Unravelling signal escape through maintained EGFR activation in advanced non-small cell lung cancer (NSCLC): new treatment options

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ABSTRACT

The discovery of activating epidermal growth factor receptor (*EGFR*) mutations has opened up a new era in the development of more effective treatments for patients with non-small cell lung cancer (NSCLC). However, patients with *EGFR*-activating mutated NSCLC treated with EGFR tyrosine kinase inhibitors (TKIs) ultimately develop acquired resistance (AR). Among known cases of patients with AR, 70% of the mechanisms involved in the development of AR to EGFR TKI have been identified and may be categorised as either secondary *EGFR* mutations such as the *T790M* mutation, activation of bypass track signalling pathways such as MET amplification, or histologic transformation. *EGFR*-mutant NSCLC tumours maintain oncogenic addiction to the EGFR pathway beyond progression with EGFR TKI. Clinical strategies that can be implemented in daily clinical practice to potentially overcome this resistance and prolong the outcome in this subgroup of patients are presented.

INTRODUCTION

Lung cancer is the third most frequent cancer (1.82 million cases) and the leading cause of cancer-related death (1.59 million deaths) worldwide according to the GLOBOCAN 2012 database.[1] The current SEER database shows that 16% of non-small cell lung cancers (NSCLCs) are diagnosed at localised stage (for which surgery remains the standard treatment for fit patients), 22% of patients are diagnosed with locally advanced disease and up to 60% with advanced stage.[2] Historically, platinum-based doublet chemotherapy has been the standard first-line treatment for non-selected patients with advanced NSCLC who have a good performance status.[3] The knowledge of genomic alterations in lung cancer has implications for the management of this disease.[4] The introduction of targeted therapies, based on the recognition of the significance of acquired genetic driver mutations, has changed the treatment paradigm of patients with lung cancer, establishing tumour genotyping as an essential routine diagnostic tool in clinical practice, notably in cases of adenocarcinoma histology.[5] Different types of mutations have been reported in lung adenocarcinomas,[4] but only 20–25% of them are actionable oncogenic driver mutations.[6] It has been reported that patients with NSCLC with a tumour harbouring known oncogenic drivers and who receive a matched targeted agent live significantly longer than those who have a driver mutation but do not receive personalised treatment (HR, 0.69; 95% CI 0.53 to 0.90; p=0.006),[7] supporting the clinical benefit of this policy.[6]

In Caucasian patients, the most frequent genetic alterations in advanced adenocarcinoma lung cancer are the *KRAS* mutation ~29%, epidermal growth factor receptor (*EGFR*) mutations ~11%, *ALK* rearrangements ~5%[6] and *MET* mutations (exon 14) in 4%.[8] Other less frequent mutations include *BRAF* and PIK3CA mutations in ~2% each, the *HER2* mutation in 1% of tumours[6] and *ROS1* rearrangements[9] in 1% of patients with NSCLC. These oncogenic drivers are almost always mutually exclusive in this patient population.[7]

There are several classes of activating somatic *EGFR* mutations, with in-frame deletions in exon 19 (ELREA, *Del1*9) and single-point mutations in exon 21 (*L858R*) being the most frequent. These mutations are markedly more frequent in the Asian than in the Caucasian population (~50% vs 10%).[10] In this review, we summarise the state of play for current treatments in the *EGFR*-mutant population for different treatment settings following acquired resistance (AR) and present the rationale behind new approaches being investigated following development resistance.

FAILURE TO FIRST-LINE TREATMENT IN PATIENTS WITH ADVANCED *EGFR*-MUTANT NSCLC

EGFR mutations predict sensitivity to the first-generation reversible EGFR tyrosine kinase inhibitors (TKIs) erlotinib and gefitinib and to the second-generation irreversible EGFR TKIs such as afatinib and dacomitinib. All four of these drugs have demonstrated improvement in the response rate (RR), progression-free survival (PFS) and quality of life over standard first-line platinum-doublet chemotherapy in at least nine randomised phase III trials in patients with advanced *EGFR*-mutant NSCLC. To date, no differences in overall survival (OS) versus standard platinum-doublet chemotherapy have been reported in these trials, possibly due to the high crossover rate to the TKI arm following disease progression in chemotherapy-treated patients.[11] A pooled analysis of two randomised phase III trials (LUX-Lung 3 and LUX-Lung 6), which compared afatinib versus first-line chemotherapy, reported that although afatinib did not improve OS in the whole population of either trial, OS was improved with the drug for patients with *Del19 EGFR* mutations.[12] In a recent meta-analysis of seven trials (1649 patients) evaluating EGFR TKIs, the EGFR TKI benefit over standard first-line chemotherapy was 50% greater for tumours with the *Del19* mutation (HR, 0.24; 95% CI 0.20 to 0.29) than for those with the exon 21 *L858R* substitution (HR, 0.48; 95% CI 0.39 to 0.58; p<0.001).[13] In a second meta-analysis, patients with the *Del19 EGFR* mutation had a significant OS benefit under TKI treatment (HR, 0.72; 95% CI 0.60 to 0.88; p=0.02) but not with the *L858R EGFR* mutation (HR, 1.15; 95% CI 0.95 to 1.39; p=0.07).[14] These results suggest that *EGFR*-mutant tumours are not equal, with different treatment impacts according to the mutation subtype in first-line setting.

There is currently no consensus as to which inhibitor maximises therapeutic efficacy in patients with *EGFR*-mutant NSCLC. The phase III study CTONG 0901 (NCT01024413) comparing erlotinib with gefitinib in 256 patients with advanced NSCLC harbouring common *EGFR* mutations presented no significant difference in outcomes (OS, PFS and ORR) or toxicity between these drugs.[15] The results from the LUX-Lung 7 study, a randomised phase IIb trial (NCT01466660) with 319 patients comparing afatinib to gefitinib as first-line therapy for patients with *EGFR*-mutant tumours, showed a modest but significant PFS prolongation (11.0 vs 10.9 months, HR, 0·73; 95% CI 0.57 to 0.95; p=0·017) and ORR (70.0% vs 56.0%; p=0.008) in favour of afatinib compared to gefitinib, independently of *EGFR* mutation subtype.[16] In a recent pooled analysis from two randomised trials, dacomitinib was an active drug with comparable outcomes to erlotinib in patients with NSCLC with common *EGFR* mutations.[17] The phase III trial ARCHER1050 (NCT01774721) comparing dacomitinib with gefitinib in patients with treatment-naive *EGFR*-mutant NSCLC has finished recruitment.

New strategies are needed to further improve PFS in patients with *EGFR*-mutant NSCLC. In a phase II trial, 154 Asian patients with *EGFR*-mutant NSCLC were randomised to erlotinib plus bevacizumab (15 mg/kg every 3 weeks) or erlotinib as first-line treatment. The combination significantly improved median PFS compared with monotherapy (16 vs 9.7 months, HR, 0.54; 95% CI 0.36 to 0.79, p=0.0015), without differences in serious adverse events between both treatments.[18] In a single-arm phase II trial in 109 Caucasian patients with *EGFR*-mutant NSCLC, erlotinib and bevacizumab reported an overall 1-year PFS of 56.7% and a median PFS of 13.8 months (95% CI 10.3 to 21.3). The median PFS was 16.0 months for patients with *T790M* at diagnosis (34% of patients) and 10.5 months for those without de novo *T790M*.[19] These data led to EMA approval for erlotinib and bevacizumab combination in this population in 28 April 2016. In another phase II study in an Asian population treated with gefitinib and bevacizumab, PFS differed significantly according to *EGFR* mutation subtype (18.0 vs 9.4 months, p=0.006, for *Del19* vs *L858R*, respectively).[20] A phase III trial (NCT02411448) of ramucirumab (anti-VEGFR2) and erlotinib is ongoing to validate this strategy.

Another combination strategy has been developed with pemetrexed. A phase II trial in 191 East Asian patients with *EGFR*-mutated NSCLC achieved a significant improvement in PFS for the combination compared with gefitinib monotherapy (15.8 vs 10.9 months; HR, 0.68; 95% CI 0.48 to 0.96; p=0.014); however, the incidence of grade 3–4 study related adverse events was significantly higher for the combination than for monotherapy (42.1% vs 18.5%; p=0.001).[21] This strategy has only been tested in the Asian population but is not considered acceptable elsewhere as a first-line strategy.

Intercalated administration of an EGFR TKI and chemotherapy has been postulated as a feasible option providing pharmacodynamic separation of the two drugs.[22] The intercalated strategy was evaluated in the randomised phase III FASTACT-2 trial in 451 unselected patients with advanced NSCLC. Among patients with *EGFR*-mutant NSCLC, an improvement was resulted in PFS (HR, 0.25; p<0.0001) and OS (HR, 0.48; p=0.0092) compared with chemotherapy plus placebo.[23] It is as yet unclear if such a strategy will be more effective than a first-line EGFR TKI followed by an adapted treatment in the event of resistance.

NSCLC tumours invariably develop AR after a median of 9–11 months from the start of the treatment.[11] Several potential mechanisms of AR have been identified: (1) development of secondary *EGFR* mutations such as the gatekeeper *T790M* point mutation in exon 20 of the EGFR gene; (2) bypass signalling pathways such *MET* amplification, *PIK3CA* mutation, *BRAF* mutation and *HER2* amplification (figure 1); and (3) phenotypic changes, specific to small cell lung cancer or to NSCLC with evidence of epithelial-to-mesenchymal transformation. However, ~20% of AR mechanisms are
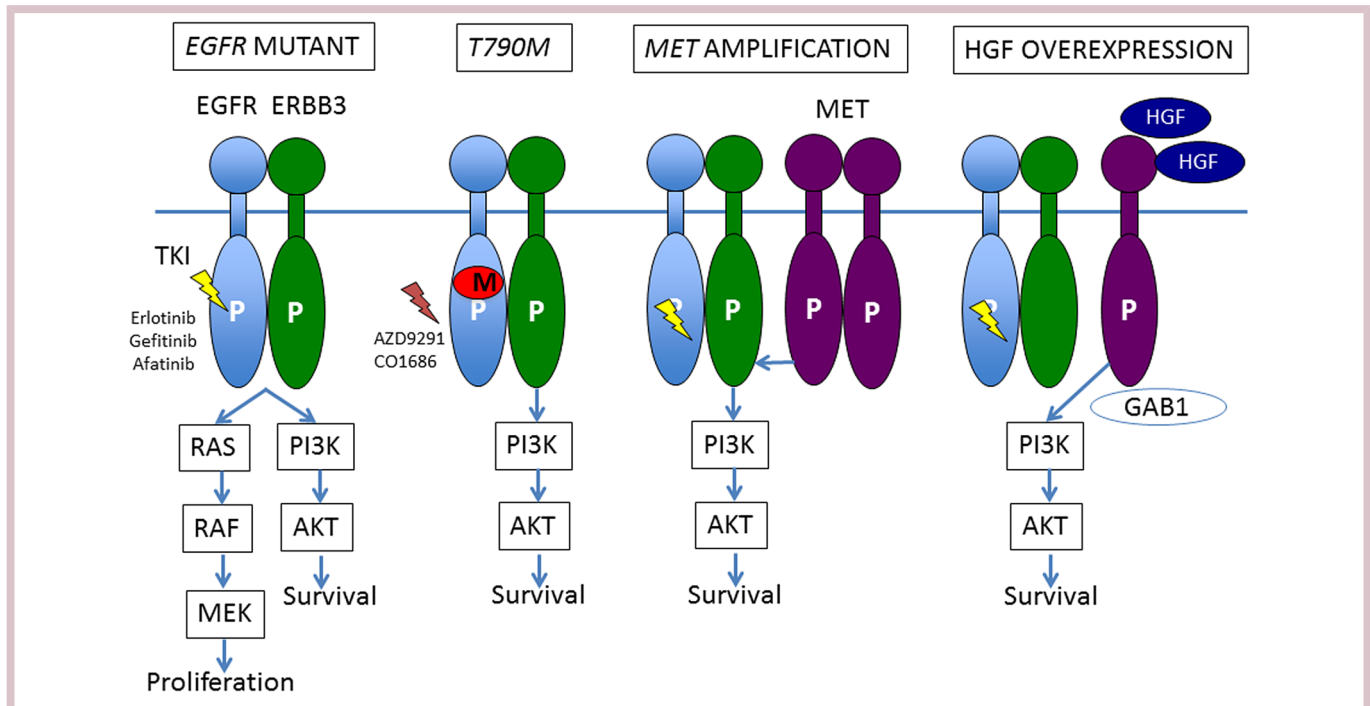
Figure 1 Main mechanisms of AR to EGFR TKI in *EGFR*-mutant NSCLC cells. AR, acquired resistance; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; M, mutated; NSCLC, non-small cell lung cancer; P, phosphorylation.

still unknown.[24] There is no well-defined strategy for EGFR TKI AR, and the patients are managed according to known mechanisms of AR or disease progression patterns.[25]

PERSISTING ONCOGENIC ADDICTION TO THE EGFR PATHWAY BEYOND PROGRESSION
Persistent inhibition of tumour-dependent pathways beyond progression is a therapeutic strategy, which can be exploited in cancers in which there is a reliance on a single pathway for growth and proliferation. This 'addiction' is seen in various cancers such as advanced prostate cancer, which remains almost uniformly dependent on androgen receptor despite acquired resistant to hormonal therapies such as castration,[26] or *HER2*-positive advanced breast cancers, which can achieve an outcome at different HER2 inhibitors.[27] Similarly, *EGFR*-mutant NSCLC maintains dependence on EGFR signalling even after the development of AR,[28 29] and many trials have studied the impact of intensifying EGFR inhibition continuing the same EGFR TKI beyond progression, or using a second-generation irreversible EGFR TKI as a monotherapy or in combination with anti-EGFR monoclonal antibodies.

Continuing single-agent EGFR TKIs beyond progression
Some patients with *EGFR*-mutant NSCLC have indolent progression, and the patients may be treated with an EGFR TKI beyond RECIST progression if there is no clinical evidence of deterioration or intolerable toxicity.[30] In the retrospective SLADB study,[31] the median

PFS according to the physician criteria was 14.0, whereas in the prospective EURTAC trial,[32] the same group had a median PFS of 9.7 months according to the RECIST criteria. Continuing EGFR TKI beyond RECIST progression may delay salvage systemic therapy for a year or more.[33] Recently, the phase II ASPIRATION trial conducted in 208 Asian patients with NSCLC, whose tumour harbours common *EGFR* mutations, and treated with first-line erlotinib reported that continuing erlotinib beyond RECIST progression improved PFS by 3.9 months (from 11.0 to 14.9 months).[34] However, the lack of an optimal control arm, the fact that the decision to continue erlotinib at progression was at the investigators' or patients' discretion and the unknown local therapies administered diminish strength of the study. Taken together, the results of these studies suggest that continuing EGFR TKI beyond RECIST progression is an adequate strategy for patients with good performance status, progression in previously identified lesions,[35] a longer time to progression on EGFR TKI[33] and no more than one metastatic site.[36]

Switching to second-generation irreversible EGFR TKIs
Second-generation irreversible EGFR TKIs such as afatinib[12] and dacomitinib[37] are effective in the treatment of untreated *EGFR*-mutant lung cancers, although, as a monotherapy, they failed to overcome *T790M*-mediated resistance.[38] Two phase II trials have tested the efficacy of afatinib in patients with advanced NSCLC who progressed after one or two lines of chemotherapy and with at least 12 weeks of erlotinib and/or gefitinib. In the

LUX-Lung 1 trial, 697 patients were randomised to afatinib or placebo. A 2-month PFS improvement was seen with afatinib (3.3 vs 1.1 months; HR, 0.38; 95% CI 0.31 to 0.48; p<0.0001), although there was no OS benefit (10.8 vs 12.0 months; HR, 1.08; 95% CI 0·86 to 1·35; p=0·74).[39] The LUX-Lung 4,[40] a single-arm trial, reported a median PFS of 4.4 months with afatinib in this pretreated population. Neither of these trials supports switching to second-generation EGFR TKIs, but rather continuing inhibition of EGFR pathway beyond EGFR TKI progression.

Combining second-generation irreversible EGFR TKIs and monoclonal antibodies

In a phase Ib clinical trial, the combination of afatinib and cetuximab (an anti-EGFR monoclonal antibody) in 126 heavily pretreated patients with advanced *EGFR*-mutant lung cancer and AR to erlotinib/gefitinib reported encouraging results in terms of RR, independently of T790M status (32% vs 25%, for *T790M* positive vs *T790M* negative, p=0.341), with a median PFS of 4.7 months. However, the 44% rate of grade 3 toxicity might limit its applicability in daily clinical practice.[41] A further phase I study was designed to find a more tolerable combination (NCT02020577), with preliminary results giving 11% grade 3 toxicity.[42] In another phase Ib/II trial with 50 pretreated patients with *EGFR*-mutant NSCLC, the combination of afatinib and nimotuzumab, a humanised anti-EGFR monoclonal antibody, gave similar outcomes for RR (23%), median PFS (4 months) and OS (11.7 months) with 16% grade 3 toxicity. No differences in RR (p=0.628) or PFS (p=0.720) according to the T790M status were reported.[43] Two randomised phase II trials (NCT 02438722 and IFCT1503 ACE) are currently evaluating afatinib with or without cetuximab as first-line treatment in patients with *EGFR*-mutant NSCLC.

Despite the efficacy outcomes with this combination approach, its toxicity and the efficacy of third-generation EGFR TKI as first- and second-line treatment may limit its widespread implementation in daily clinical practice.

THIRD-GENERATION EGFR TKIS

The substitution of threonine to methionine at amino acid position 790 (T790M) in exon 20 of the *EGFR* gene is the most frequent mechanism of AR, accounting for 49–63% of cases depending on the detection method.[44–46] The *T790M* mutation enhances the ATP affinity of the kinase domain of the EGFR-mutant receptor restoring its affinity for ATP to that of wild-type EGFR. Given that EGFR TKIs are competitive inhibitors with ATP, their ability to bind to the kinase domain is decreased by this mutation.[47] AR via the *T790M* mutation defines a subset of *EGFR*-mutant lung cancers with indolent growth in preclinical models[28] and clinical studies.[48 49] However, as not all authors confirm this finding,[50] its prognostic implication remains undetermined. Moreover, a study focusing on the discrepancies seen between tissue and plasma samples when identifying the *T790M* mutation is underway using the amplification-refractory mutation system (ARMS) and droplet digital PCR methods (NCT02418234).

Recently, de novo *T790M* mutations in EGFR TKI-naïve patients were described with a highly frequency, ranging from <1% to 80%, according to the detection method,[51–53] and it predicts shorter outcome to reversible EGFR TKI.[54 55]

Osimertinib (AZD9291),[56] rociletinib (CO1686)[57] and olmutinib (HM61713)[58] are third-generation oral EGFR TKIs, mutant-selective covalent inhibitors of commonly mutated and resistant (T790M) forms of *EGFR* (eg, in H1975 (*L858R/T790M*) and PC-9 VanR (*Del19/T790M*) resistant cell lines, osimertinib reported activity with a mean IC$_{50}$ potency of <15 nmol/L compared to 6073 nmol/L with first-generation EGFR TKI), which do not affect wild-type EGFR. They cause less frequent and less severe gastrointestinal and skin toxicity compared to first-generation or second-generation EGFR TKIs[56] (table 1).

In the phase I AURA trial, osimertinib was tested in 253 patients with advanced NSCLC who had radiologically documented disease progression after previous treatment with first-generation EGFR TKI. EGFR *T790M* was detected in 62% of patients, not detected in 28%, and the status was unknown in 10%. The overall RR was 51% with no differences by ethnicity, and the median PFS was 8.2 months. Patients with a centrally confirmed *T790M* mutation had better RR (61% vs 21%) and PFS (9.6 vs 2.8 months). Among all doses tested (20 up to 240 mg daily), the dose of 80 mg daily was considered optimal to maximise efficacy and minimise skin and

Table 1 IC$_{50}$ values for four different *EGFR*-mutant, *T790M*-resistant cancer cell lines treated with reversible (gefitinib, erlotinib) and irreversible (afatinib, dacomitinib, AZD9291) TKIs (data from Cross D[56])

	H1975 (L858R/T790M) IC50 potency (nmol/L)	PC-9 VanR (Del19/T790M) IC50 potency (nmol/L)	PC-9 (Del19)	H3255 (L858R)*	WT
Osimertinib	15	6	17	60 to 49	480
Dacomitinib	40	6	0.7	1.2 to 1.3	12
Afatinib	22	3	0.6	1 to 0.8	15
Gefitinib	3102	741	7	11 to 12	59
Erlotinib	6073	1262	6	8 to 11	91

*95% CI.
TKIs, tyrosine kinase inhibitors; WT, wild-type.

Table 2 Efficacy of third-generation EGFR TKI in patients with *EGFR*-mutant NSCLC after acquired resistance to EGFR TKIs

	Osimertinib[60]*	Rociletinib†[65]	Olmutinib[58][66]
T790M positive			
ORR (%)	At 80 mg*:71	45	At 800 mg: 56
PFS (months)	At 80 mg*:9.7	6.1	At 800 mg: NR
T790M-negative			
ORR (%)	26*	17	12
PFS (months)	3.4*	1.8	2.5

*Updated results reported in last ELCC congress (Amsterdam 2016).
†Updated results reported by Sequist *et al*[65] in NEJM 2016.
NR, not reached; ORR, overall response rate; PFS, progression-free survival.

gastrointestinal toxicity observed at higher doses.[59] In the updated results of this study, 80 mg osimertinib provided a 71% of RR and a median PFS of 9.7 months[60] (table 2). The FDA approved osimertinib in November 2015 for patients with acquired EGFR T790M NSCLC, based on data from the two AURA phase II studies (AURA extension[61] and AURA2[62]), which demonstrated efficacy in 411 patients with *T790M EGFR*-mutant NSCLC that had progressed on or after an EGFR TKI with a 59% of RR. The EMA followed suit in April 2016. Phase III clinical trials with osimertinib, as first-line treatment (FL-AURA, NCT02296125) in patients with common *EGFR* mutations and as second-line treatment (AURA3, NCT02151981) in patients with tumours harbour *T790M* mutation, are ongoing.

Rociletinib was evaluated in a phase I/II TIGER trial of 130 patients with *EGFR*-mutant NSCLC with AR to first-generation or second-generation EGFR TKIs. The RR among patients with centrally confirmed *T790M*-positive tumours was 59%, independently of the *EGFR* mutation subtype, with an estimated median PFS of 13.1 months, whereas the RR was 27% and the median PFS was 5.7 months among T790M-negative disease.[63] The updated results in 270 patients with *T790M*-positive NSCLC confirmed an overall RR of 53% and a median PFS of 8 months (10.3 months for those patients without brain metastasis) with rociletinib at 500 mg two times a day, whereas among the T790M-negative cohort the RR was 37%[64] (table 1). However, updated data from a pooled cohort of patients from TIGER-X and TIGER-2 (another phase 2 study of rociletinib) reported an RR of only 28–34%. A retrospective, independent review of data from the phase I TIGER trial reported a 45% RR and 6.1 months PFS versus 17% and 1.8 months for *T790M*-positive versus negative tumours, respectively,[65] and rociletinib development was halted.

Finally, olmutinib has been tested in a phase II trial among 76 patients with T790M-positive NSCLC as second-line treatment. Olmutinib achieved an RR of 56% with a median duration of response of 8.3 months.[66] This promising efficacy has led the first approval for this drug among the patients with EGFR

T790M mutation-positive NSCLC in South Korea in 2016.

Addiction beyond third-generation EGFR TKI

EGFR oncogenic addiction can even persist after AR to third-generation EGFR TKI. Acquisition of *C797S* mutation in exon 20 of EGFR is the main mechanism of resistance to osimertinib with or without the *T790M* mutation.[67] The context in which the *C797S* mutation develops with respect to other EGFR alleles affects the efficacy of subsequent treatments. In preclinical models, if the *C797S* and *T790M* mutations are in *trans* nature (on a different allele), cells are resistant to third-generation EGFR TKIs, but are sensitive to a combination of first-generation and third-generation TKIs. If the mutations are in *cis* nature (on the same allele), no EGFR TKIs alone or in combination can suppress activity.[68] If this preclinical approach is confirmed in the clinic, treatment-making decisions will require sequencing biopsies on progression with third-generation EGFR TKI to determining the *cis* or *trans* nature of *C797S* with respect to *T790M* mutation.

It has recently been reported that patients progressing on rociletinib achieved a response with osimertinib. The clinical benefit of this strategy may be explained by incomplete target inhibition with rociletinib, because in rociletinib-resistant tumours, a *C797S* resistance mutation has not been identified.[69] Clonal selection due to cancer cell heterogeneity in response to drug treatment pressure might explain the efficacy of sequential treatment with different EGFR TKIs (figure 2). This postprogression efficacy with sequential EGFR TKI strategies mirrors crizotinib-resistant *ALK* tumours, which can respond to sequential ALK TKI therapies based on different resistance-mutational profiles with different ALK TKIs.[70]

Additional data will help determine the optimal strategy for using third-generation EGFR TKIs in patients with *EGFR*-mutant NSCLC, notably their use as first-line therapy or after failure of first-generation or second-generation TKIs, and the optimal sequence.[68][69] Prescription of these agents requires a positive *T790M* mutation in a new tumour tissue biopsy. However, non-invasive assessment and monitoring of the *T790M*
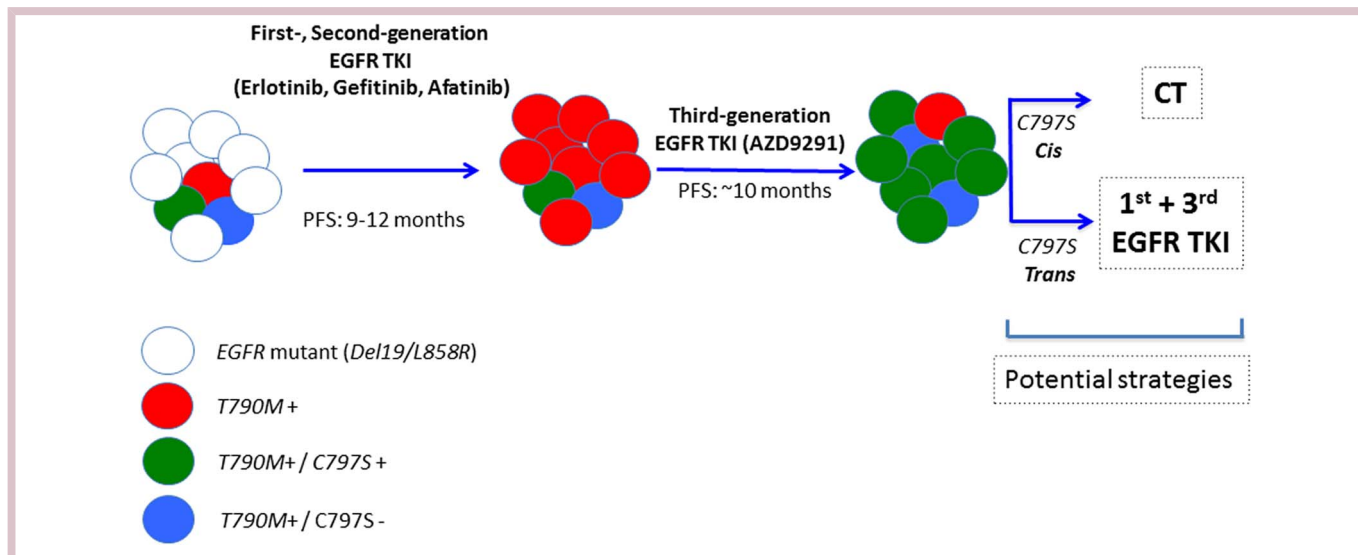
Figure 2 Mechanisms of AR after treatment pressure. AR, acquired resistance; CT, chemotherapy; PFS, progression-free survival.

mutation in plasma samples (liquid biopsies) offer a promising alternative to tissue-based biopsies and could complement tumour testing by identifying *T790M* mutations missed because of tumour heterogeneity or biopsy inadequacy.[71 72] Moreover, recent results reported equal efficacy of rociletinib independently of whether the *T790M* analysis was performed in plasma or tissue;[64] this suggests that liquid biopsies could become new standard tests in the near future and may even be used as a dynamic marker of treatment efficacy.

ONCOGENIC ADDICTION: BY-PASS MECHANISMS AND MET AMPLIFICATION

The EGFR oncogenic addiction also persists in cases of AR due to by-pass mechanisms. Amplification of the *MET* is the second most common mechanism of AR to EGFR TKIs (~20%)[73] irrespective of the T790M mutational status.[74] Targeting MET in combination with EGFR TKI to overcome resistance is a viable option from the biological standpoint (figure 1). In a phase II trial, the MET inhibitor cabozantinib administered in combination with erlotinib in patients with *EGFR*-mutant NSCLC with AR to EGFR TKI resulted in an ORR of 8.1%, a PFS of 3.7 months and an OS of 9.1 months. *MET* gene amplification was not found in any of those with postprogression biopsies (available for 41% of patients).[75] INC280, another MET inhibitor, gave a 15% of RR in combination with gefitinib in patients with *EGFR*-mutant and *MET*-positive (amplification (FISH ≥5 CN) or overexpression (IHC 2/3+)) NSCLC.[76] An INC280 and erlotinib combination is also feasible, and expansion cohorts in *EGFR*-mutant, treatment-naïve and pretreated patients are ongoing.[77] MET inhibitors in combination with EGFR inhibitors further evaluation in selected patients, but toxicity can be an issue.

SWITCHING TO CHEMOTHERAPY

For T790M-negative patients at the time of progression after a first-line EGFR TKI, other than participating in a clinical trial, second-line, platinum-based chemotherapy is a rational option, especially for those patients with systemic progression. NSCLC harbouring *EGFR*-activating mutations are more likely to express low excision repair cross-complementing 1 (ERCC1) mRNA levels,[78] which may justify the enhanced efficacy of first-line, platinum-based chemotherapy among patients with *EGFR*-mutant NSCLC reported in some clinical trials.[79] However, it remains unclear whether prior EGFR TKI impacts the efficacy of subsequent chemotherapy. Results from two retrospective analyses were inconsistent,[80 81] and a third study reported that pemetrexed as second-line treatment significantly prolonged PFS compared to second-line, platinum-doublet chemotherapy with similar RRs for the two strategies in patients with *EGFR*-mutant NSCLC with AR EGFR TKI.[82] However, the analysis from the phase III NEJ002 trial (comparing gefitinib with carboplatin plus paclitaxel) showed that second-line, platinum-based chemotherapy followed at progression by gefitinib was similar to first-line, platinum-based chemotherapy in terms of RR (partial response with chemotherapy second-line treatment vs first-line treatment: 25.4% vs 30.7%; OR 1.45; 95% CI 0.75 to 2.81; p=0.345) and OS (28.9 vs 27.6 months; HR, 0.77; 95% CI 0.52 to 1.14; p=0.188) with no influence of *EGFR* mutation subtype in the efficacy of second-line, platinum-based chemotherapy.[83]

Given the potential heterogeneity of cancer cells during AR to EGFR TKI, with some clones remaining sensitive to the original EGFR inhibitor,[28] and the risk of disease flare (a phenomenon of rapid disease progression during a washout period after EGFR TKI cessation[84]) in up to 25% of patients, chemotherapy combination and continuing EGFR TKI are likely to

have impact outcome. Four randomised phase III studies in molecularly unselected populations failed to show a better outcome with concurrent combination of EGFR TKI and chemotherapy over chemotherapy alone as first-line treatment in patients with advanced NSCLC.[85] In patients with AR to afatinib, the randomised phase III LUX-Lung 5 trial compared continuing afatinib with paclitaxel (40 mg/day; 80 mg/m^2 weekly) versus the investigator's choice of chemotherapy alone in 202 patients. The combination regimen demonstrated a significant improvement in RR (32.1% vs 13.2%; p=0.005), evaluated by the investigator, and PFS (5.6 vs 2.8 months; p=0.003) compared with chemotherapy alone with no differences in OS.[86] Benefit of continued EGFR TKI with chemotherapy in a cohort of 78 patients with *EGFR*-mutant NSCLC with AR to an EGFR TKI was evaluated in an institutional database. This also showed that continuing the EGFR TKI along with chemotherapy improved RR over chemotherapy alone (41% vs 18%; p=0.02), although no improvement in PFS and OS was observed between the groups.[87]

On the other hand, the randomised phase III IMPRESS trial compared maintenance gefitinib combined with pemetrexed and cisplatin versus chemotherapy alone in 265 patients with AR to gefitinib. No PFS difference was reported in both arms (median PFS 5·4 months in both groups; HR, 0·86; 95% CI 0.65 to 1.13; p=0.27) and had a deleterious effect on OS compared with the chemotherapy alone (14.8 vs 17.2 months; HR, 1.62; 95% CI 1.05 to 2.52; p=0.03, immature data),[88] suggesting that the EGFR TKI should be discontinued in AR patients in combination with doublet second-line chemotherapy.

Two ongoing phase II trials (NCT 02098954, NCT 02064491) may help to develop a definitive recommendation about combining chemotherapy and erlotinib in patients with erlotinib-resistant, *EGFR*-mutant NSCLC. The biomarker analyses of the IMPRESS trial addressed

the question whether T790M status affected the benefit of continuing an EGFR TKI with chemotherapy. T790M status was tested using plasma circulating cell-free, tumour-derived DNA (centrally detected using a quantitative emulsion BEAMing digital Sysmex PCR assay with positivity defined as ≥ 0.02% mutant DNA fraction). Patients without *T790M* mutation (40% of patients) had a non-significant trend towards benefit with combined treatment compared with chemotherapy alone (PFS: 6.7 vs 5.4 months; HR, 0.67; 95% CI 0.43 to 1.03; p=0.07).[89] This hypothesis thus requires further confirmation in a prospective randomised study.

Taken together, these results suggest that second-line, platinum-based doublet chemotherapy will remain the standard of care in patients without the *T790M* mutation or other targetable resistance mechanisms, as viable evidence does not support maintenance of an EGFR TKI when switching to second-line chemotherapy.

LOCAL STRATEGIES BEYOND EGFR TKI PROGRESSION
Based on the pattern of relapse, patients with *EGFR*-mutant NSCLC can be classified into three categories with different prognostic and therapeutic implications: dramatic progressors who will be treated with chemotherapy, gradual progressors and oligometastatic progressors (figure 3).[25] In cases of rapid and symptomatic progression, a biopsy is recommended to rule out phenotypic transformation to small cell lung cancer, in which chemotherapy should be adapted according to the pathological report.

For patients with oligometastatic progression, local therapies such as radiotherapy, surgery and stereotactic ablative radiotherapy in conjunction with continued EGFR TKI can give long-term survival. For gradual progressors patients, continued EGFR TKI treatment is recommended in asymptomatic patients.[90 91]

Figure 3 Patterns of clinical relapse and algorithm for the therapeutic strategy when AR to EGFR TKI occurs in patients with *EGFR*-mutant NSCLC. *After discussion with the patients. AR, acquired resistance; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.
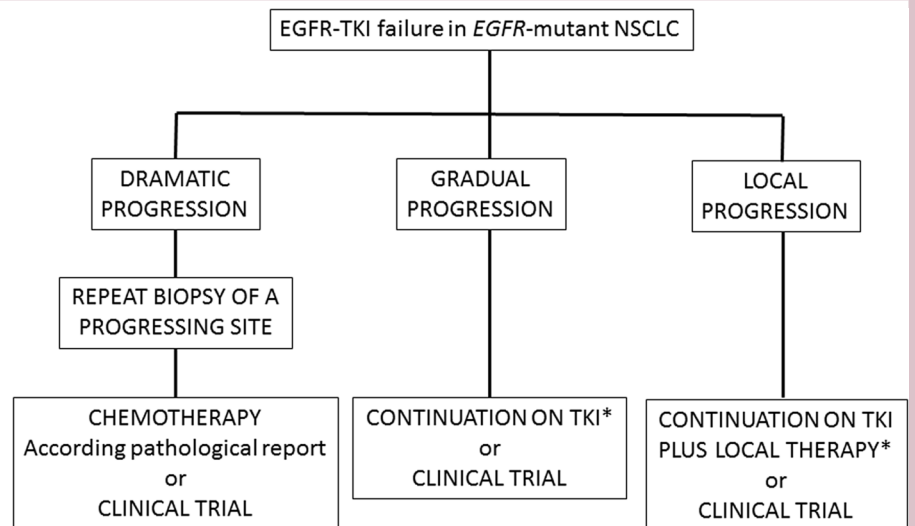
The true incidence of brain metastases in *EGFR*-mutant NSCLC is unknown, and whether EGFR TKIs are effective in these patient subgroups is unknown.[92] However, some patients develop brain metastasis during EGFR TKI treatment, in which local therapy (surgery or radiotherapy) and continued EGFR TKI may be suitable, extending disease control by over 6 months.[90] Moreover, concurrent EGFR TKI (erlotinib) plus concurrent whole brain radiation therapy is safe and well tolerated impacting the outcome of *EGFR*-mutant patients.[93] However, current first-generation EGFR TKIs generally have poor properties for penetrating across the blood–brain barrier at recommended doses.[94–96] Second-generation EGFR TKIs such as afatinib have reported higher efficacy on central nervous system metastases.[97] A novel EGFR TKI, AZD3759, which was designed to effectively cross the blood–brain barrier, has recently demonstrated promising efficacy among EGFR-mutant patients with brain metastases.[98]

IMMUNOTHERAPY AND EGFR TKIS

The ability of cancer cells to evade antitumour T cell activity in the microenvironment is a hallmark of cancer progression.[99] One means of evading immune destruction is through the expression of endogenous immune checkpoints, such as programmed cell death ligand 1 (PD-L1), that terminate immune responses after antigen activation.[100]

Three randomised phase III trials have reported a statistically significant improvement in RR and OS with checkpoint inhibitors such as nivolumab and pembrolizumab over standard second-line docetaxel chemotherapy in NSCLC.[100–102] However, the efficacy of these checkpoint inhibitors among *EGFR*-mutant patients was lower than in the wild-type population (OS HR *EGFR* mutant vs EGFR wild-type: 0.88 vs 0.66 and 1.18 vs 0.66 with pembrolizumab[102] and nivolumab in non-squamous cancers,[101] respectively). Recently, benefit from immunotherapy has been associated with tumours bearing high levels of somatic mutations.[103] Low level of mutational load in *EGFR*-mutant tumours could explain the lower efficacy of immune checkpoint therapies among this NSCLC subpopulation.

EGFR-mutant NSCLC expresses higher PD-L1 levels than wild-type, and in vitro and in vivo experiments have shown that gefitinib can reduce PD-L1 expression by inhibiting KF-*K*B, suggesting that combined strategies of EGFR TKI and immunotherapy warrant further evaluation.[104] Preliminary clinical results of combined nivolumab plus erlotinib showed clinical benefit (ORR 19%) and an acceptable safety profile in patients with *EGFR*-mutant advanced NSCLC with AR to EGFR TKI.[105] Pembrolizumab and gefitinib also reported clinical activity in heavily pretreated (up to four prior therapies) patients with *EGFR*-mutant NSCLC.[106] These results support further evaluation of checkpoint inhibitors in patients with *EGFR*-mutant NSCLC, and several

phase I/II trials are ongoing in EGFR TKI-naïve and pretreated patients (NCT 02013219: erlotinib and atezolizumab, NCT 02630186: rociletinib and atezolizumab, NCT 02323126: EGF816 and nivolumab, NCT 02364609: afatinib and pembrolizumab). However, in the phase I TATTON trial (NCT02143466) and in the randomised phase III CAURAL trial (NCT02454933) the combination of osimertinib and durvalumab (anti-PD-L1 monoclonal antibody) in patients with EGFR-mutant NSCLC with AR to EGFR TKI and *T790M* positivity have been halted due to an excess of pulmonary toxicity with the combination, suggesting that toxicity can limit the effectiveness of this combination.

CONCLUSIONS

Despite the efficacy of first-generation and second-generation EGFR TKIs, all patients develop AR to the treatment. Optimal postprogression therapy should not be systematically always tailored according to the RECIST progression criteria, with delaying the switch from first-line therapy for months after progression with maintenance EGFR and the addition of some local therapies being the optimal option in some patients. While combination targeted therapies offer promising alternatives in many AR settings, some recent studies have also raised the issue of a balancing toxicity against their potential efficacy benefits. For patients with *T790M*-positive NSCLC, third-generation EGFR TKIs are the most appropriate strategy. In this case, genomic guidance of treatment could be performed in the near future through a liquid biopsy. Chemotherapy remains the standard of care for all patients, particularly for T790M-negative patients and other targetable resistance mechanisms. EGFR TKIs should be interrupted during chemotherapy doublet treatment. Immunotherapy is a promising strategy in *EGFR*-mutant patients currently being addressed for implementation in the clinic in the future.

REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, *et al*. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–386.
2. http://www.seer.cancer.gov, (n.d.).
3. Reck M, Popat S, Reinmuth N, *et al*., ESMO Guidelines Working Group. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2014;5(Suppl 3):iii27–39.
4. Swanton C, Govindan R. Clinical implications of genomic discoveries in lung cancer. *N Engl J Med* 2016;374:1864–73.
5. Lindeman NI, Cagle PT, Beasley MB, *et al*. Null College of American Pathologists International Association for the Study of

Lung Cancer and Association for Molecular Pathology. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Mol Diagn* 2013;15:415–53.

6. Barlesi F, Mazieres J, Merlio JP, *et al*. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Intergroup (IFCT). *Lancet* 2016;387:1415–26.

7. Kris MG, Johnson BE, Berry LD, *et al*. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA* 2014;311:1998–2006.

8. Paik PK, Drilon A, Fan PD, *et al*. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring *MET* mutations causing exon 14 skipping. *Cancer Discov* 2015;5:842–9.

9. Shaw AT, Ou SHI, Bang YJ, *et al*. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;371:1963–71.

10. Gahr S, Stoehr R, Geissinger E, *et al*. EGFR mutational status in a large series of Caucasian European NSCLC patients: data from daily practice. *Br J Cancer* 2013;109:1821–8.

11. Reguart N, Remon J. Common EGFR-mutated subgroups (Del19/ L858R) in advanced non-small-cell lung cancer: chasing better outcomes with tyrosine-kinase inhibitors. *Future Oncol* 2015;11:1–13.

12. Yang JC, Wu YL, Schuler M, *et al*. Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-Lung 3 and LUX-Lung 6): analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol* 2015;16:141–51.

13. Lee CK, Wu YL, Ding PN, *et al*. Impact of specific epidermal growth factor receptor (EGFR) mutations and clinical characteristics on outcomes after treatment with EGFR tyrosine kinase inhibitors versus chemotherapy in EGFR-mutant lung cancer: a meta-analysis. *J Clin Oncol* 2015;33:1958–65.

14. Kuan FC, Kuo LT, Chen MC, *et al*. Overall survival benefits of first-line EGFR tyrosine kinase inhibitors in EGFR-mutated non-small-cell lung cancers: a systematic review and meta-analysis. *Br J Cancer* 2015;113:1519–28.

15. Yang JJ, Zhou Q, Yan HH, *et al*. A randomized controlled trial of erlotinib versus gefitinib in advanced nonsmall-cell lung cancer harboring EGFR mutations (CTONG0901). *J Thorac Oncol* 2015;10:S321. (Abstract MINI 16.13). (n.d.).

16. Park K, Tan EH, O'Byrne K, *et al*. Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): a phase 2B, open-label, randomised controlled trial. *Lancet Oncol* 2016;17:577–89.

17. Ramalingam SS, O'Byrne K, Boyer M, *et al*. Dacomitinib versus erlotinib in patients with EGFR-mutated advanced nonsmall-cell lung cancer (NSCLC): pooled subset analyses from two randomized trials. *Ann Oncol* 2016;27:423–9.

18. Seto T, Kato T, Nishio M, *et al*. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations (JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol* 2014;15:1236–44.

19. Stahel R, Dafni U, Gautschi O, *et al*. A phase II trial of erlotinib (E) and bevacizumab (B) _in patients with advanced non-small-cell lung cancer with activating epidermal growth factor receptor mutations with and without T790M mutation. Spanish Lung Cancer Group and the European Thoracic Oncology Platform BELIEF trial. ECCO 2015;25-29 September 2015. Vienna, Austria: The European Cancer Congress 2015. Abstract 3BA.

20. Ichihara E, Hotta K, Nogami N, *et al*. Phase II trial of gefitinib in combination with bevacizumab as first-line therapy for advanced non-small cell lung cancer with activating EGFR gene mutations: the Okayama Lung Cancer Study Group Trial 1001. *J Thorac Oncol* 2015;10:486–91.

21. Cheng Y, Murakami H, Yang P, *et al*., Randomized trial of gefitinib with and without pemetrexed as first-line therapy in East-Asian patients with advanced NS NSCLC with EGFR mutations. *J Thorac Oncol* 2015;10(9 suppl 2):S206. (oral 17.02) (n.d.).

22. Solit DB, She Y, Lobo J, *et al*. Pulsatile administration of the epidermal growth factor receptor inhibitor gefitinib is significantly more effective than continuous dosing for sensitizing tumors to paclitaxel. *Clin Cancer Res* 2005;11:1983–9.

23. Wu YL, Lee JS, Thongprasert S, *et al*. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. *Lancet Oncol* 2013;14:777–86.

24. Camidge DR, Pao W, Sequist LV. Acquired resistance to TKIs in solid tumours: learning from lung cancer. *Nat Rev Clin Oncol* 2014;11:473–81.

25. Yang JJ, Chen HJ, Yan HH, *et al*. Clinical modes of EGFR tyrosine kinase inhibitor failure and subsequent management in advanced non-small cell lung cancer. *Lung Cancer* 2013;79:33–9.

26. Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. *Nat Rev Cancer* 2015;15:701–11.

27. Cameron D, Casey M, Oliva C, *et al*. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. *Oncologist* 2010;15:924–34.

28. Chmielecki J, Foo J, Oxnard GR, *et al*. Optimization of dosing for EGFR-mutant non-small cell lung cancer with evolutionary cancer modeling. *Sci Transl Med* 2011;3:90ra59.

29. Riely GJ, Kris MG, Zhao B, *et al*. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. *Clin Cancer Res* 2007;13:5150–5.

30. Nishino M, Cardarella S, Dahlberg SE, *et al*. Radiographic assessment and therapeutic decisions at RECIST progression in EGFR-mutant NSCLC treated with EGFR tyrosine kinase inhibitors. *Lung Cancer* 2013;79:283–8.

31. Rosell R, Moran T, Queralt C, *et al*. Spanish Lung Cancer Group, Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med* 2009;361:958–67.

32. Rosell R, Carcereny E, Gervais R, *et al*. Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica, Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–46.

33. Lo PC, Dahlberg SE, Nishino M, *et al*. Delay of treatment change after objective progression on first-line erlotinib in epidermal growth factor receptor-mutant lung cancer. *Cancer* 2015;121:2570–7.

34. Park K, Yu CJ, Kim SW, *et al*. First-line erlotinib therapy until and beyond response evaluation criteria in solid tumors progression in Asian patients with epidermal growth factor receptor mutation-positive non-small-cell lung cancer: The ASPIRATION study. *JAMA Oncol* 2016;2:305–12.

35. Asami K, Okuma T, Hirashima T, *et al*. Continued treatment with gefitinib beyond progressive disease benefits patients with activating EGFR mutations. *Lung Cancer* 2013;79:276–82.

36. Auliac JB, Fournier C, Audigier Valette C, *et al*. Impact of continuing first-line EGFR tyrosine kinase inhibitor therapy beyond RECIST disease progression in patients with advanced EGFR-mutated non-small-cell lung cancer (NSCLC): retrospective GFPC 04-13 study. *Target Oncol* 2016;11:167–74.

37. Ramalingam SS, Jänne PA, Mok T, *et al*. Dacomitinib versus erlotinib in patients with advanced-stage, previously treated non-small-cell lung cancer (ARCHER 1009): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2014;15:1369–78.

38. Eskens FA, Mom CH, Planting AS, *et al*. A phase I dose escalation study of BIBW 2992, an irreversible dual inhibitor of epidermal growth factor receptor 1 (EGFR) and 2 (HER2) tyrosine kinase in a 2-week on, 2-week off schedule in patients with advanced solid tumours. *Br J Cancer* 2008;98:80–5.

39. Miller VA, Hirsh V, Cadranel J, *et al*. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012;13:528–38.

40. Katakami N, Atagi S, Goto K, *et al*. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. *J Clin Oncol* 2013;31:3335–41.

41. Janjigian YY, Smit EF, Groen HJ, *et al*. Dual inhibition of EGFR with afatinib and cetuximab in kinase inhibitor-resistant EGFR-mutant lung cancer with and without T790M mutations. *Cancer Discov* 2014;4:1036–45.

42. Gazzah A, Boni V, Soria JC, *et al*. Phase Ib study of afatinib plus standard-dose cetuximab in patients (pts) with advanced solid tumors. Vol 33. ASCO Meeting Abstracts. 2015:2536.

43. Lee JY, Sun JM, Lim SH, *et al*. A phase Ib/II study of afatinib in combination with nimotuzumab in non-small cell lung cancer patients with acquired resistance to gefitinib or erlotinib. *Clin Cancer Res* 2016;22:2139–45.

44. Sequist LV, Waltman BA, Dias-Santagata D, *et al.* Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011;3:75ra26.
45. Arcila ME, Oxnard GR, Nafa K, *et al.* Rebiopsy of lung cancer patients with acquired resistance to EGFR inhibitors and enhanced detection of the T790M mutation using a locked nucleic acid-based assay. *Clin Cancer Res* 2011;17:1169–80.
46. Yu HA, Arcila ME, Rekhtman N, *et al.* Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013;19:2240–7.
47. Yun CH, Mengwasser KE, Toms AV, *et al.* The T790M mutation in EGFR kinase causes drug resistance by increasing the affinity for ATP. *Proc Natl Acad Sci USA* 2008;105:2070–2075.
48. Hata A, Katakami N, Yoshioka H, *et al.* Nishimura, Rebiopsy of non-small cell lung cancer patients with acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitor: comparison between T790M mutation-positive and mutation-negative populations. *Cancer* 2013;119:4325–32.
49. Oxnard GR, Arcila ME, Sima CS, *et al.* Acquired resistance to EGFR tyrosine kinase inhibitors in EGFR-mutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. *Clin Cancer Res* 2011;17:1616–22.
50. Sun JM, Ahn MJ, Choi YL, *et al.* Clinical implications of T790M mutation in patients with acquired resistance to EGFR tyrosine kinase inhibitors. *Lung Cancer* 2013;82:294–8.
51. Rosell R, Molina MA, Costa C, *et al.* Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non-small-cell lung cancer patients with EGFR mutations. *Clin Cancer Res* 2011;17:1160–8.
52. Watanabe M, Kawaguchi T, Isa SI, *et al.* Ultra-sensitive detection of the pretreatment EGFR T790M mutation in non-small cell lung cancer patients with an EGFR-activating mutation using droplet digital PCR. *Clin Cancer Res* 2015;21:3552–60.
53. Yu HA, Arcila ME, Hellmann MD, *et al.* Poor response to erlotinib in patients with tumors containing baseline EGFR T790M mutations found by routine clinical molecular testing. *Ann Oncol* 2014;25:423–8.
54. Ding D, Yu Y, Li Z, *et al.* The predictive role of pretreatment epidermal growth factor receptor T790M mutation on the progression-free survival of tyrosine-kinase inhibitor-treated non-small cell lung cancer patients: a meta-analysis. *Onco Targets Ther* 2014;7:387–93.
55. Costa C, Molina MA, Drozdowskyj A, *et al.* The impact of EGFR T790M mutations and BIM mRNA expression on outcome in patients with EGFR-mutant NSCLC treated with erlotinib or chemotherapy in the randomized phase III EURTAC trial. *Clin Cancer Res* 2014;20:2001–10.
56. Cross DA, Ashton SE, Ghiorghiu S, *et al.* AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. *Cancer Discov* 2014;4:1046–61.
57. Walter AO, Sjin RT, Haringsma HJ, *et al.* Discovery of a mutant-selective covalent inhibitor of EGFR that overcomes T790M-mediated resistance in NSCLC. *Cancer Discov* 2013;3:1404–15.
58. Park K, Lee JS, Lee KH, *et al.* Updated safety and efficacy results from phase I/II study of HM61713 in patients (pts) with EGFR mutation positive non-small cell lung cancer (NSCLC) who failed previous EGFR-tyrosine kinase inhibitor (TKI). Vol 33. ASCO Meeting Abstracts. 2015:8084.
59. Jänne PA, Yang JC, Kim DW, *et al.* AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 2015;372:1689–99.
60. Oxnard G, Thress K, Alden R, *et al.* Plasma genotyping for predicting osimertinib benefit, ELCC 2016; Abstract 1350.
61. Yang J, Ahn M, Ramalingam S, *et al.* AZD9291 in pre-treated T790M positive advanced NSCLC: AURA study phase II extension cohort. *J Thorac Oncol* 2015;10(9 Suppl 2):S319 (n.d.).
62. Mitsudomi T, Tsai CM, Shepherd F, *et al.* AZD9291 in pre-treated T790M positive advanced NSCLC: AURA2 phase II study. *J Thorac Oncol* 2015;10(9 Suppl 2):S320 (n.d.).
63. Sequist LV, Soria JC, Goldman JW, *et al.* Rociletinib in EGFR-mutated non-small-cell lung cancer. *N Engl J Med* 2015;372:1700–9.
64. Sequist LV, Goldman JW, Wakelee HA, *et al.* Efficacy of rociletinib (CO-1686) in plasma-genotyped T790M-positive non-small cell lung cancer (NSCLC) patients (pts). Vol 33. ASCO Meeting Abstracts. 2015:8001.
65. Sequist LV, Soria JC, Camidge DR. Update to rociletinib data with the RECIST confirmed response rate. *N Engl J Med* 2016;374:2296–7.
66. Park K, Lee JS, Lee KH, *et al.* BI 1482694 (HM61713), an EGFR mutant-specific inhibitor, in T790M+ NSCLC: efficacy and safety at the RP2D. Vol 34. ASCO Meeting Abstracts. 2016:9055.
67. Thress KS, Paweletz CP, Felip E, *et al.* Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M. *Nat Med* 2015;21:560–2.
68. Niederst MJ, Hu H, Mulvey HE, *et al.* The allelic context of the C797S mutation acquired upon treatment with third generation EGFR inhibitors impacts sensitivity to subsequent treatment strategies. *Clin Cancer Res* 2015;21:3924–33.
69. Sequist LV, Piotrowska Z, Niederst MJ, *et al.* Osimertinib responses after disease progression in patients who had been receiving Rociletinib. *JAMA Oncol* 2016;2:541–3.
70. Friboulet L, Li N, Katayama R, *et al.* The ALK inhibitor ceritinib overcomes crizotinib resistance in non-small cell lung cancer. *Cancer Discov* 2014;4:662–73.
71. Karlovich CA, Goldman JW, Sun JM, *et al.* Assessment of EGFR mutation status in matched plasma and tumor tissue of NSCLC patients from a phase 1 study of rociletinib (CO-1686). *Clin Cancer Res* 2016;22:2386–95.
72. Thress KS, Brant R, Carr TH, *et al.* EGFR mutation detection in ctDNA from NSCLC patient plasma: a cross-platform comparison of leading technologies to support the clinical development of AZD9291. *Lung Cancer* 2015;90:509–15.
73. Engelman JA, Zejnullahu K, Mitsudomi T, *et al.* MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. *Science* 2007;316:1039–43.
74. Bean J, Brennan C, Shih JY, *et al.* MET amplification occurs with or without T790M mutations in EGFR mutant lung tumors with acquired resistance to gefitinib or erlotinib. *Proc Natl Acad Sci USA* 2007;104:20932–7.
75. Reckamp KL, Mack PC, Ruel N, *et al.* Biomarker analysis of a phase II trial of cabozantinib and erlotinib in patients (pts) with EGFR-mutant NSCLC with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) resistance: a California Cancer Consortium Phase II Trial (NCI 9303). Vol 33. ASCO Meeting Abstracts. 2015:8087.
76. Wu YL, Yang JCH, Kim DW, *et al.* Safety and efficacy of INC280 in combination with gefitinib (gef) in patients with EGFR-mutated (mut), MET-positive NSCLC: a single-arm phase Ib/II study. Vol 32. ASCO Meeting Abstracts. 2014:8017.
77. McCoach CE, Yu A, Gandara DR, *et al.* Phase I study of INC280 plus erlotinib in patients with MET expressing adenocarcinoma of the lung. Vol 33. ASCO Meeting Abstracts. 2015:2587.
78. Gandara DR, Grimminger P, Mack PC, *et al.* Association of epidermal growth factor receptor activating mutations with low ERCC1 gene expression in non-small cell lung cancer. *J Thorac Oncol* 2010;5:1933–8.
79. Mok TS, Wu YL, Thongprasert S, *et al.* Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–57.
80. Tseng JS, Yang TY, Chen KC, *et al.* Prior EGFR tyrosine-kinase inhibitor therapy did not influence the efficacy of subsequent pemetrexed plus platinum in advanced chemonaïve patients with EGFR-mutant lung adenocarcinoma. *Onco Targets Ther* 2014;7:799–805.
81. Zeng Z, Yan HH, Zhang XC, *et al.* Reduced chemotherapy sensitivity in EGFR-mutant lung cancer patient with frontline EGFR tyrosine kinase inhibitor. *Lung Cancer* 2014;86:219–24.
82. Park S, Keam B, Kim SH, *et al.* Pemetrexed singlet versus nonpemetrexed-based platinum doublet as second-line chemotherapy after first-line Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor failure in non-small cell lung cancer patients with EGFR mutations. *Cancer Res Treat* 2015;47:630–7.
83. Miyauchi E, Inoue A, Kobayashi K, *et al.* North-East Japan Study Group, Efficacy of chemotherapy after first-line gefitinib therapy in EGFR mutation-positive advanced non-small cell lung cancer-data from a randomized Phase III study comparing gefitinib with carboplatin plus paclitaxel (NEJ002). *Jpn J Clin Oncol* 2015;45:670–6.
84. Chaft JE, Oxnard GR, Sima CS, *et al.* Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. *Clin Cancer Res* 2011;17:6298–303.
85. Pennell NA. Integration of EGFR inhibitors and conventional chemotherapy in the treatment of non-small-cell lung cancer. *Clin Lung Cancer* 2011;12:350–9.

86. Schuler M, Yang JCH, Park K, *et al*., LUX-Lung 5 Investigators. Afatinib beyond progression in patients with non-small-cell lung cancer following chemotherapy, erlotinib/gefitinib and afatinib: phase III randomized LUX-Lung 5 trial. *Ann Oncol* 2016;27:417–23.

87. Goldberg SB, Oxnard GR, Digumarthy S, *et al*. Chemotherapy with Erlotinib or chemotherapy alone in advanced non-small cell lung cancer with acquired resistance to EGFR tyrosine kinase inhibitors. *Oncologist* 2013;18:1214–20.

88. Soria JC, Wu YL, Nakagawa K, *et al*. Gefitinib plus chemotherapy versus placebo plus chemotherapy in EGFR-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a phase 3 randomised trial. *Lancet Oncol* 2015;16:990–8.

89. Mok T, Soria JC, Kim SW, *et al*. Gefitinib/chemotherapy vs chemotherapy in EGFR mutation-positive NSCLC resistant to first-line gefitinib: IMPRESS T790M subgroup analysis. *J Thorac Oncol* 2015;10(9 suppl 2):S207 (ORAL17.08).

90. Weickhardt AJ, Scheier B, Burke JM, *et al*. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* 2012;7:1807–14.

91. Yu HA, Sima CS, Huang J, *et al*. Local therapy with continued EGFR tyrosine kinase inhibitor therapy as a treatment strategy in EGFR-mutant advanced lung cancers that have developed acquired resistance to EGFR tyrosine kinase inhibitors. *J Thorac Oncol* 2013;8:346–51.

92. Schuler M, Wu YL, Hirsh V, *et al*. First-Line Afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. *J Thorac Oncol* 2016;11:380–90.

93. Welsh JW, Komaki R, Amini A, *et al*. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J Clin Oncol* 2013;31:895–902.

94. Jamal-Hanjani M, Spicer J. Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of epidermal growth factor receptor-mutant non-small cell lung cancer metastatic to the brain. *Clin Cancer Res* 2012;18:938–44.

95. Omuro AM, Kris MG, Miller VA, *et al*. High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib. *Cancer* 2005;103:2344–8.

96. Lee YJ, Choi HJ, Kim SK, *et al*. Frequent central nervous system failure after clinical benefit with epidermal growth factor receptor tyrosine kinase inhibitors in Korean patients with nonsmall-cell lung cancer. *Cancer* 2010;116:1336–43.

97. Hoffknecht P, Tufman A, Wehler T, *et al*. Afatinib Compassionate Use Consortium (ACUC), Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. *J Thorac Oncol* 2015;10:156–63.

98. Ahn MJ, Kim DW, Kim TM, *et al*. Phase I study of AZD3759, a CNS penetrable EGFR inhibitor, for the treatment of non-small-cell lung cancer (NSCLC) with brain metastasis (BM) and leptomeningeal metastasis (LM). Vol 34. ASCO Meeting Abstracts. 2016:9003.

99. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646–74.

100. Brahmer JR. Immune checkpoint blockade: the hope for immunotherapy as a treatment of lung cancer?. *Semin Oncol* 2014;41:126–32.

101. Borghaei H, Paz-Ares L, Horn L, *et al*. Nivolumab versus Docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627–39.

102. Herbst RS, Baas P, Kim DW, *et al*. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540–50.

103. Rizvi NA, Hellmann MD, Snyder A, *et al*. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015;348:124–8.

104. Lin K, Cheng J, Yang T, *et al*. EGFR-TKI down-regulates PD-L1 in EGFR mutant NSCLC through inhibiting NF-κB. *Biochem Biophys Res Commun* 2015;463:95–101.

105. Rizvi NA, Chow LQM, Borghaei H, *et al*. Safety and response with nivolumab (anti-PD-1; BMS-936558, ONO-4538) plus erlotinib in patients (pts) with epidermal growth factor receptor mutant (EGFR MT) advanced NSCLC. Vol 32. ASCO Meeting Abstracts. 2014:8022.

106. Creelan BC, Chow LQ, Kim DW, *et al*. Safety and tolerability results from a phase I study of MEDI4736, a human IgG1 anti-programmed cell death-ligand-1 (PD-L1) antibody, combined with gefitinib in patients (pts) with non-small-cell lung cancer (NSCLC). Vol 33. ASCO Meeting Abstracts. 2015:3047.