

Three generations of epidermal growth factor receptor tyrosine kinase inhibitors developed to revolutionize the therapy of lung cancer

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Abstract: Lung cancer, ~80%–85% of which is non-small-cell lung cancer (NSCLC), is the leading cause of cancer-related mortality worldwide. Sensitizing mutations in epidermal growth factor receptor (*EGFR*) gene (*EGFRm⁺*), such as exon 19 deletions and exon 21 L858R point mutations, are the most important drivers in NSCLC patients. In this respect, small-molecule EGFR tyrosine kinase inhibitors (TKIs) have been designed and developed, which launched the era of targeted, personalized and precise medicine for lung cancer. Patients with *EGFRm⁺* could achieve good responses to the treatment with the first-generation EGFR TKIs, such as erlotinib and gefitinib. However, most patients develop acquired drug resistance mostly driven by the T790M mutation occurring within exon 20. Although the second-generation EGFR TKIs, such as afatinib, dacomitinib and neratinib, demonstrated promising activity against T790M in preclinical models, they have failed to overcome resistance in patients due to dose-limiting toxicity. Recently, the third-generation EGFR TKIs have shown to be effective against cell lines and murine models harboring T790M mutations while sparing wild-type EGFR, which represents a promising breakthrough approach in overcoming T790M-mediated resistance in NSCLC patients. This article provides a comprehensive review of the therapy revolution for NSCLC with three generations of EGFR TKIs.

Keywords: lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitors, T790M mutation

Introduction

Lung cancer, ~80%–85% of which is non-small-cell lung cancer (NSCLC), is the leading cause of cancer-related mortality around the world.¹ Due to poor prognosis with traditional chemotherapy agents, the discovery of molecular changes that drive lung cancer leads to a dramatic shift in the therapeutic landscape of this disease. The epidermal growth factor receptor (EGFR) represents an important signaling pathway that regulates tumorigenesis, invasion and metastasis of tumor. The most important drivers in NSCLC patients are mutations in *EGFR* gene, which occur in ~10%–35% of NSCLC patients.^{2,3} The so-called sensitizing mutations in *EGFR* (*EGFRm⁺*) usually refer to exon 19 deletions and exon 21 L858R point mutations. In this respect, small-molecule EGFR tyrosine kinase inhibitors (TKIs) have been designed and developed for the targeted and personalized therapy selection on molecular characteristics of tumors while avoiding a “one-size-fits-all” chemotherapy approach.² Patients with *EGFRm⁺* could achieve good responses to the treatment with the first-generation EGFR TKIs, such as erlotinib and gefitinib.^{4,5} Unfortunately, despite initial benefit, most patients develop acquired resistance to them within 1 year, which is driven in ~60% of cases

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by a second-site *EGFR* point mutation, the T790M mutation occurring within exon 20.^{6,7} Although the second-generation *EGFR* TKIs, such as afatinib, dacomitinib and neratinib, demonstrated promising activity against T790M in preclinical models, they have failed in clinical trials due to dose-limiting toxicity.^{8–10} Recently, the third-generation *EGFR* inhibitors, including osimertinib, rociletinib and olmutinib, have been developed, which could more effectively target T790M while sparing wild-type *EGFR*.¹¹ These mutant-selective *EGFR* TKIs could represent a promising approach of overcoming T790M-mediated resistance in NSCLC patients. For example, osimertinib has been classed as a breakthrough compound for fast-track development and received its first global approval by the US Food and Drug Administration (FDA) in November 2015 for patients with metastatic *EGFR* T790M-positive NSCLC who had progressed on prior systemic therapy, including an *EGFR* TKI.¹²

To date, three generations of small-molecule *EGFR* TKIs have been designed and developed, whose formula, systematic name and structure are listed in Table 1. The purpose of this article is to provide a comprehensive review of the therapy revolution for NSCLC with these *EGFR* TKIs, from the early successes with the first-generation *EGFR* TKIs to the breakthrough in overcoming resistance with the second- and third-generation ones.

First-generation *EGFR* TKIs

Erlotinib

Erlotinib was the first FDA-approved *EGFR* TKI for the targeted therapy of NSCLC patients. In the Canadian phase III BR.21 trial, patients with stage IIIB or IV NSCLC who had received one or two chemotherapy regimen were randomized to erlotinib or placebo. The results demonstrated that the response rate was 8.9% in the erlotinib group and <1% in the placebo group ($P<0.001$). Progression-free survival (PFS) of erlotinib and placebo was 2.2 months and 1.8 months, respectively (hazard ratio [HR] =0.61, $P<0.001$). Overall survival (OS) of erlotinib and placebo was 6.7 months and 4.7 months, respectively (HR =0.70, $P<0.001$). This trial is the first clinical trial to show a significant improvement in OS comparing erlotinib to placebo.¹³

Gefitinib

The Iressa Pan-Asia Study (IPASS) randomized >1,200 untreated patients with stage IV NSCLC to compare first-line gefitinib to the combination of carboplatin and paclitaxel. The 12-month rates of PFS of gefitinib and carboplatin–paclitaxel were 24.9% and 6.7%, respectively. What is more,

for patients with *EGFR*m⁺, PFS was significantly longer among those who received gefitinib than among those who received carboplatin–paclitaxel (HR for progression or death =0.48, $P<0.001$), whereas for patients with negative *EGFR* mutations, PFS was significantly longer among those who received carboplatin–paclitaxel (HR for progression or death with gefitinib =2.85, $P<0.001$). This trial is the first trial to demonstrate that *EGFR* TKI is superior to chemotherapy as an initial treatment for NSCLC patients with *EGFR*m⁺.¹⁴ Similar results have been achieved in other trials, such as the First-SIGNAL trial from South Korea, the OPTIMAL trial from China and the EURTAC trial from Europe.^{15–17}

Icotinib

Icotinib is also an oral, small-molecule *EGFR* TKI for NSCLC, which is approved in China. A phase III, double-blind, non-inferiority trial (ICOGEN) compared icotinib to gefitinib in unselected Chinese patients with advanced NSCLC who had not responded to one or more platinum-based chemotherapy regimen. In this trial, patients were randomly assigned to either icotinib or gefitinib. The results demonstrated that icotinib was non-inferior to gefitinib in terms of PFS at 4.6 months vs 3.4 months, respectively. Thus, icotinib is also a treatment option for pretreated patients with advanced NSCLC.¹⁸

These studies confirmed that the first-generation *EGFR* TKIs were effective for patients with *EGFR*m⁺ NSCLC in the first-line setting.

Second-generation *EGFR* TKIs

After initial benefit, most patients develop resistance to the first-generation *EGFR* TKIs mostly driven by T790M mutation. Thus, the second-generation *EGFR* TKIs, such as afatinib, dacomitinib and neratinib, are designed to overcome the acquired resistance.

Afatinib

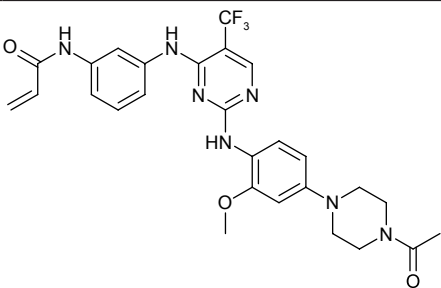
Afatinib (BIBW 2992), an aniline-quinazoline, is an irreversible *EGFR* TKI. In a phase I study, three patients with NSCLC achieved a durable partial response to afatinib, including two *EGFR*m⁺ patients.¹⁹ In the trial of LUX-Lung 1, patients with *EGFR*m⁺ NSCLC who had received a first-generation *EGFR* TKI and chemotherapy were randomized to either afatinib or placebo. PFS of afatinib and PFS of placebo were 3.3 months and 1.1 months ($P<0.0001$), respectively. Afatinib could be of some benefit to patients who have failed in previous *EGFR* TKI treatment.²⁰ Then, the drug was studied as a first-line treatment for *EGFR*m⁺ NSCLC

Table 1 Formula, systematic name and structure of small-molecule EGFR TKIs

Generic name	Trade name	Formula	Systematic name	Structure
Erlotinib	Tarceva®	C ₂₂ H ₂₃ N ₃ O ₄	<i>N</i> -(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine	
Gefitinib	Iressa®	C ₂₂ H ₂₄ ClFN ₄ O ₃	<i>N</i> -(3-chloro-4-fluoro-phenyl)-7-methoxy-6-(3-morpholin-4-ylpropoxy)quinazolin-4-amine	
Afatinib	Gilotrif®	C ₂₄ H ₂₅ ClFN ₅ O ₃	<i>N</i> -[4-[(3-chloro-4-fluorophenyl)amino]-7-[[[(3S)-tetrahydro-3-furanyl]oxy]-6-quinazolyl]-4-(dimethylamino)-2-butenamide	
Dacomitinib		C ₂₄ H ₂₅ ClFN ₅ O ₂	(2 <i>E</i>)- <i>N</i> -{4-[(3-chloro-4-fluorophenyl)amino]-7-methoxy-6-quinazolyl]-4-(1-piperidinyl)-2-butenamide	
Neratinib		C ₃₀ H ₂₉ ClN ₆ O ₃	(2 <i>E</i>)- <i>N</i> -[4-[[[3-chloro-4-[(pyridin-2-yl)methoxy]phenyl]amino]-3-cyano-7-ethoxyquinolin-6-yl]-4-(dimethylamino)but-2-enamide	
Osimertinib	Tagrisso™	C ₂₈ H ₃₃ N ₇ O ₂ ·CH ₄ O ₃ S	<i>N</i> -(2-{2-dimethylaminoethylmethylamino}-4-methoxy-5-[[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino]phenyl)prop-2-enamide mesylate salt	
Olmudinib		C ₂₆ H ₂₆ N ₆ O ₂ S	<i>N</i> -[3-({2-[4-(4-methylpiperazin-1-yl)anilino]thieno[3,2-d]pyrimidin-4-yl}oxy)phenyl]prop-2-enamide	

(Continued)

Table 1 (Continued)

Generic name	Trade name	Formula	Systematic name	Structure
Rociletinib		$C_{27}H_{28}F_3N_7O_3$	N-[3-[[2-[4-(4-acetylpiperazin-1-yl)-2-methoxyanilino]-5-(trifluoromethyl)pyrimidin-4-yl]amino]phenyl]prop-2-enamide	 The chemical structure of Rociletinib is a complex molecule. It features a central pyrimidine ring substituted with a trifluoromethyl group (CF3) at the 2-position and a prop-2-enamide group at the 4-position. The 5-position of the pyrimidine ring is linked via an amino group to a phenyl ring. This phenyl ring is further substituted with a prop-2-enamide group at the para position and a methoxy group (OCH3) at the meta position. The meta position of this phenyl ring is also linked via an amino group to another phenyl ring, which is substituted with a prop-2-enamide group at the para position. Finally, this phenyl ring is linked via an amino group to a piperazine ring, which has an acetyl group (CH3CO) attached to one of its nitrogen atoms.

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

in a phase II study (LUX-Lung 2). Overall, a response was noted in 79 (61%) of 129 patients. In all, 70 (66%) of the 106 patients with common exon 19 deletions and exon 21 L858R point mutations demonstrated a response, as did nine (39%) of 23 patients with less common EGFR mutations.²¹ Afatinib could significantly prolong PFS as compared with the pemetrexed plus cisplatin chemotherapy, at 11.9 months vs 6.9 months ($P < 0.001$), as first-line treatment for *EGFR*⁺ NSCLC patients in a global phase III study, LUX-Lung 3. Objective response rate (ORR) was also significantly higher with afatinib than that with chemotherapy (56% vs 23%, $P < 0.001$). Thus, afatinib was approved as the first-line treatment for advanced NSCLC patients with *EGFR*⁺.⁸

Neratinib

In vitro, neratinib showed activity against *EGFR*⁺ NSCLC cell lines, including ones harboring a T790M.²² However, a phase II trial demonstrated disappointing results with an ORR of 3% in patients with *EGFR*⁺ NSCLC and no responses in patients with wild-type EGFR, which resulted from insufficient bioavailability from diarrhea-imposed dose limitation.²³

Dacomitinib

Dacomitinib (PF-00299804) is another second-generation irreversible TKI.²⁴ A phase II study of dacomitinib in treatment-naïve advanced NSCLC patients with either *EGFR*⁺ or clinical characteristics associated with *EGFR*⁺ found an ORR of 53% and a median PFS of 11.5 months.²⁵ However, a phase III study (NCIC CTG BR.26) compared dacomitinib with placebo in patients with advanced NSCLC pretreated with cytotoxic chemotherapy and an EGFR-TKI failed to meet its primary objective of prolonging OS.²⁶ Thus, dacomitinib cannot be recommended for treatment of NSCLC patients previously treated with chemotherapy and an EGFR TKI.

Third-generation EGFR TKIs

So far, EGFR TKIs have been widely used in NSCLC patients. However, acquired resistance to most clinically available EGFR TKIs has been mediated by T790M. As mentioned earlier, although the second-generation EGFR TKIs show promising activity against T790M in vitro, they have failed in patients due to serious side effects. Thus, therapeutic strategies for NSCLC patients with the acquired resistance to EGFR TKIs mediated by T790M are still limited. More efforts should be focused on new-generation EGFR TKIs that could more effectively target T790M while sparing wild-type EGFR. Recently, a novel class of third-generation EGFR TKIs, such as osimertinib, rociletinib and olmutinib, has been designed and developed to overcome T790M-mediated resistance. For example, osimertinib received its first global approval by FDA in November 2015 for patients with metastatic *EGFR* T790M-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI.

Osimertinib

Osimertinib, also known as AZD9291, is a novel EGFR TKI developed by AstraZeneca, which shows 200-fold selectivity for T790M/L858R protein over wild-type EGFR.^{27,28} It has been classed as a “breakthrough” compound for fast-track development, having demonstrated perfect ORR in T790M-positive NSCLC patients who had progressed on a first-generation EGFR TKI.^{27,28} The efficacy of osimertinib for the treatment of patients with locally advanced or metastatic *EGFR*⁺ NSCLC has been investigated in several clinical trials. The phase I AURA trial was initiated to assess the safety and efficacy of osimertinib in patients with locally advanced or metastatic *EGFR*⁺ NSCLC who had documented disease progression while receiving a first- or second-generation EGFR TKI.²⁹ The result demonstrated that ORR was 51%. Of the 127 patients with confirmed *EGFR* T790M, osimertinib was associated with an ORR of 61%, while those with

no detectable *EGFR* T790M mutation (n=61) had an ORR of 21%. The median PFS was 9.6 months in *EGFR* T790M-positive patients and 2.8 months in *EGFR* T790M-negative patients. Based on these data, in April 2014, osimertinib was granted breakthrough therapy designation by the FDA for the treatment of patients with NSCLC and *EGFR* T790M mutation whose disease has progressed during treatment with a TKI. Osimertinib was further evaluated in patients with *EGFR* T790M-positive NSCLC and progression after *EGFR* TKI therapy in a phase II extension cohort of AURA and an additional phase II trial. Results from a data cutoff on November 1, 2015, for pooled analysis of two phase II studies showed that ORR was 66%, median duration of remission (DOR) was 12.5 months, median PFS was 11.0 months and the proportion of patients progression free at 12 months was 47.5%.³⁰ Thus, osimertinib received its first global approval on November 13, 2015, for patients with metastatic *EGFR* T790M-positive NSCLC who have progressed on, or after, *EGFR* TKI therapy in the USA. Now, several phase III trials are ongoing in evaluating osimertinib as second-line treatment in *EGFR* T790M-mutated NSCLC and first-line treatment for NSCLC with any *EGFR*m⁺.

Rociletinib

Rociletinib (CO-1686) is also a small-molecule, irreversible, mutant-selective third-generation *EGFR* TKI.³¹ A phase I/II study enrolled a total of 130 patients with *EGFR*-mutated NSCLC who had disease progression during previous treatment with an existing *EGFR* inhibitor. ORR among the 46 patients with T790M positive mutation was 59%, and the rate among the 17 patients with T790M negative mutation was 29%. The median PFS at the time of analysis was 13.1 months and 5.6 months for patients with and without T790M mutations, respectively. The results demonstrated that rociletinib was active in NSCLC patients with *EGFR*m⁺ associated with the T790M resistance mutation.³²

Olmutinib

In a phase I/II study of olmutinib (HM61713), another third-generation *EGFR* TKI, in patients with advanced NSCLC who had failed previous *EGFR*-TKIs, ORR was 58.8% and disease control rate was 97.1% in 34 patients with centrally confirmed T790M mutations.³³

Conclusion

Three generations of *EGFR* TKIs have revolutionized the therapy of NSCLC patients with *EGFR*m⁺. Despite great progression in this field, treatment of the molecularly selected patient poses novel challenges, such as emergence

of acquired resistance mostly mediated by T790M. Third-generation *EGFR* TKIs have been designed to overcome resistance through covalent binding to the Cys 797 residue of the enzyme, and they are effective against most clinically relevant *EGFR* mutants while sparing wild-type *EGFR*. However, the high dependence of three generations of *EGFR* TKIs on this particular interaction means that additional mutation of Cys 797 results in poor inhibitory activity, which leads to tumor relapse in initially responding patients.³⁴ In future, novel *EGFR* TKIs should be designed and developed for high inhibitory activities against the cysteine-mutated L858R/T790M/C797S *EGFR*. Even if a cure for advanced lung cancer still remains out of reach, we can hope that in the near future, lung cancer may be well controlled under the power of precision medicine in genetically defined tumors.

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Disclosure

The author reports no conflicts of interest pertaining to this review.

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