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EGFR TKIs IN NON-SMALL CELL LUNG CANCER: HEAD AND TAIL OF THE COIN

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Abstract

TKIs against the human EGFR have become standard of care for patients with advanced *EGFR* mutant NSCLC. But despite the initial good results with first generation *EGFR* TKIs, patientsâ€™ cancers will progress after a median duration of response of around 12 months. And some patient will not even show response or only for a short time.

These are due to the development of resistance. Significant research has tried to understand the mechanism behind these two different types of resistance to be able to overcome it with the development of newer drugs. Different generations of TKIs are currently approved to use in routine clinical practice but further investigations need to be carried out to ascertain the best approach to this significant group of patients to be able to extend their cancer natural history with good quality of life.

This article will review the timeline of development of EGFR-TKIs and the mechanism behind the emerging resistance to be able to understand where are we know and where our efforts should be directed.

Introduction

Primary lung cancer is the second most common malignancy and still the most frequent cause of cancer related deaths worldwide, being non-small cell lung cancer (NSCLC) the majority of them (around 80%â€“90%). [1,2]

The most frequent type of NSCLC is adenocarcinoma, accounting for around 40%. This is the most common type in smokers and non-smokers and both genders regardless their age [3]. Â

Unfortunately >50% of primary NSCLC present already with stage IV disease which continues to be incurable.

For many years, cytotoxic chemotherapy has been the only systemic treatment available aiming at improving survival by controlling disease related issues [4-6].Â

Four large multicenter randomized clinical trials assessing different regimens of hemotherapy with platinums, came to the conclusion that no regimen was superior to another, obtaining a median overall survival (mOS) of about 8-10 months [7-10]; yet not ideal.

However, when bevacizumab, an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, was added to the doublet chemotherapy regimen, better OS was reported (12.3 vs 10.3 months) [11].Â Â

In 2015, the American Society of Clinical Oncology guidelines recommended then a platinum based chemotherapy combination for patients with a performance status (PS) of 0 or 1, Â [12] and although cisplatin seemed to be slightly more effective than carboplatin, it produced Â more adverse events, therefore it was not advised for patients with a PS of 2 [13].

The addition of bevacizumab to carboplatin plus paclitaxel was recommended as long as no contraindicated.

Pemetrexed, another cytotoxic agent, had gradually become part of the systemic treatment for advanced non-squamous NSCLC based on its demonstrated activity as first-line, maintenance and second or third-line therapy for this group of NSCLC and it has been generally well tolerated [14].

But, despite all these results, chemotherapy based treatmentâ€™s benefits had plateaued, and thus more effective drugs were desperately needed.

Finding personalised treatments have become the dream in NSCLC with a double hope. First to improve OS with good control of cancer related events and second, but very important as well, to improve the tolerance profile of the new drugs or regimens by targeting cancer molecular drivers, minimising damage to healthy cells.

This dream became real following the success of imatinib, a BCR-ABL tyrosine kinase inhibitor (TKI) in chronic myeloid leukemia (CML) which was a therapeutic breakthrough.

BCR/ABL is an ideal target because this fusion protein is present in all CML cells but not in healthy cells. Thus, imatinib binds to BCR-ABL kinase domain and switches off the leukemogenesis pathway [15].

This prompted the search for key genetic alterations that stimulate proliferative signals in malignant cells

and could be targeted by a treatment [16].

In NSCLC (mainly adenocarcinomas), molecular driver mutations have been found during the past decade and subsequently several specific targeted therapies have been developed. Â

This has turned around the landscape of therapies in NSCLC. The presence of molecular driver mutations in epidermal growth factor receptor (EGFR) is, among others, in the eye of the storm of the oncogenesis in NSCLC [17-19].

The fact is that several clinical trials have shown an improvement in progression free survival (PFS) with a first line EGFR TKI in comparison with standard chemotherapy when patientsâ€™ tumours show positivity for EGFR mutations [20-25].

However, despite this initial boom of happiness, the reality shows that most patients will acquire drug resistance at some point, and some of them will not even respond at all or only for a very short period of time.

Thus further research is needed to ascertain the underlying causes for such resistances and to create either new agents or different strategies to overcome this issue and extend the treatment benefits for our patients.

This article will review these two aspects of the EGFR-TKIs (heads and tails) in NSCLC patients with metastatic disease. Â

EGFR in NSCLC

EGFR belongs to the erbB family which includes several members (erbB1 or EGFR, erbB2 (HER-2), erbB3 and erbB4.

It holds an extracellular ligand binding domain, a transmembrane area and intracellular TK domain.

When a specific ligand attaches to it, EGFR suffers a configurational adjustment and phosphorylation of the intracellular part, leading to the activation of the downstream cascade of events that will eventually impact on cell growth and blockage of apoptosis [26].

DNA mutations as identified by polymerase chain reaction (PCR), can appear in extracellular or intracellular domains of the protein.

In NSCLC, some authors have reported that EGFR is overexpressed or mutated in intracellular areas in around 43-89% [27], while others have found that 25% of NSCLC had mutations in the EGFR TK domain, associated to EGFR overexpression in 75% of cases [28,29].

These activating mutations of EGFR are identified in the first four exons (18 through 21) of the TK domain and classified into three groups: group 1 incorporates the in-frame deletions in exon 19 (44%); group 2 (41%) includes single-nucleotide replacements in exon 21 (arginine is replaced by leucine at codon 858 (L858R) and group 3 (5%) with in-frame duplications or insertions in exon 20.

The first two groups are recognised as â€œclassical mutationsâ€•, and are more frequent in females, never smokers, East Asians and adenocarcinomas [30]. In fact, those account for around 90% of all EGFR activating mutations. The presence of these will constitutively activate the signal transduction cascades in different pathways, guiding to cell proliferation and anti-apoptosis.

It is well documented that the presence of these activating mutations is linked to a response to EGFR TKIs, but unfortunately only in 70% of the patients [31,32].

The rest either do not respond or only get a benefit for a short time, generally < 3 months, due to the presence of primary resistance.

This phenomenon creates the first tail of the coin of TKIs development. Â

Moreover, [33] patients treated with EGFR-TKIs with good initial response, will eventually show evidence of progressive disease (PD), linked to the appearance of resistance to these drugs, with a mPFS of about 9 to 13 months, being this the second tail in these agents development.

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First-generation EGFR TKIs â€“ the head of the coin

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First-generation EGFR TKIs (gefitinib, erlotinib and icotinib) are drugs that will reversibly attach to the ATP-binding site of the EGFR TK domain and block the attachment of ATP to the TK domain, preventing phosphorylation of the EGFR and thus stopping cell growth and causing cell death [34].

Gefitinib and erlotinib, are globally approved for EGFR-mutant NSCLC while icotinib is only approved in China.

These agents have documented higher response rate (RR), PFS and quality of life when compared to standard platinum-based chemotherapy in patients whose tumours show an activatingÂ *EGFRÂ* mutation [20, 21, 23-25, 35-37].

In fact, as mentioned earlier in this review, EGFR activating mutations NSCLC tend to respond well to

TKIs, whereas those who carry wild-type (WT)Â *EGFRÂ* and/orÂ *KRASÂ* mutations will not respond [38-40].

Randomized phase III trials have shown that first-line EGFR TKIs have improved PFS in comparison to chemotherapy in advanced EGFR mutated NSCLC [20-25].

OS was not improved but this is probably related to the high crossover rate after PD was determined [20-25].

These findings led to the approval of these drugs as the standard of care for such patients.

Gefitinib

In initial clinical studies, gefitinib showed only some tumour responses (around 10-19%) in chemotherapy-refractory advanced NSCLC and when combined to chemotherapy, no further benefit was seen [41-44].

This drug received accelerated approval by the U.S. Food and Drug Administration (FDA) in May 2003 as monotherapy for advanced NSCLC after failure of both platinum-based and docetaxel chemotherapies [45]. Â Â

This was based on a RR of 15% as reported in two phase II clinical trials: the IRESSA Dose Evaluation in Advanced NSCLC (IDEAL)-1 and 2 [41,42].

However, in June 2005, FDA restricted its use to patients who were already on it showing a benefit or for those included in clinical trials with an Institutional Review Board approval before June 2005, being withdrawn later (April 2012) due to the negative results of three phase III trials (IBREESE, ISEL, and INTEREST) [45-47].

In 2004 the IRESSA NSCLC Trial Assessing Combination Treatment (INTACT-1 and 2) phase III clinical trials assessed the effect of gefitinib in first-line setting combined with chemotherapy [44,48]. Both studies were negative.

Once activating EGFR mutations were evidenced in 2004 [49-51] gefitinib was incorporated again to phase III trials, showing significant benefits. This finally led to its approval in 2015 for first-line of EGFR-mutant patients.

First line gefitinib vs carboplatin/paclitaxel was assessed in Asia [Iressa Pan-Asia Study (IPASS)] in a clinically selected population [35]. Results were superior for gefitinib especially when EGFR mutations were positive [35,52].

Moreover, two phase III Japanese trials (NEJ002 and WJTOG3405) [20,21,53] were carried out in NSCLC EGFR mutated, obtaining similar results.

IMPRESS is another phase 3 trial [54], assessing the benefits in PFS with the continuation of gefitinib/platinum based chemotherapy after PD, in comparison to placebo/chemotherapy. Results showed that the continuation with gefitinib does not prolong PFS, suggesting that chemotherapy would be the standard of care in that situation.

Erlotinib

The second EGFR-TKI first generation is erlotinib. This was initially approved by the FDA in November 2004 for metastatic NSCLC after failure of chemotherapy [55].

Later, the Sequential Tarceva in unresectable NSCLC (SATURN) assessed erlotinib after finishing chemotherapy, as a maintenance treatment. It showed significant improvement in OS from 11.1 months with placebo to 12.3 months with erlotinib, with even further benefit in a subgroup of patients whose tumours had EGFR mutations [56].

Therefore, it was approved in 2010 as a maintenance treatment for unselected NSCLC who had shown a benefit from first-line platinum-based cytotoxic chemotherapy.

Several randomized trials, EURTAC (European Randomized Trial of Tarceva vs Chemotherapy), the OPTIMAL (CTONG0802) and the ENSURE have shown the superiority of erlotinib compared to chemotherapy in terms of RR and PFS for first-line ofÂ *EGFR*-mutant NSCLC patients [23,25,57].

And based on those results, EMA and FDA have approved erlotinib for first-line therapy ofÂ *EGFR* -mutant NSCLC.

Further studies were carried out as the TRIBUTE [58] and the Tarceva Lung Cancer Investigation Trial [59]. These two phase III clinical trials assessed erlotinib or placebo in combination with a platinum-based chemotherapy for the first-line of NSCLC patients unselected forÂ *EGFRÂ* mutations.

Neither of them showed a survival benefit for the combination with erlotinib and chemotherapy [58,59].

And the TOPICAL phase III clinical trial is a large study to assess whether erlotinib as monotherapy in first-line for unselected advanced stage NSCLC who are not suitable for chemotherapy. Results showed no differences in OS for both groups (3.7 months for erlotinib and 3.6 for placebo), concluding that its administration is not beneficial for unselected patients [60].

As second line treatment, it has been compared to

chemotherapy in two randomized trials (TaiLOR, DELTA) again for unselected NSCLC patients. Results showed that chemotherapy significantly extended PFS compared with erlotinib [61,62].

Following these studies, a multicenter randomized phase III trial (WJOG 5108L) was carried out to compare two first generation TKIs, erlotinib vs gefitinib in NSCLC adenocarcinoma, initially regardless of the EGFR mutation status [63] but later amended to include only EGFR mutation-positive patients.

561 patients were recruited and the results showed a PFS of 8.3 and 10.0 months for gefitinib and erlotinib among EGFR mutated NSCLC patients respectively (p = 0.424). Thus, authors did not demonstrate non-inferiority of gefitinib vs erlotinib in terms of PFS. However, when comparing the Kaplanâ€“Meier survival curves for both arms, these two drugs were considered pretty similar.

These results transformed theseÂ *EGFRÂ* TKIs as the treatment of choice for newly diagnosedÂ *EGFR* -mutant advanced NSCLC.

Unfortunately, not all that glitters is gold and after a median duration of response of around 12 months, all patients will develop tumour resistance, and in >50% of cases, this will be due to the emergence of a specific mutation, theÂ *EGFRÂ* T790M mutation.

For those cases which show PD on gefitinib or erlotinib, it is vital to understand the mechanisms of resistance to be able to choose the best therapeutic approach.Â

Secondary resistance: the tail of the coin

Patients with EGFR mutant NSCLC will eventually show resistance to the EGFR TKIs and it is crucial to understand the underlying mechanisms to be able to develop a new group of agents or combination regimens to overcome this issue.Â

Several molecular processes are involved in acquired resistance to the first-generation EGFR-TKIs, but the most important one seems to be the emergence of a secondary EGFR-TK domain mutation in exon 20, known T790M. Â

This mutation is due to a single nucleotide change replacing a threonine with methionine which leads to inability of TKIs to bind [64-66]

Around 40% to 50% of NSCLC patients resistant to gefitinib or erlotinib showed positivity for T790M mutations [67].

It has been suggested that T790M causes resistance to EGFR-TKIs probably by increasing the affinity to ATP [68]. In any case, this is not the only mechanism behind this secondary resistance.

Others implicated are theÂ *NF-kBÂ* activation, which affects mainly rociletinib (a third-generation EGFR-TKI) [69]. A study showed that on H1975 NSCLC cells, with T790M mutation, therefore resistant to gefitinib and erlotinib, are sensitive to rociletinib.

And the induction of resistance to rociletinib led to NF-kB activation replacing oncogenic EGFR signalling. Also, the blockage of this pathway with the proteasome inhibitor bortezomib, made those cells sensitive again to rociletinib. This is a relevant point to explore further as could be [70-72] a promising intervention in patients showing PD after a third-generation EGFR-TKI.

Second generation TKIs: brought to resolve resistance to first generation EGFR-TKIs

As big problems need big solutions, recently EGFR irreversible inhibitors have opened new hopes for NSCLC patients who showed PD after first generation EGFR-TKIs.

These drugs were developed to delay or defeat acquired resistance by showing a wider kinases blockage and by irreversibly attaching to the TK domain.

Second generation TKIs will irreversibly block human EGFR 2 (Her2) and EGFR kinases [73] and presumably, they might as well inhibit T790M EGFR, increasing the efficacy of the drug and reducing the rate of further drug resistance [73].

AFATINIB

Afatinib is an example of this new generation [74] that further delays PD by keeping irreversible attachment to EGFR and HER2 [74].

It has higher affinity for the EGFR-TK domain than the first-generation, causing longer suppression of EGFR signalling [74].

A randomized, open label phase IIb trial (LUX-Lung 7) comparing afatinib vs gefitinib was carried out in 319 patients, in first-line for advanced lung adenocarcinoma EGFR activating mutations positive (exon-19 deletions or the L858R point mutation) [75].

Afatinib showed better PFS (11.0 vs 10.9 months; HR = 0.73, p = 0.017) and TTF (median of 13.7 vs 11.5 months; HR = 0.73, p = 0.0073) but not OS.

LUX-Lung 3 compared afatinib to cisplatin/pemetrexed in first-line advanced lung adenocarcinoma with activating EGFR mutations showing a significantly increased PFS, but not OS [76,77].

Similar results were obtained in the LUX-Lung 6 trial when compared to gemcitabine and cisplatin [25]. Â

However, when looking at the subgroup of patients with deletions in exon 19 only, OS was significantly increased with afatinib in both studies LUX-Lung 6 and 3 [76,77]. Â

In second-line afatinib significantly prolonged PFS and OS when compared with erlotinib, regardless of EGFR mutation status (LUX-Lung 8 trial) [78].Â Â

Overall, it seems that afatinib is a relevant option for first-line in patients with advanced NSCLC and activating EGFR mutations [74].Â Â

After the discovery of T790M many new agents targeting this mutation have beenÂ developed. Second-generationÂ *EGFRÂ* inhibitors (neratinib, afatinib, and dacomitinib) have shown a positive anti-T790M effect in the laboratory, but unfortunately their clinical activity has been poor, with RR of less than 10% among patients resistant to gefitinib or erlotinib [79-81]. Moreover, higher signs of toxicity, mainly skin and digestive, were seen due to WTÂ *EGFR*Â inhibition at lower concentrations than those required to inhibit T790M.

LUX-Lung 5 trial was carried out to know the efficacy of continuing with afatinib after PD. This trial compared paclitaxel alone vs in combination with afatinib for patients heavily pre-treated who had also progressed on previous EGFR TKIs (first generation and afatinib). Authors concluded that the combination achieved further benefits in PFS and RR in patients who had acquired resistance to TKIs after initial benefit.

This trial was the first in showing the improvement in efficacy by continuing ErbB targeting treatment after PD vs changing to chemotherapy single agent.

Moreover, this regimen of afatinib combined with paclitaxel warrants further investigation in patients withÂ *EGFR T790MÂ* mutation-negative who have progressed on a first-generation EGFR-TKI [82].

DACOMITINIB

Dacomitinib is a potent, second-generation EGFR-TKI that irreversibly binds EGFR, as well as the related proteins ErbB2 and ErbB4 [83].

Early-phase clinical trials have reported efficacy in NSCLC [84].

The phase III randomized trial ARCHER 1050, in first-line [85], compared dacomitinib vs gefitinib in patients with sensitizing EGFR mutations advanced NSCLC.

This trial excluded patients with brain metastases as opposed to LUX-Lung 7 (with afatinib).

The results reported a significant benefit in PFS with dacomitinib (14.7 months vs 9.2 months) vs gefitinib (HR = 0.59, p < 0.0001) [85]. OS was also improved with dacomitinib (34.1 months vs 26.8 months; HR = 0.76, p = 0.044) [85].

ARCHER 1028 is a phase III trial comparing dacomitinib vs erlotinib after one or two lines of chemotherapy in unselected patients with NSCLC [86].

To notice that despite randomization, patients included in the dacomitinib arm, had worseÂ ECOG (PS 2 - 10.1% vs 1.6%), EGFR-mutant (10.1% vs 5.8%), and heavily pre-treated (22.8% vs 16.4%) than patients on the erlotinib arm. The primary endpoint PFS was achieved with a median of 2.86 vs 1.91 months in the dacomitinib and erlotinib respectively (p 0.012). In the analysis of subgroups, dacomitinib showed further benefit if KRAS WT/any EGFR and KRAS/EGFR WT with not statistically significant advantage among EGFR mutations. Although dacomitinib obtained higher RR, OS was not different. Unfortunately, dacomitinib showed a more concerning pattern of side effects than erlotinib and needed a dose reduction more frequently (double than with erlotinib).

ARCHER 1009 is another randomized, multicentre (in Asian and non-Asian countries), double-blind trial, comparing again dacomitinib to erlotinib in advanced NSCLC previously treated with one or two chemotherapy regimens. 878 patients were recruited, 82 patients (9.3%) had an EGFR activating mutation and 136 (15.5%) had a mutated KRAS [87]. Â

PFS (2.6 months in both arms) or OS (7.9 m in dacomitinib vs 8.4 m in erlotinib) did not show significant differences.

Once again, if EGFR sensitizing mutations were present, longer PFS (11.0 months with dacomitinib and 10.9 with erlotinib) and OS (26.6 months with dacomitinib and not reached with erlotinib) were seen, in comparison to WT-EGFR (PFS 1.9 m for both and OS 6.8 with dacomitinib and 7.6m with erlotinib).

Safety profile favoured erlotinib with less diarrhoea, rash, acneiform dermatitis, paronychia and stomatitis.

All side effects associated to dacomitinib are related to the EGFR blockade. Phase IIâ€“III trials have documented rates of dose reduction of 30 to 66% and discontinuation of 6 to 10% [88]. Â

Some side-effects, such as skin toxicity, improved after adequate management.

In fact, the ARCHER 1042 study that doxycycline reduced the rate of Grade â‰¥2 skin toxicity in comparison to placebo (23.2% vs 46.6%, P=0.016) and a slight though not significant reduction in Grade â‰¥2 diarrhoea [89]. Â

Therefore, randomized studies suggest that

second-generation EGFR-TKIs are better than first-generation, at least in terms of PFS [90].Â

Overcoming T790M with second generation TKIs

Previous reports have shown that T790M mutation is the main cause of resistance to gefitinib in NSCLC [91]. Â Preclinical observations showed afatinib combined with cetuximab (an anti-*EGFR m*onoclonal antibody) overcame T790M resistance [92]. Â This led to a phase Ib study with 126 heavily treated patients with advancedÂ *EGFR*-mutant NSCLC resistant to first generation TKIs.

Results showed a RR of 29%, similar regardless of T790M status and PFS of 4.7 months. Unfortunately, the dualÂ *EGFRÂ* blockade caused higher rates of toxicity, mainly rash, diarrhoea and fatigue, documented in 46% of patients [32].

A randomized phase II/III trial (NCT02438722) of afatinib plus cetuximab vs. afatinib alone is currently open in treatment-naÃ¯ve patients with advancedÂ *EGFR*-mutant NSCLC.

Third-Generation EGFR TKIsÂ

The previous generation of EGFR-TKIs caused some disappointment when looking at the reversal of resistance to gefitinib/erlotinib.

This led to another generation of TKIs to developed, the third. These include osimertinib, EGF816, olmutinib, PF-06747775, YH5448, avitinib and rociletinib.

The common characteristics of this generation are the greater activity in EGFR mutant cells than in WT-EGFR, selective targeting of T790M mutations and irreversible attachment to EGFR-ATP site [94].

The only approved third generation TKI is osimertinib.

All these drugs show only a few toxicities related to the small activity against WT-*EGFR*.

Osimertinib is an irreversible EGFR-TKI selective for both EGFR mutated and T790M resistance mutations [95]. This was the first approved by FDA and EMA in November 2015 and February 2016, respectively, for metastaticÂ *EGFRÂ* T790M+ NSCLC, which has shown PD on or afterÂ *EGFRÂ* TKI.

Osimertinib acts as a covalent TKI with potent efficacy against severalÂ *EGFRÂ* mutations (L858R, L858R/T790M, exon 19 deletion, and exon 19 deletion/T790M) and evidenced as well nearly 200 times higher potency against L858R/T790M than WT-*EGFR*.

The drug is metabolized to two circulating metabolites, AZ5104 and AZ7550.

AZ7550 is similar in potency and selectivity to osimertinib, whereas AZ5104 showed higher potency against exon 19 deletions, T790M mutants and WT-*EGFRÂ* [95].

A phase I/II dose-escalation study of osimertinib (AURA, NCT01802632) was carried out in patients with locally advanced or metastaticÂ *EGFR*-mutated NSCLC who had shown PD on first- or second-generationÂ *EGFRÂ* TKIs.

YangÂ *et al*, published the results from the phase II extension trial.

201 patients received osimertinib, with a median treatment duration of 13.2 months at the time of data cutoff (November 1, 2015).

198 patients were evaluable and the results showed a RR of 62%, median duration of response 15.2 months and PFS of 12.3 months.

In terms of toxicities, diarrhoea followed by rash were the most frequent ones, involving around 40% of patients each with less than 1% being grade 3 or above.

The phase II study AURA2 (NCT02094261) showed a similar RR and PFS in patients with Â T790M mutation positive [96].

These authors reported as well positive PFS with osimertinib in patients with CNS metastases and a significant CNS response (64%).

AhnÂ *et alÂ* presented the results of a pre-planned pooled analysis of two phase II studies, the AZD9291 First Time in Patients Ascending Dose Study (AURA) extension trial (NCT01802632) and the AURA2 trial (NCT02094261). 411 patients were included. Most of them received osimertinib as third line or later [97].

At the data cutoff (date of November 1, 2016), the median treatment exposure was 16.4 months (range, 0?29.7 months) with a RR of 66%, median response duration of 12.3 months and PFS of 9.9 months.

At a later data cutoff (date of May 1, 2018), OS was 26.8 months and the 12?month, 24?month, and 36?month survival rates were 80%, 55%, and 37%, respectively. The most frequent side effects again diarrhoea and rash in about 40% each being grade 3 or above in 1% or less.

These results emphasise once more the relevance of osimertinib in patients with pre-treated, T790M?positive, advanced NSCLC.

But osimertinib has also demonstrated activity in first-line. SoriaÂ *et al*Â carried out a study to compare osimertinib with standard EGFR-TKIs in NSCLC,Â *EGFR*Â mutationâ€“positive (exon 19 deletion or L858R). This FLAURA trial [97] was a phase III,

double blind, that randomised 556 patients to osimertinib or either gefitinib or erlotinib). The primary end point was PFS and reported a significantly longer PFS with osimertinib (18.9 months vs. 10.2 months; P< 0.001). RR was similar in both arms, 80% with osimertinib and 76% with standard EGFR-TKIs (P=0.24). Median duration of response 17.2 months with osimertinib vs 8.5 months with standard EGFR-TKIs. OS data were immature at the interim analysis but at 18months, the survival rate was 83% with osimertinib and 71% with standard EGFR-TKIsÂ (NS). Toxicity of grade 3 or higher was less frequent with osimertinib (34% vs. 45%). These authors concluded that osimertinib showed superior efficacy to that of standard EGFR-TKIs in the first-line treatment ofÂ *EGFRÂ* mutationâ€“positive advanced NSCLC, with a similar safety profile and lower rates of serious toxicities.

The AURA 3 is an open-label, phase III, randomized, international trial that compared in a 2:1 ratio osimertinib vs pemetrexed plus carboplatin or cisplatin for up to six cycles; maintenance pemetrexed was allowed.

All patients had a T790M-positive advanced NSCLC which had progressed on first-line EGFR-TKI. The primary end point was PFS.

419 patients were recruited. PFS was longer with osimertinib (10.1 months vs. 4.4 months, P< 0.001) and RR favoured as well osimertinib (71% vs 31%; P< 0.001) compared with chemotherapy. Â

144 patients had brain metastases and in those cases, the PFS was longer with osimertinib (8.5 months vs. 4.2 months) as well. Â

Moreover, toxicity grade 3 or above was lower with osimertinib (23%) than with chemotherapy (47%) [99].

This trial showed a significant benefit of osimertinib among T790Mpositive patients after PD during first-line EGFR-TKI therapy.

Other EGFR-TKI third generationÂ -Â

Rociletinib (CO-1686)Â

Rociletinib is a third generation EGFR-TKI that shows irreversible inhibitor of frequently mutated forms ofÂ *EGFR*, including T790M, with minimal effect against wild-typeÂ *EGFRÂ* in preclinical studies [100].

It is a third generation TKI, mutant-selective, covalent inhibitor of both the activating EGFR mutations, (exon 19 deletions and L858R) and the resistance mutation T790M. It lacks activity against exon 20 insertions [101].

TIGER-X (NCT01526928) was a phase I/II study for patients with NSCLC with acquired resistance to first or second generation EGFR TKIs [101].

The phase II part of the trial required the presence of T790M mutation. At the time of the report, 130 patients had been recruited. Among the 46 evaluable patients with centrally confirmed T790M-positive cancers, RR was 59% whereas for 17 patients with T790M negative, RR was 29%. No duration of response was presented. PFS at the time of the analysis was 13.1 months with data on 82% of the patients censored [101].

In November 2015 a pooled analysis of TIGER-X and TIGER-2 (NCT02147990), another phase II trial assessing rociletinib in second line forÂ *EGFRÂ* T790M+ NSCLC.

325 patients were assessed (dose range, 500â€“750 mg twice daily) and overall RR was 30.2%. The median duration of response for the two treatment doses was 8.8 and 9.1 months, respectively. The significant difference in RR prompted an updated analysis of cases (intention-to-treat population) included in TIGER-X trial confirming RR of 45% and 17% among T790M+ and T790Mâˆ’ tumours, respectively [102].

These results led to a halt in the enrollment of all ongoing rociletinib studies, including the phase III TIGER-3 trial (NCT02322281) and its clinical development has stopped.

Olmutinib (BI-1482694/HM61713; Olitaâ„¢)Â

Olmutinib is another third generation TKI against mutantÂ *EGFR*Â including T790M, not active against WTÂ *EGFRÂ* [103].

It has been investigated in a phase I/II trial Olmutinib (NCT01588145) assessing Korean NSCLC who failed previous EGFR TKI [104].

In the phase II study of patients with T790M, RR was 56% with DCR of 90%. PFS was 7.0 months. The most frequent side effects were diarrhoea (55%), rash (39%) and nauseas (38%) [104].

The initial plan was to continue with further clinical development of this drug within the ELUXA trials. However, due to a drug safety report of a fatal case of toxic epidermal necrolysis (TEN), its development stopped there [105].

ASP8273

ASP8273 is an irreversible TKI that specifically blocks TK activity ofÂ *EGFRÂ* mutations including T790M, with poor effect against WTÂ *EGFRÂ* [106]. It might also suppress signallingÂ *viaÂ* ERK and Akt.

It is active in E*GFRÂ* cell lines resistant to other TKIs such as osimertinib and rociletinib (47).

ASP8273 was evaluated in an open-label phase I/II study (NCT02192697) for safety and efficacy [107].

In a phase I/II trial in Japanese patients with EGFR mutant NSCLC after failure of first line EGFR TKI, RR was 50% for all patients dosed with â‰¥100 mg with RR of 80% in T790 M positive patients. The most frequent toxicities were diarrhoea (56%), nausea (31%), vomiting (31%) and thrombocytopenia (31%) [106].

In a North American trial with 60 patients with EGFR mutated NSCLC who had failed after EGFR TKI, 90% of patients had T790M mutation. In the latter group, RR was 37.5% with disease control rate of 65%. PFS 6.7 months [108].

A phase III study assessed ASP8273 vs first generation EGFR TKI in NSCL with EGFR activating mutations in the first line setting (SOLAR) [109].

Primary end point was PFS. 530 were randomized 1:1 to receive ASP8273 or erlotinib/gefitinib.

PFS was 9.3â€‰months for ASP8273 and 9.6â€‰months for erlotinib/gefitinib group. (P=â€‰0.992).

RR of 33% for ASP8273 vs 47.9% in the erlotinib/gefitinib arm with similar duration of response (9.2â€‰months for ASP8273 vs 9.0â€‰months for erlotinib/gefitinib).

More grade â‰¥3 adverse events were seen in those receiving ASP8273 (54.7% vs 43.5%).

An independent data monitoring committee carried out an interim safety analysis and adviced against continuing this study due to toxicity and limited efficacy of ASP8273 relative to erlotinib/gefitinib. Authors concluded that this drug in first-line did not show improved PFS or equivalent toxicities versus erlotinib/gefitinib.

Avitinib

This agent will irreversibly inhibit EGFR TKI with activity against EGFR mutations including T790M without effect in WT EGFR. It is structurally different from other TKIs such as as osimertinib [110].

It has been assessed in a phase I/II study for EGFR mutant patients who had progressed on first line EGFR TKI [111] and had acquired T790M mutation.

136 patients were treated in seven dose cohorts (50-350 mg BID). RR (including unconfirmed responses) and disease control rate were 44% and 84% respectively. The cohorts of 150-300 mg BID showed a RR and disease control rate of 51% and 89% respectively.

It was well tolerated with diarrhoea (38%) and rash (24%) mainly grade 1 and 2 [111]. A subgroup of patients with brain metastases, the intracranial PFS of two patients were shorter than extracranial PFS. This finding may be attributed to a low blood-brain-barrier penetration rate of 0.046%-0.146% [112].

Nazartinib (EGF816)Â

Nazartinib is another irreversibleÂ *EGFRÂ* mutated inhibitor targeting bothÂ *EGFR*-activating mutations (L858R, Del19) and the resistant T790M mutation, while no active against WTÂ *EGFRÂ* [113].

NCT02108964 is a phase I/II first-in-human trial of nazartinib inÂ *EGFR*-mutated locally advanced or metastatic NSCLC [114]. Â

Patients were assigned to receive once-daily nazartinib with doses ranging from 75 to 350 mg. At the cutoff date of January 29, 2016, 152 patients had been treated in seven cohorts (51). Among them, 147 patients were evaluable for response. The confirmed RR was 46.9%. The estimated median PFS was 9.7 months. Among 69 patients with confirmed responses at the cutoff date, the estimated median duration of response was 9.5 months.

The most frequent side effects were rash (54%), diarrhoea (37%), and pruritus (34%). Curiously, these rashes had a different pattern, location, and histology than those seen with otherÂ *EGFRÂ* TKIs that target WT-*EGFR*.

This agent is also investigated in association with INC280, a specificÂ *METÂ* inhibitor (based on the potential escape pathway for third-generationÂ *EGFRÂ* TKIs) in an ongoing phase Ib/II study in patients with advancedÂ *EGFRÂ* mutant NSCLC (NCT02335944), and with nivolumab, an anti- PD-1 monoclonal antibody in a phase II study inÂ *EGFRÂ* mutant/ T790M+ NSCLC who have progressed on first-lineÂ *EGFRÂ* TKI (NCT02323126).Â

Primary resistance to EGFR TKIs

This is a complex event. While acquired resistance has been studied by checking further the tumour samples obtained at PD, it seems more difficult to recognise what factors are behind the primary resistance to TKIs [115].Â

Recently, the development of next generation sequencing (NGS) analyses has granted access to the whole genome and given further insight on the most common driver aberrations.

In fact, the concept of activating EGFR mutations

mutually exclusive, has recently changed dramatically with the demonstration of their co-existence with other driver mutations in a high proportion of patient naÃ¯ve for any treatment [116, 117].Â

A large French Biomarkers molecular database with 17664 lung cancer patients was used to assess the prevalence of multiple molecular alterations in treatment naÃ¯ve patients, and their impact on prognosis as compared to those cases with one mutation or no mutation at all. Results evidence that almost 1% of cases harboured multiple aberrations (2-3 driver mutations) [118].Â

Authors concluded that a concurrent *PIK3CA*Â orÂ *KRAS*Â mutations in cases with EGFR mutations, confer lower sensitivity to EGFR TKIs. However, the number of responses appears to be good enough as to continue to use these drugs as first or second line of treatment. The identification of the allelic fraction of each mutation would be relevant to quantify the relative importance of each of them and guide the first-line treatment.

It is generally accepted that after being treated with EGFR-TKIs, NSCLCs may develop resistance by selecting already resistant clones or the tumour changing to a different oncogenic pathway controlling proliferation and survival, even if the TKI-sensitive clones are destroyed.

This reflects once again the cancer heterogeneity and that EGFR mutated adenocarcinoma depends not only on EGFR but also on other concurrent drivers [119].Â

It has been suggested that primary and secondary TKI-resistance may share some genetic mechanisms or it may be that surviving malignant cells are able to quickly adjust to Â the targeted treatment [120,121]. Whatever the mechanism is, these resistances are usually noticed within the first 3 months after starting TKIs.

Several genetic alterations conferring resistance can be detected within the same tumour or even in different metastatic deposits within the same patient which complicates this issue even further [119].Â

Drug tolerance could explain as well primary resistance [122].Â

It seems that small groups of malignant cells can escape selective drug activity by switching to a quiet mode with negligible rate of proliferation. In fact, this has been claimed as a mechanism behind the acquired resistance as can provide with a latent group of cancer cells which will eventually develop proper resistance events, leading to cancer progression.

Rare mutations in EGFR, such as the exon 20 insertion, accounts for 5-10% of all EGFR mutations in NSCLC adenocarcinoma and it has been reported in 4% of NSCLC. This is related to TKI resistance [123,124] as well.Â Â

Vanita *et al* carried out a retrospective study of 580 NSCLC patients. 39.1% had EGFR TKI-sensitizing activating mutations and 3.4% had exon 20 insertion mutations [125].Â Â Â

Authors concluded that patients with exon 20 insertion showed a poorer OS prognosis in comparison to EGFR- L858R mutation or an exon 19 deletion. The incidence of de novo exon 20 insertions was 3.4%. Different types of exon mutations seem to have different results.

Another way of showing resistance is the activation of other downstream pathways. Some of those mechanisms are involved as well in primary resistance to first-, second- and third-generation EGFR TKIs.

The hepatocyte growth factor (HGF)-cMET pathway, where amplification of cMET will give the ability of evading EGFR-TKI. This has been reported in 3% of TKI-naÃ¯ve NSCLC patients and in 10%-20% of EGFR-TKI treated [126,127].Â Â Â

This pathway is important for both the first- and third generation EGFR-TKIs [128-130].Â Â Â .

KRAS mutations usually appear in codon 12 (G12C/D/S/V) and codon 13 (G13C) and [131]Â Â Â

KRAS will generally become activated after stimulation of EGFR. This will turn KRAS permanently active regardless EGFR-stimulation and unlikely to respond to EGFR-TKIs [38]Â Â Â Â

This is relevant again for first and third generation of EGFR-TKIs [132,133].

Upregulation of the receptor TK Axl or its ligand GAS6 is another mechanism [134].

Axl is involved in epithelial to mesenchymal transition (EMT) and its increased activation can bypass EGFR-inhibition [135].

The insulin growth factor receptor 1 (IGF-1R) induces EMT in NSCLC cells with *EGFR* exon 19 deletion [136].

The activation of the downstream pathway signalling of IGF-1R will produce EGFR TKI resistance and this is relevant for first [137,138], second [139] and third [140] generation.

However, double inhibition of EGFR and IGF-1R at the same time can overcome this resistance [141,142].

Furthermore, fibroblast growth factor (FGF) family is involved in intrinsic and acquired resistance against EGFR-TKIs. FGFR1 and 2 as well as ligands FGF2

and 9 are overexpressed in NSCLC [143,144].

The activation of FGFR entails more mesenchymal phenotype and activates MEK-ERK and PI3K signalling [145].

Through response to an EGFR inhibitor (erlotinib or gefitinib) [146], FGF ligands become active and this will produce EGFR-TKI resistance [147]. This mechanism has been involved in resistance to afatinib, but not for acquired resistance to osimertinib [148].

The PIK3CA signalling is involved in primary resistance to first- and second-line EGFR TKIs. Through either a mutation or a gain in copy number, will confer poor prognosis. Mutations are present in 1%-10% of *EGFR*-mutant NSCLC whereas increased copy number in about 40% of NSCLC [149,150].

A meta-analysis assessed the effects of concurrent presence of *EGFR* and *PIK3CA*Â mutations in NSCLC on treatment with TKIs first and second generation. Authors concluded that the concurrency might not preclude a response [151].

BRAF mutations are a rare primary resistance pathway in NSCLC (1.5%-3.5%) and

It consists of a V600E mutation in 50% of the cases [152].

Finding this mutation at the same time as *EGFR* mutations is very rare (< 1%) in NSCLC but

its activation can bypass EGFR inhibition [153]. It has been seen in patients during treatment with osimertinib [154].

Combinations with BRAF inhibitors could be contemplated in cases of EGFR TKI resistance due to BRAF activation although further studies are needed.

PTEN is a tumour suppressor whose loss of *PTEN* is present in 5% of *EGFR* mutant NSCLC and linked to primary resistance against EGFR-TKIs [155].

PTEN is a connector link between EGFR and Akt. When *PTEN* is lost, the connection is lost as well resulting in resistance to EGFR-TKIs [156].

Overexpression of PTEN in cell lines with low/no PTEN levels resulted in increased sensitivity to erlotinib or gefitinib [157].

Loss of *PTEN* is involved in primary and acquired resistance. For the latter, around 10% of patients without any other known resistance mechanisms are reported to have *PTEN* loss [155].

TP53 in NSCLC is mutated in 50% of patients and it has been reported as showing lower PFS in cases of concurrent *TP53* exon 8 mutations and exon 19 deletions in *EGFR* [158].

However, two studies did not find any significant effect, thus the role of *TP53* mutations in EGFRTKI resistance is not clear [159,160].

The yes-associated protein (YAP) is a part of the HIPPO-pathway, and seems involved in primary and acquired resistance to EGFR-TKI. The MEK1/2 inhibitor trametinib decreases YAP levels and HIPPO-signalling and in cell lines resistant against erlotinib, gefitinib or osimertinib, YAP is found activated [161,162].

Overexpression of YAP confers resistance to erlotinib [163].

YAP expression increases after EGFR-TKIs and when active, it increases Axl activation and a change to EMT-phenotype of the cells.

Blocking YAP and inhibiting Axl resensitize the cells to EGFR-TKIs [164].

Further mutations involved in resistanceÂ Â

As is the case with first and second-generationÂ *EGFRÂ* TKIs, mutations mediating resistance to third-generationÂ *EGFRÂ* TKIs are emerging [165].

The recurrent acquisition of EGFR C797S mutation in exon 20 is considered the most frequent mechanism of resistance to osimertinib [166,167].

This mutation cancels the link of osimertinib to EGFR and it appears in between 22% to 40% of cases who have progressed on osimertinib [168-170].

It also confers resistance to other third generation TKIs, such as olmutinib [168-171], rociletinib [172] and nazartinib [173].

By-pass mechanisms affecting MET amplification or activation of the MAPK pathway may be involved as well in the development of resistance to third-generation EGFR TKIs [166].

This occurs in less than 3% of patients treated with rociletinib [174].

The C797S mutation was also reported in one case that led to resistance to olmutinib [174].

Recently, the acquired L798I mutation observed with T790M in one patient following rociletinib [174].

And another mutation in the same codon (L798Q) described in one patient at the time of progression under osimertinib [174].

The acquired resistance linked toÂ *EGFRÂ* T790M mutation may appear by either selection of pre-existingÂ *EGFRÂ* T790M+ clones or through genetic evolution ofÂ *EGFRÂ* T790Mâˆ' drug-tolerant cells. This suggests that malignant cells that survive third-generation TKIs may act as a reservoir from

which acquired resistance can emerge while on therapy [174].

AdditionalÂ *EGFR*-independent mechanisms of resistance have been reported such asÂ *NRASÂ* mutations orÂ *KRASÂ* that have been connected with secondary resistance to osimertinib, Â gefitinib and afatinib [174].

Amplifications inÂ *HER2Â* andÂ *METÂ* genes involved in acquired resistance to osimertinib and rociletinib inÂ *EGFRÂ* T790M+ NSCLC patients [174].

Loss of T790M at the time of progression which could be due to overgrowth of cells showingÂ *HER2Â* amplification, orÂ *BRAFÂ* V600E orÂ *PIK3CAÂ* mutations, as recently detected in plasma of patients included in the phase I AURA study [174].

Small-cell lung cancer transformation has been reported in two cases of rociletinib resistance and one osimertinib-resistant; in these cases, the T790M was lost while kept the originalÂ *EGFRÂ* mutation in the small cell transformed cancer [174].

The future: EGFR TKIs under development

Further third generation TKIs are under development such as PF-06747775 whish is a potent irreversible inhibitor of the four common mutants (exon 19 deletion (Del), L858R, and double mutants T790 M/L858R and T790 M/Del), with activity against *EGFR* T790M and barely effect in WT*EGFR* [175].

There is a phase I study, with 44 EGFR mutant NSCLC after progression on first line EGFR TKI. Results are still pending.

HS-10296 is another inhibitor under evaluation within the trial NCT02981108, which is under recruitment.

And a fourth generation EGFR TKIs are also under development.

Current EGFR TKIs target the ATP binding site, however, the C797S mutation blocks the attachment of these agents, conferring resistance.

Despite the initial good results with 3rd generation EGFR TKIs, acquired resistance invariably develops. Several mechanisms of resistance that are EGFR-dependent and EGFR-independent have been described. EGFR-dependent mechanisms include the development ofÂ *EGFR*Â C797S mutation whereas examples of EGFR-independent mechanisms include activation of pathways downstream of EGFR and parallel signalling pathways

Preclinical studies have demonstrated the acquired C797S mutation in cells resistant to 3rd generation TKIs and of interest was the finding that the allelic context in which C797S was acquired may predict responsiveness to subsequent TKI treatments [176].

EAI001 and EAI045 are new drugs that bind allosterically to EGFR away from the usual binding site, with specificity for mutant EGFR over WT-EGFR [176].

EAI001 has activity against L858R/T790 M mutant EGFR, but less active against individual L858R or T790 M mutant EGFR.

EAI045 is active in L858R or T790 M mutations, or both [176].

In cell lines with L858R/T790 M/C797S mutations, EAI045 has reported effect in controlling cell growth when combined with cetuximab, not as a monotherapy.

Further novel EGFR TKIs are under development as well. These agents showed activity cells expressing the triple mutation (T790 M/C797S/L858R) and had more than 300-fold selectivity for double EGFR mutant (T790 M/L858R) over WT-EGFR. Further studies are required to assess clinical efficacy and safety of these new agents.

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First generation EGFR TKIs after acquired resistance to third generation TKIs

Niederst et al. reported that cell lines with C797S and EGFR activating mutations (C797S/del19) without the T790 M mutation were resistant to third-generation TKIs but kept sensitivity to first generation [177].

This implies that those cases who received a third generation TKIs in first line and develop secondary resistance by C797S but still undetectable for T790 M may respond to first-generation TKIs.

First and third generation EGFR TKI combinationsÂ

The T790M and C797S mutations of EGFR cause resistance to first- and third-generation EGFR TKIs respectively in NSCLC harbouring EGFR activating mutations.

C797S has been identified in cis or in trans with T790M in tumour specimens from patients who showed PD with first- and third-generation EGFR-TKIs.

When the mutations occur in trans (i.e. on separate alleles), cells become resistant to third generation EGFR TKIs but sensitive to a combination of first and third generation EGFR TKIs. However, when the

mutations are in cis, no EGFR TKIs alone or in combination are effective [178].

In a patient who developed the triple mutation (T790 M/C797S/del19) in trans after PD on osimertinib, the combination of erlotinib and osimertinib achieved partial response. After showing PD again, C797S in cis to T790 M appeared and the patient did not further respond with EGFR TKIs, requiring chemotherapy for disease control [179].

Overcoming resistance to third generation TKIs with new agentsÂ

The favourable toxicity profiles of the third-generationÂ *EGFRÂ* TKIs make them particularly attractive for combination, and many trials are currently ongoing.

Navitoclax is a BCL-2 inhibitor which increased the apoptotic response of late-resistantÂ *EGFRÂ* T790M cells with reduced sensitivity toÂ *EGFRÂ* blockage. When combined with a third-generationÂ *EGFRÂ* TKI WZ4002 (in preclinical development) induced more apoptosis compared to WZ4002 aloneÂ *in vivoÂ* andÂ *in vitroÂ* analyses [180].

This could be a promising strategy forÂ *EGFRÂ* T790M-positive cancers that have a minimal apoptotic response toÂ *EGFRÂ* inhibition [180].

When combined to trametinib, anotherÂ *MEKÂ* inhibitor, it prevents the appearance of acquired resistance inÂ *EGFR*-mutant lung cancer models. A phase Ib trial is ongoing to assess the tolerability of the osimertinib/navitoclax in patients withÂ *EGFR* -mutant NSCLC following resistance to priorÂ *EGFRÂ* TKIs (NCT02520778).

Conclusion

The identification of EGFR activating mutations in NSCLC and the development of targeted treatment has revolutionised the therapeutic landscape of NSCLC.

Different generations of EGFR-TKIs have been implemented in clinical practice as a step forward to personalised medicine.

However, despite the initial success, hopes were limited by the emergence of resistance.

The identification of the mechanisms behind this resistance will eventually lead us to the development of newer active drugs able to block multiple pathways at the same time to overcome this resistance.

The FLAURA trial has established osimertinib (third generation TKI) as an effective treatment for advanced EGFR mutant NSCLC in the first-line setting.

But further research is mandatory to develop newer generations of EGFR-TKIs and to understand the optimal therapeutic approach to achieve the goal of extending the natural history of the cancer with the lowest rate of side effects as possible.

Patient selection has already improved, which is crucial to decide what would be the best strategy to get durable OS and quality of life.

Several EGFR-TKIs are now available in clinical practice, but the best sequence for administration of these drugs to optimise the blockage of the EGFR signalling has not been determined.

Comprehensive characterization of resistance mechanisms for each EGFR-TKI will serve to a better understanding of how to develop more effective strategies.

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Tables

Table 1 Selected trials of gefitinib in NSCLC

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Trial	Phase	N	Eligibility criteria	Primary end-points	Conclusion
IDEAL 1	II	210 Gef 250mg/day vs Gef 500mg/day	After â‰¥ 1 chemoÂ lines, including at least one platinum	RR safety	18.4% vs 19% NS >50% DCR both mPFS2.7 vs 2.8m NS mOS 7.6vs7.9m NS
IDEAL 2	II	250 (2/3 adc) Â Gef 250mg/day vs Gef 500mg/day	PD after two previous chemo lines, including docetaxel and cis or carbo	RR Reduction in symptoms	12% vs 9% mOS 6.5vs5.9m
INTACT 1	III	1093 Gef two doses/Gem/Cis Plac/Gem/Cis Â	First line	OS	No differences in efficacy
INTACT 2	III	1037 Gef/paclit/carbo Plac/paclit/carbo	First line	OS	No added benefit
INTEREST	III	1433 Â	Second line vs Docetaxel	Â	non-inferior survival
ISEL	III	1692 Â	Second or third line vs placebo	OS whole population OS in adc	OS favoured Asian and non-smokers
IBREESE	III	Gef vs BSC	Second or third line vs placebo	Â	Closed due to feasibility issues
IPASS	III Retrospective analysis of EGFR pos	1217 Gef vs paclit/carbo	First-line Asian, non-smokers adc Retrospective analysis in EGFR mut	OS	RR and PFS benefit over platinum-doublet
NEJ002	III	Gef vs paclit/carbo	First line EGFR mut	PFS	Better RR and PFS for Gef
WJTOG3405	III	172 Gef vs doce/cis	First line EGFR mut (either the exon 19 deletion or L858R point mutation) Â	PFS	9.2 vs 6.3m favouring Gef
IMPRESS	III	265 Continuation of Gef/chemo vs Plac/chemo	EGFR mut with PD after first line Gef	PFS	Gef does not prolong PFS after PD
IFUM	IV	106	First line in caucasian EGFR mut	RR	70%

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Table 2 Selected trials with erlotinib

Trial	Phase	N	Eligibility criteria	Primary end-point	Conclusion
EURTAC	III	174	First line, EGFR mut, european Erlo vs Cis/doce or Gem	PFS	9.9 vs 5.2
OPTIMAL	III	165	First line, EGFR mut Erlo vs gem/carbo	PFS	13.1 (erlo) vs 4.6m
ENSURE	III	217	First line, EGFR mut Erlo vs gem/cis	PFS	11 vs 5.5m OS NS (26.3 vs 25.5m)
TRIBUTE	III	1059	First line Erlo/pacli/carbo Plac/pacli/carbo	OS	Never smokers OS 22.5 vs 10.1 Overall â€“ OS 10.6 vs 10.5m
Tarceva lung cancer investigation trial	III	1172	First line Erlo/gem/cis Plac/gem/cis	OS	43 vs 44.1weeks NS Never smokers â€“ OS better in erlo
TAILOR	III	222	WT EGFR Second line Erlo vs Docetaxel	OS	5.4 vs 8.2m (docetaxel)
Delta	III	301	Second line EGFR unselected Erlo vs Docetaxel	PFS	2 vs 3.2m (docetaxel) In EGFR WT: 1.3 vs 2.9m (docetaxel)
WJOG 5108	III	561	Previously treated unselected Gef vs erlo	PFS	6.5 vs 7.5m NS In EGFR pos: 8.3 vs 10m NS
TOPICAL	III	670	Unsuitable for chemo First line Unselected Erlo vs plac	OS	3.7 vs 3.6 (plac) NS If first-cycle rash - better OSÂ

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Table 3 Selected trials with afatinib

Trial	Phase	Line of treatment	Â	PFS	OS
LUX-Lung 3	III	First line	Afa vs cis/peme	11.1 vs 6.9	All: 28.2 vs 28.2m Exon 19 del: 33.3 vs 21.1m Leu858arg mutÂ : 27.6 vs 40.3m
LUX-Lung 6	III	First line	Afa vs cis/gem	11 vs 5.6m	All: 23.1 vs 23.5m Exon 19 delÂ : 31.4 vs 18.4m Leu858arg mut: 19.6 vs 24.3m Â Â
LUX-Lung 7	III	First line	Afa vs gefi	11 vs 10.9	27.9 vs 24.5m
LUX-Lung 5	III	heavily treated PD after â‰¥1 chemo and after disease controlled â‰¥12 weeks on erlotinib or gefitinib and later on afatinib monotherapy	Afa + pacli vs pacli Â	5.6 (combo) vs 2.8m Â RR 32.1 vs 13.2% p+ 0.005	12.2 vs 12.2m NS

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Table 4 Selected dacomitinib trials

Trial	Phase	N	Eligibility	Other mutations	Efficacy
ARCHER 1001	I	121 (57NSCLC)	Pretreated with TKIs	5 ptes insertion exon 20	DCR 60%
ARCHER 1003	I/II	12 (I) 43 (II)	KRAS WT advanced NSCLC pretreated with at least one chemo line and a first-gen EGFR-TKI	one patient T790M mut Â	1PR on T790M
ARCHER 1017	II	89	First line Â Never-smokers or former light smokers, with KRAS WT if non-Asian. Â	Later amended to EGFR mut regardless of smoking status. EGFR exon 19 or 21 â€“ 51%	RR 53.9% PFS 11.5m OS 29.5m
ARCHER 1002	II	66	After erlotinib + 1-2 chemo lines	Â	EGFR 19 or 21 28.8% EGFR others 10.1% T790M 9.01%
ARCHER 1028	II	188	Daco vs erlo After one or two chemo lines	Unselected patients EGFR 31.9% KRAS 32.9%	2.86 vs 1.91m Benefit seen in KRAS WT, any EGFR, KRAS/EGFR WT NS if EGFR mut Â OS 9.53 vs 7.4m NS
ARCHER 1009	III	878	Daco vs erlo After one or two chemo lines	EGFR exon 19,20,21 â€“ 9.3% KRAS 15.3% EGFR others 1%	OVERALL: PFS 2.6 vs 2.6m OS 7.9 vs 8.4m (erlo) NS WT KRAS: PFS 2.6 vs 2.6m OS 8.1 vs 8.5 NS EGFRmutÂ : PFS 11 vs 10.9m (erlo) OS 26.6 vs not reached with erlo WT EGFR: PFS 1.9 vs 1.9 OS 6.8 vs 7.6m (erlo) Â
ARCHER 1050	III	452	First line Daco vs gefi	EGFR del exon 19 â€“ 59% EGFR L858R â€“ 41%	PFS 14.7 vs 9.2 m (gefi) p < 0.001
NCIC CTG BR-26	III	720	Daco vs plac Up to three chemo lines and a first-generation EGFR-TKI	EGFR 23.3% KRAS 10.8%	OS 6.83 vs 6.31 m (NS) NS differences with EGFR or KRAS mut PFS 2.66 vs 1.38mÂ p < 0.0001

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Table 5 Selected trials with osimertinib

Trial	Phase	N	End point	Efficacy	Mutations and efficacy
AURA	I/II	252 After progression on EGFR-TKIS	PFS	RR 51% PFS 8.2 Â	T790 M (N= 127) DCR of 95% RR of 61% PFS of 9.6 m
AURA 2	II	201 After progression on EGFR-TKI All had T790M-positive	RR	70% PFS 9.9m	EGFRm T790M advanced NSCLC who progress after EGFR-TKI osimertinib provides a high RR, encouraging PFS, and durable response.
Poole analysis of AURA extension and AURA 2	II	411	RR	66%	Â
AURA 3	III	419 T790 M mutations Second line after progression on TKIs Osi vs peme/cisp	PFS	10.1 vs 4.4m p< 0.001 RR 71 (osi) vs 31% p < 0.001	Â
FLAURA	III	556 First line Ex19del/L858R EGFR mutated Osi vs gefi or erlo	PFS OS	18.9 vs 10.2m (gefi) 38.6 vs 31.8m	Crossover permitted but T790M should be identified post-PD

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