

Advances on EGFR mutation for lung cancer

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Abstract: Patients with advanced non-small-cell lung cancer (NSCLC) and somatic activating mutations of the tyrosine kinase (TK) domain of the *epidermal growth factor receptor* (EGFR) gene represent a biologically distinct disease entity that shows exquisite sensitivity to the reversible EGFR-TK inhibitors (TKIs) gefitinib or erlotinib. Phase III randomized studies have clearly demonstrated that a reversible EGFR-TKI is significantly superior in terms of response rate, progression-free survival and quality of life to platinum-based chemotherapy in advanced NSCLC patients who carry an activating EGFR mutation, thus resulting into a new standard of care for this biologically selected group of patients. Unfortunately, approximately one third of EGFR-mutated patients show primary resistance to gefitinib or erlotinib, whereas virtually all patients who initially benefit from treatment will eventually develop acquired resistance. Importantly, revealing the molecular mechanisms that underlie resistance to reversible EGFR-TKIs is key to the development of EGFR-targeting strategies with the potential to prevent, delay or overcome such resistance. Early results of clinical trials with irreversible EGFR-TKIs or dual combination strategies aiming to block EGFR-mediated signaling at different levels have shown encouraging results in EGFR-mutated patients pretreated or not with a reversible EGFR-TKI. Therefore, in the near future it is reasonable to hypothesize that EGFR-mutated NSCLCs could be treated with multiple lines of EGFR-targeting therapies beyond disease progression, limiting chemotherapy to selected cases of resistant disease. This evolving treatment scenario highlights once again how important is the identification of a single oncogenic “addiction” that functions as unique determinant of progression and survival of NSCLC.

Keywords: Epidermal growth factor receptor mutation; gefitinib-erlotinib; non-small cell lung cancer; tyrosine kinase inhibitors



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Introduction

Lung cancer is among the most commonly diagnosed cancers worldwide, representing the first cause of cancer-related death in both the U.S. and Europe (1,2). Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers, being often diagnosed at an advanced stage when treatment options are limited. First-line chemotherapy for NSCLC patients with advanced disease is generally platinum-based, yielding a median overall survival of 8-11 months (3). Unfortunately, the addition of a targeted agent to a platinum-based chemotherapy backbone either in combination regimens and or as sequential treatment has only marginally improved overall prognosis of patients with advanced disease (4-6).

Against this background, the recent recognition that certain genetic abnormalities play a major role in the oncogenic process of NSCLC, has allowed in some cases for appropriate selection of patients candidate to targeted therapies based on well-defined biological characteristics (7,8).

EGFR as a target in NSCLC

Since its identification in 1986, the epidermal growth factor receptor (EGFR) has emerged as a crucial factor for the development and growth of human malignancies, including lung cancer (9). In fact, EGFR signal transduction network plays an important role in multiple tumorigenic processes

such as proliferation of cancer cells, angiogenesis, and metastasization. Consistently, EGFR aberrant activation has been shown to be prognostic in NSCLC, which provided a solid rationale for the development of EGFR-targeting strategies for NSCLC (10).

EGFR belongs to the Erb family of transmembrane receptor tyrosine kinases which includes also HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4). Upon ligand binding, EGFR undergoes homo- or hetero-dimerization with other receptors of the same family with subsequent autophosphorylation and activation of the intracellular tyrosine-kinase (TK) domain, recruitment of second messengers and intensification of the anti-apoptotic signaling (11). Interestingly, no ligand has been identified for the HER2 orphan receptor while no kinase activity has been documented for HER3, which allow both HER2 and HER3 to be actively involved in EGFR-mediated signaling as preferred hetero-dimerization partners of EGFR itself. There are several ways through which EGFR can be aberrantly activated including receptor overexpression, gene amplification and gene mutation (10). However, because of its crucial role as oncogenic determinant, the presence of an activating (meaning ligand-independent activation of the TK) EGFR mutation in NSCLC carries major therapeutic implications. The present review will focus on the most recent acknowledgements on *EGFR* gene mutations in NSCLC, also discussing their potential applicabilities in the clinic.

EGFR gene mutations in NSCLC

In 2004, the identification of somatic mutations of the *EGFR* gene in NSCLC has led to the recognition of a biologically distinct disease entity which has been termed ‘oncogene addicted’ to reflect its dependence on EGFR-mediated pro-survival signalling (12-14). Consistently, EGFR-mutated NSCLC patients represents a subgroup which seems to experience a more indolent course of disease irrespective of treatment (15,16). However, the clinical relevance of detecting an activating EGFR mutation in NSCLC as assessed by *DNA* gene sequencing cannot be understated given the exquisite sensitivity that EGFR-mutated NSCLCs show to the ‘reversible’ EGFR-TK inhibitors (-TKIs) gefitinib or erlotinib (to which we will also refer to as ‘first-generation’ EGFR-TKIs) (7), which allows patients to experience a particularly extended survival in the presence of EGFR-TKI treatment, thus in contrast with the historical data reported for NSCLCs when considered as a single disease entity (3).

Importantly, although the incidence of EGFR mutations is higher in patients with certain clinical characteristics such

as never smoking history, Asian ethnicity (where they can be found in up to 30% of advanced NSCLCs as opposed to 15% for the western population), female sex and adenocarcinoma histology (17), it is not possible to rule out the possibility of an EGFR mutation solely on the basis of clinical characteristics (18-22). This concept is the basis for testing for an EGFR mutation all NSCLC tissues (preferentially adenocarcinoma) irrespective of clinical characteristics in order not to exclude from a very active targeted treatment patients who are discovered to carry an EGFR mutation.

Specific activating EGFR mutations are either short, in-frame nucleotide deletions, in-frame duplications/insertions or single-nucleotide substitutions clustered around the adenosine triphosphate (ATP) binding pocket of the TK domain (23). To date, in-frame deletions in exon 19 around the LeuArgGluAla motif (del19) at residues 746-750 (the most common being del E746_A750) and exon 21 Leu858Arg (L858R) point mutation are the best characterized mutations, together representing 85-90% of all EGFR mutations in NSCLC (23). The frequency of classic EGFR mutations seem to differ according to ethnic backgrounds. In fact, EGFR genotyping from large prospective studies have shown a higher frequency of del19 mutation compared with L858R for European patients (18,22), whereas the incidence of del19 mutation appear to be only slightly superior in Asiatic patients (19-21). Interestingly, clinical data seem to indicate that patients harboring the del19 mutation are more susceptible to the activity of a reversible EGFR-TKI compared to those carrying the L858R mutation (24). However, the molecular mechanisms underlying this apparent inter-mutation discrepancy in drug sensitivity are not clearly understood, possibly being related to a higher EGFR-dependence of the tumor owing to common association of del 19 mutations with EGFR amplification (25). Moreover, it cannot be excluded that gefitinib or erlotinib possess a different inhibitory effect on del19 mutation favoring the erlotinib, as suggested by biochemical studies (26).

Nevertheless, activating EGFR mutations other than del19 or L858R have been described, usually defined as ‘other uncommon mutation’. However, their ability to predict sensitivity to a reversible EGFR-TKI is less striking compared with del 19 or L858R mutations. A recent report exploring the sensitivity of uncommon EGFR mutations to gefitinib or erlotinib showed that two types of uncommon EGFR mutations, namely point mutations in position Gly719 of exon 18 (G719) and Leu861Gln mutation in exon 21 (L861) may have unaltered sensitivity to a reversible EGFR-TKI, being associated with clinical responses in approximately half of cases (27). On the other hand, exon 20 insertions have

Table 1 Phase III studies comparing gefitinib or erlotinib versus a standard platinum-based doublet in the first line treatment of advanced NSCLC patients selected based on the presence of EGFR mutation

Study	EGFR-TKI	No. of patients	Type of EGFR mutation	Population	RR (EGFR-TKI vs. chemotherapy)	PFS (EGFR-TKI vs. chemotherapy)	OS (EGFR-TKI vs. chemotherapy)	Quality of life (EGFR-TKI vs. chemotherapy)
WJTOG 3405 (19)	Gefitinib	172	del19 or L858R	Asiatic	62.1% vs. 32.2% [†] P<0.0001	9.2 vs. 6.3 months P<0.0001	Not available	Not assessed
NEJ002 (20,34)	Gefitinib	228	Any [‡]	Asiatic	73.7% vs. 30.7% P<0.001	10.4 vs. 5.5 months P<0.001	30.5 vs. 23.6 months P=0.31	Significant less deterioration [§]
OPTIMAL (21)	Erlotinib	154	del19 or L858R	Asiatic	83% vs. 36% P<0.0001	13.1 vs. 4.6 months P<0.0001	Not available	Significant improvement [¶]
EURTAC (22)	Erlotinib	173	del19 or L858R	Caucasian	58% vs. 15% P<0.05	9.7 vs. 5.2 months P<0.0001	Not available	Not available

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; No., number; OS, overall survival; PFS, progression-free survival; RR, response rate. [†]Only patients with measurable disease considered. [‡]Excluded the T790M resistant mutation. [§]As assessed by a Care Notebook (QOL Res 2005, <http://homepage3.nifty.com/care-notebook/>) questionnaire. [¶]As assessed with the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and the Lung Cancer Subscale (LCS).

been associated with primary resistance to EGFR-TKIs (28). However, owing to their rarity, it is not possible to draw definitive conclusions on the true relationship between uncommon EGFR mutations and sensitivity to gefitinib or erlotinib and even case reports may orientate in the decision making process of patients with uncommon activating mutations of the *EGFR* gene (29).

EGFR gene mutations and sensitivity to gefitinib or erlotinib

Gefitinib or erlotinib are orally bioavailable anilinoquinazoline small molecules that act by selectively and reversibly blocking the phosphorylation of the EGFR-TK domain through competition with ATP for binding at the active site of EGFR itself (30). Early phase III studies comparing gefitinib or erlotinib to placebo in chemotherapy pretreated NSCLCs showed a survival improvement for individuals receiving the EGFR-TKI (31,32) which, in case of gefitinib, was statistically significant only for patients with certain clinical characteristics such as never-smoking history and Asian ethnicity (31). However, only one of these two trials, namely the BR.21 study, showed for erlotinib a statistically significant improvement in overall survival (OS) for the whole population (6.7 months versus 4.7 months, respectively, HR =0.70, P<0.001). Therefore, based on these data, erlotinib was granted approval by American and European regulatory agencies for use as second or third-line therapy after failure of cytotoxic chemotherapy.

Nevertheless, since their identification, activating *EGFR* gene mutations have emerged as the most important predictor of response to reversible EGFR-TKIs (12-14). From that moment on, several retrospective and prospective studies confirmed that patients carrying an EGFR mutation were particularly sensitive to a first-generation EGFR-TKI, with responses observed in up to 90% of cases (33). Recently, four large phase III trials comparing a reversible EGFR-TKI to standard platinum-based chemotherapy in untreated advanced NSCLCs biologically selected for the presence of an activating EGFR mutation clearly stated the superiority of gefitinib or erlotinib over chemotherapy in terms of response rates (RR) and progression-free survival (PFS) (*Table 1*) (19-22). Also, as expected, gefitinib and erlotinib were associated with a significantly lower incidence of grade ≥ 3 adverse events. Notably, the fact that OS was not statistically in favor of gefitinib or erlotinib does not come as a surprise given the high rate of cross-over to an EGFR-TKI in the experimental arm at the time of disease progression. In addition, the particularly long median survival (>24 months) experienced by EGFR-mutated patients treated with a reversible EGFR-TKI might have led to miscalculation of the optimal sample size required to detect a statistically significant difference in survival (35).

At the present time, no head-to-head randomized comparison exists between gefitinib and erlotinib for EGFR-mutated advanced NSCLCs. However, although preclinical studies have shown a differential sensitivity to gefitinib or erlotinib according to the type of activating EGFR mutation expressed by the tumor (del19 or L858R) (26), indirect

Table 2 Known mechanisms of either primary or acquired resistance to gefitinib or erlotinib in advanced NSCLC patients with activating *EGFR* gene mutations

Mechanisms of resistance
Primary
Exon 20 insertions (42,43)
T790M mutation (48,49)
HGF overexpression (52)
Acquired
Secondary T790M mutation (44-47)
Non-T790M secondary EGFR mutation (46,50,51)
<i>MET</i> gene amplification (47,53)
PI3KCA mutation (54)
Histologic change from NSCLC to SCLC (54)
HGF overexpression (52,55)
IGF-1R hyperphosphorylation (56)
EGFR, epidermal growth factor receptor; HGF, hepatocyte growth factor; IGF-1R, insulin-like growth factor-1; NSCLC, non-small cell lung cancer; PI3KCA, phosphatidylinositol 3-kinase catalytic subunit; SCLC, small cell lung cancer.

evidence suggests that it is unlikely that this difference would translate into a clinically meaningful benefit in favor of one of the two agent (*Table 1*) (19-22). Interestingly, a recent randomized phase III study compared a new reversible EGFR-TKI, icotinib, to gefitinib in chemotherapy pretreated advanced NSCLCs showing comparable efficacy in the EGFR-mutated subgroup of patients (36).

Importantly, if EGFR-mutated patients benefit much from first-line treatment with gefitinib or erlotinib, the replacement of chemotherapy with a reversible EGFR-TKI as front-line therapy in biologically unselected patients with unknown EGFR mutation status is associated with a worse clinical outcome in terms of both PFS and OS (37,38). Moreover, selection of patients candidate to gefitinib or erlotinib according to clinical characteristics known to be associated with enrichment for the presence of an activating EGFR mutation is per se not sufficient to identify individuals who benefit the most from up-front therapy with a reversible EGFR-TKI (39,40). This question was matter of the IPASS and First-SIGNAL trials in which gefitinib was compared with standard chemotherapy in East-Asian advanced NSCLC patients with adenocarcinoma histology who were only (First-SIGNAL) or mostly (IPASS) never smokers. Although in both studies gefitinib was associated with a significant improvement in the primary PFS endpoint (HR =0.74, $P<0.0001$ and HR=0.81, $P=0.044$, for IPASS and First-Signal respectively), this benefit was shown to be driven by the high proportion of EGFR-mutated patients present in the studies population, since the

analysis of EGFR wild type patients showed a significantly longer PFS in favor of chemotherapy.

These data strongly support the use of a reversible EGFR-TKI in EGFR-mutated advanced NSCLC patients and allowed recent approval of gefitinib by the European Medicines Agency with this indication. As for erlotinib, it is likely that its current indication will soon be extended to include also treatment-naïve patients with activating EGFR mutations.

Mechanisms of resistance to gefitinib or erlotinib

Unfortunately, approximately 20% to 30% of EGFR-mutated patients do not undergo tumor shrinkage on a first generation EGFR-TKI (19-22,39,40). Moreover, virtually all EGFR-mutated patients who initially benefit from gefitinib or erlotinib eventually develop progressive disease, usually after approximately a year since treatment initiation. Since no standard treatment exists for EGFR-mutated patients who progress while on a reversible EGFR-TKI, strict criteria for definition of acquired resistance have been proposed for better interpretation of clinical trials investigating novel agents in this setting (41). Against this background, the identification of the molecular mechanisms that underlie either primary or acquired resistance to gefitinib or erlotinib is of crucial importance in order to prevent, delay or overcome resistance to treatment. To date, a few mechanisms of resistance to reversible EGFR-TKIs have been identified (*Table 2*). Preclinically, primary resistance has been associated with in-frame insertion mutations in exon 20 (42). Consistent with these data, most patients with tumors harboring exon 20 insertions have been shown to be resistant to gefitinib (43). As for acquired resistance, in approximately 50% of patients this can be attributed to the occurrence of a secondary threonine-to-methionine missense mutation in codon 790 (T790M) in exon 20 of the *EGFR* gene, which is located in the “critical” catalytic region of the ATP binding pocket of the EGFR-TK domain (44-47). The way through which the T790M mutation induce resistance to gefitinib or erlotinib is thought to be due to an increased binding affinity between EGFR and ATP rather than to a decreased affinity between EGFR and EGFR-TKI (57). Nevertheless, recent evidence suggests that the T790M mutation might pre-exist in minor clones in almost all reported cases of T790M-related acquired resistance, becoming evident during exposure to a reversible EGFR-TKIs as a result of evolutionary selection during treatment (58). Importantly, a poorer clinical outcome is usually experienced by patients with pre-treatment T790M compared with those without it (58). However, an interesting prospective clinical study suggested that EGFR-mutated patients with

T790M-related acquired resistance may have a more favorable prognosis as opposed to non-T790M resistant patients, which might have important clinical implications for the design of clinical trials in this setting (59). Notably, although extremely rare, T790M mutations may exist as major clones irrespective of EGFR-TKI administration in certain patients, thus being implicated also in primary resistance (48,49). More recently, three other less common secondary mutations have been identified as 'de novo' alterations in patients with acquired resistance to first generation EGFR-TKIs, namely the D761Y (exon 19), L747S (exon 19) and T854A (exon 21) mutations (46,50,51).

On the other hand, amplification of the MET proto-oncogene, which encodes a transmembrane TK receptor for the hepatocyte growth factor (HGF) and is involved with invasion, metastasis and angiogenesis in tumors, has been implicated in approximately 20% of the cases of acquired resistance to gefitinib and erlotinib (47,53). MET amplification causes resistance through activation of HER3, which in turn sustains the activity of the phosphatidylinositol 3-kinase (PI3K)/Akt downstream signalling pathway (47). Therefore, even with gefitinib inhibiting the phosphorylation of HER3 by EGFR, the proliferation signal is not inhibited because of the maintenance of the phosphorylation of HER3 by MET. Interestingly, similarly to the T790M mutation, *MET* gene amplification might be the result of selection of minor clones of pre-existing MET amplified tumor cells becoming dominant during exposure to an EGFR-TKI (52). Occasionally, resistant tumors with MET amplification may have a concurrent secondary T790M mutation (53,59).

A recent study identified mutations in the catalytic subunit of PI3K and phenotypic change into small cell lung cancer (SCLC) as two other mechanism of acquired resistance to reversible EGFR-TKIs in EGFR-mutated patients (54). Intriguingly, the latter mechanism might have important clinical implications since it implies that a rebiopsy at the time of progression would result into significant change in disease management. However, it is still not known whether this phenotypic change reflects the selection of a population of SCLC from a histologically mixed tumor following eradication of the majority of NSCLC clones. Even more intriguingly, EGFR mutations are maintained in SCLCs arising in EGFR-TKIs resistant patients, although the relevance of this phenomenon is uncertain given that EGFR-mutated SCLCs do not seem to be addicted to EGFR pro-survival signalling (60).

Finally, HGF overexpression has been advocated as another possible mechanism of acquired resistance (52,55), probably acting by inducing downstream signal activation independently of HER3

or EGFR (55). Notably, HGF overexpression is likely to be implicated also in primary resistance to a reversible EGFR-TKI in patients with activating *EGFR* gene mutations (52).

In conclusion, these proposed mechanism of resistance, strongly encourage the use in the clinic of certain strategies to prevent/overcome resistance to reversible EGFR-TKIs in advanced NSCLC patients with activating *EGFR* gene mutations. Among these, the use of irreversible EGFR-TKIs or combination regimens of an EGFR-TKI with a MET-inhibitor appear to be the most appealing ones.

Irreversible EGFR-TKIs

Similarly to gefitinib or erlotinib, irreversible EGFR-TKIs are anilinoquinazoline inhibitors that, however, unlike them, irreversibly bind EGFR to the amino acid position 797 which enables blockade of EGFR kinase activity even in the presence of an EGFR T790M mutation (61-63). In addition to irreversible binding, simultaneous blockade of two or more members of the EGFR family represents another key feature through which these agents might prove clinically active in delaying/preventing resistance to first-generation EGFR-TKIs.

The dual irreversible EGFR/HER2 inhibitor afatinib (BIBW 2992) is among the most promising drugs for use in the setting of gefitinib- or erlotinib-resistant NSCLCs. Recently, a large randomized phase IIb/III trial comparing afatinib versus placebo was conducted in advanced adenocarcinomas of the lung who had progressed after ≤ 2 lines of chemotherapy (including at least one platinum-based regimen) and ≥ 12 weeks of treatment with gefitinib or erlotinib (64). Interestingly, afatinib showed signs of activity by significantly prolonging PFS over placebo in this population of patients with clinically acquired resistance to a reversible EGFR-TKI (3.3 months versus 1.1 months, respectively, HR =0.38, $P < 0.0001$) (64). More importantly, this benefit was particularly evident when the analysis was restricted to key subgroup populations that were likely to be enriched for the presence of EGFR mutations such as those who had experienced prior response or treatment duration ≥ 48 weeks with a reversible EGFR-TKI (4.4 months versus 1.0 month, respectively, HR =0.28) (65).

More recently, afatinib was tested in combination with the anti-EGFR monoclonal antibody cetuximab, based on the solid preclinical background that this combination would overcome resistance to gefitinib or erlotinib in EGFR-mutated NSCLCs (66,67). Crucial prerequisites for trial participation were the presence of EGFR-mutated tumors with clinically acquired resistance to gefitinib or erlotinib (stable disease ≥ 6 months or prior response to gefitinib or erlotinib) and acquisition

of tumor tissue at baseline for molecular analysis. Of note, out of the 47 patients so far enrolled, the afatinib/cetuximab combination reported a RR of 40% with an overall disease control rate (RR + stable disease) of 92% (67). Importantly treatment activity seemed to be independent of the presence of the T790M mutation.

Current areas of research of afatinib in advanced NSCLC include its use in EGFR-mutated and gefitinib or erlotinib-naïve patients where a RR of 61% with an outstanding median PFS of 14 months was observed in a recently conducted phase II study (68). Also, two relevant phase III studies are currently being run in order to compare afatinib with platinum-based chemotherapy in EGFR-mutated advanced adenocarcinomas of the lung (33).

Dacomitinib (PF-00299804) is another irreversible EGFR-TKI under clinical testing for advanced NSCLC, which acts also as inhibitor of other EGFR family members, namely HER2 and HER4. As monotherapy in clinically (adenocarcinoma, never or light smokers) or biologically (presence of EGFR mutation) selected treatment-naïve advanced NSCLC patients it showed a RR of 45% (69). More importantly, in a subset analysis of 29 evaluable patients with EGFR-mutation positive disease, 51% of responses were observed, including one case of exon 20 insertion, and some degree of tumor shrinkage was observed overall in >90% of EGFR-mutated patients (69).

Currently a double-blind, randomized phase III study is being conducted in chemotherapy-pretreated advanced NSCLC to compare dacomitinib to erlotinib, the primary endpoint being PFS (70). Notably, collection of tissue samples is mandatory for study inclusion, this in order to molecularly characterized whether exists a group of patients (iEGFR mutated or not) who derive more benefit from dacomitinib than from erlotinib.

MET-inhibitors

Importantly, because MET amplification and T790M mutation often occur in the same patient, probably the best strategy is to combine the second-generation irreversible EGFR-TKIs with MET inhibitors. Preclinically, in MET amplified NSCLC cell lines treatment resistance could be suppressed by the addition of erlotinib to a MET inhibitor (71). There are several ways to inhibit the MET signaling pathway, including anti-MET antibodies, inactivation of MET ligand, namely the hepatocyte growth factor (HGF) or inhibition of MET kinase activity. Currently, the anti-MET monoclonal antibody MetMab and the MET-TKI tivantinib have been tested in randomized phase II studies of chemotherapy pretreated advanced NSCLCs,

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which were hypothesis-generating for identifying biomarkers of sensitivity to MET inhibition such as MET expression by immunohistochemistry and *MET* gene copy number as assessed by fluorescence in situ hybridization (72,73). However none of the ongoing studies with these agents has been thought for the EGFR-mutated NSCLC population undergoing resistance to a reversible EGFR-TKI.

Conclusions

EGFR-mutated NSCLC is a totally distinct disease entity whose EGFR “addiction” is maintained despite progression and/or prior exposure to a first-generation EGFR-TKIs (67,74,75). Therefore, therapeutic advances beyond gefitinib and erlotinib should keep focusing on EGFR blockade, possibly by means of revealing novel mechanisms of EGFR-interference or biological combinations of EGFR-targeting agents. Future scenarios include the possibility to develop therapeutic strategies that can delay further the onset of treatment resistance to EGFR-TKIs such as covalent pyrimidine EGFR inhibitors (76). These agents are 30 to 100-fold more potent against EGFR T790M, and up to 100-fold less potent against EGFR wild type, thus possibly resulting in greater efficacy and better tolerability compared with quinazoline-based inhibitors such as gefitinib, erlotinib or afatinib. To conclude, in recent years the rapid clinical development of EGFR targeting drugs for EGFR-mutated NSCLC represents a proof of concept of how important can be the discovery of a target to which the tumor is addicted for proliferation and survival. Against this background only rationally designed clinical trials can help research move faster toward a personalized therapeutic approach based on patients’ biological characteristics.

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