease (with slight decrease), and 1 patient progressed on therapy[55]. In a similarly designed dose escalation study of AZD9291, 35 patients were treated with doses ranging from 20-80 mg. Fifteen of 35 patients (43%) had a confirmed or unconfirmed partial response, including those with and without documented T790M mutation. The majority of patients had some degree of tumor control, and only 4 patients progressed initially on treatment. Interestingly, wild-type EGFR toxicity for both agents appears quite mild, with rash and diarrhea infrequently reported[56].

FIRST-GENERATION ALK TKI

Activating EGFR mutations are not the only actionable genetic alterations in NSCLC. In 2007, Japanese researchers working with NSCLC cells discovered an inversion in chromosome 2p resulting in a novel fusion gene comprised of portions of the echinoderm microtubule-associated protein-like 4 (*EML4*) gene and the anaplastic lymphoma kinase (*ALK*) gene, including its entire intracellular tyrosine kinase domain. The *EML4* fusion partner mediates ligand-independent dimerization of ALK, leading to constitutive kinase activity. EML4-ALK fusion protein was tumorigenic in mice, and the Japanese researchers detected this transcript in about 5 out of 75 (6.7%) tumors from NSCLC patients[57]. Subsequent published series have suggested that the frequency of *ALK* gene rearrangement in unselected NSCLC patients is about 3% to 6%[58-63]. Besides *EML4*, several other fusion partners of *ALK*, *e.g.*, *KIF5B* and *TFG*, have been identified[64,65]. Similar to activating *EGFR* mutations, *ALK* gene rearrangements are associated with younger age, never or light smoking status, and adenocarcinoma histology; however there is equal distribution by sex[66,67].

Crizotinib, an oral, small-molecule inhibitor of ALK and c-Met, was originally developed as a potential therapeutic agent for *ALK*-positive anaplastic large cell lymphoma (ALCL)[68]. The drug has indeed demonstrated activity in *ALK*-positive ALCL[69] as well as *ALK*-positive diffuse large B cell lymphoma and inflammatory myofibroblastic tumors[70,71]. However, crizotinib has been most widely applied in the treatment of NSCLC with *ALK* gene rearrangements after marked activity was noted in the patient population in the phase I trial, leading to FDA approval of the drug[72]. In a phase Ⅲ study, 347 patients with locally advanced or metastatic *ALK*-rearranged NSCLC who had received one prior platinum-based regimen were randomized to crizotinib or chemotherapy with either pemetrexed or docetaxel. The median PFS was 7.7 mo in the crizotinib group, significantly superior to the 3.0 mo in the chemotherapy group (HR for progression or death with crizotinib, 0.49; 95%CI: 0.37-0.64; $P < 0.001$). Common adverse events associated with crizotinib were visual disorders, nausea, diarrhea, vomiting, constipation, and elevated liver enzymes[73]. Rare cases of esophageal ulceration associated with crizotinib have also been reported[74]. In August 2011, only four years after the discovery of *ALK* gene rearrangements in NSCLC, the FDA granted accelerated approval to crizotinib for patients with *ALK*-positive NSCLC[75]. An ongoing clinical trial seeks to demonstrate superiority of crizotinib compared to first-line platinum/pemetrexed chemotherapy for *ALK*-rearranged (ClinicalTrials.gov identifiers: NCT01154140 and NCT01639001). Accrual is complete and results are awaited, though crizotinib is commonly used in the first line setting without this evidence.

OVERCOMING RESISTANCE TO CRIZOTINIB

Unfortunately, many tumors with *ALK* gene rearrangements eventually acquire resistance to crizotinib, frequently within one year, similar to *EGFR*-mutant NSCLC

developing resistance to erlotinib or gefitinib. Researchers from Massachusetts General Hospital and collaborators analyzed 18 patients with crizotinib-resistant NSCLC and discovered that almost one-quarter of the patients had either secondary mutations in the *ALK* tyrosine kinase domain or *ALK* fusion gene amplification. About half of the patients were found to have tyrosine kinase activity via EGFR or KIT, thus bypassing the inhibited ALK-mediated pathway[76]. The L1196M mutation has been shown to be a gatekeeper mutation in the *ALK* kinase domain, conferring resistance to crizotinib[76-79], similar to the *EGFR* T790M mutation that confers resistance to erlotinib. Besides *EGFR* mutations[76,78], *KRAS* mutations have also been identified as a possible mechanism of crizotinib resistance in a separate series of crizotinib-resistant patients from the University of Colorado[78].

Multiple second-generation ALK inhibitors have been developed with increased potency and potential to overcome acquired resistance to crizotinib, including ceritinib (LDK378), AP26113, and alectinib (CH/RO5424802). Ceritinib has recently been shown to have efficacy against crizotinib-naive as well as crizotinib-resistant *ALK*-positive lung cancer. In a multicenter phase I study, 131 patients with advanced malignancies harboring a genetic alteration in *ALK*, including 123 patients with *ALK*-rearranged NSCLC, received ceritinib orally at doses of 50 mg to 750 mg once daily. Among the 88 NSCLC patients who received ceritinib at 400-750 mg daily, the ORR was 70%. In the subset of 64 crizotinib-resistant patients, the ORR was similar at 73%, with responses observed in patients with different crizotinib resistance mutations, patients without detectable mutation, and even patients with untreated CNS metastases. In all 123 NSCLC patients, the median PFS was 8.6 mo (95%CI: 4.3-19.3). Ceritinib appeared to have more toxicities than crizotinib, however, with the most common adverse events, including all grades, being nausea (72%), diarrhea (69%), vomiting (50%), and fatigue (31%)[80]. The drug has advanced to phase Ⅲ clinical trials, being compared *vs* chemotherapy for *ALK*-rearranged NSCLC in the first-line setting (ClinicalTrials.gov identifier NCT01828099) or in the third-line setting for patients previously treated with chemotherapy and crizotinib (ClinicalTrials.gov identifier NCT01828112).

Another promising second-generation ALK inhibitor is AP26113, which exhibits activity against all 9 clinically-identified crizotinib-resistant mutants, including the L1196M gatekeeper, in preclinical experiments[81,82]. Like most other ALK inhibitors, AP26113 also inhibits ROS1, an actionable target to be discussed later in this review, and selectively inhibits EGFR T790M without affecting the native receptor[83]. In a phase Ⅰ/Ⅱ multicenter study, 55 patients with advanced malignancies, including 47 with NSCLC refractory to available therapies, received daily doses of AP26113. Of the 24 patients who had *ALK*-positive solid tumors, 15 responded. Among *ALK*-rearranged NSCLC patients with prior crizotinib only, 12 out of 16 (75%) responded. The drug appeared to have activity in the CNS as well. Four out of 5 *ALK*-positive patients with untreated or progressing CNS lesions had evidence of radiographic improvement in the CNS, including 1 patient resistant to both crizotinib and LDK378. The most common adverse events were fatigue (40%), nausea (36%), and diarrhea (33%), generally at CTCAE grade 1/2[84].

A third ALK inhibitor in development is alectinib, previously known as CH/RO5424802. In a phase Ⅰ/Ⅱ study of 58 patients with *ALK*-rearranged NSCLC and no prior ALK inhibitor therapy, the overall response rate for alectinib in 46 patients on the phase Ⅱ part of the study was 93.5% (95%CI: 82.1-98.6) with 2 CRs and 41 PRs. With a median follow-up period of 12.6 mo, 47 out of 58 patients were still on study treatment, and the median treatment duration had passed 10.3 mo[85]. Alectinib has been shown to have activity post crizotinib as well. In a phase Ⅰ study of alectinib in 37 patients with *ALK*-rearranged NSCLC who progressed after crizotinib and chemotherapy, partial response (PR) was observed in 48% of all patients and 59.5% of the subgroup of patients receiving doses of 460 mg or higher twice a day. Median PFS had not been reached, with the median duration on study ranging from 39 d to over 347 d[86]. Sixteen of these *ALK*-rearranged NSCLC patients had CNS metastases. Although PFS had not been reached by June 2013, alectinib demonstrated rapid benefit in brain metastases in a number of patients, including those resistant to crizotinib[87]. The most common side effects of the drug were fatigue, myalgia, cough, liver enzyme elevation, peripheral edema and rash[86,87].

There are also other second-generation ALK inhibitors in earlier stages of clinical development. For example, X-396, a potent and highly specific ALK TKI, demonstrated preclinical activity against the most common *ALK* fusions as well as against secondary *ALK* mutations that conferred resistance to crizotinib[88]. X-396 is currently in phase Ⅰ development (ClinicalTrials.gov identifier NCT01625234). PF-06463922 is a promising next-generation ALK/ROS1 inhibitor that has potent and selective inhibitory activity against all known acquired crizotinib-resistant mutations. PF-06463922 is also capable of penetrating the blood brain barrier in preclinical animal models[89]. The drug is also currently in phase Ⅰ development (ClinicalTrials.gov identifier NCT01970865). ASP3026 is another potent ALK inhibitor that also has activity against crizotinib-resistant tumors in mouse model[90]. ASP3026 is currently in phase Ⅰ development (ClinicalTrials.gov identifier NCT01401504).

OTHER "ACTIONABLE" MOLECULAR TARGETS

The discovery of the oncogenic alterations involving *EGFR* and *ALK* and their inhibitors has revolutionized the treatment of non-small cell lung cancer over the past decade. However, *EGFR*-mutant and *ALK*-rearranged cancers make up less than one-fifth of all NSCLC cases

Table 1 Selected current targeted therapies for non-small cell lung cancer and their stages of development

Drug	Company	Stage of development in NSCLC
EGFR activating mutations		
Gefitinib	AstraZeneca	Approved
Erlotinib	Roche	Approved
Afatinib	Boehringer Ingelheim	Approved
Dacomitinib	Pfizer	Phase Ⅲ
CO-1686	Clovis	Phase Ⅰ / Ⅱ
AZD9291	AstraZeneca	Phase Ⅰ / Ⅱ
ALK gene rearrangements		
Crizotinib	Pfizer	Approved
LDK378	Novartis	Phase Ⅲ
AP26113	ARIAD	Phase Ⅱ
Alectinib	Chugai	Phase Ⅱ
X-396	Xcovery	Phase Ⅰ
PF-06463922	Pfizer	Phase Ⅰ
ROS1 gene rearrangements		
Crizotinib	Pfizer	Phase Ⅱ (approved for ALK-positive NSCLC)
LDK378	Novartis	Phase Ⅱ
PF-06463922	Pfizer	Phase Ⅰ
HER2 activating mutations		
Trastuzumab	Genentech	Phase Ⅱ
Afatinib	Boehringer Ingelheim	No HER2-mutant NSCLC specific trial
Neratinib	Puma Biotechnology	Phase Ⅱ
BRAF activating mutations		
Dabrafenib	GlaxoSmithKline	Phase Ⅱ

NSCLC: Non-small-cell lung cancer; ALK: Anaplastic lymphoma kinase.

in the United States. Several other potentially actionable molecular targets have recently been found.

ROS1 gene rearrangements, involving the receptor tyrosine kinase ROS1 and partners CD74, SLC24A2, and FIG, are the driver oncogenes in a small subset of NSCLC[91-93] also responsive to crizotinib[91]. An expansion cohort of the phase I crizotinib study PROFILE 1001 included 40 patients with *ROS1*-positive NSCLC. In the 35 patients who were evaluated, the ORR was 60% with 2 complete response (CR), 19 PR, and 10 stable disease (SD) cases. Six-month PFS probability was 76% (95%CI: 55-88). Median PFS had not been reached when the results were reported at the World Conference on Lung Cancer in October 2013[94]. Unfortunately, acquired resistance to crizotinib in *ROS1*-positive patients has also been reported. A patient with the *ROS1-CD74* fusion oncogene initially responded dramatically to two mo of crizotinib treatment but then progressed in the third month. Her tumor was found to have a novel G2032R mutation in the *CD74-ROS1* fusion junction that had not been observed before crizotinib treatment[95]. Recently a promising ROS1 inhibitor, foretinib, has been shown to demonstrate efficacy against ROS1-rearranged tumor cells, including crizotinib-resistant cells. Foretinib, which also inhibits other kinases including MET and VEGFR2, is being studied in phase I and Ⅱ studies in a variety of cancers.

About 1% to 2% of NSCLC tumors have mutations in *HER2* exon 20[96,97], which is not clearly associated with *HER2* amplification. Although anti-Her2 therapies are ineffective in *HER2*-amplified NSCLC[98,99], *HER2*-mutant NSCLC has been shown to be responsive to trastuzumab plus chemotherapy, with an overall response rate of 50% and median PFS of 5.1 mo in one case series[96]. Afatinib, the ErbB family inhibitor approved for *EGFR*-mutant NSCLC as discussed earlier in this review, also has clinical activity against *HER2*-mutant NSCLC in a small case series[96,100]. As HER family members signal via the PI3K-AKT-mTOR cascade, recent attempts have been made to inhibit both HER2 and mTOR in HER2-driven cancers. In a phase I study of the combination of neratinib (a small molecule pan-HER inhibitor) and temsirolimus (an mTOR inhibitor), 7 patients with *HER2*-mutant NSCLC were treated, with 2 showing partial responses[101]. An ongoing phase Ⅱ study compares neratinib *vs* neratinib plus temsirolimus in patients with *HER2*-mutant NSCLC (ClinicalTrials.gov identifier NCT01827267).

BRAF activating mutations can be observed in 1%-3% of NSCLC[102,103]. In one case series, about half of these *BRAF* mutations are the V600E mutation that is also seen in melanoma. Unlike *EGFR*, *ALK*, and *ROS1* genetic alterations that are associated with light or never smoking status, *BRAF* mutations in NSCLC are often reported in current or former smokers[103]. In a phase Ⅱ study, 17 patients with *BRAF* V600E-mutant NSCLC received dabrafenib, which had previously shown activity in *BRAF* V600E-mutant melanoma. Seven patients out of 13 (54%) evaluable patients had PR, with 1 patient having stable disease. The drug was generally well tolerated, and the median duration of treatment was 9 wk, with the longest duration of response being 49 wk when the results were reported at the 2013 ASCO Annual Meeting[104]. An ongoing phase Ⅱ study tests dabrafenib *vs* dabrafenib and trametinib, an inhibitor of MEK that is downstream of BRAF, in patients with *BRAF* V600E mutation-positive NSCLC (ClinicalTrials.gov identifier NCT01336634).

Other rare genetic alterations in NSCLC have been found and have potentially therapeutic agents include *MET* amplification, *FGFR1* amplification, *RET* translocations, and *MEK1* mutations. Investigations using inhibitors of these oncogenic pathways are ongoing, with anecdotal responses reported in some cases. A detailed discussion of these targets is beyond the scope of this review. Table 1 summarizes the targeted therapies for NSCLC that have already been approved or are still in ongoing clinical trials.

CONCLUSION

Until several years ago, the only therapeutic option for advanced NSCLC was cytotoxic chemotherapy. The discovery of activating *EGFR* mutations and the unprecedented efficacy of erlotinib and gefitinib in *EGFR*-mutant NSCLC ushered in an era of truly personalized cancer care. There is increasing evidence that targeted therapies yield better outcomes than traditional chemotherapy in appropriate patients. The Lung Cancer Mutation Consortium recently reported that an actionable

driver was detected in 64% of patients with pulmonary adenocarcinoma and that among the 938 patients the consortium tracked, the median survival was 3.5 years for the 264 with an oncogenic driver treated with genotype-directed therapy, 2.4 years for the 318 with an oncogenic driver with no genotype-directed therapy, and 2.1 years for the 360 with no driver identified ($P < 0.0001$)[105].

With the advance of next-generation sequencing, one can foresee a future in which every single tumor will be sequenced at the time of diagnosis to find potential driver mutations that can be therapeutically targeted. While some rare patients have had astounding disease remission, defined as long-term complete responses to EGFR TKI therapy[106,107], these patients are still usually receiving active therapy and therefore cannot truly be considered "cured". Therefore, challenges remain on how to overcome the seemingly inevitable acquired resistance to these therapies. The optimal sequence for the use of multiple inhibitors of the same target and the efficacy and tolerability of combinations of inhibitors of various oncogenic pathways are being actively studied. In addition, the emerging promise of immunotherapies such as PD-1/PDL-1 directed antibody therapy opens the door for studies of potential synergy with these drugs and tyrosine kinase targeted therapeutics. Even if a cure for advanced lung cancer still remains out of reach, one can hope that in the near future advanced NSCLC may be controlled like other chronic diseases with well-tolerated and effective therapies.

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