

# The role of epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of advanced stage non-small cell lung cancer

Pei-Jye Voon<sup>1</sup>, Byoung Chul Cho<sup>2</sup>, Wee-Lee Yeo<sup>1,3</sup>, Ross A Soo<sup>1,3</sup>

<sup>1</sup>Department of Hematology-Oncology, National University Cancer Institute, National University Health System, Singapore; <sup>2</sup>Division of Medical Oncology, Yonsei Cancer Center, Seoul, South Korea; <sup>3</sup>Cancer Science Institute of Singapore, Singapore

### ABSTRACT

The epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) like erlotinib and gefitinib have been extensively studied. Multiple randomized trials have evaluated the role of EGFR TKIs in advanced stage non-small cell lung cancer (NSCLC) as a monotherapy in the first line, or subsequent lines of therapy, and in the first line in the maintenance setting or in combination with chemotherapy. Most of these trials showed positive results in particular for selected patients with specific clinical characteristic and somatic activating mutation of EGFR. A further understanding of the mechanism of primary and secondary resistance has led to the development of promising novel agents designed to overcome resistance to EGFR.

### Key Words:

non-small cell lung cancer; epidermal growth factor receptor; tyrosine kinase inhibitors; Gefitinib; Erlotinib

*J Thorac Dis 2010; 2: 144-153. DOI: 10.3978/j.issn.2072-1439.2010.02.03.6*

## Introduction

Lung cancer is one of the leading causes of death worldwide with the majority of patients presenting with advanced unresectable or metastatic non-small cell lung cancer (NSCLC). Despite the advances in palliative chemotherapy, the survival for patients with advanced disease treated with chemotherapy remains poor with a median survival of 8-10 months (1). The development of the specific molecular-targeted therapeutic agents has provided more treatment options to improve survival. One such molecular target is the epidermal growth factor receptor (EGFR). EGFR is an attractive target for various antitumor strategies including small-molecule agents that selectively inhibit the intracellular tyrosine kinase activity and anti-EGFR monoclonal antibody which inhibit extracellular ligand-induced phosphorylation and receptor degradation (2). This review will further discuss on the role of EGFR tyrosine inhibitors (TKIs) in the management of advanced stage NSCLC.

## EGFR pathway in NSCLC

EGFR is one of the four members of the human epidermal growth factor receptor (HER) family of tyrosine kinase. Structurally, EGFR consist of an extracellular ligand binding domain, a transmembrane domain and an intracellular tyrosine kinase domain (3). Dimerization of the EGFR occurs after stimulation by a ligand such as epidermal growth factor (EGF). This results in autophosphorylation and downstream increased of cell proliferation, inhibition of apoptosis, activating invasion and metastasis (2).

Aberrant tyrosine kinase activity is a hallmark of malignant cells in particular for NSCLC. Overexpression of EGFR is reported to occur in 60% of metastatic NSCLC cases and correlates with poor disease prognosis and reduced survival (5). Apart from EGFR overexpression, NSCLC also produce EGF and transforming growth factor-alpha. Both of these growth factors induce autocrine stimulation for EGFR. The inhibition of EGFR signaling with small molecule inhibitors for tyrosine kinase domain of EGFR on malignant cells can be effective and potentially less toxic (6).

## Pharmacology of EGFR TKIs

Small-molecule EGFR tyrosine kinase inhibitors, such as gefitinib and erlotinib, are orally active low molecular weight compound (40-600kD) that reversibly compete with ATP to bind to the intracellular catalytic domain of EGFR. This

No potential conflict of interest.

Corresponding author: Ross A Soo, MD. Department of Hematology-Oncology, National University Health System, 1E Kent Ridge Road, Tower Block Level 7, Singapore 119228. Tel: (65) 6779 5555; Fax: (65) 6775 0913. Email: ross\_soo@nuhs.edu.sg.

Submitted Jul 25, 2010. Accepted for publication Aug 30, 2010.  
Available at [www.jthoracdis.com](http://www.jthoracdis.com)

ISSN: 2072-1439 © 2010 Journal of Thoracic Disease. All rights reserved.

**Table 1.** Phase III studies of EGFR TKI in pre-treated advanced stage NSCLC

Study	Treatment	Patient number	Response rate (%)	Progression free survival (months)	Median survival (months)
BR21 (15)	Placebo	243	<1	1.8	4.7
	Erlotinib 150mg daily	488	8.9*	2.2*	6.7*
ISEL (17)	Placebo	563	1.3	2.6	5.1
	Gefitinib 250mg daily	1129	8*	3.0*	5.6
INTEREST (18)	Docetaxel 75mg/m <sup>2</sup>	733	7.6	2.2	7.6
	Gefitinib 250mg daily	733	9.1	2.7	8.0
V-15-32 (19)	Docetaxel 60mg/m <sup>2</sup>	244	12.8	2.0	14
	Gefitinib 250mg daily	245	22.5*	2.0	11.5
ISTANA (20)	Docetaxel	79	7.6	3.4	HR 0.870; 95% CI
	Gefitinib 250mg daily	82	28.1*	3.3	0.613-1.236

EGFR (epidermal growth factor receptor), TKI (tyrosine kinase inhibitor), NSCLC (non-small cell lung cancer)

\* Statistically significant

inhibits autophosphorylation and downstream signaling cascades of RAS-RAF-MEK-MAPK (gene transcription, cell cycle progression, and cell proliferation) and PI3K-Akt pathway (antiapoptotic and prosurvival) (7).

## Determinants of response to EGFR TKI

Whilst EGFR TKIs are active in unselected patients with NSCLC, differences in response rates were observed in certain patient subgroups. Retrospective analysis have suggested certain clinical characteristics such as female gender, adenocarcinoma histology, Asian ethnicity and a history of never/ light smoking were associated with increased response to EGFR TKIs. Molecular predictors of EGFR TKIs sensitivity include somatic activating mutations in exon 18-21 of EGFR (commonly exon 19 deletions and L858R point mutation in exon 21) (8-10) and account for 80% to 95% of the EGFR mutations in NSCLC (9). Such mutations are present predominantly in patients with the clinical features mentioned previously (10). Other molecular determinants of EGFR TKIs response include KRAS mutations and EGFR gene copy number detected by fluorescence in situ hybridization (FISH) (11).

## Single agent EGFR TKIs in pretreated patients

The efficacy of erlotinib and gefitinib were initially evaluated in the second- or third-line setting in several phase II and phase III studies (Table 1). In two randomized phase II studies, the Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) studies I and II, patients with pre-treated NSCLC were randomized to gefitinib at 250 mg or 500 mg daily. In IDEAL-1 where patients

who received one or two lines of chemotherapy, a similar response rate of 18.4% and 19% was seen patients receiving gefitinib 250mg daily or 500mg daily respectively. In addition, the disease control rate (54.4% vs. 51.4%), progression-free survival (PFS) (2.7 months vs. 2.8 months), median overall survival (7.6 months vs. 8 months), and 1-year survival (35% vs. 29%) were also similar. Subset analysis showed that Japanese patients had a better response rate compared to non-Japanese (27.5% vs. 10.4%;  $P = 0.002$ ) (12).

In IDEAL-2, a multicentre US study, patients with advanced NSCLC treated with two or more regimens, including a platinum agent and docetaxel were randomised to gefitinib at 250mg or 500mg daily. The response rate was 12% vs. 10%, and the median survival was 7 vs. 6 months for 250 mg and 500 mg daily respectively (13). Treatment was well tolerated in both IDEAL-1 and -2, with skin rash the most common side effect. The 250mg daily was selected for further trials as the efficacy was similar between the two doses and as grade 3-4 toxicity was more frequent in patients receiving 500 mg daily. Clinical predictors for response included Japanese patients, women, adenocarcinoma histology, never smokers, and good performance status (0 or 1). Based on these results, gefitinib received accelerated Food and Drug Administration (FDA) approval in 2003 as monotherapy for patients with advanced stage NSCLC after progression with platinum-based therapy and docetaxel (14).

The efficacy of erlotinib in pre-treated advanced NSCLC was established in a phase III study, BR21. Patients with NSCLC who had received one or two prior chemotherapy regimens were randomized to erlotinib or best supportive care. A significant improvement in median survival was seen in patients receiving erlotinib compared with placebo (6.7 months vs. 4.7 months, HR 0.70; 95% CI 0.58-0.85). In addition, a

significant improvement in response rate and progression free survival was also seen in the erlotinib arm. In the BR21 study, subset analyses reported female gender, adenocarcinoma, Asian ethnicity and a history of never smoking were clinical indicators of increased survival (15). Additional biomarker studies were also reported in this study. Erlotinib treatment was associated with prolonged survival when EGFR overexpressed by immunohistochemistry (HR 0.68; 95% CI 0.49-0.95) or by polysomy or amplification of EGFR gene number (HR 0.44; 95% CI 0.23-0.82). EGFR mutational status had no significant effect on survival (16).

In a multicentre phase III study Iressa Survival Evaluation in Lung Cancer (ISEL) assessing the benefit of gefitinib in the second or third line setting, patients with advanced stage NSCLC refractory to or intolerant to their chemotherapy were randomized to gefitinib 250mg daily or placebo. No significant difference in median survival was seen with 5.6 vs. 5.1 months respectively (HR 0.89; 95% CI 0.77-1.02). A superior response rate (8% vs. 1%) and time to treatment failure (3 vs. 2.6 months) was seen in gefitinib compared with placebo. Pre-planned subset analysis showed an improvement in overall survival for gefitinib compared with placebo in never smokers (8.9 months vs. 6.1 months; HR 0.67; 95% CI 0.49-0.92) and patients of Asian origin (9.5 months vs. 5.5 months; HR 0.66; 95% CI 0.48-0.91) (17). Exploratory subset analyses found an increased response rate in patients with EGFR mutations compared with wild-type (37.5% vs. 2.6%). In addition, EGFR gene copy number was a borderline predictor survival for patients treated with gefitinib with HR 0.61 95% CI 0.36-1.04 for high copy number and HR 1.16; 95% CI 0.81-1.64 for low copy number. A comparison of high vs. low EGFR copy number hazard ratio was significant ( $P = 0.045$ ).

Based on the results from the ISEL study, gefitinib was withdrawn in the US and European Union. The contrast in the lack of survival benefit with gefitinib in the ISEL study compared with the BR21 study may possibly be due to the large number of patients refractory to chemotherapy in the ISEL study (90%) as these patients represent a population who are difficult to treat and have a poor prognosis.

## Second-line EGFR TKI compared to chemotherapy

In a phase III global study Iressa in NSCLC Trial Evaluating Response and Survival vs. Taxotere (INTEREST), patients with NSCLC previously treated with platinum based chemotherapy were randomized to gefitinib or docetaxel. The primary endpoint of non-inferiority in terms of overall survival was met. The median survival (HR 1.02; 96% CI 0.905-1.15) and response rate (9.1% vs. 7.6%) for gefitinib vs. docetaxel. The co-primary endpoint of superiority in patients with high EGFR

gene-copy number was not met (HR 1.09; 95% CI 0.78-1.51; median survival 8.4 months vs. 7.5 months). An improvement in quality of life was seen in patients receiving gefitinib. Additional treatment administered post study were well balanced between the arms. In the gefitinib group, 54% received no systemic therapy apart from further EGFR tyrosine kinase inhibitor, 31% received docetaxel, and 15% received other chemotherapy only. In the docetaxel arm, 53% received no systemic therapy apart from further docetaxel, 37% received an EGFR tyrosine kinase inhibitors, and 10% received other chemotherapy only (18). Biomarker analysis showed no differences in survival between gefitinib and docetaxel irrespective of EGFR protein expression, EGFR gene mutation or KRAS gene mutation status.

In another phase III study V-15-32, Japanese patients with pre-treated advanced stage NSCLC were randomized to gefitinib or docetaxel. The median survival was 11.5 months vs. 14 months respectively (HR 1.12; 95.24% CI 0.89-1.40). In contrast to the INTEREST study, non-inferiority of survival for gefitinib however was not met according to the pre-specified criteria of upper confidence interval  $< 1.25$ . This may be due to imbalances in post discontinuation treatment as more docetaxel-treated patients received additional systemic therapy, thus complicating the interpretation of the overall survival result. Response rate was 22.5% and 12.8% for gefitinib and docetaxel respectively ( $P = 0.009$ ). An improvement in quality of life was seen in patients treated with gefitinib (19).

In a Korean phase III study Iressa as Second Line Therapy in Advanced NSCLC-Asia (ISTANA), gefitinib and docetaxel was compared in patients with advanced stage NSCLC. An improvement in the progression free-survival (HR 0.73; 90% CI 0.533-0.998) and response rate (28% vs. 7.6%,  $P < 0.0007$ ) was seen in the gefitinib arm. Quality of life was similar between the two treatment arms (20).

## First-line EGFR TKI in advanced stage NSCLC

Several trials have examined the role of EGFR TKIs administered concurrently with cytotoxic chemotherapy in the first line treatment of advanced stage NSCLC or as maintenance therapy following cytotoxic chemotherapy.

In INTACT-1 (Iressa NSCLC Trial Assessing Combination Treatment), patients were randomized to three treatment arms: gemcitabine and cisplatin and placebo or to the same chemotherapy in combination with gefitinib at 250mg daily or gefitinib 500mg daily. The median survival was similar in the three arms at 10.9 months, 9.9 months and 9.9 months respectively. Time to progression and response rates were also similar (21). INTACT-2 was a three-arm phase III study with similar design to INTACT-1. Standard chemotherapy in this study was paclitaxel and carboplatin. The median overall survival

was 9.9 months, 9.8 months and 8.7 months for placebo, gefitinib 250mg daily and gefitinib 500mg daily respectively (22).

In a phase III study of patients randomized to either gemcitabine and cisplatin and placebo or same chemotherapy in combination with erlotinib (Tarceva Lung Cancer Investigation [TALENT]), no differences in time to progression, response rate or survival were seen. The median survival was 43 weeks vs. 44.1 weeks for erlotinib and placebo respectively (23). In a multi-center US phase III study, Tarceva responses in conjunction with paclitaxel and carboplatin (TRIBUTE), patients were randomly assigned to erlotinib or placebo in combination with carboplatin and paclitaxel. Similar to the other studies, there were no difference in survival, response rate and time to progression. Median survival for was 10.6 months and 10.5 months for patients treated with erlotinib and placebo respectively (HR 0.99; 95% CI 0.86- 1.16) (24).

Taken together, these results indicate there is no clinical benefit with the addition of an EGFR TKI given concurrently with chemotherapy (Table 2). Other approaches administering EGFR TKI with chemotherapy in the first line setting have been used such as sequential administration of chemotherapy followed by EGFR TKI or administration of maintenance EGFR TKI after the completion of all chemotherapy treatment. Using the first approach, in a multicenter, phase II study, First-Line Asian Sequential Tarceva and Chemotherapy Trial (FAST-ACT), patients were randomized to erlotinib or placebo on days 15-28 of a 4-week cycle of a platinum and gemcitabine regimen. Whilst the primary endpoint of non progression rate at 8 weeks was not met, 80.3% vs. 76.9% for erlotinib and chemotherapy vs. placebo and chemotherapy respectively, a significant improvement in progression free survival of 29.4 weeks vs. 23.4 weeks (adjusted HR 0.47; 95% CI 0.33 to 0.68) was reported (25). Based on these promising results, a phase III study is ongoing using this treatment strategy (26).

Two recent studies have used the latter approach (Table 3). The West Japan Thoracic Oncology Group conducted a Phase III study (WJTOG0203) of maintenance gefitinib therapy following first line chemotherapy. Patients were randomized to a platinum doublet (carboplatin/paclitaxel, cisplatin/irinotecan, cisplatin/gemcitabine) for up to six cycles (arm A) or platinum-doublet chemotherapy for three cycles followed by gefitinib 250 mg orally daily, until disease progression (arm B). An improvement in progression-free survival was reported in patients on arm B compared with arm A, 4.6 months vs. 4.3 months respectively (HR 0.68; 95% CI 0.57-0.80) but the primary endpoint of overall survival results did not reach statistical significance with a median survival of 12.9 months for chemotherapy alone and 13.7 months with chemotherapy followed by gefitinib (HR 0.86; 95% CI 0.72-1.03). Exploratory subset analysis of overall survival by histologic group showed patients in arm B with adenocarcinoma did significantly better than patients in arm A with adenocarcinoma with a median survival of 12.9 and 13.7 months for arm A and B respectively (HR 0.79; 95% CI 0.65-0.98) (27).

In a second study, the phase III Sequential Tarceva in Unresectable Lung Cancer (SATURN), patients were initially treated with four cycles of platinum based chemotherapy. Patients without disease progression were randomized to erlotinib or placebo. Progression free survival (PFS) was significantly longer for erlotinib compared to placebo at 12.3 weeks

**Table 2.** Phase III studies of EGFR TKI concurrent with cytotoxic chemotherapy in the first line treatment of advanced stage NSCLC

Study	Treatment	Patient number	Response rate (%)	Time to progression (months)	Median survival (months)
INTACT-1 (21)	Gemcitabine/ cisplatin/ placebo	363	47.2	6.0	10.9
	Gemcitabine/ cisplatin/ gefitinib 250mg daily	365	51.2	5.8	9.9
	Gemcitabine/ cisplatin/ gefitinib 500mg daily	365	50.3	5.5	9.9
INTACT-2 (22)	Paclitaxel/ carboplatin/ placebo	345	28.7	5.0	9.9
	Paclitaxel/ carboplatin/ gefitinib 250mg daily	345	30.4	5.3	9.8
	Paclitaxel/ carboplatin/ gefitinib 500mg daily	347	30.0	4.6	8.7
TRIBUTE (24)	Paclitaxel/ carboplatin/ placebo	533	19.3	4.9	10.5
	Paclitaxel/ carboplatin/ erlotinib 150mg daily	526	21.5	5.1	10.6
TALENT (23)	Gemcitabine/ cisplatin/ placebo	586	29.9	24.6 weeks	44.1 weeks
	Gemcitabine/ cisplatin/ erlotinib 150mg daily	586	31.5	23.7 weeks	43.0 weeks

EGFR (epidermal growth factor receptor), TKI (tyrosine kinase inhibitor), NSCLC (non-small cell lung cancer)



**Table 3.** Phase III studies of EGFR TKI as maintenance therapy following first line cytotoxic chemotherapy in advanced stage NSCLC

Study	Treatment	Patient number	Response rate (%)	Progression free survival (months)	Median survival (months)
WJTOG0203 (27)	Observation	301	29.3	4.3	12.9
	Gefitinib 250mg daily	302	34.2	4.6*	13.7
SATURN (28)	Placebo	451	5.4	11.1 weeks	11.0
	Erlotinib 150 mg daily	438	11.9	12.3 weeks*	12.0

EGFR (epidermal growth factor receptor), TKI (tyrosine kinase inhibitor), NSCLC (non-small cell lung cancer)

\* Statistically significant

and 11.1 weeks respectively (HR 0.71; 95% CI 0.62-0.82). A secondary endpoint of overall survival was significantly longer in patients receiving erlotinib compared with placebo at 12 months and 11 months respectively (HR 0.81, 95% CI 0.70-0.95). The co-primary endpoint of PFS in EGFR immunohistochemistry positive tumors was also met with a median PFS of 12.3 weeks vs. 11.1 weeks (HR 0.69; 95% CI 0.58-0.82). EGFR mutation status showed that erlotinib improved PFS in patients with EGFR activating mutations (HR 0.10; 95% CI 0.04-0.25) and EGFR wild-type (HR 0.78; 95% CI 0.63-0.96) (28).

## First line monotherapy

The Iressa Pan-Asia Study (IPASS), a randomized phase III conducted in Asia where patients were selected by clinical characteristics for EGFR mutation (never/ light smoker, adenocarcinoma subtype), were randomised to gefitinib or carboplatin and paclitaxel. A superior PFS favoring gefitinib (HR 0.74; 95% CI 0.65-0.85) was seen. Furthermore, in patients receiving gefitinib, higher response rates (43% vs. 32.2%) and superior quality of life were reported. In the IPASS study, in pre-planned subset analysis, patients with EGFR mutations had a prolonged PFS with gefitinib compared with chemotherapy (HR 0.48; 95% CI 0.36-0.64) whilst patients without EGFR mutation had a poorer PFS with gefitinib (HR 2.85; 95% CI 2.05-3.98). Response rate for EGFR mutation positive and negative patients was 71.7% and 1.1%, respectively (29). Based on these analyses, gefitinib is a novel treatment option for patients with EGFR mutations and but should not be offered to patients without the mutation (Table 4).

The role of monotherapy erlotinib in the first line setting in unselected patients has been reported in several phase II studies. Response rates and survival were comparable with results from cytotoxic chemotherapy (30, 31). Based on these phase II studies, several phase III studies have been initiated. The Tarceva or Chemotherapy (TORCH) study, designed to evaluate the efficacy of erlotinib and chemotherapy in an unselected population has been completed and results are awaited (32).

## First-line EGFR TKI in advanced stage NSCLC in patients with EGFR mutations

As EGFR mutations are associated with greater sensitivity to EGFR TKIs, investigators have examined the efficacy of EGFR TKI compared with chemotherapy in this molecularly selected patient group in the first line setting (Table 4). In an open label phase III Japanese study (WJTOG3405), chemo-naïve patients with advanced stage NSCLC or postoperative recurrence with an EGFR mutation (exon 19 deletion or L858R point mutation) were randomized to gefitinib or cisplatin/docetaxel. An improvement in PFS of 9.2 months vs. 6.3 months was seen in patients receiving gefitinib compared with chemotherapy (HR 0.489; 95% CI 0.336-0.71). Response rates were 62.1% and 32.2% for gefitinib and chemotherapy respectively (33).

In a more recent Japanese study, chemo naïve patients with sensitizing EGFR mutations were randomly assigned to gefitinib or carboplatin/paclitaxel. The PFS was longer in the gefitinib arm compared to the chemotherapy arm at 10.8 months and 5.4 months respectively (HR 0.30; 95% CI 0.22-0.41) whilst the response rates were 73.7% and 30.7% respectively. No difference in overall survival was seen (30.5 months vs. 23.6 months) (34).

Results from the above Japanese studies, together with the EGFR mutation subset analysis from the IPASS study (Table 4), suggest that first line gefitinib is superior to cytotoxic chemotherapy in patients with advanced stage NSCLC harbouring sensitive EGFR mutations on the basis of improved PFS with acceptable toxicity. Furthermore, the European Medicines Agency has approved the use of gefitinib for the treatment of patients with locally advanced or metastatic NSCLC with activating mutations of EGFR (35). We recommend that the selection of patients for first line treatment of patients with advanced stage NSCLC should be based on EGFR mutation status.

## EGFR TKIs in poor performance patients

Concern of potential chemotherapy related toxicities have

**Table 4.** Phase III studies of single agent EGFR TKI monotherapy in the first line treatment of advanced stage NSCLC

Study	Treatment	Patient number	Response rate (%)	Progression free survival (months)	Median survival (months)
IPASS (29) (All patients)	Paclitaxel/ carboplatin	608	32.2	HR 0.74; 95% CI 0.65-0.85	HR 0.91; 95% CI 0.76-1.10
	Gefitinib 250mg daily	609	43.0*		
IPASS (29) (Patients with sensitizing EGFR mutations)	Paclitaxel/ carboplatin	129	47.3	HR 0.48; 95% CI 0.36-0.64	HR 0.78; 95% CI 0.50-1.20
	Gefitinib 250mg daily	132	71.2*		
WJTOG3405 (33)	Cisplatin/ docetaxel	89	32.2	6.3	NR
	Gefitinib	88	62.1*	9.2*	NR
NEJSG (34)	Carboplatin/ paclitaxel	114	30.7	5.5	23.6
	Gefitinib	114	73.7*	10.4*	30.5

EGFR (epidermal growth factor receptor), TKI (tyrosine kinase inhibitor), NSCLC (non-small cell lung cancer), NR (not reported)

\* Statistically significant

deprived many poor performance patients with advanced NSCLC from deriving benefits from palliative chemotherapy. The oral administration and potential better toxicity profile of TKIs may offer some advantages for chemotherapy-naive poor performance status patients.

Two phase II trials from North America and Europe reported no benefit with the use of EGFR TKIs compare with either chemotherapy or best supportive care in this group of patients (36, 37). However, these two trials were conducted in unselected patients. In contrast, in a Japanese study of patients with untreated, advanced stage NSCLC with sensitising EGFR mutations treated with gefitinib, the response rate was 66% (90% CI, 51%-80%) and was associated with an improvement in performance status (38).

In a recent phase III trial, the Tarceva Or Placebo In Clinically Advanced Lung Cancer (TOPICAL) study, patients with chemo-naïve advanced stage NSCLC with a poor performance (ECOG PS 2/3 or PS 0/1 and unfit for platinum chemotherapy) were randomized to erlotinib or placebo. Preliminary results presented in abstract form reported no difference in overall survival (HR 0.98; 95% CI 0.82-1.15). In pre-specified subgroup analysis, erlotinib use in females improved overall survival (HR 0.75; 95% CI 0.57-0.99) and PFS (HR 0.64; 95% CI 0.49-0.83) (39).

## Toxicity of EGFR TKIs

EGFR TKIs are generally well tolerated. The two most common toxicities include dermatologic and gastrointestinal side effects. High levels of EGFR expression in the basal layer of the epidermis is thought to be the cause of the dermatologic toxicity (40). In BR21, erlotinib was found to cause rash in 76% overall and 9% of grade  $\geq 3$  toxicity (15). The efficacy of the drug has been correlated with the occurrence and severity of the skin adverse event (40, 41). However, conflicting evidence has been shown in IDEAL-2 study where the presence of skin toxicities did not correlate with tumour response to gefitinib and was not a marker for antitumor activity (13).

In addition, diarrhea is also a common side effect of erlotinib (<1%-4% for grade  $\geq 3$  toxicity) (15, 30) and gefitinib (2-5% for grade  $\geq 3$  toxicity) (17, 18, 29). Cases of gastrointestinal perforation, some of which were fatal, have also been reported in patients receiving erlotinib (42).

Reports of severe or fatal drug-related interstitial lung disease associated with the EGFR TKIs had been reported in particularly Japanese patients with a prevalence of 3.5% and mortality of 1.6% (43). However, other clinical trial including placebo control trial with erlotinib (15) and trials combining EGFR TKIs with chemotherapy, mainly conducted in non-Asian populations, the incidence of interstitial lung disease was similar across the groups (approximately 1% in all groups) (21-24).

Hepatic toxicity has been observed in erlotinib use and caution need to be exercised for patients with liver impairment.

## Mechanism of resistance of EGFR TKIs

Resistance of EGFR TKIs can be divided into primary or secondary (acquired) resistance. Preexisting somatic mutations in KRAS are associated with primary resistance to EGFR TKIs (44). KRAS and EGFR mutations are usually

mutually exclusive and are rarely found in the same tumour. Activating mutations of KRAS occur in about 13-30% of lung adenocarcinomas (44-46). A meta-analysis suggests KRAS mutations are negative predictors for response of EGFR TKIs (47).

Insertion mutations in the exon 20 in EGFR TK domain also has been found to cause primary resistance by reducing efficacy of the TKIs. It reduces the inhibitory activity of TKIs 100 fold but is rare and is not a predominant cause of primary TKIs resistance (48).

Despite initial good response to EGFR TKIs, almost all patients will subsequently develop acquired resistance. Multiple acquired resistance mechanisms have been implicated. One of the mechanisms extensively studied is a secondary mutation of EGFR at exon 20 involving substitution of methionine for threonine at 790 (T790M). This mutation is present in approximately 50% of patients with acquired resistance to EGFR TKIs (49, 50). The mechanism of this resistance is unclear with hypothesis that T790M are usually present in small fraction of tumour cell before treatment with EGFR TKIs and clonal selection after the treatment has resulted in this resistance (51). The proto-oncogene c-Met has been implicated in causing acquired resistance to EGFR TKIs. MET amplification activates EGFR independent PI3K/AKT pathway through HER-3 dependent activation (52).

Other mechanisms of acquired resistance that have been intensively looked into include epithelial-to-mesenchymal transition (EMT), downregulation of PTEN pathways and Insulin-like Growth Factor-1 (53, 54, 55, 56). Further studies are needed to establish the clinical significance of these resistance mechanisms.

## Novel agents

Despite the efficacy the current EGFR TKIs, novel agents are needed to improve the efficacy as well as to overcome the resistance to EGFR TKIs. These therapies are broadly divided into irreversible TKIs and multikinase inhibitors.

In preclinical studies, irreversible EGFR TKIs have demonstrated potential of overcoming the resistance conferred by T790M (57). Most of these agents have activities not only against EGFR but also other Erb/Her family and most of them are undergoing phase II and III studies. One of the promising agents is BIBW 2992 that has both irreversible binding to EGFR and Her2. It has showed activity in patients who have developed resistance to erlotinib (58). Currently, this agent is being tested in randomized studies comparing with placebo or cytotoxic chemotherapy after encouraging results in phase II studies (59, 60).

A recent phase II study of the irreversible pan-EGFR TKIs, HKI-272 (neratinib) in patients of advanced stage NSCLC

with or without prior TKIs showed only low activity with a response rate of 0-3% (61). Other similar agents that potentially overcome resistance conferred by T790M mutation are currently undergoing clinical trials. These include PF00299804 and EKB-569 (62, 63).

The multikinase inhibitor vandetanib is an orally active low molecular weight inhibitor of EGFR, VEGFR and RET receptor. Several phase II trials of vandetanib have shown an improvement in PFS when combined with chemotherapy or as monotherapy. However, phase III trials of vandetanib in combination with docetaxel or perimetrexed or as monotherapy have shown only modest activity. A randomized, double-blind phase III trial of second line therapy with perimetrexed with or without vandetanib (ZEAL), a positive trend was seen for vandetanib with pemetrexed for PFS (HR 0.86; 97.58% CI 0.69-1.06) (64). Another randomized phase III study comparing vandetanib vs. erlotinib after failure of the cytotoxic therapy also did not meet its primary objective of PFS prolongation with vandetanib (HR 0.98; 95.22% CI 0.87-1.10) (65). In a recently published randomized phase III trial (ZODIAC) with combination of docetaxel and vandetanib compared with docetaxel alone showed a minor improvement in PFS in patients with advanced NSCLC after progression following first-line therapy with a median survival of 4 months vs. 3.2 months (HR 0.79; 97.58% CI 0.70-0.90) (66).

BMS-690514, another orally active multikinase inhibitor of EGFR, Her-2, VEGFR-2 and VEGFR-3 also has shown promising activity in both erlotinib-naive and erlotinib failure patients (67).

## Summary

The development of the EGFR TKIs in NSCLC have expanded treatment options in the treatment of advanced stage NSCLC. However, these agents are associated with response and improvement in survival for selected patients with specific clinical and molecular characteristics. Further evaluation of the best strategies especially in terms of molecular assays in identifying and selecting these favourable patients are crucial in ensuring the success of these agents. As resistance to gefitinib and erlotinib will occur with time, an understanding of the mechanisms of resistance and further development of novel agents are needed.

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