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REVIEW

EGFR mutations as a prognostic and predictive marker in non-small-cell lung cancer

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Abstract: Non-small-cell lung cancer (NSCLC) has entered the age of individual treatment, and increasing point mutations of specific oncogenes and rearrangement of some chromosomes are biomarkers used to predict the therapeutic effect of targeted therapy. At present, there is a consensus among clinicians that epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have shown favorable efficacy in NSCLC patients with *EGFR* mutation, and some relevant research has suggested that the presence of *EGFR* mutations is a favorable prognostic marker. However, the association of *EGFR* mutation status with the responsiveness to conventional chemotherapy agents and survival in NSCLC patients is still unclear. This review provides an overview of and assesses the role of *EGFR* as a prognostic marker for postoperative patients and as a predictive marker for response to cytotoxic chemotherapy. In addition, we review the comparison of response to chemotherapy between *EGFR* mutations in exon 19 and in exon 21 and the predictive role of p.T790M mutation.

Keywords: epidermal growth factor receptor, prediction, prognosis

Introduction

At present, lung cancer is the leading cause of carcinoma-related death in industrialized countries,[1] and 75%–80% of primary lung cancers are non-small-cell lung cancer (NSCLC).[2] Although surgical operation is the most effective therapy for NSCLC, many cases with advanced stage are unresectable,[3–5] and, for these patients, the preferred treatment is chemotherapy. Even though NSCLC patients have a chance to receive complete resection, they also face the risk of recurrence.[6] Therefore, whether certain biomarkers could exist as predictive factors of the chemotherapy and be used for decisions about treatment options is extremely important in clinical decision-making.

Epidermal growth factor receptor (*EGFR*) is a member of the ErbB receptor tyrosine kinase (TK) family and has an essential action in the development and progression of NSCLC.[7–9] It has been reported that the signaling pathways of *EGFR* could influence angiogenesis, activation and regulation of cellular proliferation, and the epithelial–mesenchymal transition (Figure 1).[10–13] The gene with the most frequent mutations in NSCLC is *EGFR*. The most common *EGFR* mutations reported are deletions in exon 19 and the p.L858R point mutation in exon 21 (85%–90%).[14,15] It has been reported that *EGFR* mutations usually occur in a subset of NSCLC patients with the following features: nonsmoker, female, East Asian, adenocarcinoma with bronchioloalveolar carcinoma, and well- or moderately differentiated tumor cells.[16–18] During the past decade, some research demonstrated that EGFR TK inhibitor (EGFR-TKI) sensitivity was influenced by the presence of *EGFR* mutations and increased *EGFR* copy numbers.[19–25] Some Phase III trials also revealed that, compared with those treated with erlotinib or gefitinib, the *EGFR*-mutated NSCLC

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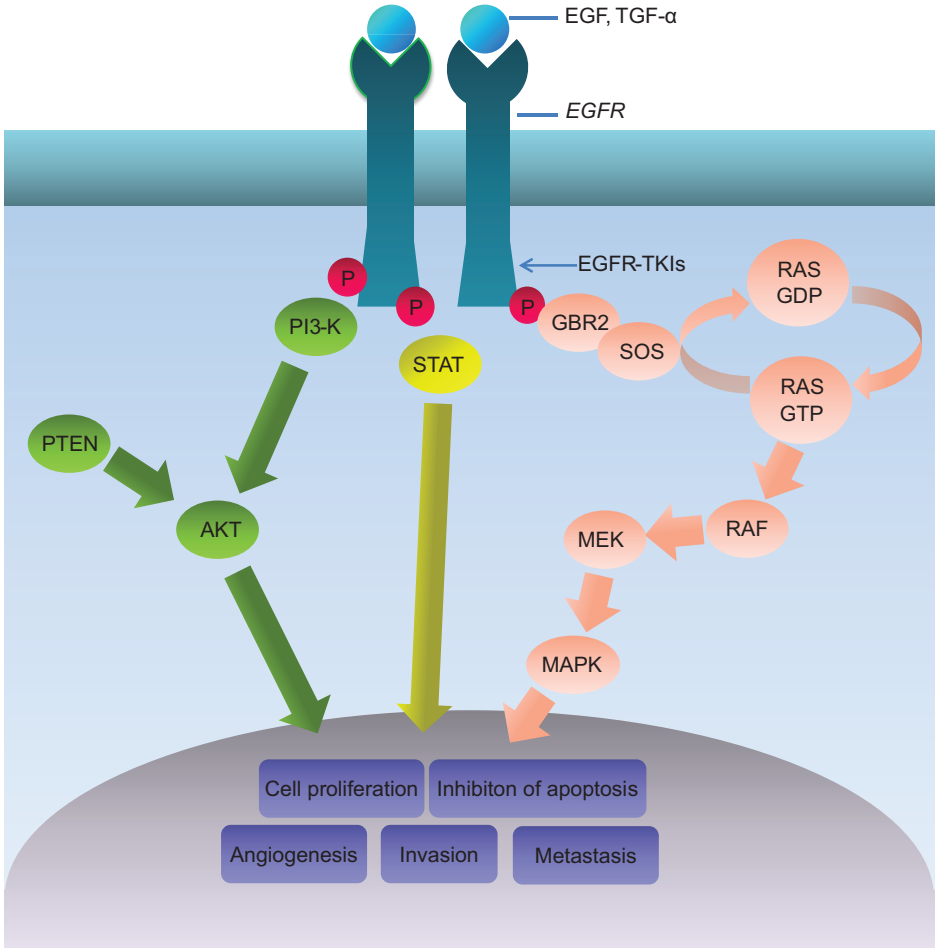

Figure 1 *EGFR* signaling pathway.
Abbreviation: *EGFR*, epidermal growth factor receptor; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; P, phosphorylate.

patients who were treated with normal chemotherapy had poorer clinical outcomes.[26,27] Currently, relevant research results suggest that the mutant status of *EGFR* can likely be a predicting factor for the response to cytotoxic chemotherapy and prognosis of advanced NSCLC patients; however, this issue remains debatable.

In this review, we aim to summarize the role of *EGFR* as a prognostic marker for postoperative patients and as a predictive marker for response to cytotoxic chemotherapy. In addition, we review the comparison of response to chemotherapy between *EGFR* mutations in exon 19 and in exon 21 and the predictive role of p.T790M mutation.

Materials and methods

Search strategy

PubMed was searched using the following keywords: "non-small-cell lung cancer", "*EGFR*", "erlotinib", "gefitinib", "afatinib", "chemotherapy", "p.T790M", "mutation", "predictive", and "prognostic". The online proceedings of the American Society of Clinical Oncology annual meeting and the World Conferences on Lung Cancer were searched for publications from 2004 to 2014 using the same keywords. In addition, the reference lists of relevant articles were searched. Search results were limited to articles in English.

Trial identification criteria

Clinical randomized trials, prospective cohort studies, and retrospective studies were included. Studies that evaluated the relationship between *EGFR* mutations and the outcomes of NSCLC patients were included. In addition, the included studies had to satisfy the following criteria: patients had a pathological diagnosis of NSCLC; patients had a clear *EGFR* mutation status; and at least one outcome regarding response rate (RR) or survival time was reported.

Data extraction

Data recorded from each single study included authors' names, publication year, study design, objectives, sample

size, *EGFR* mutation rate, and effects on patient outcomes (RR, survival, recurrence). Two reviewers independently conducted a data extraction from the original reports. Disagreements were resolved by consensus or by arbitration of a third reviewer.

Outcome definition

Based on the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guidelines,[28] complete response and partial response (PR) were defined as the RR, and complete response, PR, and stable disease were defined as the disease control rate (DCR). Disease-free survival (DFS) was defined as the time from the date of surgery to proven recurrence or death. Progression-free survival (PFS) was defined as the time from the date of starting the therapy to disease progression or death. Overall survival (OS) was defined as the time from the date of surgery or starting the therapy to death or last follow-up. Post-recurrence survival was defined as the time from the date of recurrence to death or last follow-up. Time to treatment failure (TTF) was defined as the time from the date of starting the treatment to disease progression or death. Two-sided *P*-values <0.05 were considered statistically significant.

EGFR mutations as a prognostic marker for postoperative patients with NSCLC

Recently, the predictive factors of postoperative prognosis in NSCLC patients have received much attention. Although outcomes after curative resection are improving, long-term survival time is still poor, resulting from a high rate of relapse.[29–31] Several studies have shown that the 5-year OS rates remained at 24%–58% after complete resection in stage IA–IIIA NSCLC patients.[32–34] Therefore, clarifying the role of *EGFR* mutation status in predicting the outcome of NSCLC patients with resection is essential clinical work.

The prognostic value of *EGFR* mutations in resected NSCLC remains debatable (Table 1). Several studies have indicated that the presence of *EGFR* mutations meant longer survival times for patients with NSCLC who received surgical treatment. In a study by Lee et al[35] 117 patients with surgically resected pulmonary adenocarcinoma were reviewed, including 53 patients with *EGFR* mutations and 64 patients with wild-type *EGFR*. The results revealed that *EGFR* mutations were significantly associated with longer DFS (34.4 versus 20.1 months, *P*=0.003), but *EGFR* mutations had no correlation with OS (*P*=0.39). In multivariate analysis of DFS, wild-type *EGFR* was associated with a higher risk of recurrence after curative resection (hazard ratio [HR] 1.42, 95% confidence interval [CI]: 1.10–2.41, *P*=0.04). Although there was not a statistically significant difference, isolated brain metastasis as the first recurrence was found more frequently in patients with *EGFR* mutations (24% versus 9%, *P*=0.15).

In a recent study performed by Jeon et al[36] 138 patients who underwent surgical resection with adenocarcinoma and had postoperative recurrence were included in the research. *EGFR* mutation was an independent prognostic factor for post-recurrence survival (HR 0.552, *P*=0.013) and survival time (HR 0.552, 95% CI: 0.345–0.882, *P*=0.013) in multivariable analysis.

Similarly, Sasaki et al[37] analyzed the information of 95 NSCLC patients who underwent surgical resection. Compared with those with wild-type *EGFR*, they found that the patients with *EGFR* mutations had a longer survival time (*P*=0.0143). However, a multivariate analysis did not prove that *EGFR* mutation was the significant factor (*P*=0.1824). Kosaka et al[38] analyzed 397 Japanese patients who were treated with curative pulmonary resection with lung adenocarcinoma. Although the results of multivariate analysis showed *EGFR* mutations were not independent factors related to the prognosis (*P*=0.3225), the authors found that the *EGFR* mutation patients had a longer survival time than those with wild-type *EGFR*.

A study by D'Angelo et al[39] enrolled the largest cohort ever reported (n=1,118) in an investigation of whether EGFR mutations could be used to predict the prognosis of postoperative patients with NSCLC *EGFR* mutation was detected in 222 (19.9%) patients. The results showed that patients with *EGFR* mutations had a lower risk of death (HR 0.51, $P<0.001$) and a longer OS (HR 0.51, 95% CI: 0.34–0.76, $P<0.001$) than those with *EGFR* wild-type. They also found that a survival time of more than 10 years (n=286) only occurred in patients with *EGFR* mutation in lung cancer.

However, several studies revealed that *EGFR* mutation status had no prognostic value in patients who underwent surgical resection with adenocarcinomas. A total of 131 patients with completely resected lung adenocarcinoma whose pathologic stage was IA–IIIA were included in a study by Liu et al[40] in which no significant correlation was observed between median DFS (36.6 versus 25.7 months, *P*=0.533), OS (*P*=0.564), the recurrence rate, and *EGFR* mutation status. The results of multivariate analysis revealed that the lymph node (N) status (*P*=0.037) and distant metastasis ($P<0.001$) were significant predictive factors for OS.

Kobayashi et al[41] performed a retrospective study to evaluate the factors related to poor outcomes of stage IA lung adenocarcinoma patients with surgical resection; 127 patients

Table 1 Select studies related to the association of *EGFR* mutations with prognosis in patients with resected NSCLC

Author/trial (year)	Number	*EGFR* mutation status, n		DFS/PFS (months)		OS (months)	
		Mutation	Wild-type	Mutation	Wild-type	Mutation	Wild-type
Kosaka et al (2004)[42]	224	110 (49.1%)	114 (50.9%)		NR		*P*=0.9933
Sasaki et al (2006)[37]	95	35 (36.8%)	60 (63.2%)		NR		*P*=0.1824
Lim et al (2007)[43]	27	15 (55.6%)	12 (44.4%)	DFS			*P*=0.45
				18.13	16.87		
					P=0.83		
Kobayashi et al (2008)[41]	127	64 (50.4%)	63 (49.6%)	DFS			
					HR 1.55 (0.54–4.49)		HR 1.60 (0.49–5.23)
					P=0.42		*P*=0.44
Lee et al (2009)[35]	117	53 (45.2%)	64 (54.8%)	DFS			NR
				34.4	20.1		
					HR 1.42 (1.10–2.41)		
					P=0.04		
Nose et al (2009)[44]	393	147 (37.4%)	246 (62.6%)		*P*=0.367		NR
Kosaka et al (2009)[38]	397	196 (49.4%)	201 (50.6%)		NR		*P*=0.3225
D'Angelo et al (2012)[39]	1,118	222 (19.9%)	896 (80.1%)		NR		HR 0.51 (0.34–0.76) *P*< 0.001
Liu et al (2013)[40]	131	58 (44.3%)	73 (55.7%)	DFS			HR 0.946 (0.500–1.791)
				36.6	25.7		*P*=0.865
					P=0.533		
					HR 1.133 (0.716–1.794)		
					P=0.595		
Jeon et al (2014)[36]	138	73 (52.9%)	65 (47.1%)	PRS			HR 0.552 (0.345–0.882)
					HR 0.552		*P*=0.013
					P=0.013		

Note: The number ranges given after HR values are 95% confidence interval.

Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; PFS, progression-free survival; OS, overall survival; PRS, post-recurrence survival; DFS, disease-free survival; NR, not reported; HR, hazard ratio.

were included in the study. The results indicated that there was no correlation between *EGFR* mutations and recurrence (HR 1.42, 95% CI: 0.38–5.29, *P*=0.60) or survival (HR 1.60, 95% CI: 0.49–5.32, *P*=0.44) in patients with lung adenocarcinoma 20 mm or less. These results were consistent with those of a study by Kosaka et al[42] who revealed that *EGFR* mutations did not influence the prognosis of patients with adenocarcinoma who underwent surgical resection (*P*=0.9933).

A total of 27 patients with resected lung adenocarcinomas were enrolled in a study performed by Lim et al.[43] *EGFR* mutations were detected in 15 patients (55.6%). The results showed there was no significant difference in DFS (16.87 versus 18.13 months, *P*=0.83) and OS (*P*=0.45) between *EGFR* mutation patients and those with wild-type *EGFR*. Similarly, among 393 Japanese patients who underwent a complete resection of adenocarcinoma in a study by Nose et al[44] there was no significant DFS difference between *EGFR* mutation patients and patients with wild-type *EGFR* (*P*=0.367).

At present, *EGFR* and *KRAS* mutations are known for having biologic relevance. Marks et al[45] analyzed the clinical outcomes data of 296 patients with stage I–III lung adenocarcinoma who underwent resection and compared outcomes between patients with *EGFR* mutation and *KRAS* mutation. The results revealed that patients with *EGFR* mutation had a higher 3-year OS than patients with *KRAS* mutant tumors (90% versus 66%) and suggested the NSCLC patients with *EGFR* mutation might have a more favorable prognosis.

Based on the previous studies,[35–45] the prognostic role of *EGFR* mutations was not clear in patients with resected NSCLC. Although several studies did not report a significant difference in survival time between patients with and without *EGFR* mutations who underwent a resection of NSCLC,[40–44] we believe that the presence of *EGFR* mutations is related to improved prognosis because of the better clinicopathologic characteristics. However, we cannot obtain a certain conclusion on this issue because of different postoperative treatments and the small population of patients in previous research. Therefore, further prospective studies are needed to investigate the prognostic value of *EGFR* mutations after surgical resection.

EGFR mutations as a predictive marker for response to cytotoxic chemotherapy in NSCLC

First-line treatment

Platinum-based doublet chemotherapy is the standard first-line therapy for advanced-stage NSCLC.[46–48] Currently, although chemotherapy regimens are continuously updated, the curative effect of chemotherapy for NSCLC has reached a plateau.[49,50] There is an urgent need to develop individualized treatments for NSCLC patients. Some research has indicated that *EGFR* mutations may be used as a predictive marker for the response to conventional cytotoxic chemotherapies (Table 2).[51–69] Although the results of these studies differed, they may suggest that there is a certain correlation between *EGFR* mutations and the response to cytotoxic agents.

The IRESSA Pan-Asia Study (IPASS)[51,52] was a randomized Phase III study that included 1,217 patients with advanced lung adenocarcinoma from 87 clinical research centers of nine Asian countries. The purpose of the study was to compare the efficiency of gefitinib and carboplatin/paclitaxel. The researchers found that the RR was higher in *EGFR* mutation patients compared with wild-type *EGFR* cases (47.3% versus 23.5%). The research revealed that *EGFR* mutations may be a favorable predictive factor for the response to cytotoxic chemotherapy in NSCLC patients. However, the results of another Phase III trial indicated that patients with *EGFR* mutations had a similar RR to *EGFR* wild-type patients after receiving chemotherapy.[53] In the first-line randomized Phase III Iressa NSCLC Trial Assessing Combination Treatment (INTACT) trials, Bell et al[54] found that *EGFR* mutation-positive patients treated only with chemotherapy had a better OS (19.4 versus 9.2 months) than those with wild-type mutations, but there was no significant difference in RR between the two groups (40.0% versus 39.0%).

Similar results were found in other studies. The study by Eberhard et al[55] indicated that the presence of *EGFR* mutations was associated with higher RR (38% versus 23%, *P*=0.01) and longer time to progression despite a therapeutic regimen (8.0 versus 5.0 months, $P<0.001$). The study by Hotta et al[56] demonstrated that *EGFR* mutations were significantly correlated with a better PFS (HR 0.422, *P*=0.0422) and OS (HR 0.263, *P*=0.0074) in 54 Japanese patients with advanced NSCLC receiving first-line cytotoxic regimens, whereas they observed that the objective response was not affected by the presence of *EGFR* mutations (*P*=0.6842). However, the correlation of *EGFR* mutation with PFS was not found in the patients who received chemotherapy after the failure of the first-line gefitinib (*P*=0.0764).

Kalikaki et al[57] evaluated the clinical outcome of 162 patients with advanced NSCLC who received first-line chemotherapy and divided patients with *EGFR* mutations into two groups, which included those who had classical activating mutations (Del19, p.L858R, p.G719D, and p.E746V) and those who carried other mutations of unknown effect. The data indicated that patients with

Table 2 Select studies related to the association of *EGFR* mutations with the response to cytotoxic chemotherapy in non-small-cell lung cancer

Author/ trial (year)	Number	*EGFR* mutation status, n		RR			PFS (months)			OS (months)		
		Mutation	Wild-type	Mutation		Wild-type	Mutation		Wild-type	Mutation		Wild-type
Eberhard et al (2005)[55]	228	29 (12.7%)	199 (87.3%)	38.0%	*P*=0.01	23.0%	TTP 8.0	*P*<0.001	5.0		NR	
Lee et al (2006)[60]	90	17 (18.9%)	73 (81.1%)	42.9%	*P*=0.553	34.4%	TTP 7.97	*P*=0.96	6.67		NR	
Hotta et al (2007)[56]	54	14 (25.9%)	40 (74.1%)	21.4%	*P*=0.6842	15.0%	0.422 (0.179–0.991)	*P*=0.0422			0.263 (0.099–0.699) *P*=0.0074	
INTEREST (2010)[66,67]	142	19 (13.4%)	123 (86.6%)	21.1%		9.8%	NR			16.6	*P*=0.59	6.0
Kalikaki et al (2010)[57]	162	Classical 31	Wild-type		WT vs classical		TTP				WT vs Classical	
		Other 9	122 (75.3%)		HR 4.85 (1.13–20.83) *P*=0.034		4.4	*P*=0.69	4.1		HR 2.25 (0.81–6.24) *P*=0.117	
Wu et al (2010)[3]	145	55 (37.9%)	90 (62.1%)	34.5%	*P*=0.881	33.3%	4.0	*P*=0.2148	3.0	23.0	*P*=0.0273 HR (0.372–0.961) *P*=0.0355	16.0 0.598
IPASS (2011)[51,52]	214	129 (60.3%)	85 (39.7%)	47.3%		23.5%	6.3		5.5	21.9		12.7
Park et al (2012)[59]	217	137 (63.1%)	80 (36.9%)	33.6%		35.0%	4.9	*P*=0.840	4.4		NR	
Dong et al (2013)[58]	229	120 (52.4%)	109 (47.6%)	35.0%		34.9%	9.1	*P*=0.008	8.3		NR	

Note: The number ranges given after HR values are 95% confidence interval.

Abbreviations: *EGFR*, epidermal growth factor receptor; HR, hazard ratio; INTEREST, Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere; IPASS, IRESSA Pan-Asia Study; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, response rate; TTP, time to progression; vs, versus; WT, wild-type.

classical *EGFR* mutations had a higher effectiveness of first-line chemotherapy than those with wild-type *EGFR* mutations patients (55.6% versus 21.8%, *P*=0.023), while, among patients treated with platinum-based regimens as the first-line treatment, OS was significantly longer in patients with classical *EGFR* mutations than in those without mutations (35.9 versus 15.3 months, *P*=0.043). In multivariate analysis, the presence of *EGFR* mutations was an independent factor associated with response to first-line chemotherapy (HR 4.85; 95% CI: 1.13–20.83; *P*=0.034).

Wu et al[3] retrospectively analyzed 145 cases of stages IIIB and IV NSCLC patients who received first-line chemotherapy. The results indicated that no statistical difference in RR to the first-line chemotherapy between *EGFR* mutation carriers and wild-type *EGFR* patients was observed (34.5% versus 33.3%, *P*=0.881). The mutated *EGFR* patients had a longer median survival time and higher 1- and 2-year survival rates than those with wild-type *EGFR* (23 versus 16 months, 86.38% versus 62.64%, and 38.78% versus 27.16%, respectively, *P*=0.0273). Among stage IV patients, those with *EGFR* mutations had a longer PFS than wild-type *EGFR* patients (5 versus 3 months, *P*=0.040*)*. Multivariate analysis demonstrated that the efficiency of the first-line chemotherapy and *EGFR* mutation status were independent prognostic factors (HR 0.461, *P*=0.0042 and HR 0.598, *P*=0.0335, respectively) for advanced NSCLC patients. The results of the study[3] suggested that *EGFR* mutations had a relationship with survival time rather than with the response to first-line chemotherapy in patients with advanced NSCLC.

There are some related studies which indicate that certain therapies could demonstrate higher efficiency in NSCLC patients with *EGFR* mutation. Dong et al[58] reviewed 229 patients with advanced NSCLC who received platinum-based doublet chemotherapy as the first-line treatment. Although the RRs were not influenced by *EGFR* mutation status, there was significant difference in the PFS between patients with wild-type *EGFR* and *EGFR* mutations (8.3 versus 9.1 months, *P*=0.008). In 120 patients with *EGFR* mutation, DCR was higher in patients treated with docetaxel when compared with patients treated with gemcitabine (88.6% versus 67.5%, *P*=0.031), and docetaxel- or vinorelbine-based treatment showed a longer PFS compared to gemcitabine (9.4, 9.6, and 8.3 months, respectively, *P*=0.033 and *P*=0.028). Multivariate analysis indicated that the presence of an *EGFR* mutation was an independent predictive factor for PFS to first-line chemotherapy (95% CI: 1.086–1.840, *P*=0.01).

Park et al[59] included 217 patients with advanced NSCLC who had received platinum doublet chemotherapy as a first-line regimen, with gemcitabine-based and taxane-based therapies administered in 131 (60.4%) and 86 (39.6%) cases, respectively. They found that taxane-based therapies had a higher DCR (71.8% versus 88.5%, *P*=0.022) and longer PFS (5.7 versus 4.1 months, *P*=0.002) compared with gemcitabine-based treatment in patients with *EGFR* mutations, particularly in those with deletions in exon 19 (5.3 versus 3.7 months, *P*=0.012). The results suggested that an optimal cytotoxic chemotherapy regimen could be selected based on the *EGFR* mutation status in patients with NSCLC.

However, the results of some research showed that there was no relationship between *EGFR* mutations and the response to cytotoxic chemotherapy. Lee et al[60] investigated 90 patients, of whom 75 received platinum and 45 received paclitaxel as first-line chemotherapy agents. RR to first-line chemotherapy for patients with *EGFR* mutations was 42.9%, which was similar to that for wild-type *EGFR* patients (34.4%, *P*=0.55). Similarly, Takano et al[61] reported that the RRs to first-line cytotoxic chemotherapy were not significantly different between *EGFR* mutation patients and *EGFR* wild-type cases (31.0% versus 28.0%, respectively, *P*=0.50).

In contrast, a chemosensitivity test performed by Yoshimasu et al[62] demonstrated that the sensitivity to docetaxel was lower in lung cancers with *EGFR* mutations compared with in tumors with wild-type *EGFR*.

Second-line treatment

At present, international recommendations for second-line drugs in NSCLC patients are docetaxel, pemetrexed, and EGFR-TKIs. However, patients with *EGFR* mutations receiving EGFR-TKIs after progression on chemotherapy demonstrated a lower RR compared with those on first-line therapy.[63–65] The Phase III Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST) trial[66,67] compared the response to gefitinib and docetaxel as a second-line therapy in advanced NSCLC. The results showed that the RR to docetaxel was higher in patients with *EGFR* mutation-positive tumors compared with those with wild-type *EGFR* (21.1% versus 9.8%). Moreover, among patients who were treated with docetaxel, those with *EGFR* mutations had a longer OS than wild-type patients, although there was no significant difference (16.6 versus 6.0 months, *P*=0.59).

Wu et al[68] analyzed 95 patients with stage IIIb or IV NSCLC after treatment with gefitinib as the first-line therapy who received a second-line treatment with a platinum-based or taxane-containing regimen. The results showed that the

gemcitabine-plus-platinum regimen achieved better OS than erlotinib in patients with *EGFR* mutations (27.1 versus 10 months, *P*=0.035) but not in patients with wild-type *EGFR* (10.1 versus 12.7 months, *P*=0.785).

In the BR.21 trial,[63,69] researchers compared erlotinib with a placebo in advanced NSCLC patients. Among the placebo subgroup, the data showed that patients with classical mutations had a longer median survival time than patients with *EGFR* wild-type or novel *EGFR* mutations (9.1, 3.5, and 3.5 months, respectively). However, there was no significant survival difference between *EGFR* classical or novel mutation patients and patients with wild-type *EGFR* (HR 0.65, 0.67, and 0.73, respectively).

As we can see from the results of the abovementioned studies, it has not been established whether *EGFR* mutations could predict the outcomes in NSCLC patients treated with cytotoxic chemotherapy. Regarding the results that showed that NSCLC patients with *EGFR* mutations achieved better therapeutic effect and longer survival time, one possible reason is that *EGFR* mutation patients have a favorable natural process, regardless of the efficacy of chemotherapy itself. Although a better outcome was found in mutation-positive NSCLC patients, this was not always obvious. Moreover, a majority of the previous related studies involved retrospective analysis and had a relatively small sample size, which could lead to some biases. Therefore, it is necessary to conduct further prospective studies to determine the predictive role of *EGFR* mutations for cytotoxic chemotherapy and the detailed prediction mechanism.

Comparison of the response to chemotherapy or EGFR-TKIs between *EGFR* mutations in exon 19 and mutations in exon 21 in NSCLC

In different types of *EGFR* mutations, in-frame deletions in exon 19 and amino acid replacements in exon 21 (leucine to arginine at condon 858, p.L858R) were the most common mutations, and accounted for about 85% of all *EGFR* mutations in patients with NSCLC.[70–72] The predictive and prognostic value in patients with *EGFR* exon 19 mutation or with *EGFR* exon 21 mutation remains unclear (Table 3). In research performed by Cappuzzo et al[73] *EGFR* mutation was detected in 24 patients, which included deletion in exon 19 in 15 cases and point mutation in exon 21 in seven cases. The authors found a 46.6% RR to chemotherapy in patients with *EGFR* deletions in exon 19 compared with 0% RR in patients with other *EGFR* mutations (*P*=0.02), which suggested that patients with *EGFR* exon 19 mutation might be more sensitive to EGFR-TKIs than patients with other *EGFR* mutations.

Jackman et al[74] compared the clinical data and outcomes of patients whose tumors had an *EGFR* exon 19 mutation to those with *EGFR* exon 21 mutation in 36 NSCLC patients who were treated with gefitinib or erlotinib. The results indicated that patients with deletions in exon 19 (delp.729–761) had a significantly improved time to progression (24 versus 10 months, *P*=0.04) and OS (38 versus 17 months, *P*=0.0384) than patients with a p.L858R mutation. Although there were no significant differences in multivariate analysis, patients with exon 19 mutation showed a higher RR than those with exon 21 mutation (73% versus 50%, *P*=0.25).

Riely et al[75] noted that patients with *EGFR* exon 19 mutation had a longer median PFS (12 versus 5 months, *P*=0.01) and OS (34 versus 8 months, *P*=0.01) compared with those with *EGFR* exon 21 mutation after receiving EGFR-TKI treatment. Similar results were shown in a study by Rosell et al.[76] A pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials[77] indicated that the patients with deletions in exon 19 receiving first-line afatinib had a longer OS than those treated with standard chemotherapy (HR 0.59; 95% CI: 0.45–0.77, *P*<0.001); however, in patients with p.L858R mutation, HR =1.25 (95% CI: 0.92–1.71, *P*=0.160). The results suggested that the patients with a particular *EGFR* mutation (eg, deletion in exon 19) could acquire more obvious benefit from the first-line afatinib therapy.

In a study by Liu et al[40] which enrolled 131 patients with completely resected lung adenocarcinoma, the results showed that, compared with the patients with exon 21 mutation, those with exon 19 mutation (delp.746–750) had longer DFS (46.2 versus 21.9 months, *P*=0.056) and 1-, 2-, and 3-year OS (100%, 96.7%, and 93.3%, respectively, versus 91.3%, 82.6%, and 60.9%, respectively, *P*=0.01). However, several randomized Phase III studies reported no significant difference in PFS with EGFR-TKIs between the patients with deletions in exon 19 and those with exon 21 p.L858R mutation.[52,78,79]

Conversely, Shigematsu et al[80] analyzed early-stage NSCLC patients who underwent resections and never received EGFR-TKIs. After comparing the outcomes of 31 cases with *EGFR* p.L858R and 31 cases with *EGFR* deletions in exon 19 (delp.729–761), they reported that patients with p.L858R attained a longer survival time (*P*=0.05).

However, the study by Lee et al[35] found that patients with exon 19 mutation recurred more frequently compared

Table 3 Select studies related to the association of *EGFR* mutations in exon 19 and exon 21 with the response to treatment in NSCLC

Author/trial (year)	Number		RR		PFS (months)		OS (months)	
	Exon 19	Exon 21	Exon 19	Exon 21	Exon 19	Exon 21	Exon 19	Exon 21
Shigematsu et al (2005)[80]	62	52	NR		NR		*P*=0.05	
Riely et al (2006)[75]	43	27	NR		12	5	34	8
					P=0.01		*P*=0.01	
Jackman et al (2006)[74]	22	10	73.0%	25%	24	10	38	17
			P=0.25		*P*=0.04		*P*=0.0384	
Cappuzzo et al (2007)[73]	15	7	46.6%	0%	NR		NR	
			P=0.02					
Rosell et al (2009)[76]	135	82	HR 3.08 (1.63–5.81) *P*=0.001		HR 1.92 (1.19–3.10) *P*=0.02		NR	
WJTOG3405 (2010, 2012)[78,79]	EGFR-TKIs		NR		9	9.6	NR	
	50	36			HR 1.13 (0.63–2.03) *P*=0.681			
	Cisplatin and docetaxel				6	6.7		
	37	49			HR 1.23 (0.75–2.01) *p*=0.405			
IPASS (2011)[51,52]	140	111	NR		HR 0.78 (0.51–1.19)		NR	
Liu et al (2013)[40]	30	23	NR		DFS		*P*=0.01	
					46.2	21.9		
					P=0.056			

Note: The number ranges given after HR values are 95% confidence interval.

Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; RR, response rate; PFS, progression-free survival; DFS, disease-free survival; OS, overall survival; NR, not reported; HR, hazard ratio; IPASS, IRESSA Pan-Asia Study; WJTOG3405, West Japan Thoracic Oncology Group 3405; EGFR-TKIs, *EGFR* tyrosine kinase inhibitors.

Table 4 Select studies related to T790M mutation as a prognostic marker for patients with NSCLC

Author/trial (year)	Number	*EGFR* T790M mutation, n		PFS (months)			OS (months)		
		Mutation	Wild-type	Mutation		Wild-type	Mutation		Wild-type
Oxnard et al (2011)[91]	93	58 (62.4%)	35 (37.6%)	19.0		12.0	39.0		26.0
					P=0.036			*P*=0.007	
Fujita et al (2012)[92]	38	30 (78.9%)	8 (21.1%)	TTF				NR	
				9.0		7.0			
					P=0.44				
Sun et al (2013)[95]	70	36 (51.4%)	34 (48.6%)	14.7		14.1	43.5		36.8
					P=0.26			*P*=0.23	
Kuiper et al (2014)[93]	66	34 (51.5%)	32 (48.5%)	14.2		11.1	45.9		29.8
					P=0.034			*P*=0.213	
Li et al (2014)[94]	54	29 (53.7%)	25 (46.3%)	PFS1					
				13.0		10.5			
					P=0.894				
				PFS2			OS2		
				6.3		2.6	39.8		23.2
					P=0.002			*P*=0.044	

Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; TTF, time to treatment failure; PFS, progression-free survival; PFS1, the time from the date of starting; PFS2, the time from the date of the first disease progression to the second disease progression; OS, overall survival; OS2, the time from the date of starting the therapy to death or last follow-up; NR, not reported.

with patients with exon 21 mutations (HR 4.13, 95% CI: 1.14–14.88, *P*=0.03).

The results of several studies have suggested that the tumor biology of patients with different *EGFR* mutations is different, which indicates that specific types of *EGFR* mutation may have an additional predictive role in NSCLC patients. The cause resulting in the different clinical outcomes between NSCLC patients with deletions in exon 19 and p.L858R point mutations remains unknown. One possible reason is that *EGFR* mutations in exon 19 are more sensitive to EGFR-TKIs or chemotherapy than exon 21 mutations. However, such differences also exist in patients who only receive surgical resection with lung cancer. In in vitro research, however, EGFR-TKIs had similar growth inhibitions to NSCLC cell lines with deletions in exon 19 or p.L858R mutations.[21,81] There is a question about whether we should treat the two *EGFR* mutations equally when making clinical decisions. Prospective studies are needed to further investigate this difference.

p.T790M mutation as a prognostic marker for patients with NSCLC

Some mechanisms of acquired resistance to EGFR-TKIs have been identified, such as MET amplification, small-cell histologic transformation, and HER2 amplification.[82–84] However, the p.T790M mutation is the most prevalent mechanism. p.T790M mutation was reported in 2.7%–40% of TKI-naïve patients.[20,85] Currently, almost all patients with activating mutations (deletion in exon 19 or point mutation in exon 21) eventually develop acquired resistance while receiving EGFR-TKI therapy,[20] and about 50% of these patients have a secondary mutation in exon 20 (p.T790M).[86–90] The p.T790M mutation abolishes the influence of EGFR-TKIs by increasing the affinity for adenosine triphosphate (ATP).[87] There is a major clinical problem in that NSCLC patients with *EGFR* mutations achieve acquired resistance after treatment with EGFR-TKIs.

Several studies have evaluated the predictive and prognostic role of p.T790M mutations in patients with NSCLC (Table 4). The results of the study by Oxnard et al[91] showed that patients with p.T790M mutation at post-TKI biopsy had a longer post-progression survival compared with patients without p.T790M mutation after progression on EGFR-TKIs (19.0 versus 12.0 months, *P*=0.036). Moreover, those without p.T790M suffered a lower Karnofsky performance status at time of progression (*P*=0.007).

In the research of Fujita et al[92] 38 EGFR-TKI-naïve patients with *EGFR* mutations who underwent curative pulmonary resection were included, and the *EGFR* p.T790M mutation at pre-TKI biopsy was detected in 30 patients (78.9%). There was no significant difference in TTF between those with and without p.T790M mutation (9.0 versus 7.0 months, *P*=0.44) after receiving EGFR-TKIs. However, the authors divided the patients with p.T790M mutation mutation into strongly positive and modestly positive groups according to the frequency of positive signals, and revealed that the patients who were strongly positive had a longer TTF compared with those without p.T790M mutation (*P*=0.0097) and those with modest positivity *(P*=0.0019). This was the first report to reveal a positive relationship between the

presence of p.T790M mutation before receiving EGFR-TKIs and prognosis of patients. The results suggested that the abundance rather than the presence of p.T790M mutation caused the benefits of EGFR-TKI treatment in NSCLC.

Kuiper et al[93] analyzed the clinical data of 66 patients with *EGFR* mutations, and the results showed that patients with p.T790M mutation at post-TKI biopsy attained a longer PFS (14.2 versus 11.1 months, P=0.034) and longer OS (45.9 versus 29.8 months, P=0.213) than those without p.T790M mutation on EGFR-TKI therapy.

Similar results were reported in a study by Li et al.[94] p.T790M mutation was detected in 29 patients after the failure of EGFR-TKIs, and the authors found that the time from the date of starting EGFR-TKI treatment to disease progression or death (PFS1) was not influenced by p.T790M mutation (13.0 versus 10.5 months, P=0.894). However, among 41 patients treated with EGFR-TKIs beyond progression, the results showed that patients with p.T790M mutation had a longer time from the date of the first disease progression to the second disease progression (PFS2) (6.3 versus 2.6 months, P=0.002) and OS (39.8 versus 23.2 months, P=0.044) than those with p.T790M wild-type. The data indicated that patients with p.T790M mutation after acquired resistance to EGFR-TKIs had better therapeutic effect to the continuous EGFR-TKI therapy. This conclusion requires further investigation.

In contrast, Sun et al[95] analyzed 70 NSCLC patients who had acquired resistance to EGFR-TKIs and of whom 36 (51%) had *EGFR* p.T790M mutation at post-TKI biopsy. No significant difference was found in post-progression survival (14.7 versus 14.1 months, P=0.26) and OS (43.5 versus 36.8 months, P=0.23) between patients with and without p.T790M mutation. Thirty-four patients were treated with subsequent afatinib after progression on EGFR-TKIs, and the patients with p.T790M mutation had a higher RR than those without p.T790M mutation (5% versus 38%, P=0.01). However, the median PFS for afatinib was 3.2 months in the p.T790M mutation group and 4.6 months in the p.T790M wild-type group (P=0.33).

A meta-analysis[96] was performed to identify the role of *EGFR* p.T790M mutation in the prognosis of patients receiving EGFR-TKI therapy. The incidence of patients who had pretreatment p.T790M mutation ranged from 34.88% to 80.00%. The authors found that patients with p.T790M mutation had a shorter PFS on EGFR-TKI treatment compared with p.T790M wild-type patients.

The studies above evaluated whether there was a prognostic value to the p.T790M mutation in NSCLC patients with *EGFR* mutations, but this remains unclear. Rather than finding a negative prognostic effect of p.T790M mutation with EGFR-TKI treatment, some research has indicated that the p.T790M mutation might have a positive prognostic value after progression on EGFR-TKIs. In a fundamental study, the existence of p.T790M mutation was correlated with a slow speed of tumor growth,[86] which may be the reason why patients with *EGFR* p.T790M mutation were usually found to have a longer survival time in clinical research. Knowledge of p.T790M mutation is essential for determining the optimal treatment for these patients and we expect that the p.T790M mutation will become the first acquired molecular marker with prognostic significance.

Some studies have demonstrated that there were activities against p.T790M mutation tumors in vitro and in vivo,[97,98] and some clinical trials are ongoing.[99,100] The results of CO-1686 indicated that three-quarters of patients with p.T790M mutation who progressed following EGFR-TKIs treatment could have PR in a Phase I trial.[101] Preliminary data from a Phase I study in NSCLC patients with acquired resistance to EGFR-TKIs also showed that about one-half of the patients receiving AZD9291 treatment could achieve responses.[100,102] Moreover, a Phase II trial suggested that the combination of cetuximab and afatinib had modest clinical activity in NSCLC patients with p.T790M mutation.[103] However, there is still no standard therapy for patients with p.T790M mutation.

First-line therapy in NSCLC patients with *EGFR* mutations

Six randomized Phase III trials indicated that NSCLC patients with *EGFR* mutations receiving EGFR-TKIs as the first-line therapy could achieve higher RR and longer PFS than those receiving chemotherapy; however, no significant difference was found in OS between the two groups (Table 5).[51,51,78,79,105–108,110,111] However, a pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials reported an improvement in OS in *EGFR* mutant patients receiving EGFR-TKIs in 2014.[77]

Among the subgroup of NSCLC patients with *EGFR* mutation, the results of IPASS[51,52] indicated that the gefitinib arm had a higher RR (71.2% versus 47.3%, $P<0.001$) and a longer PFS (9.5 versus 6.3 months, $P<0.001$) compared to the carboplatin/paclitaxel group, while no significant difference was found in OS between these two groups (21.6 versus 21.9 months, P=0.990).

WJTOG (West Japan Thoracic Oncology Group) 3405[78,79] was a Phase III study that analyzed the outcomes of 177 Japanese patients harboring *EGFR* mutations with advanced NSCLC. The researchers found that the patients who received gefitinib showed a significantly higher RR (62.1% versus 32.2%,

Table 5 Select studies related to first-line therapy in NSCLC patients with *EGFR* mutations

Author/trial (year)	Number	RR		PFS (months)		OS (months)	
		TKI	Chemotherapy	TKI	Chemotherapy	TKI	Chemotherapy
IPASS (2008, 2011)[51,52]	261	71.2% *P*<0.001	47.3%	9.5 HR 0.48 (0.34–0.64) *P*<0.001	6.3	21.6 HR 1.00 (0.76–1.33) *P*=0.990	21.9
WJTOG 3405 (2010, 2012)[78,79]	177	62.1% *P*<0.001	32.2%	9.2 HR 0.489 (0.336–0.710) *P*<0.001	6.3	35.5 HR 1.185 *P*=0.443	38.8
OPTIMAL (2011)[104]	154	83.0% *P*<0.001	36.0%	13.7 HR 0.16 (0.10–0.26) *P*<0.001	4.6	22.6 HR 1.065 *P*=0.685	28.8
First-SIGNAL (2012)	42	84.6% *P*=0.002	37.5%	8.0 HR 0.544 (0.269–1.100) *P*=0.086	6.3	27.2 HR 1.043 (0.498–2.182) *P*=0.984	25.6
EURTAC (2012)[105]	173	58.0% *P*<0.001	15.0%	9.7 HR 0.37 (0.25–0.54)	5.2	19.3 HR 1.04 *P*=0.87	19.5
NEJ002 (2013)[106]	228	73.7% *P*<0.001	30.7%	10.8 HR 0.322 (0.236–0.438) *P*<0.001	5.4	27.7 HR 0.887 (0.634–1.241) *P*=0.483	26.6
LUX-Lung 3 (2013)[108]	345	56.0% *P*=0.001	23.0%	11.1 HR 0.58 (0.43–0.78) *P*=0.001	6.9	HR 1.12 (0.73–1.73) *P*=0.60	
LUX-Lung 6 (2014)[109]	364	66.9% *P*<0.0001	23.0%	11.0 HR 0.28 (0.20–0.39) *P*<0.0001	5.6	22.1 HR 0.95 (0.68–1.33) *P*=0.76	22.2

Note: The number ranges given after HR values are 95% confidence interval.

Abbreviations: *EGFR*, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; IPASS, IRESSA Pan-Asia Study; WJTOG, West Japan Thoracic Oncology Group; First-SIGNAL, First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers With Adenocarcinoma of the Lung; EURTAC, European Tarceva versus Chemotherapy; RR, response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; TKI, tyrosine kinase inhibitors.

$P<0.001$) and longer PFS (9.2 versus 6.3 months, $P<0.001$) than those receiving cisplatin plus docetaxel.

The randomized Phase III First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never-Smokers With Adenocarcinoma of the Lung (First-SIGNAL) trial enrolled 313 Korean never-smokers with advanced lung adenocarcinoma. Ninety-six patients were evaluated for *EGFR* mutation status and *EGFR* mutation was detected in 42 patients. Of the patients who had *EGFR* mutation-positive tumors, the gefitinib group had a higher objective response rate (ORR) (84.6% versus 37.5%, $P=0.002$) and a longer PFS (8.0 versus 6.3 months, $P=0.086$); however, the results failed to show a significant difference in OS. Similar results were shown in OPTIMAL study,[104] European Tarceva versus Chemotherapy (EURTAC) study,[105] and NEJ002 study.[106]

In 2013, a meta-analysis[107] was performed to evaluate the favored therapy for first-line treatment in NSCLC patients with *EGFR* mutations. The results demonstrated that patients receiving EGFR-TKI therapy showed a higher RR (66.60% versus 30.62%, HR 5.68, 95% CI: 3.17–10.18, $P<0.001$) and an improved PFS (9.5 versus 5.9 months, HR 0.37, 95% CI: 0.27–0.52, $P<0.001$) compared with those receiving chemotherapy treatment. There was no significant difference in OS (30.5 versus 23.6 months, HR 0.94, 95% CI: 0.77–1.15, $P=0.57$).

Recently, in two randomized Phase III trials,[108,109] patients with *EGFR* mutations treated with second-generation EGFR-TKIs such as afatinib had better outcomes than those receiving chemotherapy (Table 5). The results of the LUX-Lung 3 study[108] demonstrated that significantly improved RR and PFS were found with afatinib compared to chemotherapy in *EGFR* mutation patients (56% versus 23%, $P=0.001$ and 11.1 versus 6.9 months, $P=0.001$, respectively). Similar results were found in the LUX-Lung 6 trial.[109] At the American Society of Clinical Oncology 2014 meeting, a pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials[77] provided new efficacy and safety data to support treatment with afatinib. The analysis included 631 advanced NSCLC patients with common *EGFR* mutations (deletions in exon 19 or p.L858R substitutions) and demonstrated that the patients attained longer OS when treated with first-line afatinib compared to standard chemotherapy (27.3 versus 24.3 months, HR 0.81, 95% CI: 0.66–0.99, $P=0.037$). This is the first time an actual survival benefit not seen in previous trials with gefitinib or erlotinib was shown.

The pooled analysis of the LUX-Lung 3 and LUX-Lung 6 trials[77] suggested that patients with *EGFR* mutations receiving EGFR-TKIs had a greater improvement in OS than those treated with chemotherapy, which provided the latest evidence toward determining whether EGFR-TKIs should be used as first- or second-line treatment. The results may influence the therapeutic regimen of the *EGFR* mutant patients in clinical practice. Afatinib is an irreversible inhibitor against p.T790M mutation and all *EGFR* family members. Although several related studies have been carried out,[110–113] whether different EGFR-TKIs have different effects in *EGFR*-mutant patients is still unclear.

Conclusion

At present, *EGFR* mutation is the strongest predictive biomarker for the efficiency of EGFR-TKIs.[114,115] Through analyzing relevant research of the past 20 years, we found that the prognostic and predictive value of *EGFR* mutation status in NSCLC remains uncertain, and it is difficult to understand the detailed mechanism by which cytotoxic agents influence *EGFR*-mutant and wild-type tumors differently. One study reported the differences in carcinogenic molecular genetic pathways between *EGFR* mutation tumors and tumors with wild-type *EGFR*.[116] The results showed that mutant *EGFR* selectively activated Akt and signal transducer and activator of transcription (STAT) signaling is related to cell survival; however, mutant *EGFR* could not act on extracellular signal-regulated kinase signaling, the function of which is to induce proliferation. Wild-type *EGFR* was proved to promote cellular proliferation and cell survival. Future molecular studies are needed to support this mechanism.

Although the majority of the selected research was performed retrospectively, and the studies achieved various conclusions, the results provide new information which can play an essential role in choosing the best treatment option for patients with NSCLC according to the *EGFR* mutation status. We believe that the presence of *EGFR* mutations has an intrinsic relationship with the outcomes in patients with NSCLC. With improvements in technology for detecting gene mutations, some novel mutations in *EGFR* have been reported to be sensitive to TKIs, such as p.V765A, p.T783A, p.V774A, p.S784P, and p.V769A.[117–121] The role of *EGFR* should be evaluated in more detail in prospectively designed research so that we can have a deeper understanding of the association of *EGFR* mutation with the curative effect and survival benefit of chemotherapy in the future.

Disclosure

The authors report no conflicts of interest in this work.

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