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EDITORIAL

Molecularly targeted therapies for advanced or metastatic non-small-cell lung carcinoma

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Abstract

Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related death in both men and women in the United States. Platinum-based doublet chemotherapy has been a standard for patients with advanced stage disease. Improvements in overall survival and quality of life have been modest. Improved knowledge of the aberrant molecular signaling pathways found in NSCLC has led to the development of biomarkers with associated targeted therapeutics, thus changing the treatment paradigm for many NSCLC patients. In this review, we present a summary of many of the currently investigated biologic targets in NSCLC, discuss their current clinical trial status, and also discuss the potential for development of other targeted agents.

Key words: Non-small cell lung cancer; Molecular targeted therapy; Vascular endothelial growth factor; Epidermal growth factor receptor; Tyrosine kinase inhibitors; BRAF; Anaplastic lymphoma kinase

Core tip: Targetable molecular abnormalities have not yet been identified in approximately 80% of non-small-cell lung cancer patients. In addition to anaplastic lymphoma kinase, epidermal growth factor receptor, vascular endothelial growth factor targeted therapies, the results from ongoing trials will determine if the newer targeted agents will be incorporated into clinical practice.

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INTRODUCTION

Non-small-cell lung cancer (NSCLC) remains a therapeutic challenge. Despite some progress, it remains the leading cause of cancer-related death in the United States in both men and women. The estimated incidence of NSCLC is 226160 cases with 160340 deaths in the United States in 2012. The 5-year survival rates for advanced and metastatic NSCLC are only 24% and 4%, respectively[1].

The core drug and backbone of treatment in locally advanced and metastatic settings of NSCLC has been a platinum agent. In a large randomized clinical trial, Schiller *et al*[2] compared the efficacy of three commonly used regimens (cisplatin and gemcitabine, cisplatin and docetaxel, carboplatin and paclitaxel) with that of a reference regimen of cisplatin and paclitaxel. No significant difference in survival was observed among the four commonly used regimens, although the regimen of carboplatin and paclitaxel had a lower rate of toxic effects than the other regimens. On the basis of these results, Eastern Cooperative Oncology Group had chosen carboplatin and paclitaxel as its reference regimen for future studies; and it is still the most commonly used taxane-platinum combination in the United States[3] which produces 15%-32% objective response rates (ORR), with 7.9-10.6 mo median overall survivals (OS)[4-6].

Further attempt at subclassification is now accepted as a standard of care; separating squamous cell carcinoma from adenocarcinoma and large-cell carcinoma as the distinction carries implications for prognosis and treatment decisions. For example, a phase Ⅲ study in patients with advanced NSCLC treated with cisplatin plus pemetrexed (an inhibitor of purine and pyrimidine synthesis), showed no improvement in tumor response rate and survival over cisplatin plus gemcitabine for all histologies; however, an improvement in survival was noted in the non-squamous histology subset while a decrement in the squamous histology subset was observed[7]. Due to safety concerns observed in the phase Ⅱ trial, the addition of bevacizumab to carboplatin/taxol was subsequently studied in phase Ⅲ trial and improved efficacy was observed in patients with non-squamous histology (ORR, 35%; OS, 12.3 mo)[5].

In addition to making distinction in cytotoxic chemotherapy based on histology, over the past decade, a large number of studies have been published that aimed to target the molecular abnormalities implicated in NSCLC tumor growth, invasion, metastasis, angiogenesis and resistance to apoptosis. Currently, detection of the presence of mutations involving the epidermal growth factor receptor (*EGFR*) gene and fusion of the N-terminal portion of the protein encoded by echinoderm microtubule-associated protein-like 4 (*EML4*) gene with the intracellular signaling portion of the receptor tyrosine kinase encoded by anaplastic lymphoma kinase (*ALK*) gene - that is, EML4-ALK - has become routine in many centers because patients having tumors harboring such alterations benefit from novel targeted inhibitors as part of their treatment regimen. This review describes some of the important developments and targeted agents that have been tested in clinical trials; and the potential future biologics in the treatment of advanced or metastatic NSCLC.

MOLECULARLY TARGETED THERAPIES IN ADVANCED OR METASTATIC NSCLC

EGFR inhibition

EGFRs are a group of transmembrane proteins that regulate key processes in the cell, such as proliferation, division, migration, and differentiation. This family has 4 different members: EGFR (HER1 or ErbB1), HER2 (ErbB2), HER3 (ErbB3), and HER4 (ErbB4); all of which share a similar structure[8]. Upon binding to its ligands, EGFR induces receptor homo- or hetero-dimerization and results in the activation of an intracellular tyrosine kinase domain. Receptor activation cause downstream signaling events through activation of the Ras/Raf/MEK/MAPK and PI3K/AKT/mTOR pathways that regulate cell proliferation, differentiation, and survival[9]. The two most common EGFR mutations are short in-frame deletions of exon 19 and a point mutation in exon 21[10]. Tumors with EGFR mutations occur at a higher frequency in East Asians than in non-Asians (30% *vs* 8%), in women than in men (59% *vs* 26%), in never-smokers than in ever-smokers (66% *vs* 22%), and in adenocarcinoma than in other NSCLC histologies (49% *vs* 2%)[11]. In the United States, activating EGFR mutations are estimated to occur in 15% of patients with primary lung adenocarcinoma[12].

Monoclonal antibodies against EGFR: Cetuximab is a chimeric monoclonal antibody against EGFR. One of the first phase Ⅱ studies assessing combination chemotherapy with cetuximab (cisplatin or carboplatin and gemcitabine with or without cetuximab) showed an increased ORR, progression-free survival (PFS), and OS in the cetuximab group[13]. A similar phase Ⅱ study in which cisplatin and vinorelbine were administered with or without cetuximab also showed enhanced survival indices in the cetuximab arm[14]. However a subsequent large phase Ⅲ trial investigating paclitaxel or docetaxel and carboplatin, with or without cetuximab in 676 patients with NSCLC did not find any notable differences in PFS or ORR[15].

The recently published FLEX study demonstrated that adding cetuximab to cisplatin-based chemotherapy resulted in a small but significant improvement in median OS in patients with advanced NSCLC [11.3 mo *vs* 10.1 mo; hazard ratio (HR): 0.87; $P = 0.04$][16]. A retrospective analysis of FLEX data showed that 31% of patients with high EGFR expression, adding cetuximab increased the median OS from 9.6 to 12 mo (HR: 0.73; $P = 0.011$)[17]. Ultimately, a meta-analysis looking at the four trials in which 2018 previously untreated NSCLC patients were analyzed concluded that cetuximab improved OS and ORR regardless of the presence of EGFR mutations[18]. In accordance with the above results, a more in-depth analysis of these subgroups in phase Ⅲ trials revealed that specific activating mutations in the tyrosine kinase domain of the *EGFR* gene were associated with sensitivity to gefitinib but not to cetuximab[19]. In addition, no significant cetuximab treatment-specific correlations between EGFR or K-RAS mutation status and PFS, OS, or ORR were observed in the phase Ⅲ trials[20,21]. Therefore, we can conclude that EGFR or K-RAS mutations may not be useful as biomarkers in cetuximab therapy. At present, a number of clinical trials are still evaluating the efficacy of cetuximab in combination with other treatment modalities in combination with tyrosine kinase inhibitors (TKIs), and other chemotherapeutic drugs. Most of these trials are also assessing biomarker status that could be predictive or prognostic in value.

EGFR-Tyrosine kinase inhibitors: EGFR-TKIs are small molecules administered orally and are subdivided in reversible, gefitinib and erlotinib, and irreversible, afatinib on the basis of their straight binding with the specific site of the EGFR intracellular domain. These drugs inhibit the phosphorylation and tyrosine kinase activity of the intracellular adenosine triphosphate (ATP)-binding domain of the EGFR through competitive binding to this site, and were initially investigated in unselected patients reporting contrasting results depending on the type of population/enrolled in each study. However, the discov-

ery that response to EGFR-TKIs is associated with the presence of activating EGFR mutations in NSCLC has led to the design of clinical trials in which patients were selected on the basis of the EGFR mutational status. Almost all patients who respond to EGFR-TKIs have been shown to carry activating mutations usually found in exons 18 through 21 of the TK domain of EGFR, and are either point mutations or in-frame small deletions or insertions[22]. Although more than 250 mutations of the EGFR have been described up to now, two mutations, one single point mutation in exon 21, the L858R, and a series of small in-frame deletions in exon 19 account for approximately 90% of all EGFR mutations.

Erlotinib: EGFR mutations have been defined "activating" and "sensitizing" and both definitions are correct. In fact, EGFR mutations lead to increased response of the EGFR to exogenous growth factors, thus producing a more significant and more persistent activation of intracellular signaling pathways, resulting in increased cell proliferation and survival. On the other hand, the mutant receptor is more sensitive to EGFR-TKIs as compared with wild type EGFR, since lower concentrations of drugs are required to inhibit its phosphorylation. Retrospective analyses have demonstrated that patients with EGFR mutations have high ORRs to EGFR-TKIs in any line of treatment[23]. These findings sustain the hypothesis that tumors with EGFR mutations are addicted to the EGFR pathway, *i.e.* depend on these pathways for their growth. In agreement with this hypothesis, tumors with EGFR mutations have shown to homogeneously carry this molecular alteration in all tumor cells[24]. As discussed above, erlotinib was first studied in unselected patients with NSCLC, and a subsequent analysis of the patients who had experienced dramatic tumor responses were found to have the activating mutations in the kinase domain of EGFR[25]. The response rate was as high as 81% in patients harboring EGFR tyrosine kinase domain mutations, but less than 10% in patients with wild-type EGFR[26]. The OPTIMAL trial was the first phase Ⅲ study directly comparing erlotinib with standard chemotherapy in the first-line setting of advanced NSCLC in Chinese patients with an activating EGFR mutation. That trial showed a PFS of 13.1 mo with erlotinib compared with 4.6 mo with gemcitabine-carboplatin chemotherapy (HR: 0.16; 95%CI: 0.1-0.26; $P < 0.001$)[27]. An updated analysis also showed median PFS of 13.7 mo *vs* 4.6 mo; HR: 0.164; $P < 0.0001$[28]. A second trial called EURTAC, the first to involve a Western European population, randomized patients to a platinum-based doublet chemotherapy regimen (docetaxel-gemcitabine) or to erlotinib in patients with an EGFR activating mutation. Patients treated with erlotinib experienced a PFS advantage (9.7 mo *vs* 5.2 mo; HR: 0.37; 95%CI: 0.25-0.54)[29]. Based on these results, erlotinib was approved as a first-line treatment in patients with advanced or metastatic NSCLC harboring the EGFR mutations.

Recent phase Ⅱ/Ⅲ trials have shown single agent activity of erlotinib in the second-line setting in either selected or unselected patients with metastatic NSCLC[30,31]. In the TITAN phase Ⅲ trial, the efficacy and tolerability of second-line erlotinib was compared with either pemetrexed or docetaxel in 425 patients with advanced NSCLC who were treated with first-line platinum doublet chemotherapy and had disease progression during or immediately after chemotherapy. The second-line erlotinib was associated with a similar median OS duration to pemetrexed or docetaxel in patients with advanced NSCLC (5.3 mo *vs* 5.5 mo; HR: 0.96 in the overall population; 95%CI: 0.78-1.19). Similarly, there was no difference in OS between the treatment groups (HR: 0.85; 95%CI: 0.59-1.22) in 149 patients with EGFR wild type tumors[32].

The phase Ⅲ SATURN trial examined erlotinib as maintenance therapy after platinum-based chemotherapy. That trial met the primary endpoint of significantly longer PFS in patients treated with erlotinib (12.3 wk) than in patients receiving placebo (11.1 wk; HR: 0.69; 95%CI: 0.58-0.82; $P < 0.0001$). The overall response rate was 11.9% in the erlotinib arm compared with 5.4% in the placebo arm ($P = 0.0006$)[33]. Importantly, the benefit of erlotinib maintenance on PFS and OS was also seen in EGFR wild-type patients (HR: 0.78, 95%CI: 0.63-0.96, $P = 0.0185$, and HR: 0.77, 95%CI: 0.61-0.097, $P = 0.008$, respectively).

Gefitinib: Two large phase Ⅲ studies highlighted the role of gefitinib in tumors harboring EGFR mutations[34,35]. In IPASS trial, the efficacy of gefitinib was compared with carboplatin/paclitaxel in previously untreated never-smokers and light ex-smokers with advanced pulmonary adenocarcinoma. Of 1217 enrolled patients, OS was similar for gefitinib and carboplatin/paclitaxel (HR: 0.90; 95%CI: 0.79-1.02; $P = 0.109$) in overall, or in EGFR mutation-positive (HR: 1.00; 95%CI: 0.76-1.33; $P = 0.990$) or EGFR mutation-negative (HR: 1.18; 95%CI: 0.86-1.63; $P = 0.309$) subgroups. Of importance, PFS was significantly longer with gefitinib for patients whose tumors had both high *EGFR* gene copy number and EGFR mutation (HR: 0.48; 95%CI: 0.34-0.67) but significantly shorter when high *EGFR* gene copy number was not accompanied by EGFR mutation (HR: 3.85; 95%CI: 2.09-7.09)[34]. Likewise, another multicenter phase Ⅲ trial demonstrated that patients with advanced-stage NSCLC containing EGFR mutations and treated with first-line gefitinib (compared with standard chemotherapy) had improved PFS[35]. Based on these results, the American Society of Clinical Oncology recommended EGFR mutation testing for patients with advanced NSCLC who are being considered for first-line therapy with an EGFR-TKI[12].

Two phase Ⅲ clinical trials suggested that gefitinib was more efficacious and less toxic than docetaxel as a second-line treatment in patients with previously-treated advanced NSCLC[36,37]. In the ISTANA trial, the primary endpoint of PFS was longer with gefitinib than

Table 1 Selected phase Ⅲ and randomized phase Ⅱ trials comparing epidermal growth factor receptor tyrosine kinase inhibitor and chemotherapy as first-line therapy in patients with advanced non-small cell lung cancer

Trial	*n*	Type of study	Study design	OS (mo) HR (95%CI)	*P* value	PFS (mo) HR (95%CI)	*P* value	ORR (%) HR (95%CI)	*P* value
Fukuoka *et al*[34]	261	Retrospective	Gefitinib *vs* PC	21.6 *vs* 21.9 1.00 (0.76-1.33)	0.99	9.6 *vs* 6.3 0.48 (0.36-0.64)	0.0001	71.2 *vs* 47.3 2.75 (1.65-4.6)	0.0001
Han *et al*[98]	42	Retrospective	Gefitinib *vs* Cis + G	27.2 *vs* 25.6 1.04 (0.49-2.18)	NA	8.0 *vs* 6.3 0.54 (0.26-1.1)	0.086	84.6 *vs* 37.5 9.16 (2.10-39.84)	0.002
Mitsudomi *et al*[99]	172	Prospective	Gefitinib *vs* Cis + D	35.5 *vs* 38.8 1.18 (0.76-1.8)	0.44	9.6 *vs* 6.6 0.52 (0.37-0.71)	0.001	62.1 *vs* 32.1 3.44 (1.60-7.37)	0.0001
Maemondo *et al*[35], Inoue *et al*[100]	228	Prospective	Gefitinib *vs* PC	27.7 *vs* 26.6 0.88 (0.63-1.24)	0.48	10.8 *vs* 5.4 0.32 (0.23-0.43)	0.001	73.7 *vs* 30.7 6.32 (3.55-11.25)	0.001
Chen *et al*[28]	154	Prospective	Erlotinib *vs* C + G	22.7 *vs* 28.85 1.04 (0.69-1.58)	0.69	13.7 *vs* 4.6 0.16 (0.10-0.26)	0.0001	83 *vs* 36 NA	0.0001
Rosell *et al*[29]	173	Prospective	Erlotinib *vs* platinum-based doublets	19.3 *vs* 19.5 1.04 (0.65-1.68)	0.87	9.7 *vs* 5.2 0.37 (0.25-0.54)	0.0001	58[1] *vs* 15[1] NA	NA
Yang *et al*[2][101]	345	Prospective	Afatinib *vs* Cis + P	NM		11.1[3] *vs* 6.9[3] 0.58 (0.43-0.78)	0.0004	56.1[3] *vs* 22.6[3] NA	0.001
Jänne *et al*[102]	345	Prospective	Erlotinib *vs* erlotinib + PC	24.6 *vs* 19.8 NA	NA	5.0 *vs* 6.6 NA	NA	35 *vs* 46 NA	NA

[1]Intention-to-treat population; [2]Only lung adenocarcinoma patients; [3]By independent review. PC: Paclitaxel and carboplatin; Cis: Cisplatin; C: Carboplatin; G: Gemcitabine; D: Docetaxel; P: Pemetrexed; OS: Overall survival; HR: Hazard ratio; NM: Not yet mature; NA: Not available; PFS: Progression-free survival; ORR: Objective response rate; *n*: Number of patients enrolled in the study.

docetaxel (HR: 0.729; 90%CI: 0.533-0.998; $P = 0.0441$), and the secondary endpoints showed superior ORR (28.1% *vs* 7.6%; $P = 0.0007$), good tolerability, and similar quality-of-life (QoL) improvement rates for gefitinib compared to docetaxel[37]. In the INTEREST trial, of 1433 patients analyzed (723 in gefitinib group and 710 in docetaxel group), non-inferiority of gefitinib compared with docetaxel was confirmed for OS (593 events *vs* 576 events; HR: 1.020, 95%CI: 0.905-1.150). Interestingly, superiority of gefitinib in patients with high *EGFR*-gene-copy number was not proven (72 *vs* 71 events; HR: 1.09, 95%CI: 0.78-1.51; $P = 0.62$; median survival 8.4 mo *vs* 7.5 mo)[36]. Table 1 summarizes the selected phase Ⅲ and randomized phase Ⅱ trials comparing EGFR-TKIs and chemotherapy as first-line therapy in patients with advanced NSCLC.

Vascular endothelial growth factor inhibition

Bevacizumab, a monoclonal antibody against circulating vascular endothelial growth factor (VEGF), was approved by Food and Drug Administration for the treatment of NSCLC in 2006. The combination of bevacizumab with carboplatin and paclitaxel was shown to prolong OS compared with chemotherapy alone (median OS, 12.3 *vs* 10.3 mo, respectively) in patients with nonsquamous advanced NSCLC[5]. Bevacizumab has also been combined with gemcitabine and cisplatin, with a modest benefit observed in PFS but no differences seen in OS[38]. Many other antiangiogenic agents have been under development.

Triple angiokinase inhibitors, which inhibit VEGF, platelet derived growth factor and/or fibroblast derived growth factor were thought to have the potential to improve the therapeutic outcomes for patients with NSCLC. Clinical trials have been ongoing involving several new antiangiogenic therapies, including ramucirumab, aflibercept, vandetanib, cediranib, nintedanib, sunitinib, pazopanib, brivanib, linifinib, axitinib, and motesanib (http://www.clinicaltrials.gov). To date, none of these agents in combination with chemotherapy have resulted in improvements in OS for patients with advanced NSCLC. Moreover, in a phase Ⅱ trial (ESCAPE), patients with squamous histology treated with chemotherapy plus sorafenib had a shorter OS than those receiving chemotherapy plus placebo (HR: 1.85; 95%CI: 1.22-2.81)[6]. A recent meta-analysis comparing the efficacy and toxicity of chemotherapy plus multitargeted antiangiogenic TKI with chemotherapy alone in patients with advanced NSCLC showed that chemotherapy plus a TKI significantly increased the ORR (HR: 1.71, 95%CI: 1.43-2.05) and PFS (HR: 0.83, 95%CI: 0.76-0.90], but not OS (HR: 0.93, 95%CI: 0.83-1.03). The toxicity was comparable between the two therapies[25]. Table 2 summarizes the phase Ⅲ clinical trials testing antiangiogenic TKIs in combination with chemotherapy in NSCLC.

There is evidence from the 3 phase Ⅱ clinical trials supporting the potential use of sorafenib as a monotherapy in chemotherapy refractory NSCLC[26,27]. Particularly, the BATTLE trial showed a promising response rate (8-wk disease control rate in 58% of patients) in heavily pretreated patients with single agent sorafenib. More impressively, in patients whose tumor harbored a KRAS mutation, sorafenib had a disease control rate of 79% while on a separate phase Ⅱ trial in NSCLC, the response rate to erlotinib was only 14% ($P = 0.016$)[28]. This indicates that the significant disease control rate in KRAS mutant NSCLC patients may be due to sorafenib's effects on KRAS downstream pathways such as Raf inhibition rather than its antiangiogenic effects. The randomized,

Table 2 Phase Ⅲ clinical trials testing antiangiogenic tyrosine kinase inhibitors in combination with chemotherapy in non-small cell lung cancer

Trial	*n*	Study design	PE	OS (mo)	PFS (mo)	ORR (%)
Vandetanib second-line						
ZEAL[103]	534	PV *vs* P	PFS	10.5 *vs* 9.2	17.6 wk *vs* 11.9 wk	19 *vs* 8
ZEST[104]	1240	EV *vs* E	PFS	6.9 *vs* 7.8	2.6 *vs* 2.0	12 *vs* 12
ZODIAC[105]	1391	DV *vs* D	PFS	10.6 *vs* 10.0	4.0 *vs* 3.2	NA
Vandetanib second or third-line						
ZEPHYR[106]	924	V *vs* placebo	OS	8.5 *vs* 7.8	NA	2.6 *vs* 0.7
Sorafenib first-line						
NEXUS[107]	904	G + Cis + S f/b S *vs* G + Cis f/b placebo	OS	376 d *vs* 379 d	183 d *vs* 168 d	28 *vs* 26
Motesanib first-line						
MONET[6]	1090	PC + M *vs* PC	OS	13.0 *vs* 11.0	5.6 *vs* 5.4	40 *vs* 26
Cediranib first-line						
BR29 (active, no longer recruiting, NCT00795340)	750	PC + Ced *vs* PC	OS	NA	NA	NA
Nintedanib second-line						
LUME-Lung 1 (active, no longer recruiting, NCT00805194)	1300	D + Nin *vs* D	PFS	NA	NA	NA
LUME-Lung 2 (active, no longer recruiting, NCT00806819)	1302	P + Nin *vs* P	PFS	NA	NA	NA

PC: Paclitaxel and carboplatin; P: Pemetrexed; E: Erlotinib; D: Docetaxel; V: Vandetanib; DV: Docetaxel-vandetanib; EV: Erlotinib-vandetanib; G: Gemcitabine; Cis: Cisplatin; S: Sorafenib; f/b: Followed by; M: Motesanib; Ced: Cediranib; Nin: Nintedanib; OS: Overall survival; PE: Primary endpoint; PFS: Progression-free survival; ORR: Objective response rate; NSCLC: Non-small cell lung cancer; NA: Not available.

placebo-controlled, multicenter international phase Ⅲ trial (NCT00863746 MISSION Trial) is currently underway to evaluate single agent sorafenib as third- or fourth-line therapy in patients with NSCLC. The enrollment for MISSION Trial has been concluded and data should be available later this year.

EML4-ALK inhibition

Rearrangements of the *ALK* gene are felt to be mutually exclusive of EGFR and KRAS mutations and occur in approximately 4% of NSCLC. The ALK mutations are more common in adenocarcinomas and in light smokers or non-smokers[39]. The phase I trial of the ALK-inhibitor crizotinib in advanced ALK-positive NSCLC revealed a response rate of 57% (95%CI: 46%-68%) and an estimated 6-mo PFS probability of 72% (95%CI: 61%-83%)[40]. A retrospective review of 82 ALK-positive patients (including patients who had received multiple lines of therapy) treated with crizotinib revealed an impressive 1-year survival of 74% (95%CI: 63%-82%) and 2-year survival of 54% (95%CI: 40%-66%)[41]. Crizotinib was approved in the United States in 2011, primarily based on response rates of 50% on the first 136 patients with *ALK*-rearranged NSCLC enrolled on PROFILE 1005[42] and secondarily on a response rate of 61% from the first 119 patients with *ALK*-rearranged NSCLC enrolled on PROFILE 1001[43]. Table 3 lists the major ongoing trials with crizotinib for advanced NSCLC.

New ALK inhibitors are under investigation, with phase I trials of LDK378 (not yet recruiting) and AP26113 (currently recruiting). NCT01449461, a phase I trial of AP26113, will be conducted in two parts, with the second part including expansion cohorts. The 4 cohorts include ALK mutations with no previous exposure to ALK inhibitors, ALK mutation with resistance to an ALK inhibitor, EGFR mutation with resistance to EGFR inhibitors, and non-lung malignancies with ALK mutations.

KRAS and BRAF mutations and MEK inhibition

Mutations in KRAS have been found in 15%-30% of patients with NSCLC and are considered to be one of the more frequent mutations in these tumors[44,45]. Approximately 97% of K-RAS mutations in NSCLC involve codons 12 or 13[46]. As with EGFR mutations, KRAS mutations are detected mainly in lung adenocarcinomas and are less frequently observed in squamous cell carcinomas of the lung[47,48]. In contrast with lung adenocarcinomas harboring EGFR mutations, tumors having KRAS mutations are seen at a higher frequency (20%-30%) in Caucasian patients than in East Asian patients (5%)[49]. Also, compared with EGFR mutations, KRAS mutations are more common in current or former smokers than in never-smokers[50].

Although the value of KRAS status as a prognostic and predictive biomarker for anti-EGFR therapy is less clear in NSCLC, several studies have demonstrated that KRAS mutations are a factor correlated with poor survival in patients with NSCLC[51-53]. A recent prospective biomarker-driven phase Ⅲ trial conducted in 889 patients comparing placebo with sequential erlotinib maintenance in unresectable NSCLC (SATURN, BO18192) showed that the presence of KRAS mutations was not predictive for erlotinib efficacy and was prognostic significantly associated with reduced PFS[54]. The predictive significance of KRAS mutation status is being further evaluated in BATTLE-2 clinical trial.

Table 3 Major ongoing clinical trials with crizotinib for advanced non-small cell lung cancer[1]

Trial number	Phase	Study design	Key entry criteria	PE
PROFILE 1007 (NCT00932893)	Ⅲ	Crizotinib *vs* Pem or Doc as second-line	ALK(+) and 1 prior platinum-based chemo	PFS
PROFILE 1014 (NCT01154140)	Ⅲ	Crizotinib + Pem + Cis/Carbo *vs* Pem + Cis/Carbo as first-line	ALK(+) and chemotherapy-naive	PFS
PROFILE 1005 (NCT00932451)	Ⅱ	Crizotinib *vs* placebo as third-line	ALK(+) and PD in arm B of study PROFILE 1007	RR
PROFILE 1001 (NCT00965731)	Ⅰ/Ⅱ	Crizotinib + erlotinib *vs* erlotinib as second or third-line	Adenocarcinoma NSCLC and 1-2 prior chemo	MTD
PROFILE 1001 (NCT01121575)	Ⅰ	Crizotinib + PF0299804	Acquired resistance to erlotinib or gefitinib	MTD

[1]Data available at URL: http://www.cancer.gov/clinicaltrials. chemo: Chemotherapy; Pem: Pemetrexed; Doc: Docetaxel; Cis: Cisplatin; Carbo: Carboplatin; PD: Progressive disease; NSCLC: Non-small cell lung cancer; ALK: Anaplastic lymphoma kinase; PFS: Progression-free survival; RR: Response rate; MTD: Maximum tolerated dose; PE: Primary endpoint.

BRAF encodes a non-receptor serine/threonine kinase that is a member of the Ras/MAPK signaling pathway downstream of Ras protein. Upon activation, BRAF directly phosphorylates MEK, which in turns phosphorylates ERK, thereby regulating cellular responses to growth signals[55]. BRAF mutations were first identified in melanoma cells, with 80% of mutations involving the Val600 residue in the kinase domain. By contrast, BRAF mutations account for only 1%-3% of NSCLC and they are mostly non-Val600Glu mutations including Gly468Ala and Leu596Val[56,57]. BRAF mutations were shown to be mutually exclusive with EGFR mutations within exons 18-21, KRAS codon 12 mutations, ERBB2 codon 20 mutations, and translocations in ALK[58]. Furthermore, V600E mutated NSCLCs showed a more aggressive tumor histology characterized by micropapillary features and were associated with poor prognosis[59].

A number of studies are currently examining the effect of MEK inhibitors on BRAF or KRAS-mutated solid tumors. As a downstream effector of the EGFR pathway that signals through K-RAS, MEK inhibition has also been suggested to play a role in patients who become resistant to EGFR inhibitors. A number of trials to examine MEK inhibitors alone or in combination with other targeted treatments are currently recruiting. The NCT00888134 phase Ⅱ trial is examining the effects of MEK inhibitor AZD6244 in patients with metastatic malignancy and a BRAF mutation. Dasatinib was shown to selectively induce senescence in NSCLC cells with inactivating BRAF mutations[60]. The NCT01514864 phase Ⅱ trial is now recruiting patients to examine the effect of dasatinib in patients with NSCLC or melanoma harboring a BRAF mutation (Clinicaltrials.gov).

GSK2118436 is a potent MEK inhibitor that has been shown to have preclinical activity in BRAF mutant NSCLC and melanoma. A phase Ⅱ trial (NCT01336634) is currently recruiting patients with previous exposure to platinum chemotherapy, and will examine GSK2118436 in advanced NSCLC patients with a BRAF mutation. The primary outcome will be ORR, and the trial is expected to be completed in late 2013. A phase Ⅰ trial (NCT01324258) of GSK1120212, another potent MEK inhibitor, in combination with gemcitabine is currently recruiting patients with solid tumors in Japan. An Open-Label, Phase Ⅰ / Ⅰb Dose Escalation Study to assess the safety and tolerability of GSK1120212 in combination with docetaxel, erlotinib, pemetrexed, pemetrexed + carboplatin, pemetrexed + cisplatin, or nab-paclitaxel in patients with advanced metastatic lung and/or pancreatic cancers is currently recruiting patients (NCT01192165). A number of phase Ⅰ trials are currently examining the combination of MEK162, a MEK1/2 inhibitor, with PI3K (BYL719) or Raf (Raf265) inhibitors in advanced solid tumors with documented KRAS or BRAF mutations (NCT01449058, and NCT01352273). Selumetinib (AZD6244, a potent MEK inhibitor) is being investigated in NSCLC patients with tumors harboring KRAS mutations[52]. Table 4 lists the ongoing clinical trials involving targeted agents for patients with advanced or metastatic NSCLC.

OVERCOMING ACQUIRED DRUG RESISTANCE TO EGFR TARGETED THERAPIES IN NSCLC

Despite the significant improvement in outcomes for these highly selected patients, treatment failures secondary to resistance have been described since 2005[61]. Known mechanisms of resistance include secondary EGFR mutations (T790M mutant) or persistent phosphorylation of EGFR that reduces the inhibitory ability of gefitinib or erlotinib, and MET amplification with subsequent activation of downstream pathways[61,62]. The discovery of resistance to the EGFR-TKIs has led to the development of second-generation EGFR-TKIs, or the use of combination of EGFR inhibitors with other targeted therapies. Moreover, a third generation of EGFR-TKIs is now entering clinical trials; these compounds bind covalently to the ATP-binding cleft of mutant EGFR and appear to have selective activity against the T790M mutant[63].

Second-generation EGFR-TKIs

Many trials have studied intensification of EGFR inhibition through use of second-generation TKIs such as neratinib, afatinib, and dacomitinib[64]. These inhibitors are different from erlotinib and gefitinib in 2 main ways: each forms a covalent, irreversible bond with the EGFR protein, and each also inhibits other members of the ERBB family of kinases[64].

Dacomitinib (PF0299804): PF0299804 is an oral irreversible inhibitor of the EGFR/HER1, HER2, and

Table 4 Ongoing phase Ⅱ/Ⅲ clinical trials involving targeted agents for patients with advanced or metastatic non-small cell lung cancer

Study design	Clinical trial ID	Phase	Status	Key entry criteria
EGFR inhibition				
Erlotinib *vs* docetaxel	NCT00637910	Ⅲ	Recruiting	WT EGFR, prior platinum chemo, no prior taxanes
Erlotinib *vs* pazopanib	NCT01027598	Ⅱ	Active, not recruiting	1 prior chemo
Erlotinib + OSI-906	NCT01221077	Ⅱ	Recruiting	EGFR mutation (+), chemotherapy-naive
Erlotinib + ARQ197	NCT01377376	Ⅲ	Recruiting	WT EGFR, prior platinum-based chemo
Erlotinib + ARQ197	NCT01244191	Ⅲ	Recruiting	2 prior lines of chemo
Erlotinib + PC + Bev	NCT00976677	Ⅱ	Active, not recruiting	Non-squamous, nonsmokers
Gefitinib (maintenance)	NCT01404260	Ⅲ	Active, not recruiting	Stable disease after chemo, EGFR unknown, never or light smokers
Gefitinib *vs* Pem	NCT00891579	Ⅱ	Recruiting	WT EGFR, prior platinum-based chemo
Afatinib	NCT00525148	Ⅱ	Active, not recruiting	EGFR mutation (+)
Afatinib	NCT00711594	Ⅱ	Active, not recruiting	Prior platinum-based chemo, progressed after erlotinib or gefitinib
PF00299804	NCT01000025	Ⅲ	Recruiting	1 prior chemo
PF00299804 *vs* erlotinib	NCT01360554	Ⅲ	Recruiting	1 prior chemo
BRAF inhibition				
AZD6244 + erlotinib	NCT01229150	Ⅱ	Recruiting	KRAS WT or KRAS mutant
Dasatinib	NCT01514864	Ⅱ	Recruiting	Tumors harboring DDR2 mutation or inactivating B-RAF mutation
AKT inhibition				
MK-2206 + erlotinib	NCT01294306	Ⅱ	Recruiting	Progressed after initial response to erlotinib
MEK inhibition				
GSK2118436	NCT01336634	Ⅱ	Recruiting	BRAF mutation (+)
HDAC inhibitor				
Vorinostat + gefitinib	NCT01027676	Ⅱ/Ⅲ	Recruiting	prior platinum-based chemo
Vorinostat + bortezomib	NCT00798720	Ⅱ	Completed recruiting	2 prior chemo
Belinostat + Bev + PC	NCT01090830	Ⅱ	Recruiting	Chemotherapy-naive
LBH589 + Pem	NCT00907179	Ⅱ	Recruiting	1 prior chemo
KRAS mutations				
AZD6244 + erlotinib	NCT01229150	Ⅱ	Recruiting	Prior platinum-based chemo
Erlotinib + ARQ197 *vs* single-agent chemo	NCT01395758	Ⅱ	Recruiting	KRAS mutation (+)
GSK1120212 *vs* docetaxel	NCT01362296	Ⅱ	Recruiting	KRAS mutation (+)

PC: Paclitaxel and carboplatin; Bev: Bevacizumab; Pem: Pemetrexed; NSCLC: Non-small cell lung cancer; chemo: Chemotherapy; WT: Wild-type; EGFR: Epidermal growth factor receptor; HDAC: Histone deacetylase inhibitor.

HER4 tyrosine kinases. Preclinical data showed activity for PF0299804 against EGFR mutations and T790M[61,65]. Two phase Ⅱ studies highlighted the agent's clinical antitumor effect, both in first-line therapy and in treatment-refractory settings. In the first of the studies, PF0299804 was compared with erlotinib[66]. That trial enrolled a range of molecular subgroups, including a group of patients with wild-type KRAS. In all subgroups, PF0299804 showed a PFS advantage (12.4 wk *vs* 8.3 wk; HR: 0.704; $P = 0.030$). In the second phase Ⅱ trial, dacomitinib demonstrated significantly improved PFS over erlotinib (2.86 mo for patients treated with dacomitinib and 1.91 mo for patients treated with erlotinib, HR: 0.66; 95%CI: 0.47-0.91; $P = 0.012$), with an acceptable toxicity. PFS benefit was observed in most clinical and molecular subsets, notably KRAS wild-type/EGFR any status, KRAS wild-type/EGFR wild-type, and EGFR mutants[67].

Afatinib: Afatinib has been shown to suppress the kinase activity of wild-type and activated EGFR, including erlotinib-resistant isoforms with the T790M mutation. The phase Ⅱb/Ⅲ LUX-Lung 1 randomized, double-blind trial examined best supportive care plus afatinib or placebo in patients in whom chemotherapy and a reversible EGFR inhibitor had failed. No difference in OS was observed; however, PFS was significantly improved with afatinib (3.3 mo *vs* 1.1 mo; HR: 0.38; 95%CI: 0.306-0.475; $P < 0.001$), as were tumor-related symptoms and QoL[68]. The most exciting clinical trial of afatinib in the acquired-resistance setting was a phase I b study in the United States and Netherlands. Patients who had progressed on erlotinib or gefitinib were given afatinib and cetuximab. Approximately 94% of patients, regardless of T790M mutation status, had a partial response or stable disease[69].

A number of phase Ⅱ trials continue to examine the safety and efficacy of afatinib as a second-line therapy. LUX-Lung 2 phase Ⅱ trial (NCT00525148) has completed enrollment of patients with activating EGFR mutations in whom first-line chemotherapy has failed. Similarly, LUX-Lung 4 phase Ⅰ/Ⅱ Japanese trial (NCT00711594) has completed accrual; results are awaited from this group of patients with first generation EGFR-TKI-resistant advanced NSCLC.

The phase Ⅲ LUX-Lung 3 trial reported the efficacy and safety data of first-line afatinib *vs* cisplatin and pemetrexed (PC) in patients with EGFR mutation-positive tumors. Treatment with afatinib led to a significantly prolonged PFS *vs* PC (median 11.1 mo *vs* 6.9 mo; HR: 0.58; 95%CI: 0.43-0.78; $P = 0.0004$). In 308 patients with common mutations (Del19/L858R), median PFS was 13.6 *vs* 6.9 mo, respectively (HR: 0.47; 95%CI: 0.34-0.65; $P < 0.0001$). ORR was significantly higher with afatinib (56%

vs 23%; $P < 0.0001$). Significant delay in time to deterioration of cancer-related symptoms of cough (HR: 0.60, $P = 0.0072$) and dyspnea (HR: 0.68, $P = 0.0145$) was seen with afatinib *vs* PC. Drug-related adverse events led to discontinuation in 8% (afatinib; 1% due to diarrhea) and 12% of patients (PC). Given the promising results of this pivotal trial, afatinib is now being compared with gefitinib as first-line treatment in patients with stage ⅢB/Ⅳ lung adenocarcinoma with EGFR activating mutations (LUX-Lung 7; NCT01466660).

Dual inhibitors

Increasing evidence has suggested that solid tumors have multiple salvage and resistance pathways that allow them to circumvent inhibition of a single signaling pathway[70]. In fact, EGFR is known to regulate the production of VEGF and other proangiogenic factors[71], and increased VEGF expression has been associated with resistance to EGFR inhibition in a human tumor xenograft model of NSCLC[72]. Thus, it is likely that blocking only one of these pathways will be insufficient for providing any meaningful therapeutic outcomes. Based on the logical strategy for improving anti-tumor efficacy by inhibition of multiple signaling pathways, a number of clinical trials are currently dual-inhibition strategies [*e.g.* mTOR, c-MET, PIK3CA, insulin-like growth factor 1 receptor (IGF-1R) or histone deacetylase (HDAC) inhibitor plus EGFR inhibitor].

Combination of EGFR and VEGF inhibitors: There have been promising results from combination of sorafenib with erlotinib. The combination has shown encouraging disease stabilizing effects with tolerable toxicity profiles[73-75]. In a randomized, double-blind, placebo controlled, phase Ⅱ trial in 168 patients with previously treated advanced NSCLC, sorafenib plus erlotinib was compared with erlotinib plus placebo. Overall, there were no significant differences in OS, PFS, or ORR between these two groups. However, in 67 patients with tumors bearing wild-type EGFR, sorafenib/erlotinib group showed a superior median PFS (3.38 mo in sorafenib/erlotinib group *vs* 1.77 mo in placebo/erlotinib group; $P = 0.018$) and a superior mean OS (8 mo for sorafenib/erlotinib *vs* 4.5 mo for placebo/erlotinib; $P = 0.019$)[74]. Another phase Ⅱ study evaluated sorafenib in combination with gemcitabine or erlotinib in 60 elderly patients with previously untreated advanced NSCLC[52]. ORR and median OS were 6.5% and 6.5 mo with sorafenib plus gemcitabine, and 10.3% and 12.6 mo with sorafenib plus erlotinib[75]. Similarly designed randomized phase Ⅱ/Ⅲ trials failed to show any improvement in OS from the addition of sunitinib to erlotinib (9.0 mo *vs* 8.5 mo with placebo plus erlotinib; HR: 0.922; 95%CI: 0.797-1.067)[74]. In a phase Ⅲ trial, the addition of bevacizumab to erlotinib suggested a non-significant OS benefit with the combined inhibition therapy in patients with EGFR-mutant tumors (median OS: 18 mo for bevacizumab plus erlotinib *vs* 12 mo for erlotinib; HR: 0.44; 95%CI: 0.11-1.67)[76].

A recent meta-analysis[77] evaluated the safety and efficacy of the combined inhibition of the VEGFR and EGFR signaling pathways with single-targeted therapy. Patients receiving combined inhibition therapy had a significant longer PFS than the group with single-targeted therapy (HR: 0.80; 95%CI: 0.67-0.95; $P = 0.011$). The combined therapy was associated with a non-significant 3% improvement in OS (HR: 0.97; 95%CI: 0.89-1.05; $P = 0.472$) confirming the previous studies. Also, no difference in the ORR between the study groups were detected (HR: 1.44; 95%CI: 0.95-2.18; $P = 0.085$). Subgroup analysis revealed that combined inhibition therapy using combination regimens was associated with statistically significant improvement in both ORR and PFS in the expense of increased toxicity in combined inhibition therapy. Currently, there is no evidence to support the use of combined inhibition of the VEGFR and EGFR signaling pathways in unselected patients with advanced NSCLC. Nonetheless, combined inhibition therapy may have a potential advantage in the treatment of advanced NSCLC compared with single inhibition therapy if the subsets of patients who may benefit from this treatment are well identified.

MET inhibitors: Investigation of resistance to current EGFR inhibitors has highlighted the role of the c MET/ALK pathway. MET amplification leads to EGFR-independent activation of the PI3K/Akt pathway through the activation of erbB3-dependent signaling and thereby could lead to EGFR inhibitor resistance[78,79]. Thus, combinations of EGFR and c-MET/ALK inhibitors hold potential for overcoming resistance[80].

The addition of c-MET inhibitor to erlotinib has demonstrated promising clinical activity in phase Ⅱ studies[81,82] when compared with erlotinib alone, particularly among patients with MET overexpression and non-squamous histology. The subset analyses of the trial by Spigel *et al*[82] suggested that METMab plus erlotinib was associated with increased PFS and OS as compared with erlotinib alone in patients with MET overexpression. In the study[81] comparing ARQ 197-209 (c-MET inhibitor) plus erlotinib *vs* erlotinib alone, a statistically significant improvement in OS was also found in non-squamous patients favoring ARQ 197-209 and erlotinib combination. In another randomized phase Ⅱ study[83] investigating second-line erlotinib with or without ARQ-197 in patients with advanced NSCLC, primary objective of the trial (PFS) was met in 167 patients (HR: 0.68, 95%CI: 0.47 to 0.98; $P < 0.05$) and the phase Ⅲ trial is ongoing[84]. Furthermore, albeit in a small subgroup of patients, that trial showed an advantage in terms of PFS for the combination of erlotinib and ARQ-197 in K-RAS-mutated, EGFR wild-type and c-MET amplified subjects.

HDAC inhibitors: The HDACs act to tighten the bond between histones and DNA, thus inhibiting gene transcription by blocking binding sites on promoters[55]. Inhibition of HDAC leads to induction of apoptosis in ma-

lignant cells[56]. Vorinostat is currently the furthest along in the development. A phase I trial (NCT00702572) with carboplatin, paclitaxel, bevacizumab and vorinostat for patients with advanced NSCLC is recruiting patients. A number of other phase I clinical trials to examine the effect of vorinostat with other targeted treatments including inhibitors of EGFR, mTOR, and a proteasome inhibitor, NP10052 are ongoing.

PI3K-AKT-mTOR inhibitors: One downstream mutation that has been described in lung cancers with acquired resistance to TKIs is in PIK3CA, a gene encoding a protein in the PI3K/AKT/mTOR pathway[85]. The PI3K/AKT pathway up-regulates mTOR in response to stimulation by growth factors[86]. Loss of inactivating mutations of phosphatase and tensin homolog (PTEN) results in a gain in function of the *PI3KCA* gene[87]. Phosphorylated AKT overexpression and loss of PTEN expression in NSCLC was shown to confer poor prognosis[88]. Phase Ⅱ study of everolimus (an oral mTOR inhibitor) plus erlotinib in previously treated patients with advanced NSCLC yielded a 11% difference in disease-control rate at 3 mo favoring the combination but did not meet the prespecified threshold to support a phase Ⅲ study[89]. Preclinical trials of PI3K inhibitors have shown efficacy, and research is ongoing[90,91]. A phase Ib trial is going to evaluate the combination of BYL719 (a selective inhibitor of PI3Kα) and the MEK inhibitor (MEK162). This international multicenter trial is not recruiting patients yet, but is expected to be completed by 2014 (NCT01449058).

IGF-1R inhibitors: Activation of the IGF-1R pathway has been noted as a consequence of EGFR inhibition in a variety of NSCLC cell lines, leading to cellular proliferation and evasion of apoptosis[92]. Studies have also documented heterodimerization of EGFR and IGF-1R in response to stimulation with either EGF or IGF-1, the ligands for the two receptors[91]. In a preclinical study, coinhibition of EGFR and IGF-1R resulted in synergistic growth inhibition of H1299NSCLCxenografts *in vivo* compared with treatment with erlotinib alone[93].

Unfortunately, the clinical studies have not been promising. A randomized phase Ⅱ study of erlotinib in combination with R1507 (a recombinant monoclonal antibody against IGF-1R) did not provide PFS or survival advantage over erlotinib alone in an unselected group of patients with advanced NSCLC[94]. The absence of therapeutic benefit with EGFR inhibitor in combination with an IGF-1R-targeted agent was further substantiated by other phase Ⅲ clinical trials[95,96]. The study evaluating the use of OSI-906 (IGF-1R TKI) in combination with erlotinib in patients with advanced NSCLC with activating mutations of the EGFR is ongoing but not actively recruiting patients (NCT01221077).

CONCLUSION

Recent research in NSCLC has focused on understanding the molecular abnormalities associated with NSCLC cell growth and proliferation and their impact on response to treatment and survival. In addition to histology, testing EGFR mutation and ALK rearrangement has now become the standard of care for treatment selection in NSCLC patients. However, only 20% of Western NSCLC patients have an activating EGFR mutation or ALK translocation[97]. Targetable molecular abnormalities have not yet been identified in approximately 80% of NSCLC patients. Multiple targeted agents, including monoclonal antibodies and receptor TKIs, are at various stages of development and hold promise. The results from ongoing trials will determine if the newer targeted agents will be incorporated into clinical practice.

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