Review Article

EGFR first- and second-generation TKIs—there is still place for them in *EGFR*-mutant NSCLC patients

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Abstract: Identification of epidermal growth factor receptor (EGFR) as a molecular target has radically changed the treatment of metastatic non-small cell lung cancer (NSCLC) from standard chemotherapy to personalized, targeted therapy. First-, second- and third-generation EGFR tyrosine kinase inhibitors (TKIs) are now available for the treatment of EGFR-mutant NSCLC patients. This review will focus on the clinical development of first- and second-generation EGFR TKIs. We will emphasize on essential points like the head-to-head comparison among EGFR TKIs, their activity on brain metastases, mechanisms of resistance, as well as their combination with anti-angiogenic compounds, other targeted therapies, or immunotherapy. The efficacy of first- and second-generation EGFR TKIs in early-stage *EGFR*-mutant NSCLC will be also finally reviewed.

Keywords: Gefitinib; erlotinib; icotinib; afatinib; dacomitinib; epidermal growth factor receptor (EGFR); non-small cell lung cancer (NSCLC)

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Introduction

The discovery of somatic mutations in the tyrosine kinase (TK) domain of epidermal growth factor receptor (EGFR) was a paradigm shift in the understanding of the relevance of lung cancer molecular biology to therapeutic strategy and identified a subset of patients with a unique susceptibility to EGFR tyrosine kinase inhibitors (TKIs) (1). Protein TK gene families are regulators of cell proliferation, metabolism, migration, differentiation, and survival. Receptor tyrosine kinases (RTKs) are transmembrane proteins known to have a ligand-controlled TK activity. The EGFR family consists of four members: EGFR (HER1, ErbB1), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4) (2). Under physiological conditions, the EGFR family members bind ligands on their extracellular ligand-binding domains, promoting homo- and hetero-dimerization among them, and consequently activating their intracellular TK domains (3). This process induces activation of signaling pathways, such as phosphatidylinositol 3-kinase (PI3K)/AKT, Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3), and Ras/mitogen-activated protein kinase (MAPK) and stimulates downstream components involved in cell proliferation, cell cycle progression, survival and motility (4,5).

EGFR is a frequently over-expressed and aberrantly

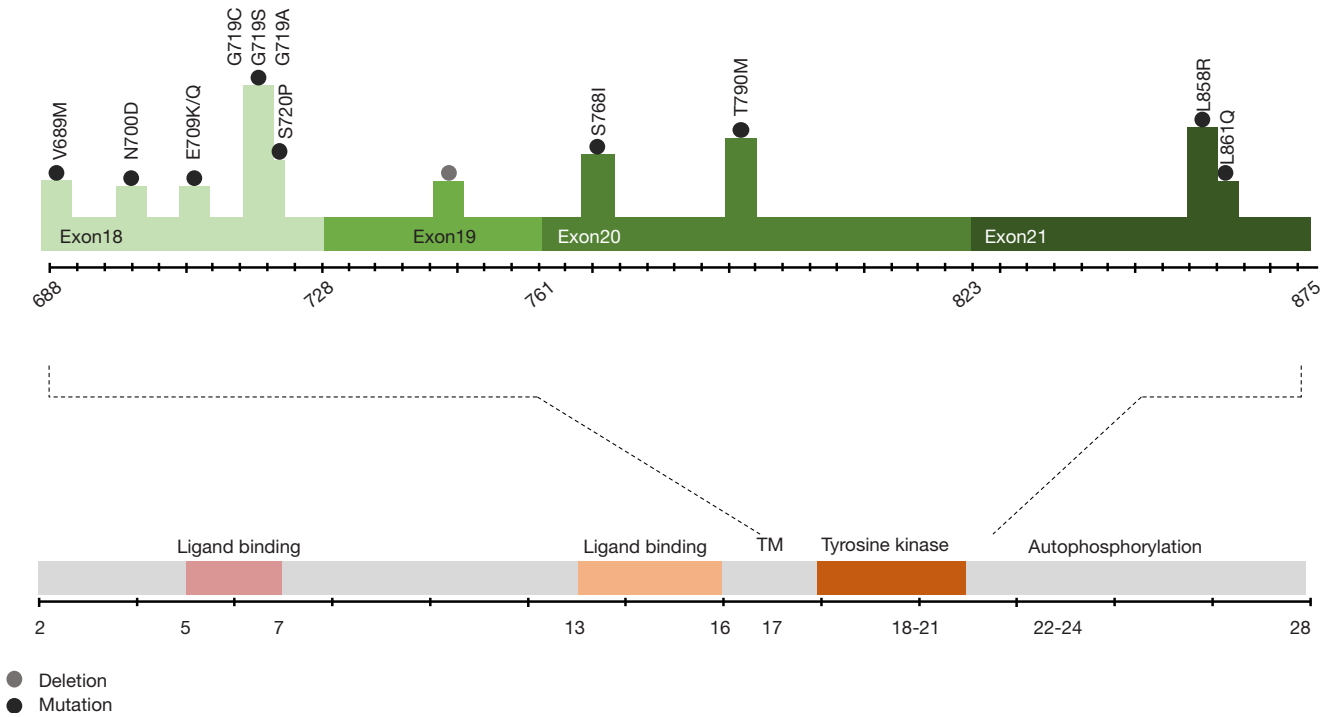

Figure 1 Schematic view of EGFR and key domains, with an expanded view of the TK domain encoded by exons 18–21 (amino acids 688–875). EGFR, epidermal growth factor receptor; TK, tyrosine kinase; TM, transmembrane.

activated trans-membrane protein in non-small cell lung cancer (NSCLC) patients, described for the first time in 2004 (4,6,7). *EGFR* mutations are more often detected in females and never-smokers (1). Activation of EGFR can occur through mutations, deletions, and amplifications, in sequences that code for the TK domain. Furthermore, altered EGFR protein or ligand expression can lead to constitutively active downstream signaling (8). Mutations in the kinase domain of EGFR cluster in exons 18–21, around the adenosine triphosphate (ATP)-binding pocket of the enzyme (*Figure 1*). Of all patients with *EGFR* mutations, 90% have in-frame exon 19 deletions or exon 21 missense mutations (9,10). First-generation and second-generation EGFR TKIs have more than doubled progression-free survival (PFS) for patients with NSCLC with actionable *EGFR* mutations, in comparison with chemotherapy. Also, they have improved objective response rates (ORRs), duration of response, quality of life and decreased treatment-related toxicity.

In the present review, we will summarise the results of the most critical studies with first- and second-generation EGFR inhibitors, highlighting those who have led to their regulatory approval. Mechanisms of resistance, activity on brain metastases, combinatorial therapies as well as the efficacy of these compounds in early-stage disease will be thoroughly reviewed.

First-generation EGFR TKIs

First-generation EGFR TKIs (gefitinib, erlotinib and icotinib) reversibly bind to EGFR and inhibit the binding of ATP to the TK domain. This block hampers cell proliferation, ultimately leading to cell death (11). Gefitinib and erlotinib, are globally approved for the treatment of *EGFR*-mutant NSCLC patients while icotinib is approved in China.

Gefitinib

The drug development history of gefitinib (ZD1839, Iressa, AstraZeneca Inc.; London, UK) has been complicated. It became available as the first small TKI against EGFR, in 2002 in Japan for the treatment of advanced NSCLC, before the discovery of activating mutations in the

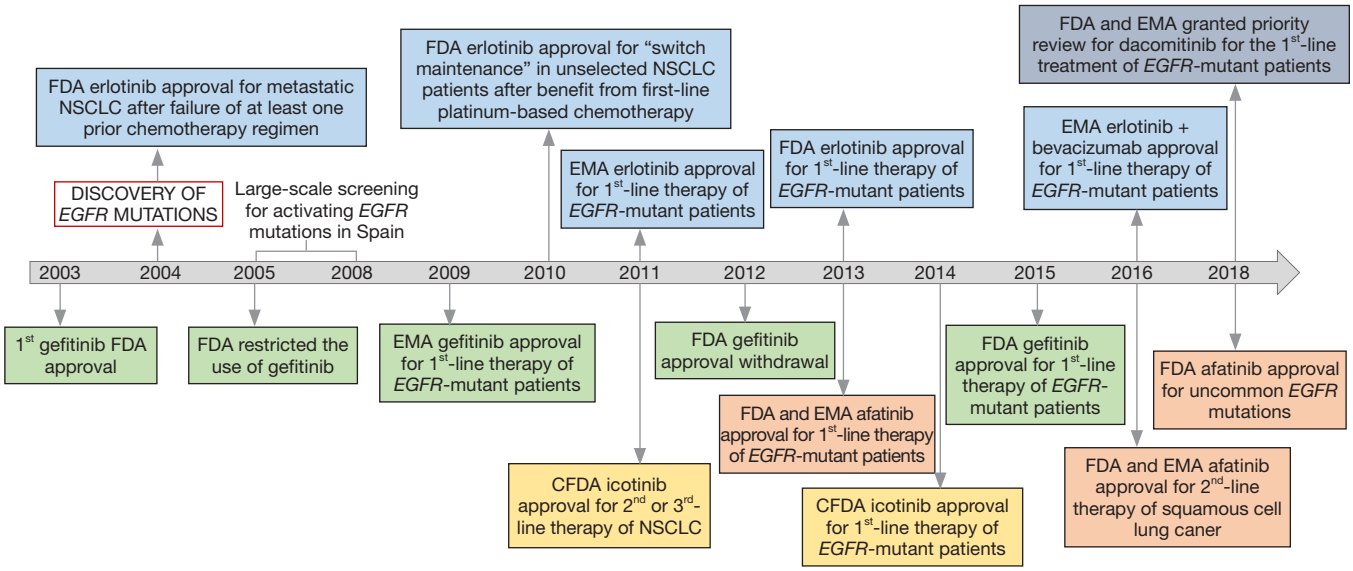

Figure 2 Regulatory approvals of first- and second-generation EGFR TKIs through the time. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

EGFR kinase domain. In May 2003, gefitinib received accelerated U.S. Food and Drug Administration (FDA) approval as monotherapy for advanced stage NSCLC patients after failure of both platinum-based and docetaxel chemotherapies (12) (*Figure 2*). The approval was based on an ORR of around 15% in this setting, as shown in two phase II clinical trials, the IRESSA Dose Evaluation in Advanced NSCLC (IDEAL)-1 and 2 (13,14). However, in June 2005, FDA restricted the use of gefitinib only for NSCLC patients who were already receiving and benefited from the drug or for new patients included in clinical trials with an Institutional Review Board approval before June 2005. Finally, FDA withdrew gefitinib approval in April 2012 (*Figure 2*). These regulatory approval changes were due to the negative results of three phase III clinical trials (IBREESE, ISEL, and INTEREST) (12,15,16), after IDEAL-1 and 2, in which gefitinib failed to demonstrate its benefit in previously treated NSCLC patients. In 2004 the IRESSA NSCLC Trial Assessing Combination Treatment (INTACT-1 and 2) phase III clinical trials were carried out (17,18). INTACT-1 and 2 evaluated the effect of gefitinib in the first-line setting combined with chemotherapy. Both studies were negative.

After the discovery of activating *EGFR* mutations in 2004 (4,6,7), gefitinib was tested in many phase III clinical trials until receiving FDA approval on 13th of July 2015 for the first-line treatment of *EGFR*-mutant patients. Earlier, in 2009, the European Medicines Agency (EMA) approved gefitinib for the same indication (*Figure 2*). At the beginning of the discovery of *EGFR* mutations, the scientific community was confused, and studies were claiming that high EGFR expression, rather than *EGFR* mutations, is relevant for the efficacy of EGFR TKIs (19,20). We were among the first to perform a large-scale screening for activating *EGFR* mutations in Spain, from 2005 to 2008 (1). Rosell's group described that *EGFR* mutations are more frequent in women, never smokers and lung adenocarcinoma patients, while median PFS and OS to first-line erlotinib, the other first-generation EGFR TKI, were 14 and 27 months, respectively (1). From 2006 to 2007, the first line iressa versus carboplatin/paclitaxel in Asia [Iressa Pan-Asia Study (IPASS)] study was conducted and evaluated gefitinib versus platinum-based chemotherapy as first-line therapy in a clinically selected Asiatic population (21). The study demonstrated the superiority of gefitinib especially for the population carrying *EGFR* mutations (21,22) (*Table 1*). Similar results were shown in two phase III Japanese studies (NEJ002 and WJTOG3405) (23,25,35) and a phase III Korean study (36), all conducted in NSCLC patients carrying *EGFR* mutations (*Table 1*). Together with the IPASS, NEJ002 and WJTOG3405 are considered as key clinical trials for the FDA and EMA approval of gefitinib for the first-line therapy of *EGFR*-mutant NSCLC (12). In the European Union, the Iressa Follow-Up Measure (IFUM)

Table 1 Selected trials of gefitinib, erlotinib, icotinib and afatinib, compared to chemotherapy as first-line therapy for *EGFR*-mutant NSCLC patients

Study name	Design	Population (N of patients)	Median PFS (months)	Median OS (months)	ORR (%)	Ref.
IPASS	Gefitinib *vs.* carboplatin-paclitaxel in pulmonary adenocarcinoma; phase 3	261 *EGFR* mutant (1,217 total)	9.5 (gefitinib) *vs.* 6.3 (chemotherapy); P<0.001	21.6 (gefitinib) *vs.* 21.9 (chemotherapy); ns	71.2% (gefitinib) *vs.* 47.3% (chemotherapy); P<0.001	(21,22)
WJTOG3405	Gefitinib *vs.* cisplatin plus docetaxel in EGFR mutant NSCLC patients; phase 3	117	9.2 (gefitinib) *vs.* 6.3 (chemotherapy); P<0.0001	34.8 (gefitinib) *vs.* 37.3 (chemotherapy); ns	62.1% (gefitinib) *vs.* 32.2% (chemotherapy); P<0.0001	(23,24)
NEJ002	Gefitinib *vs.* chemotherapy in EGFR mutant NSCLC patients; phase 3	230	10.8 (gefitinib) *vs.* 5.4 (chemotherapy); P<0.001	30.5 (gefitinib) *vs.* 23.6 (chemotherapy); ns	73.7% (gefitinib) *vs.* 30.7% (chemotherapy); P<0.001	(25)
NEJ009	Gefitinib plus chemotherapy *vs.* gefitinib in EGFR mutant NSCLC patients; phase 3	334	20.9 (gefitinib plus chemotherapy) *vs.* 11.2 (gefitinib); P<0.001 PFS2[1], 20.9 (gefitinib plus chemotherapy) *vs.* 20.7 (gefitinib); P=0.0774	52.2 (gefitinib plus chemotherapy) *vs.* 38.8 (gefitinib); P=0.013	84.0 (gefitinib plus chemotherapy) *vs.* 76.4 (gefitinib)	(26)
EURTAC	Erlotinib *vs.* chemotherapy in EGFR mutant NSCLC patients; phase 3	173	9.4 (erlotinib) *vs.* 5.2 (chemotherapy); P<0.0001	19.3 (erlotinib) *vs.* 19.5 (chemotherapy); ns	64% (erlotinib) *vs.* 18% (chemotherapy); P<0.0001	(27)
OPTIMAL	Erlotinib *vs.* chemotherapy in EGFR mutant NSCLC patients; phase 3	165	13.1 (erlotinib) *vs.* 4.6 (chemotherapy); P<0.0001	22.8 (erlotinib) *vs.* 27.2 (chemotherapy); ns	83% (erlotinib) *vs.* 36% (chemotherapy); P<0.0001	(28,29)
ENSURE	Erlotinib *vs.* chemotherapy in EGFR mutant NSCLC patients; phase 3	217	11 (erlotinib) *vs.* 5.5 (chemotherapy); P<0.0001	26.3 (erlotinib) *vs.* 22.5 (chemotherapy); ns	62.7% (erlotinib) *vs.* 33.6% (chemotherapy); P<0.0001	(30)
CONVINCE	Icotinib *vs.* chemotherapy in EGFR mutant NSCLC patients; phase 3	217	11.2 (icotinib) *vs.* 7.9 (chemotherapy); P=0.006	30.5 (icotinib) *vs.* 32.1 (chemotherapy); ns	–	(31)
LUX-Lung 3	Afatinib *vs.* chemotherapy in EGFR mutant NSCLC patients; phase 3	345	11.1 (afatinib) *vs.* 6.9 (chemotherapy); P=0.001	Overall: 28.2 (afatinib) *vs.* 28.2 (chemotherapy); ns. Exon 19 deletion: 33.3 (afatinib) *vs.* 21.1 months; P=0.0015. L858R mutation: 27.6 (afatinib) *vs.* 40.3 months; ns	56% (afatinib) *vs.* 23% (chemotherapy); P=0.001	(32,33)

Table 1 *(continued)*

Table 1 *(continued)*

Study name	Design	Population (N of patients)	Median PFS (months)	Median OS (months)	ORR (%)	Ref.
LUX-Lung 6	Afatinib *vs.* chemotherapy in EGFR mutant NSCLC patients; phase 3	345 (Asiatic)	11.0 (afatinib) *vs.* 5.6 (chemotherapy); P<0.0001	Overall: 23.1 (afatinib) *vs.* 23.5 (chemotherapy); ns Exon 19 deletion: 31.4 (afatinib) *vs.* 18.4 (chemotherapy); P=0.023 L858R mutation: 19.6 (afatinib) *vs.* 24.3 (chemotherapy); ns	66.9% (afatinib) *vs.* 23% (chemotherapy); P<0.0001	(33,34)
LUX-Lung 3 and LUX-Lung 6	–	–	–	Exon 19 deletion: 31.7 (afatinib) *vs.* 20.7 (chemotherapy); P<0.0001 L858R mutation: 22.1 (afatinib) *vs.* 26.9 (chemotherapy); ns	–	(33)

ns, not significant; 1PFS2, progression after the next line of therapy; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; ORR, objective response rate.

study, which was conducted in order to address the efficacy of gefitinib in non-Asian patients, supported the results of the previous studies (37).

Finally, the results of the phase 3 NEJ009 study (26) (*Table 1*) were presented at the 2018 ASCO Annual Meeting. The results of the NEJ009 study were among the most impressive results at the meeting, at least for *EGFR*-mutant patients. Although one of the primary endpoints of the study, time to second objective disease progression (PFS2), was not achieved, since patients who started on gefitinib and received chemotherapy at progression had similar PFS as those who received the concurrent therapy upfront (20.9 versus 20.7), the patients who started with gefitinib plus chemotherapy combination had a significantly longer overall survival (OS) of 52.2 versus 38.8 months (P=0.013) (26). Despite these results, it is not at all likely that gefitinib plus standard chemotherapy will be favored over osimertinib, considering its good tolerability and activity in the central nervous system (CNS) (38). However, maybe the results can lead us to pursue clinical trials combining osimertinib with chemotherapy in the first-line setting.

Erlotinib

Erlotinib (OSI-774, CP-358774, Tarceva; OSI Pharmaceuticals, Inc., Melville, NY, USA and Genentech, Inc., South San Francisco, CA, USA) was discovered in 1997 (39) and was initially FDA approved in November 2004 for the treatment of metastatic NSCLC after the failure of at least one prior chemotherapy regimen (19,40). In 2010, erlotinib was approved for "switch maintenance" in unselected NSCLC patients who had benefited from first-line platinum-based chemotherapy based on statistically significant OS improvement of 1 month in the SATURN trial (41,42).

Randomized trials have demonstrated the superiority of erlotinib compared to chemotherapy regarding response and PFS for the first-line therapy of *EGFR*-mutant NSCLC patients (27,28). The EURTAC (European Randomized Trial of Tarceva versus Chemotherapy), the OPTIMAL (CTONG0802) and the ENSURE phase III clinical trials have shown that erlotinib is better than platinum-based chemotherapy, concerning PFS and responses, as first-line treatment in *EGFR*-mutant European and Asiatic patients (27-30) (*Table 1*). Based on the results of the pivotal EURTAC study, in May, 2013, the FDA approved erlotinib for the first-line therapy of *EGFR*-mutant NSCLC patients (*Figure 2*). The FDA also approved the cobas® EGFR Mutation Test, which was developed by Roche and validated in the EURTAC study (43). Based on the results of the

Table 2 Phase IIb and III, head to head comparative trials with first- and second-generation EGFR TKIs in several settings

Study name	Details of the study	PFS (months)	OS (months)	ORR (%)	Ref.
ICOGEN	Icotinib [200] *vs.* gefitinib [199]; 51% *EGFR*-mutant; previously treated; phase III	4.6 (icotinib) *vs.* 3.4 (gefitinib); ns	13.3 (icotinib) *vs.* 13.9 (gefitinib); ns	27.6 (icotinib) *vs.* 27.2 (gefitinib); ns	(52)
LUX-Lung 8	Afatinib [398] *vs.* erlotinib [397]; squamous-cell lung cancer; previously treated; phase III	2.4 (afatinib) *vs.* 1.9 (erlotinib); P=0.0103	7.9 (afatinib) *vs.* 6.8 (erlotinib); P=0.0077	6.0 (afatinib) *vs.* 3.0 (erlotinib); ns	(53)
CTONG 0901	Erlotinib [128] *vs.* gefitinib [128]; *EGFR*-mutant; 66% in 1st-line; phase III	13.0 (erlotinib) *vs.* 10.4 (gefitinib); ns	22.9 (erlotinib) *vs.* 20.1 (gefitinib); ns	56.3 (erlotinib) *vs.* 52.3 (gefitinib); ns	(54)
LUX-Lung 7	Afatinib [160] *vs.* gefitinib [159]; *EGFR*-mutant; 1st-line; phase IIb	11.0 (afatinib) *vs.* 10.9 (gefitinib); P=0.017	27.9 (afatinib) *vs.* 24.5 (gefitinib); ns	72.5 (afatinib) *vs.* 56.0 (gefitinib); P=0.0018	(55,56)
ARCHER 1050	Dacomitinib [227] *vs.* gefitinib [225]; *EGFR*-mutant; 1st-line; phase III	14.7 (dacomitinib) *vs.* 9.2 (gefitinib); P<0.0001	34.1 (dacomitinib) *vs.* 26.8 (gefitinib); P=0.0438	75.0 (dacomitinib) *vs.* 72.0 (gefitinib); ns	(57,58)

ns, not significant; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; PFS, progression-free survival; OS, overall survival; ORR, objective response rate.

same study, EMA approved erlotinib in 2011 for the first-line therapy of *EGFR*-mutant NSCLC patients (*Figure 2*).

After the abovementioned studies of gefitinib and erlotinib, the scientific community should have gained a much better appreciation of the clinical efficacy of EGFR TKIs and the design of clinical trials, however, other phase III clinical trials that evaluated the efficacy of erlotinib in different settings had rather disappointing results. For instance, the TRIBUTE (44) and the Tarceva Lung Cancer Investigation Trial (45) were two phase III clinical trials in which erlotinib or placebo was combined with platinum-based chemotherapy for the first-line therapy of NSCLC patients unselected for *EGFR* mutations. In both studies, no survival benefit was found for the combination of erlotinib with chemotherapy (44,45). Perhaps the TOPICAL phase III clinical trial was the last study with erlotinib as first-line therapy in unselected advanced stage NSCLC, which demonstrated the futility of EGFR inhibitors in patients without *EGFR* mutations (46,47). The EMPHASIS trial was another negative trial comparing erlotinib versus docetaxel in squamous cell lung cancer after failure to platinum-based chemotherapy (48). Two randomized trials (TaiLOR, DELTA) comparing single-agent chemotherapy to erlotinib as second-line treatment of unselected NSCLC reported that, statistically, chemotherapy significantly improved PFS compared with erlotinib (49,50). All these futile studies reinforce the backdrop of the standard of care with EGFR TKIs. Erlotinib is also approved but rarely used in combination with gemcitabine in metastatic pancreatic cancer (51).

Icotinib

Icotinib hydrochloride is the first self-developed small molecular drug in China, synthesized in 2002, that has a similar structure to erlotinib and gefitinib. It is designed and patented by Beta Pharma (Zhejiang, People's Republic of China). In the phase III ICOGEN trial, icotinib was compared with gefitinib in NSCLC patients who have progressed to one or two lines of chemotherapy, and it was found to be equivalent regarding efficacy (*Table 2*). Icotinib was less toxic and better tolerated than gefitinib (52). The overall incidence of adverse events was 61% with icotinib versus 70% with gefitinib (P=0.046) (52). Based on the results of the ICOGEN study, icotinib was approved by the China Food and Drug Administration (CFDA) in June 2011 for the second- or third-line therapy of metastatic NSCLC (*Figure 2*). Some years later followed the open-label randomized phase III CONVINCE trial, in which first-line icotinib was compared with platinum-pemetrexed in *EGFR*-

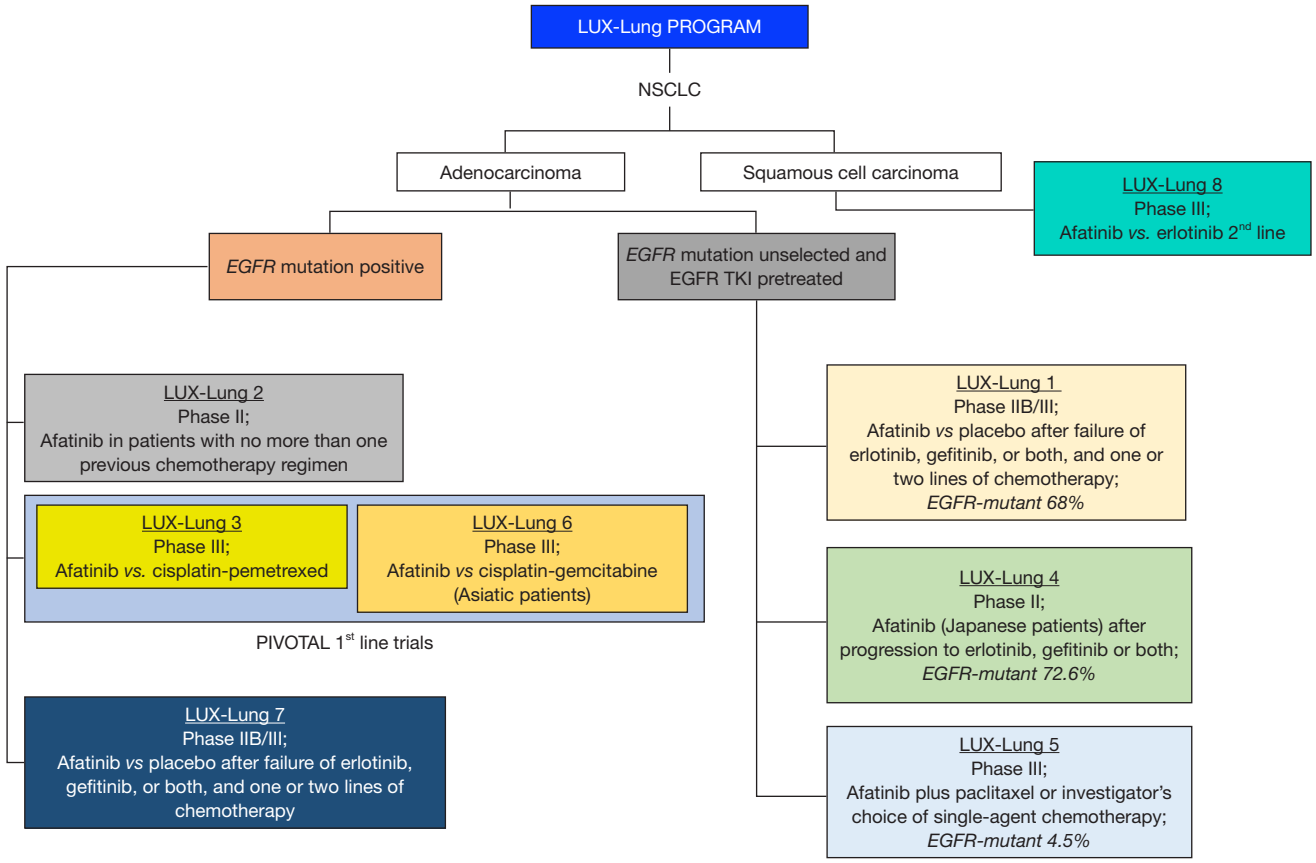

Figure 3 Schematic representation of the LUX-Lung program for the development of afatinib in NSCLC. NSCLC, non-small cell lung cancer.

mutant NSCLC patients. Icotinib significantly improved PFS compared to chemotherapy (31) (*Table 1*). On the 13th of November 2014, icotinib was approved in China for the first-line treatment of *EGFR*-mutant NSCLC patients (59) (*Figure 2*).

Second-generation EGFR TKIs

The second-generation inhibitors, including afatinib and dacomitinib, are irreversible inhibitors, which covalently bind to EGFR. Just as gefitinib and erlotinib, afatinib is globally approved for the first-line therapy of *EGFR*-mutant patients, while dacomitinib is also under consideration for regulatory approval.

Afatinib

Afatinib (Gilotrif/Giotrif; Boehringer Ingelheim, Germany) is an ATP-competitive anilinoquinazoline derivative harboring a reactive acrylamide group. It covalently binds and irreversibly blocks enzymatically active ErbB receptor family members (60). Afatinib contains an electrophilic group capable of Michael addition to conserved cysteine residues within the catalytic domains of EGFR (Cys797), HER2 (Cys805), and ErbB-4 (Cys803) (60). The efficacy of afatinib in NSCLC has been evaluated in the LUX-lung program (*Figure 3*). Many of the trials in the program initially evaluated afatinib in unselected for EGFR populations, until we reached the pivotal 1st line trials of afatinib in *EGFR*-mutant NSCLC, LUX-Lung 3 and 6 (*Figure 3*).

Afatinib is approved in U.S (July 2013) and Europe (September 2013) for the first-line therapy of *EGFR*-mutant NSCLC patients (*Figure 2*). The LUX-Lung 3 and 6 trials compared the efficacy of afatinib versus pemetrexed plus cisplatin (LUX-Lung 3) (32) or gemcitabine plus cisplatin (LUX-Lung 6) (34) and demonstrated its superiority regarding PFS and responses compared to chemotherapy

Table 3 Responses in 32 NSCLC patients with uncommon *EGFR* mutations from LUX-Lung 2, LUX-Lung 3 and LUX-Lung 6

Afatinib treated patients (N=32)	Confirmed responses (N=21)
L861Q (N=12)	7 out of 12 (58%)
G719X (N=8)	6 out of 8 (75%)
S768I + G719X (N=5)	4 out of 5 (80%)
G719X + L861Q (N=3)	2 out of 3 (67%)
S768I + L858R (N=2)	1 out of 2 (50%)
S768I (N=1)	1 out of 1
L861Q + deletion 19 (N=1)	0 out of 1

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

(*Table 1*). The pooled analysis of LUX-Lung 3 and LUX-Lung 6 (33) was performed in order to assess the effect of afatinib on OS of patients with *EGFR*-mutant lung adenocarcinoma. In the whole population, there was no survival benefit with afatinib compared to platinum-based chemotherapy, but patients with *EGFR* deletion 19 derived a significant OS benefit in comparison with those carrying exon 21 L858R mutations (*Table 1*).

The LUX-Lung 8 study compared afatinib versus erlotinib as second-line therapy in patients with metastatic squamous-cell lung cancer (53). Afatinib was superior to erlotinib concerning PFS and OS (*Table 2*). The absolute improvement in PFS with afatinib over erlotinib was only half a month and was also associated with increased toxicities. Afatinib is approved in Europe and U.S. since April 2016, for the treatment of locally advanced or metastatic squamous-cell NSCLC after progression to platinum-based chemotherapy (*Figure 2*). At the time that the LUX-Lung 8 study was conceived, there were limited therapies for squamous-cell lung cancer after progression to platinum-based chemotherapy. Still, under these conditions, erlotinib was not the appropriate comparator in the LUX-Lung 8 study. As mentioned above in the EMPHASIS study, erlotinib was compared with docetaxel in the same setting and was not able to show a superiority of the EGFR TKI (48). The LUX-Lung 8 is far from being clinically relevant for this subset of patients, and, despite the regulatory approvals, afatinib should not be considered a standard second-line treatment in squamous-cell NSCLC.

In January 2018, FDA approved a supplemental New Drug Application for afatinib for the first-line treatment of patients with metastatic NSCLC whose tumors have non-resistant *EGFR* mutations including three additional *EGFR* mutations: L861Q, G719X, and S768I (*Figures 1*,*2*). The approval is based on a pooled analysis of the phase II LUX-Lung 2 and the phase III LUX-Lung 3 and LUX-Lung 6 studies. All three studies included patients with uncommon *EGFR* mutations, including L861Q, G719X or S768I (*Table 3*). Afatinib was active in 32 patients with rare nonresistant *EGFR* mutations based on ORR, duration of response, disease control, PFS and, OS (61,62).

We report the case of a 62-year-old woman, ex-smoker, who was diagnosed in April 2017, with a stage IV (brain, bone and liver metastases) lung cancer. A biopsy of a bone metastasis with significant soft-tissue component revealed that it was a pan-negative lung adenocarcinoma. The patient started platinum-based chemotherapy after completing whole brain radiotherapy for the symptomatic brain metastases, and palliative pelvic radiotherapy for the right iliac and sacral symptomatic bone metastasis (*Figure 4*). She was included in the observational Spanish Lung Liquid versus Invasive biopsy Program (SLLIP, NCT03248089). Blood was collected before chemotherapy initiation, and her plasma DNA genome profile was performed with a clinically validated cell-free DNA (cfDNA) assay (Guardant360, Guardant Health Inc., CA, U.S.) (63,64). The results of the study revealed that the patient was carrying a double exon 18 (G719X) and exon 20 (S768I) *EGFR* mutation (*Figure 4*). After less than two months of treatment, we had to interrupt platinum-based chemotherapy due to grade IV hematologic toxicity and grade III asthenia. Based on the results of the SLIPP, we decided to switch therapy to afatinib 40 mg per day. After two weeks of therapy, she had to reduce afatinib to 30 mg per day due to grade III diarrhea and rash. The patient is still in therapy with no toxicity and almost complete response of her disease after 16 months from the diagnosis and 13 months from afatinib initiation (*Figure 4*).

Dacomitinib

Dacomitinib was developed by Pfizer as a second-generation irreversible EGFR TKI. It is a pan-HER inhibitor that was initially thought to inhibit the acquired resistance EGFR mutation T790M (65). However, the inhibitory concentration needed to inhibit 50% of the purified kinase activity of T790M is in the range of hundreds of nanomolar (65). The development of dacomitinib in NSCLC has been performed through the Advanced Research for Cancer targeted pan-HER therapy (ARCHER) program. As

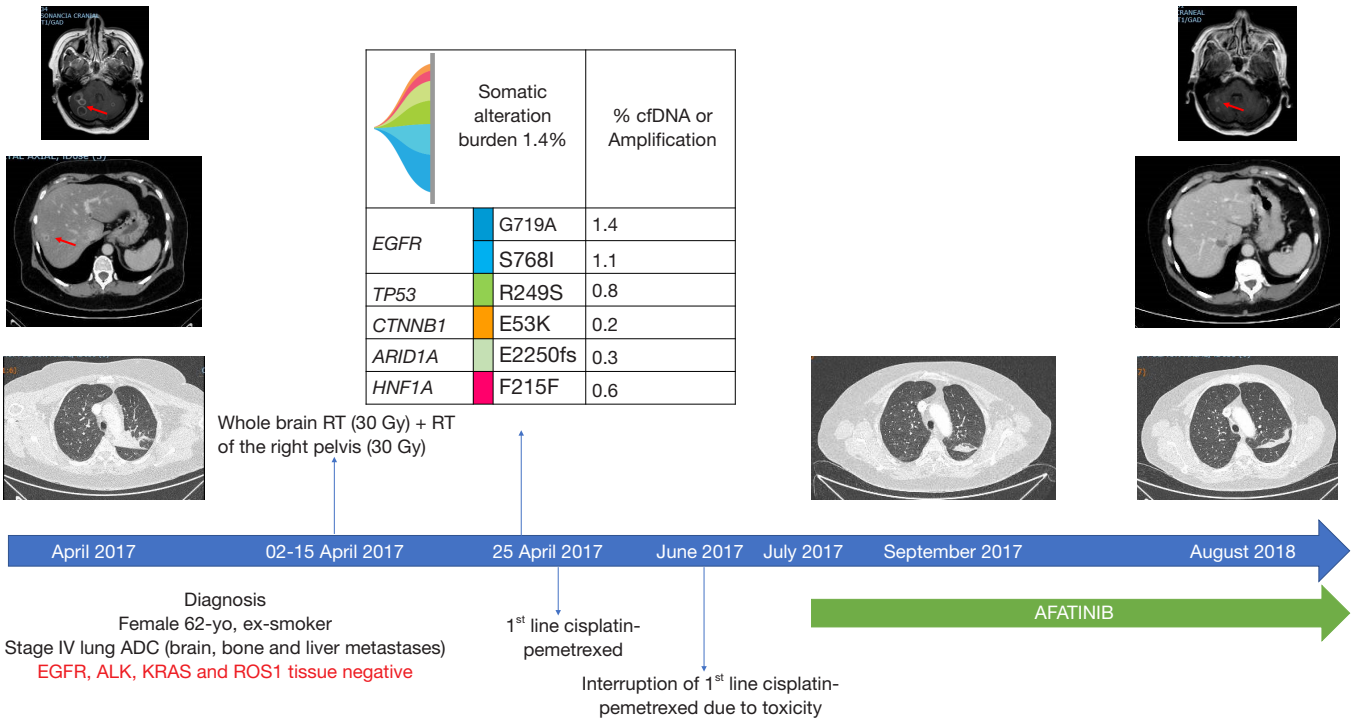

Figure 4 A case report of a patient with an uncommon double *EGFR* mutation responding to afatinib therapy. EGFR, epidermal growth factor receptor.

it is shown in *Table 4*, dacomitinib has been tested in several clinical studies and overall has failed to show better clinical efficacy over first-generation EGFR TKIs and with more toxicities in unselected NSCLC patients. Maybe the failure of ARCHER 1009 and NCIC BR-26 to achieve their primary endpoints delayed the approval and potential use of dacomitinib in NSCLC (72,73). For example, in the ARCHER 1009, dacomitinib was found to have similar efficacy to erlotinib as second-line therapy of NSCLC patients unselected for EGFR mutations. However, dacomitinib was more toxic than erlotinib, and the trial was not powered to be a non-inferiority trial (72). Dacomitinib failed to improve OS compared to placebo in the NCIC BR-26 trial in patients who had progressed to first-generation EGFR TKIs (73). These results remind us of those of the LUX-Lung-1 trial, where afatinib improved PFS over placebo, but there was no OS difference (74). Still, in the LUX-Lung-1 trial, there was OS benefit in the subgroup of patients whose best response to first-generation EGFR TKIs was not disease progression (74). Therefore, we consider that the negative results from the ARCHER 1009 and NCIC-BR-26 trials have delayed, and may have diminished, the clinical relevance of dacomitinib approval.

In addition, the era of enrolling molecularly unselected NSCLC patients into clinical trials involving EGFR TKIs (or other targeted agents) has come to an end. A lot of time was lost during the development of dacomitinib, until the ARCHER 1050 was finally conducted and the results were recently presented (57,58), now that the third-generation EGFR TKIs have taken the lead in the first line setting.

Comparison of first and second-generation EGFR TKIs

Studies have head-to-head compared first and second-generation EGFR TKIs, but until now have failed to become clinically relevant. The phase III CTONG 0901 study compared gefitinib with erlotinib in a Chinese population, but did not identify a superior drug regarding PFS, OS or toxicity (54). Randomized clinical trials have compared the efficacy of gefitinib or erlotinib with the second-generation EGFR TKIs. Gefitinib has been compared with afatinib and dacomitinib in the LUX-Lung-7 (55,56) and the ARCHER-1050 (57,58) studies, respectively. In both studies, the second-generation EGFR TKIs, afatinib and dacomitinib were found to be superior to

Table 4 ARCHER program for the development of dacomitinib in NSCLC

ARCHER	Design title	Population	Endpoints	Ref.
1001	Phase I dose-escalation study of the pan-HER inhibitor, PF299804, in patients with advanced malignant solid tumors	121 (U.S)	RP2D =45 mg orally once daily	(66)
1003	Safety and efficacy of dacomitinib in Korean patients with KRAS wild-type advanced NSCLC refractory to chemotherapy and erlotinib or gefitinib: a phase I/II trial	12 (South Korea)	RP2D =45 mg orally once daily; PFS at 4 mo =47.2%; median PFS 15.4 weeks, median OS =46.3 weeks; ORR 17.1%	(67)
1005	Phase I and pharmacokinetic study of dacomitinib (PF-00299804), an oral irreversible, pan-HER inhibitor in Japanese patients with advanced solid tumors	13 (Japan)	RP2D = 45 mg orally once daily	(68)
1002	A phase 2 trial of dacomitinib (PF-00299804), an oral, irreversible pan-HER inhibitor, in patients with advanced NSCLC after failure of prior chemotherapy and erlotinib	66. ADC: 4.8%; non-ADC: 6.3%; *EGFR*-mutant: 8%	ADC: ORR=5%; non-ADC: ORR=6%; median PFS =12 weeks; median PFS for *EGFR*-mutant =18 weeks	(69)
1017	Dacomitinib as first-line treatment in patients with clinically or molecularly selected advanced NSCLC: a multicenter, open-label, phase 2 trial	89. *EGFR*-mutant: 60% (51% with del 19 or L858R)	Median PFS=11.5 mo; median PFS for *EGFR*-mutant =18.2 mo; median OS= 29.5 mo; median OS for *EGFR*-mutant =40.2 mo; ORR =53.9%; ORR for *EGFR*-mutant =75.6%	(70)
1028	Randomized phase II study of dacomitinib (PF-00299804), an irreversible pan-HER inhibitor, *vs.* erlotinib in patients with advanced NSCLC	188. *EGFR*-mutant: 15.9%	Median PFS=2.86 mo (dacomitinib) *vs.* 1.91 mo (erlotinib); P= 0.012; KRAS wild-type/EGFR any type: median PFS =3.71 mo (dacomitinib) *vs.* 1.91 mo (erlotinib); P= 0.006; KRAS wild-type/EGFR wild-type: median PFS =2.21 mo (dacomitinib) *vs.* 1.84 mo (erlotinib); P=0.043; median OS =9.53 mo (dacomitinib) *vs.* 7.44 mo (erlotinib); ns	(71)
1009	Dacomitinib *vs.* erlotinib in patients with advanced-stage, previously treated NSCLC (ARCHER 1009): a randomized, double-blind, phase 3 trial	878. *EGFR*-mutant: 10%	Median PFS =2.6 mo for both dacomitinib and erlotinib; KRAS wild-type: median PFS =2.6 mo for both dacomitinib and erlotinib; median OS =7.9 mo (dacomitinib) *vs.* 8.4 mo (erlotinib); ns; KRAS wild-type: median OS =8.1 mo (dacomitinib) *vs.* 8.5 mo (erlotinib); ns	(72)
BR-26	Dacomitinib compared with placebo in pretreated patients with advanced or metastatic NSCLC (NCIC CTG BR.26): a double-blind, randomized, phase 3 trial	720. *EGFR*-mutant: 25.3%	Median OS =2.38 mo (dacomitinib) *vs.* 6.31 mo (placebo); ns. No differences in the subgroups	(73)
1050	Dacomitinib versus gefitinib as first-line treatment for patients with EGFR-mutation-positive NSCLC (ARCHER 1050): a randomized, open-label, phase 3 trial	452 *EGFR*-mutant	Median PFS =14.7 mo (dacomitinib) *vs.* 9.2 mo (gefitinib); P<0.0001; median PFS =34.1 mo (dacomitinib) *vs.* 26.8 mo (gefitinib); P=0.0438	(57,58)

RP2D, recommended phase II dose; mo, months; ADC, adenocarcinoma; ns, not significant; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; ORR, objective response rate.

gefitinib, but with some caveats. For instance, in the LUX-Lung-7, although the difference in PFS between the two compounds was statistically significant, from the clinical point of view a PFS of 11 months with afatinib versus 10.9 months with erlotinib is not clinically relevant (55). There were no differences in OS, while ORR was significantly higher with afatinib (56) (*Table 2*). In the most recent ARCHER-1050 study, PFS was significantly longer with dacomitinib compared to gefitinib (14.7 versus 9.2 months, P<0.0001). Patients with brain metastases were excluded from the study, and the benefit of dacomitinib in comparison with gefitinib was more evident for Asian patients with a hazard ratio (HR) of 0.51 (0.39–0.66), compared to non-Asians HR of 0.89 (0.57–1.39) (57). In addition, the patients in the dacomitinib arm suffered more toxicity in comparison with gefitinib. Besides these caveats, dacomitinib is the first EGFR TKI (among the first- and second-generation EGFR TKIs) that shows a significant improvement in OS, with an estimated HR for OS of 0.760 (95% CI, 0.582–0.993; two-sided P=0.044) and a median OS of 34.1 months with dacomitinib versus 26.8 months with gefitinib (58) (*Table 2*). On the 4th of April 2018, FDA granted priority review for dacomitinib for the first-line treatment of EGFR-mutant NSCLC patients (*Figure 2*). The European Medicines Agency has also accepted the Marketing Authorization Application for dacomitinib for the same indication.

Although any comments on third-generation EGFR TKIs is out of the scope of the present review, it is worth mentioning that both erlotinib and gefitinib were compared with the third-generation inhibitor, osimertinib in the phase III FLAURA clinical trial (38). Based on a significant improvement in PFS with osimertinib compared to standard EGFR TKIs (18.9 versus 10.2 months) (38), osimertinib has received FDA (April 2018) and EMA (June 2018) approval for the first-line therapy of *EGFR*-mutant NSCLC patients. We are running the AZENT clinical trial (NCT02841579), which is testing the efficacy of osimertinib as first-line therapy in *EGFR*-mutant NSCLC patients that carry concomitant pre-treatment T790M mutation.

First- and second-generation EGFR TKIs and brain metastases

Lung cancer patients with *EGFR* mutations have high prevalence of brain metastases at the time of diagnosis (1) which increases more during the disease (75), making the role EGFR TKIs on brain metastases of great relevance (76). Gefitinib has a limited brain penetration rate of only 1% (77,78), while studies have shown that erlotinib penetrates the cerebrospinal fluid (CSF) (79-81). *EGFR* mutations were discovered in 2004 (4,6,7), and 1 year later we were shown the case of a Spanish female patient with an *EGFR*-mutant (deletion 19) lung adenocarcinoma and severe neurologic symptoms with impairment of walking, eating, and speaking that required a gastric feeding tube (82). The brain computed tomography showed multiple brain metastases. Gefitinib was given through a gastric feeding tube, and rapid recovery of neurologic functions was observed, accompanied by a regression of the brain metastases (82). We and others have found an activity of erlotinib against brain metastases (80,83).

Most of the information about the activity of gefitinib and erlotinib in brain metastases comes from retrospective or prospective studies not focused on *EGFR*-mutant patients [see also *Table 1* in reference (76)]. It was in 2004, before understanding the role of *EGFR* mutations and targeted therapies, that gefitinib showed some activity in two reports of NSCLC patients with brain metastases, (84,85). Later, in a cohort of Korean patients with NSCLC and asymptomatic brain metastases, not previously irradiated, gefitinib or erlotinib therapy resulted in an intracranial response rate of 74% (86). An intracranial response rate of 57% was observed with gefitinib or erlotinib in a cohort of 43 Chinese NSCLC patients with brain metastases (87). Prospective studies have reported a response rate with gefitinib ranging from 10–33% in European (88) and Taiwanese (89) to 31–81% in Chinese (90) NSCLC patients with brain metastases.

It was only in 2013 that a Japanese phase II study of gefitinib concentrated on NSCLC patients with *EGFR* mutations and brain metastases (91). In this study, among 41 patients, an ORR of almost 90% with 13 complete responses was found with gefitinib. Twenty of the patients required brain radiotherapy (91). A phase II open-label single-institution clinical trial evaluated erlotinib or gefitinib for NSCLC patients harboring *EGFR* mutations with measurable metastatic brain disease (92). Among 28 patients enrolled, 83% achieved a partial response, and 11% had stable disease (92). No differences on efficacy (PFS and OS) were observed between the two EGFR TKIs used in the study (92). Dose escalation of erlotinib has been studied for increasing their CNS permeability. In a retrospective analysis, nine *EGFR*-mutant NSCLC patients with brain or leptomeningeal metastases occurring under regular doses of EGFR TKIs, were treated with 1,500 mg of erlotinib weekly (93). Six of them (67%) obtained a partial response.

However median time to CNS progression was less than three months (93). Subsequently, a phase I study found that 1,200 mg of erlotinib given for two days of the week (D1 + D2) and then 50 mg of erlotinib for the rest of the week (D3 + D7) is the maximum tolerated dose. Among the patients who had brain metastases at study entry, none of them progressed in an untreated brain metastasis or had a new brain metastasis while on the study (94). In a retrospective analysis including patients with leptomeningeal carcinomatosis, erlotinib was superior to gefitinib with a cytologic conversion rate of 64.3% compared to 9.1% with gefitinib (95). Also, erlotinib offered clinical benefit in a series of NSCLC patients with leptomeningeal metastasis who had failed gefitinib treatment (96). The BRAIN phase III clinical trial comparing icotinib versus whole brain radiotherapy for EGFR-mutant patients with brain metastases demonstrated that icotinib was superior to radiotherapy regarding intracranial and overall PFS, response, and disease control rate (97). Still, these results have not established the role of icotinib in this setting (98).

As far as the second-generation EGFR TKIs concerns, subgroup analyses of patients with asymptomatic brain metastases from the LUX-Lung 3 and 6 trials, have shown that afatinib is more efficacious than compared to chemotherapy (99). However, the rates of CNS progression were similar among patients treated with afatinib or chemotherapy. Furthermore, in both studies, those patients who had received whole brain radiation therapy appeared to have better PFS benefit from afatinib than those who did not receive radiation (32,34). In the compassionate use program of afatinib, the activity of the drug in CNS has also been reported (100). In the LUX-Lung 7 trial, no statistically significant differences were found between afatinib and gefitinib in the subgroup of patients with asymptomatic brain metastasis (55). Finally, in most of the dacomitinib studies, patients with brain metastases are excluded.

In conclusion, data about the potential efficacy of first- and second-generation EGFR TKIs in patients with brain metastases need to be interpreted with caution, because they are derived from mainly retrospective reports and from small numbers of patients. We are still not confident to defer radiotherapy in *EGFR*-mutant patients with brain metastases that are about to start therapy with a first- or second-generation EGFR TKI. Furthermore, a recent pooled analysis has shown that the upfront use of an EGFR TKI (mainly erlotinib), in *EGFR*-mutant NSCLC patients with brain metastases and deferred radiotherapy is associated with shorter OS compared with radiotherapy followed by EGFR TKI (101). Of course, we are in the era of the CNS-active EGFR TKI osimertinib that has become the EGFR TKI of choice in newly diagnosed *EGFR*-mutant NSCLC patients considering that it triples median PFS, but also has high CNS response rate compared to gefitinib or erlotinib (38).

Mechanisms of resistance to first- and second-generation EGFR TKIs

It is very well known that after a median PFS of 11 months in the 50–80% of initially responding patients to first-and second-generation EGFR TKIs, different mechanisms of resistance occur (10,11,102,103). Acquirement of the T790M mutation in exon 20 is one such example and was detected in 50–60% of patients who were resistant to EGFR-TKIs (102). This secondary mutation causes impaired binding of the TKI, by increasing the binding pocket affinity for ATP. The result is a blockage of reversible first-generation TKI binding, and thus steric hindrance (104).

We have shown that besides being induced by EGFR-TKIs, the T790M mutation is detected in treatment-naive patients. According to our experience, pre-treatment T790M can be present in more than 30% of the patients and diminishes the magnitude of response to erlotinib (105-107). We have also demonstrated that redundant signaling pathways (108,109) can sustain and even hyper-activate pro-survival signaling, despite EGFR inhibition (110-116). Recently, we convincingly demonstrated that no EGFR TKI can abrogate STAT3 and Src-YAP1 (Yes-associated protein 1) (117-119). EGFR is co-expressed with other receptor and non-RTK, like AXL, MET, CUB domain-containing protein 1 (CDCP1) or Src homology-2 domain containing phosphatase (SHP2) which undermines responses to single EGFR TKIs, forbids complete responses and ultimately deprives patients of cure (117-119). Rational combinatorial therapies that target STAT3 and Src-YAP1 overcome this problem at least in culture and *in vivo* (117-119).

Combinations of first- and second-generation EGFR TKIs with chemotherapy, antiangiogenic agents, and immunotherapy

Considering the abundance of mechanisms of resistance that indeed can similarly occur with the third-generation EGFR TKIs, many efforts are ongoing, combining EGFR TKIs with other drugs, including anti-angiogenic, chemotherapy,

immunotherapy or other targeted agents.

With anti-angiogenic agents

The addition of the vascular endothelial growth factor (VEGF) inhibitor, bevacizumab, to erlotinib was started to be tested in unselected populations, in several phase II and III clinical trials, before the clinical relevance of *EGFR* mutations was established (120-123). Retrospective analyses of *EGFR*-mutant patients demonstrated that the combination of erlotinib plus bevacizumab was better than the control arms. The phase II JO25567 clinical trial was conducted in Japan showing a significant benefit in PFS with the addition of the anti-angiogenic agent to erlotinib [HR, 0.54; 95% CI: 0.36–0.79; P=0.0015; median PFS 16.0 months for erlotinib plus bevacizumab and 9.7 months for erlotinib alone] (124,125). The combination has manageable toxicity, and it is well tolerated (125). Our BELIEF phase II single-arm clinical trial evaluated the combination of erlotinib plus bevacizumab in the first-line setting of *EGFR*-mutant patients, all of whom have been evaluated for the presence of the pre-treatment exon 20 missense mutation T790M (126). The study was based on a biological rational from preclinical studies. As previously mentioned, we and others have explored the role of pre-treatment T790M (105,107,127,128), and we have seen a worse outcome to erlotinib for patients with the double mutation (105,107). Preclinical studies had shown that the combination of gefitinib with bevacizumab inhibits tumor growth in H1975 xenograft tumors (129,130) carrying the 21 missense mutation (L858R) and T790M (4). The BELIEF study found that pre-treatment T790M was present in 37 out of the 109 patients included in the study. Median PFS was 16 months in the T790M-positive versus 10.5 months in the T790M-negative group (unadjusted HR, 0.52, 95% CI: 0.30–0.88; P=0.016) (126). From the results of the JO25567 and the BELIEF trials, erlotinib plus bevacizumab has received EMA (June 2016) approval for the first-line therapy of *EGFR*-mutant NSCLC patients (*Figure 1*). The NEJ026 and the BEVERLY studies are the first phase III clinical trials that compare erlotinib plus bevacizumab versus erlotinib alone as first-line therapy in Japanese and Caucasian *EGFR*-mutant patients, respectively (*Table 5*). A preplanned interim analysis of the NEJ026 study was presented at the 2018 ASCO Annual Meeting showing a median PFS of 16.9 months with erlotinib plus bevacizumab compared to 13.3 months with erlotinib alone (131). Finally, a meta-analysis of 2,802 unselected for *EGFR*-mutation patients showed that the combination of erlotinib plus bevacizumab did not improve OS, responses or PFS overall, but enhanced OS in *EGFR* mutant patients (132). The premise of a combination of an EGFR TKI plus bevacizumab in *EGFR*-mutant NSCLC is strong, given the signals from the already performed and the ongoing (*Table 5*) clinical trials. However, considering that both FDA an EMA have approved the third-generation EGFR TKI osimertinib for first-line treatment of metastatic NSCLC with most common *EGFR* mutations, the erlotinib plus bevacizumab combination may be obsolete and will not change the standard of care.

With other targeted agents

The group of Dr. Rosell was among the first to be in favor of upfront combinatorial therapies for *EGFR*-mutant patients. Besides the abovementioned BELIEF study, we have carried out the GOAL phase I/II trial that compares gefitinib plus the poly (ADP-ribose) polymerase (PARP) inhibitor olaparib versus gefitinib alone as first-line therapy in *EGFR*-mutant NSCLC patients (133). The rationale of the GOAL study comes from previous findings that low levels of breast cancer type 1 susceptibility (BRCA1) gene expression can be related with a better outcome to erlotinib and furthermore they can neutralize the nefarious effect of pre-treatment T790M (105). Although the results of the phase I part of the study were promising (134), in the phase II part of the study in which 186 *EGFR*-mutant patients were included, we were not able to find statistically significant differences in PFS between the two treatment arms. Specifically, the median PFS was 12.8 months for gefitinib plus olaparib versus 10.4 months for gefitinib alone (P=0.329) (135). We are now actively working to see whether the prespecified assessment of BRCA1, p53-binding protein 1 (53BP1), and other biomarkers including C-terminal binding protein interacting protein (CtIP) could determine whether a subgroup of patients may derive benefit from the combination.

There are multiple clinical trials ongoing, combining first- or second-generation EGFR TKIs with other targeted agents, like MET, AXL, PI3K, MEK or Src inhibitors (*Table 6*). There are also trials combining gefitinib or erlotinib with third-generation inhibitors as well as others that combine EGFR TKIs with monoclonal antibodies against EGFR (*Table 6*). We are carrying out in Spain and

Table 5 Ongoing clinical trials of first- and second-generation EGFR TKIs in combination with anti-angiogenic therapies in *EGFR*-mutant NSCLC patients

ClinicalTrials.gov identifier or other identifier	Phase; population	Treatment	Status
UMIN000017069	Phase III; 1st-line; NEJ026	Erlotinib + bevacizumab *vs.* erlotinib	Recruiting
NCT02633189	Phase III; 1st-line; BEVERLY	Erlotinib + bevacizumab *vs.* erlotinib	Recruiting
NCT00436332	Phase II; EGFR TKI-naive; BAC[1] and ADENOBAC[2]; S0635	Erlotinib + bevacizumab	Ongoing, not recruiting
NCT02655536	Phase II; with brain metastases; EGFR TKI-naive; BRILLIANT	Erlotinib + bevacizumab *vs.* erlotinib	Recruiting
NCT02411448	Phase III; EGFR TKI-naive; RELAY	Erlotinib + ramucirumab *vs.* erlotinib (part A and B); gefitinib + ramucirumab *vs.* gefitinib (part C)	Recruiting
NCT03461185	Phase II; EGFR TKI-pretreated (stable disease for at least 2 months	Erlotinib or gefitinib + anti-angiogenic drugs (endostatin[3] or apatinib[4] or anlotinib[5]) *vs.* erlotinib or gefitinib	Not yet recruiting
NCT03050411	Phase I; EGFR TKI-pretreated	Erlotinib + apatinib[4]	Recruiting
NCT03628521	Phase I; EGFR TKI-naive patients	Erlotinib + apatinib[4] (arm A)	Recruiting
NCT03602027	Phase I; EGFR TKI-naive patients	Gefitinib + apatinib[4]	Not yet recruiting

[1]BAC, bronchioloalveolar carcinoma; [2]ADENOBAC, adenocarcinoma with BAC features; [3]endostatin, naturally occurring, 20-kDa C-terminal fragment derived from type XVIII collagen with anti-angiogenic activity; [4]anlotinib, receptor tyrosine kinase (RTK) inhibitor (including vascular endothelial growth factor receptor type 2 (VEGFR2) and type 3 (VEGFR3); [5]apatinib (also known as YN968D1), TKI against VEGFR2. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

Latin America (Colombia) the phase Ib EPICAL clinical trial, which evaluates the safety and efficacy of afatinib with EGF pathway targeting immunization (EGF-PTI) in treatment-naive patients with *EGFR*-mutant NSCLC (136). The study was designed based on preclinical findings, generated in our laboratory, showing that the addition of EGF-PTI (that is already in phase III clinical trials) to EGFR TKIs, delays the emergence of resistance and more efficiently than EGFR TKI alone abrogates the EGFR downstream signaling pathways among them STAT3 and NOTCH (137). The study is currently accruing patients (NCT03623750).

With immunotherapy

The effect of immunotherapy in *EGFR*-mutant NSCLC is debatable. In most of the studies with immune checkpoint inhibitors, *EGFR*-mutant patients derive no benefit (138). Whether this can be because patients with *EGFR* mutations are light or never smokers, with therefore low tumor mutational burden, or because *EGFR*-mutant tumors have low PD-L1 expression and infiltrating CD8+ T cells, is still not very clear (139). The only exception until now comes from the IMpower 150 trial, in which there was a PFS benefit with the combination of atezolizumab plus bevacizumab plus chemotherapy for EGFR-mutant patients compared to those receiving bevacizumab and chemotherapy (median PFS 9.7 months *vs.* 6.1 months; unstratified HR, 0.59; 95% CI: 0.37–0.94) (140). However, the comparison of the triple combination (atezolizumab plus bevacizumab plus chemotherapy) versus atezolizumab plus chemotherapy is not reported in the study. Indeed, the main biological question behind the IMpower 150 trial was whether VEGF blockade enhanced the efficacy of immunotherapy. Considering that this important information is omitted, we cannot rely on the findings of the IMpower 150 trial (140).

There are several trials ongoing exploring the combination of first and second-generation EGFR TKIs with immunotherapy (*Table* 7). Preliminary results from the CheckMate 012 study suggest that nivolumab plus erlotinib may provide some benefit with

Table 6 Ongoing clinical trials of first- and second-generation EGFR TKIs in combination with other targeted therapies in *EGFR*-mutant NSCLC patients

ClinicalTrials.gov identifier	Phase; population	Treatment	Status
NCT01487265	Phase II; erlotinib-pretreated (sensitive)	Erlotinib + buparlisib (BKM120; selective PI3K inhibitor)	Ongoing, not recruiting
NCT01570296	Phase Ib; EGFR TKI-pretreated; molecular alterations of PI3K pathway; EGFR overexpression	Gefitinib + buparlisib	Ongoing, not recruiting
NCT02424617	Phase I/II; erlotinib-pretreated	Erlotinib + BGB324 (bemcentinib, R428; AXL inhibitor)	Recruiting
NCT03599518	Phase I; EGFR TKI-pretreated	Gefitinib + DS-1205c (AXL inhibitor)	Not yet recruiting
NCT03333343	Phase Ib; EGFR TKI-naive or not	Gefitinib + nazartinib (EGF816)[1]	Recruiting
NCT03292133	Phase II; EGFR TKI-naive	Gefitinib + nazartinib	Recruiting
NCT00600496	Phase I; EGFR TKI-pretreated	Erlotinib + selumetinib (arm 3)	Ongoing, not recruiting
NCT03076164	Phase I/II; erlotinib-pretreated	Erlotinib + trametinib	Recruiting
NCT01859026	Phase I/Ib; EGFR TKI-naive or not	Erlotinib + MEK162 (binimetinib; selective MEK inhibitor)	Recruiting
NCT02468661	Phase I/II; EGFR TKI-pretreated; c-MET amplified	Erlotinib + INC280 (capmatinib; c-MET inhibitor) *vs.* chemotherapy (phase II)	Recruiting
NCT01610336	Phase IB/II; EGFR TKI-pretreated; c-MET amplified	Gefitinib + INC280	Ongoing, not recruiting
NCT02374645	Phase Ib; EGFR TKI-pretreated; c-MET amplified	Gefitinib + volitinib (c-MET inhibitor)	Ongoing, not recruiting
NCT01982955	Phase Ib/II; EGFR TKI-pretreated; c-MET amplified and T790M negative	Gefitinib + tepotinib (c-MET inhibitor)	Ongoing, not recruiting
NCT03122717	Phase I; EGFR TKI-naive	Gefitinib + osimertinib (combined or alternative)	Recruiting
NCT02535338	Phase I/II; EGFR TKI-pretreated	Erlotinib + onalespib lactate[2]	Ongoing, not recruiting
NCT02716311	Phase II; EGFR TKI-naive	Afatinib + cetuximab	Recruiting
NCT03623750	Phase I/II; EGFR TKI-naive; EPICAL study	Afatinib + EGF-PTI[3]	Recruiting
NCT03054038	Phase I; EGFR TKI-pretreated	Afatinib + necitumumab	Recruiting
NCT02438722	Phase II/III; EGFR TKI-naive; S1403	Afatinib + cetuximab *vs.* afatinib	Recruiting
NCT01999985	Phase I; EGFR TKI-pretreated; objective response, or stable disease for at least 6 months	Afatinib + dasatinib	Ongoing, not recruiting

[1]EGF816, irreversible, third-generation, mutant-selective EGFR, with activity against T790M; [2]onalespib lactate, the lactate form of onalespib, a synthetic, orally bioavailable, small-molecule inhibitor of heat shock protein 90 (Hsp90); [3]EGF-PTI, EGF pathway targeting immunisation. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

Table 7 Ongoing clinical trials of first- and second-generation EGFR TKIs in combination with immunotherapy

ClinicalTrials.gov identifier	Phase; population	Treatment	Status
NCT01998126	Phase I; EGFR TKI-naive or not	Nivolumab/ipilimumab + erlotinib	Ongoing, not recruiting
NCT01454102	Phase I; EGFR TKI-naive or not; CheckMate 012	Nivolumab + erlotinib (arm E)	Ongoing, not recruiting
NCT02574078	Phase I/II; EGFR TKI-naive or not (maintenance)	Nivolumab + erlotinib	Ongoing, not recruiting
NCT02039674	A Phase I/II; EGFR TKI-naive	Pembrolizumab + erlotinib (cohort E); pembrolizumab + gefitinib (cohort F)	Ongoing, not recruiting
NCT02364609	Phase I; erlotinib-resistant	Pembrolizumab + afatinib	Recruiting
NCT03157089	Phase II; squamous cell lung cancer; 3rd-line and more; (LUX-Lung IO)	Pembrolizumab + afatinib	Recruiting
NCT02013219	Phase I; EGFR TKI-naive	Atezolizumab + erlotinib	Ongoing, not recruiting
NCT02088112	Phase I; EGFR TKI-naive or not	Durvalumab + gefitinib	Ongoing, not recruiting
NCT01998126	Phase I; EGFR TKI-naive or not	Ipilimumab + erlotinib	Ongoing, not recruiting
NCT02040064	Phase I; EGFR TKI-pretreated; GEFTREM	Tremelimumab + gefitinib	Ongoing, not recruiting
NCT02906163	Phase I/II; EGFR TKI-naive	Afatinib, gefitinib, erlotinib + thymosin alpha 1 (a peptide immune modulator) (phase II) *vs.* afatinib, gefitinib, erlotinib	Ongoing, not recruiting

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

acceptable safety profile EGFR TKI-resistant (141). In an ongoing phase Ib study 10 EGFR TKI-naive patients were treated with concurrent durvalumab and gefitinib (arm 1) or with gefitinib monotherapy for 4 weeks followed by concurrent durvalumab plus gefitinib (arm 2) (142). No clinically relevant differences in the ORR (approximately 79%) compared to what is already known for gefitinib monotherapy (73.7%) (25) were observed, and 55% of the patients suffered grade 3 adverse events (142). In the GEFTREM study that combined the anti-cytotoxic T-lymphocyte associated protein 4 (anti-CTLA4) antibody, tremelimumab, with gefitinib in previously treated *EGFR*-mutant patients, the best overall response was stable disease in 67% of patients, and all patients discontinued treatment after median duration of 8 weeks mainly due to disease progression (143).

Currently, there are several clinical studies in progress, and data will soon be published about the combination of EGFR TKIs and immunotherapy (*Table* 7). Until then, we should deprioritize immunotherapy (alone or in combinations) for the first- or second-line therapy of *EGFR*-mutant patients and relegate it to a later treatment, if at all.

First and second-generation EGFR TKIs in early-stage disease

It is still not clear whether EGFR TKIs have similar efficacy in metastatic disease as in patients with early-stage disease. Caution should be taken, since single therapy with EGFR TKIs abrogates EGFR downstream signaling, but also activates parallel signaling pathways and factors involved in cell migration, invasion, and metastasis (117-119,144,145). When, for instance, gefitinib was compared with placebo (the NCIC CTG BR19 study) for the post-operative treatment of operated stage IB–IIIA NSCLC patients, no benefit, or even worse outcome with gefitinib was found, even for the subpopulation carrying *EGFR* mutations (146). The trial was prematurely closed (146). Similar results were generated from the RADIANT phase III clinical trial, in which erlotinib was not able to prolong DFS in resected IB-IIIA EGFR overexpressing NSCLC patients (147).

However, there are also studies with promising results. Gefitinib has been tested as six-month maintenance after platinum-based chemotherapy in a phase II study which included surgically resected stage IIIA (N2 positive) *EGFR*-

Table 8 Studies of first- and second-generation EGFR TKIs in early-stage EGFR-mutant NSCLC

EGFR TKI	Study	Number of patients, population	Design	Primary endpoint	Ref.
Gefitinib	ADJUVANT, phase III	222, II–IIIA *EGFR*-mutant	Gefitinib *vs.* platinum-based chemotherapy	HR for DFS =0.60; P=0.0054	(149)
	NCIC CTG BR19, phase III	503 stage IB–IIIA, unselected	Gefitinib *vs.* placebo for 2 years	HR for OS =1.24; P=0.14	(146)
	Phase II, randomized	60, IIIA (N2), *EGFR*-mutant	Platinum-based chemotherapy followed by gefitinib for 6 months *vs.* platinum-based chemotherapy	HR for DFS =0.37; P=0.014	(148)
Erlotinib	SELECT, phase II, non-randomised	100, IA–IIIA, *EGFR*-mutant	Platinum-based chemotherapy followed by erlotinib for 2 years	2-year DFS rate =90%	(150)
	EVAN, phase II	100 IIIA *EGFR*-mutant	Erlotinib (2 years) *vs.* platinum-based chemotherapy	HR for DFS =0.26; P<0.001	(151)
	RADIANT, phase III	973, IB–IIIA, EGFR overexpression (IHC or FISH)	Erlotinib *vs.* placebo for 2 years	HR for DFS =0.90; P=0.324	(147)
	RECEL, phase II	41, unresectable stage III, *EGFR*-mutant	Erlotinib + RT (erlotinib for 2 years) *vs.* cisplatin-etoposide + RT	HR for PFS =0.053; P<0.001	(152)
Icotinib	Phase II, randomized	41, IB–IIIA, *EGFR*-mutant	Platinum-based chemotherapy followed by icotinib for 4–8 months *vs.* platinum-based chemotherapy	24 months DFS 90.5% *vs.* 66.7%; P=0. 066	(153)

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer; DFS, disease-free survival; HR, hazard ratio; PFS, progression-free survival.

mutant NSCLC patients (148). The combination was related to a significant improvement in disease-free survival (DFS) in comparison with adjuvant chemotherapy alone (148) (*Table 8*). The phase III ADJUVANT study followed in China. The ADJUVANT study is the only phase III clinical trial in which gefitinib was associated with longer DFS compared with platinum-based chemotherapy for the adjuvant therapy of surgically resected stage II–IIIA *EGFR*-mutant NSCLC patients (149). Still, the study has been strongly criticized (154-156), due to its several caveats, including the non-proportionality of the Kaplan-Meier curves. The ADJUVANT study has not changed the clinical practice for postoperative therapy of *EGFR*-mutant NSCLC patients. The EVAN phase II study, similar to the ADJUVANT trial, was conducted in Asia in stage IIIA *EGFR*-mutant, surgically resected patients. Patients were allocated to cisplatin plus vinorelbine for four cycles or erlotinib for 2 years (151). The study demonstrated a longer DFS with erlotinib compared to chemotherapy (*Table 8*). In the phase II, non-randomized SELECT trial, adjuvant erlotinib after standard chemotherapy conferred a 90% 2-year DFS (150). The phase II RECEL study compared erlotinib versus etoposide plus cisplatin both with concurrent radiotherapy in unresectable stage III *EGFR*-mutant NSCLC. The results were in favor of erlotinib (152) (*Table 8*).

Icotinib was combined with chemotherapy in a phase II clinical trial for the adjuvant therapy of surgically resected stage IB–IIIA *EGFR*-mutant Chinese NSCLC. The study demonstrated a non-statistically significant trend for better 2-year DFS when icotinib was combined with adjuvant chemotherapy (153) (*Table 8*). There are several phase II

clinical trials ongoing that explore the effect of adjuvant EGFR TKIs (including the third-generation EGFR TKI, osimertinib) for *EGFR*-mutant NSCLC patients [see for details *Table 2* in ref (157)].

Conclusions

With the availability of multiple compounds for *EGFR*-mutant NSCLC, treatment needs to be considered with a long-term plan to maximize survival. There is evidence that the second-generation EGFR TKIs, and even more so, the third-generation EGFR TKI, osimertinib, are more potent than gefitinib or erlotinib. However, several factors should be considered when deciding on the first-line therapy of an *EGFR*-mutant patient, including the presence of brain metastases, the type of EGFR-mutation and the tolerability profile. It is unavoidable that research in the next few years will focus on outcomes and tolerability of different sequences so that we finally turn *EGFR*-mutant NSCLC into a chronic disease.

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