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Second Generation Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors In Lung Cancers

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Abstract

EGFR mutations identify patients who are more likely to respond to treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) than cytotoxic chemotherapy. The distinct success of the first generation EGFR TKIs erlotinib and gefitinib has been accompanied by the observation that acquired resistance to these treatments develops after a median of one year of treatment. Newer, second-generation, EGFR TKIs have been developed with the intent to delay or overcome acquired resistance by the broader inhibition of kinases (e.g. HER2 and VEGFR) and/or altering the interactions with EGFR by irreversibly binding to the kinase domain. In this review, we will discuss many of these agents (including afatinib, dacomitinib, XL647, AP26113, and CO-1686) which have the potential for greater efficacy compared to first generation EGFR TKIs, and may also have clinical activity against other oncogenic mutations within the *EGFR* family including *HER2*.

EGFR

The epidermal growth factor receptor (EGFR) family includes four receptor tyrosine kinases: EGFR (HER1), ERBB2 (HER2), ERBB3 (HER3) and ERBB4 (HER4). The EGFR is composed of an extracellular ligand binding region, a transmembrane region and an intracellular tyrosine kinase domain. Ligand binding to the extracellular region of EGFR induces a conformational change in the receptor that promotes dimerization. Dimerization of the receptor results in auto-phosphorylation of the intracellular domain which in turn recruits proteins involved in downstream signaling. The resultant signal transduction cascade activates pathways including the RAS/RAF/MEK and PI3K/AKT pathways leading to cell proliferation and survival[1].

Activating mutations in *EGFR* were discovered to be oncogenic in a subset of lung cancers in 2004[2,3]. Somatic *EGFR* mutations increase the activity of the receptor by allowing activation of the kinase receptor in the absence of ligand binding and thereby inducing a constitutively active state that leads to sustained downstream signaling. *EGFR* mutated tumors appear to be dependent on *EGFR* signaling for growth and survival making inhibition of *EGFR* an attractive therapeutic target.

First generation EGFR TKIs

Gefitinib and erlotinib were the first EGFR tyrosine kinase inhibitors that were approved for the treatment of patients with non-small cell lung cancer. These drugs inhibit kinase activity by competitively interacting with the ATP-binding site of EGFR, preventing auto-phosphorylation and consequently inhibiting downstream signaling. This inhibition leads to apoptosis in cells dependent upon EGFR signaling, such as those with *EGFR* mutations.

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Gefitinib efficacy was first evaluated in two single-arm phase 2 studies in patients with non-small cell lung cancer (NSCLC) who had received prior chemotherapy. The success of these trials led to the accelerated approval of gefitinib in 2003[4,5] as well as initiation of a phase 3 trial[6] (ISEL) which randomized patients to gefitinib versus placebo and found no difference in median survival (5.6 vs 5.1 months respectively). The lack of an overall survival benefit in ISEL prompted the FDA to restrict gefitinib use. Notably, these early studies did not select or evaluate patients based upon EGFR mutation status.

Subsequent trials of gefitinib focused on subsets of patients more likely to respond to gefitinib. IPASS enrolled East Asian patients with adenocarcinoma who were former light or never smokers (the key clinical characteristics associated with response to EGFR TKI and presence of *EGFR* mutations) to receive either gefitinib or the combination of carboplatin and paclitaxel as first-line treatment[7]. Gefitinib prolonged progression-free survival (PFS) (9.5 vs 6.3months for gefitinib vs chemotherapy), with the positive study results largely driven by the predominance of *EGFR* mutations in the study population (60% of patients had tumors with *EGFR* mutations). Of note, patients with these clinical characteristics who did not have *EGFR* mutations and received initial gefitinib had a median progression-free survival less than 2 months and a response rate of 1%. Based on IPASS and other studies, the EMEA approved gefitinib for use in patients with *EGFR* mutant advanced NSCLC. Gefitinib has also been studied specifically in patients with *EGFR* mutant lung cancers. In both the WJOTG 3405[8] and NEJ2002[9] studies, patients were randomized to gefitinib or platinum based chemotherapy, and gefitinib led to improved PFS and objective response rates (ORR) compared to cytotoxic chemotherapy in these patients with *EGFR* mutations.

Similar to gefitinib, erlotinib was also compared to placebo in patients with advanced, previously treated NSCLC without determination of *EGFR* mutation status[10]. Median overall survival (OS) in these unselected patents was longer in those treated with erlotinib compared with placebo (6.7 vs 4.7 mo), with a radiographic response rate (RR) of 9% vs <1% with placebo. These led to the US FDA approval of erlotinib in advanced NSCLC in the United States. Subsequent studies, including OPTIMAL and EURTAC[11,12], evaluated erlotinib in the first line setting compared to chemotherapy in patients with *EGFR* mutant NSCLC. Both OPTIMAL and EURTAC led to improved PFS and RR with the use of erlotinib compared to cytotoxic chemotherapy with results very similar to what was seen with trials which compared gefitinib to chemotherapy. Taken together, the data indicate that the benefits of first-generation EGFR TKI are dramatic, particularly in patients with somatic EGFR mutations.

Acquired resistance to first generation EGFR TKI

Patients with lung adenocarcinomas harboring *EGFR* mutations respond to treatment with erlotinib and gefitinib, but eventually progress, developing acquired resistance after a median of 12–16 months [7,9,13]. The study of tumor samples of patients with acquired resistance to EGFR TKI therapy has elucidated various mechanisms of resistance, with a specific mechanism identified approximately 70% of the time[14,15]. The most common etiology of resistance is the acquisition of the T790M missense mutation encoded by exon 20 of EGFR which is found in >60% of patients with clinical acquired resistance[16,17]. Other secondary mutations within *EGFR* have been described including EGFR D761Y and T854A that are associated with the development of acquired resistance to EGFR TKIs[18,19]. Amplification of *MET* is another finding observed at the time of acquired resistance[20,21]. Small cell histologic transformation has also been seen associated with the development of acquired resistance[22]. More recent work has identified HER2 amplification and acquired BRAF mutations as potential mechanisms of resistance both of which have potential therapeutic implications that will require further study[23,24].

2nd generation EGFR TKIs

Acquired resistance to first generation EGFR TKIs has prompted the clinical development of second-generation EGFR tyrosine kinase inhibitors (see Table 1). Second-generation EGFR TKIs may be able to overcome some of the mechanisms of resistance to first generation EGFR TKIs and have the potential to be more effective than erlotinib or gefitinib as first EGFR TKI. Most of the 2nd generation TKIs form irreversible, covalent attachments to the EGFR kinase domain, and may have additional activity against other receptors in the EGFR family or structurally similar receptors such as VEGF (Table 1). In addition, due to their covalent binding, they may have more activity against T790M or other secondary mutations against which first generation TKI's are relatively ineffective. Several ongoing trials are also evaluating EGFR TKIs in combination with other agents that target parallel signaling pathways, or target the EGF receptor in a different manner in order to circumvent resistance to first generation EGFR TKIs.

Neratinib (HKI-272)

Neratinib is an oral, irreversible inhibitor of both EGFR and HER2 with preclinical studies suggesting neratinib is active against EGFR T790M[25] and also against cells with *HER2* mutations[26,27]. A phase 1 study[28] conducted among patients with advanced solid tumors established the maximum tolerated dose (MTD) of neratinib at 320mg daily due to a dose limiting toxicity of grade 3 diarrhea. Neratinib was studied further in a multicenter phase 2 study[29] in patients with advanced NSCLC. During the study, the dose of neratinib needed to be decreased to 240mg orally daily due to the development of grade 3 diarrhea in more than 50% of patients at the higher dose. The response rate was 2%, with no responses seen in patients with clinical acquired resistance whose tumors harbored EGFR T790M or in patients who did not have a sensitizing *EGFR* mutation. The lack of efficacy may be related to the high concentrations of neratinib required in preclinical studies to inhibit EGFR T790M and the limitations of clinical dosing of neratinib that resulted from excessive toxicity[30]. There are no current ongoing studies of neratinib in non-small lung cancer.

Dacomitinib (PF-00299804)

Dacomitinib is an irreversible pan- HER tyrosine kinase inhibitor with activity against EGFR, HER2 and HER4. Preclinical studies and xenograft models showed activity against EGFR T790M and *HER2* mutated cell lines[31,32]. Results from a phase 1 study[33] of dacomitinib in patients with NSCLC established the safety of 45mg orally daily in a population enriched for *HER* gene amplifications, *EGFR/HER2* mutations and *KRAS* wild type patients. A phase 2 study was then performed in patients with NSCLC who had progressed on chemotherapy and erlotinib[34]. At the time of study presentation, 62 patients were evaluable with 3 confirmed partial responses and 35 patients with stable disease for greater than 6 weeks. Because of relative safety and potential signals of efficacy, a randomized phase 2 study of either erlotinib or dacomitinib was undertaken in 188 patients with advanced NSCLC after progression on cytotoxic chemotherapy[35]. Dacomitinib led to a longer median PFS (12.4 vs 8.3 weeks) compared to erlotinib and a randomized phase 3, ARCHER, in this same population is ongoing. Dacomitinib is also being evaluated in the first line setting in a phase 2 study in patients with light smoking histories or adenocarcinoma with a sensitizing *EGFR* mutation[36]. Thirty-four of 46 evaluable patients had a partial response to dacomitinib therapy, and the preliminary median PFS was 17 months. This study is ongoing with a specific cohort evaluating patients with *HER2* mutations as well.

Afatinib (BIBW 2992)

Afatinib, an irreversible inhibitor of both the EGFR and HER2 kinase, is the most extensively studied second-generation EGFR TKI. In preclinical studies, afatinib inhibits both the wild type and mutant forms of *EGFR* and is active against EGFR T790M[37]. In a phase 1 trial which established the MTD of 50mg orally daily, the dose limiting toxicities were rash and dyspnea secondary to pneumonitis[38]. Common side effects of afatinib include nausea, vomiting, fatigue and rash. Extensive clinical studies of afatinib have been completed and other studies are in progress in both the first line setting in patients with *EGFR* mutant tumors and in the setting of acquired resistance to first generation EGFR TKIs (see Tables 3 and 4).

In patients with advanced lung adenocarcinoma who have *EGFR* mutations and have not received prior EGFR TKI, three studies with afatinib were performed or are in progress, including a single-arm phase 2 study and a pair of randomized studies that compare afatinib to chemotherapy in this population of patients (NCT01121393, NCT00949650). In the phase 2 study (LUX Lung2), 129 patients with advanced *EGFR* mutant lung adenocarcinoma were treated with afatinib[39]. The objective response rate was 66% with a median OS and PFS of 24 and 14 months respectively. To validate these findings and compare the efficacy of afatinib in this population with that of cytotoxic chemotherapy, two randomized phase 3 trials were performed. The trial of cisplatin/gemcitabine vs afatinib is ongoing with no preliminary results available. The preliminary results of the trial randomizing patients with previously untreated lung adenocarcinoma to afatinib or cisplatin/pemetrexed chemotherapy (LUX Lung3) were recently presented. In the overall population, the median PFS was 11 months for those treated with afatinib compared to 7 months with cisplatin and pemetrexed chemotherapy[40]. When only patients with the most common EGFR sensitizing mutations were included, the median PFS for afatinib treatment was 14 months and 7 months for cisplatin and pemetrexed.

Three prospective studies of afatinib have been conducted in patients with advanced NSCLC who have progressed on first generation EGFR TKIs. The first reported trial (LUX Lung1) was a phase 3 study that randomized 585 patients with advanced lung adenocarcinoma who had progression of disease after platinum based chemotherapy and at least 3 months of gefitinib or erlotinib 2:1 to afatinib or placebo[41]. PFS (3 months vs 1 month) and response rate (7% vs 0%) were increased with afatinib, but the primary endpoint of overall survival was not different. Only 37% of patients met the standard criteria for acquired resistance which includes previous treatment with a single agent EGFR TKI, and either a known sensitizing *EGFR* mutation or prior clinical benefit with an EGFR TKI, and documented systemic progression on EGFR TKI[42]. *Post hoc* subset analysis of this subgroup showed no differences from the overall study results.

To evaluate the hypothesis that continued EGFR inhibition is important after progression of disease on EGFR TKI (supported by some prospective and retrospective data[43]), there is a phase 3 trial evaluating continued afatinib plus chemotherapy versus chemotherapy alone (Lux Lung5) in patients who have progressed on single agent afatinib. This study is ongoing with a primary endpoint of overall survival (NCT01085136).

There is preclinical data to suggest that dual targeting of EGFR with both a second generation EGFR TKI and an EGFR monoclonal antibody may be especially effective at inducing shrinkage of *EGFR* mutant tumors that have developed resistant to erlotinib or gefitinib by way of acquired EGFR T790M[44]. An earlier phase 1/2 study of erlotinib and cetuximab did not show any significant activity in patients with acquired resistance to erlotinib[45]. A recently completed study looked at the combination of afatinib and cetuximab

in patients with advanced NSCLC who have progressed on erlotinib or gefitinib (NCT0109001). Confirmed partial responses were seen in 35% of patients, including 11/35 patients with EGFR T790M+ NSCLC[46]. Ninety percent of patients had PR or SD. This is the first targeted therapy in the setting of *EGFR* acquired resistance that has shown significant activity in T790M+ *EGFR* mutant tumors.

EGFR T790M specific inhibitors

Another strategy has been development of pyrimidine-based EGFR T790M inhibitors that have potent selectively for EGFR T790M and other mutant receptors rather than wild-type EGFR, with the goal of improving efficacy and reducing toxicity associated with wild type EGFR inhibition[47]. While the prototype compound initially reported has not been further developed, another compound is in development. CO-1686 (Clovis Oncology) is a covalent, irreversible small molecule that specifically inhibits mutant EGFR. A phase 1/2 trial of C0-1686 in patients with EGFR mutant advanced NSCLC who have received prior EGFR directed therapy is currently ongoing (NCT01526928).

Dual EGFR/VEGF inhibitors

XL647, vandetanib and BMS-690514 are all dual EGFR and VEGF kinase inhibitors that may prevent or overcome acquired resistance to EGFR TKIs by dual inhibition of these parallel signaling pathways. A phase 2 study of XL647 was performed in a patient population enriched for *EGFR* mutations in the first line setting and found a 28% partial response rate with all 8 patients with *EGFR* mutations experiencing tumor shrinkage (7 PR/ 1SD)[48]. A subsequent phase 2 study was completed in 41 patients with advanced *EGFR* mutated NSCLC who had either progressed on erlotinib or gefitinib or whose tumor contained a documented EGFR T790M mutation. The objective response rate was 3% indicating inadequate activity to warrant further study in this population[49].

Vandetanib has been extensively studied in advanced NSCLC although no current studies are ongoing. Combining vandetanib with chemotherapy has not led to significant improvements in overall survival as evidence by both the ZEAL and ZODIAC trials[50,51]. The ZEPHYR study evaluated vandetanib versus placebo in patients who have progressed on an EGFR TKI and found no difference in the primary endpoint of overall survival compared to placebo[52].

BMS-690514 was evaluated in a phase 2 study in patients with advanced NSCLC that were either TKI naïve or had progressed on EGFR TKI therapy and found a disease control rate of 39% and 22% in these two groups respectively[53]. A clinical trial of BMS-690514 versus erlotinib in patients with advanced NSCLC that have progressed on platinum therapy is ongoing, with no results yet presented (NCT00743938).

Dual EGFR/ALK inhibitors

AP26113 is a reversible, dual EGFR/ALK inhibitor that has selective activity against mutant EGFR including EGFR T790M compared to wild-type *EGFR* in pre-clinical studies [54]. AP26113 is being evaluated in a phase 1/2 trial currently, with a planned expansion cohort of patients with *EGFR* mutant lung cancer that have progressed on an EGFR TKI (NCT01449461).

Conclusions

EGFR tyrosine kinase inhibitors have dramatically altered our treatment paradigm for *EGFR* mutant lung cancers. However, their utility is limited by the universal development of

acquired resistance. Second generation EGFR TKIs have been developed with the intent to improve responses in the first line setting and to provide additional treatment options in the acquired resistance setting. Despite encouraging preclinical data suggesting efficacy, most of the second generations EGFR TKIs have not shown meaningful clinical activity after acquired resistance to gefitinib and erlotinib. The most promising clinical activity has been seen with dacomitinib and afatinib in patients with *EGFR* mutant lung cancer in the TKI naïve, first line setting. In the acquired resistance setting, there is promising preliminary data for afatinib in combination with cetuximab, although we await final results. Initial studies evaluating the most recently developed EGFR TKIs such as AP-26113 and CO-1686 are just beginning phase 1 trials.

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Table 1

EGFR TKIs and their receptor targets

Drug	EGFR	HER2	ERBB4	VEGFR	Other	Reversible
Erlotinib	x					x
Gefitinib	x					x
CO-1686	x					
Neratinib	x	x				
Afatinib	x	x				
Dacomitinib	x	x	x			
XL-647	x	x	x	x		x
Vandetanib	x			x	RET	x
BMS-690514	x	x	x	x		x
AP26113	x				ALK	x

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Table 2

First line clinical trials of 2nd generation TKI – unselected patients

Phase	Population (number)	Treatment	Primary endpoint	Results
Dacomitinib				
2	Advanced NSCLC, PD on chemo, no prior E (n=188)	E or Dacomitinib	PFS	Prelim results: PFS, ORR favored D over E[35]
3	Advanced NSCLC, PD on chemo, no prior E (n=800, ongoing)	E or Dacomitinib	PFS	None, actively recruiting patients
Vandetanib				
3	Advanced NSCLC, previously treated (n=534)	Peme +/− Vandetanib	PFS	Negative, no difference in PFS, although improved ORR (19% vs 8%)[49]
3	Advanced NSCLC, PD on 1st line platinum chemo (n=1391)	Doce +/− Vandetanib	PFS	PFS 4mo w/Vandetanib vs 3mo, no OS difference[50]
BMS-690514				
1/2	Advanced NSCLC, either E naïve or previous E w/ AR (n=60)	BMS-690514	DCR, safety	Prelim results: DCR 39% (11/28) in E naïve, 22% (7/32) E AR[53]
2	Advanced NSCLC, PD on 1st line platinum chemo (n=140)	BMS-690514 vs Erlotinib	PFS	None

Table 3

First line clinical trials of 2nd generation TKI – EGFR mutant pts

Phase	Population (no)	Treatment	Primary endpoint	Results
Dacomitinib				
2	Advanced NSCLC, no prior trtmt, EGFR+ or <10 pk yr hx (n=92)	Dacomitinib	PFS @ 4mo	Prelim results: In EGFR mutant, PFS 4mo 96%, mPFS 17mo[36]
Afatinib				
2	LUX Lung 2: EGFR mutant, TKI naïve (n=129)	Afatinib	ORR	ORR 62%, mPFS 14mo, mOS 24mo[39]
3	LUX Lung 3: EGFR mutant, TKI naïve, first line (n=345)	Afatinib vs cis/peme	PFS	Prelim results: mPFS afatinib 11.1 vs Chemo 6.9[40]
3	Lux Lung 6: EGFR mutant, TKI naïve, first line (n=330)	Afatinib vs cis/gem	PFS	None
XL-647				
2	Advanced NSCLC, at least one: Asian, female, light/no smoking hx (n=41)	XL-647	Tumor response by RECIST	Prelim results: 28% PR (10/36), 70% PR (7/10) in EGFR+, 36% SD [48]

Table 4

Clinical trials after acquired resistance – EGFR mutant pts

Phase	Population (no)	Treatment	Primary endpoint	Results
Neratinib				
2	Advanced NSCLC, previous G/E and either A)EGFR+ B)EGFR WT C)light smoker, TKI naïve (n=167)	Neratinib	ORR	Negative, ORR 2%[29]
Dacomitinib				
2	Advanced NSCLC, KRAS WT, PD on chemo and E (n=65)	Dacomitinib	ORR	Prelim results: 3/62 PR, 35/62 SD[34]
Afatinib				
3	LUX Lung 1: Adv. adeno w/ POD on platinum based chemo and G/E (n=585)	Afatinib vs Placebo	OS	Negative, OS endpoint not met, although PFS/OR/DCR improved with afatinib[41]
1/2	LUX Lung 4: Asian pts w/ POD on platinum based chemo and G/E (n=90)	Afatinib	Ph1: safety Ph2: ORR	Prelim results: mPFS 4.4mo, DCR 66%[55]
3	LUX Lung 5: Pts w/ progression on afatinib (n=900, ongoing)	Afatinib +/− Paclitaxel	OS	None, actively recruiting patients
1/2	Advanced NSCLC, clinically defined AR[42] (n=240)	Afatinib + Cetuximab	Ph1: safety Ph2: ORR	Prelim results: overall PR 35%, 11/35 PR in T790M+[46]
CO-1686				
1/2	Advanced EGFR+ NSCLC, previous EGFR TKI (n=70, ongoing)	CO-1686	Ph1: safety Ph2: ORR	None, actively recruiting patients
XL-647				
2	Advanced NSCLC, PD on G/E or +T790M (n=41)	XL-647	ORR	Negative, ORR 3%[49]
Vandetanib				
3	Advanced NSCLC, previous G/E and chemo (n=924)	Vandetanib vs placebo	OS	Negative, no difference in OS, 8.5mo (V) vs 7.8mo (P), although improved PFS, ORR w/ V[52]
BMS-690514				
1/2	Advanced NSCLC, either E naïve or previous E w/ AR (n=60)	BMS-690514	DCR, safety	Prelim results: DCR 39% (11/28) in E naïve, 22% (7/32) E AR[53]
AP-26113				
1/2	Ph1: all advanced malignancies Ph2: Several cohorts including advanced NSCLC w/ AR to EGFR TKI (n=130, ongoing)	AP 26113	Ph1: safety Ph2: ORR	None, actively recruiting patients