Introduction

Lung cancer is the leading cause of cancer death globally (1). In North America and Western Europe, 50–70% of non-small cell lung cancers (NSCLCs) are adenocarcinomas and therefore are the dominant subtype (2). The most common cause of lung cancer is tobacco exposure, but an important proportion of cases occur in never-smokers. While somatic oncogenic driver mutations (mutations in a gene which confer a selective growth advantage) occur in both smoking and non-smoking related tumours, they are more commonly found in tumours from non-smoking patients. These so called “oncogene addicted” tumours are dependent upon driver mutations to spur their development and maintain their malignant phenotype (3). Driver mutations have been identified in both adenocarcinoma and squamous carcinoma histologies but, to date, therapeutic success in targeting and inhibiting these drivers has been confined to drivers of adenocarcinomas.

Mutations in the epidermal growth factor receptor (EGFR) gene are among the most common genomic drivers of NSCLC, occurring in an estimated 50% of adenocarcinoma
cases in Asia and in 10–15% of adenocarcinomas in Western populations (4-6). As a percentage, these mutations are detected more commonly in tumours of never-smokers, females, patients of East Asian ethnicity and those with adenocarcinoma histology (6-8).

EGFR is a transmembrane receptor tyrosine kinase member of the ErbB family of receptors. Binding of a number of ligands, including epidermal growth factor (EGF), among others, causes receptor dimerization and triggers the activation of proliferative and cell-survival signals (9,10). EGFR protein overexpression in NSCLC was the basis for the development of gefitinib and erlotinib, two small molecule first-generation EGFR tyrosine kinase inhibitors (TKIs). Initially studied in unselected NSCLC populations, they were found to be most efficacious in patients whose tumours harboured activating somatic mutations in exons 18–21 of EGFR, with either small multi-nucleotide in-frame deletions in exon 19 (ex19del) or a point mutation in exon 21, p.Leu858Arg (L858R), making up 90% of detected EGFR mutations (5-7,11). In in vitro assays, these mutations were primarily heterozygous and compared to wild-type (WT) EGFR, demonstrated stronger and more prolonged signal activation, different tyrosine phosphorylation patterns and activation of primarily prosurvival pathways (12,13).

Following the discovery of increased sensitivity to erlotinib and gefitinib in lung cancers harbouring activating EGFR mutations, these agents quickly became the globally recommended treatment for EGFR mutation-positive NSCLC based on a number of pivotal phase III studies (14-17). Not surprisingly, given the genomic instability of cancers, tumours which are initially sensitive to oncogene inhibition may escape control via a number of resistance mechanisms. This led to the development and regulatory approval of second-generation irreversible EGFR inhibitors afatinib and dacomitinib (18,19). In the first-line setting, first- and second-generation EGFR TKIs led to significant improvements in both objective response (range of 65% to 90%) and progression-free survival (PFS) (range of 9 to 14.7 months) in NSCLC harbouring activating EGFR mutations (11,14-17,20-23), however resistance eventually develops in most patients [see article in this issue by Martinez-Marti et al. for a more detailed look at first-generation EGFR TKIs (24)].

**Necessity, the mother of invention—overcoming mechanisms of resistance to first- and second-generation EGFR TKIs**

A full description of the mechanisms of resistance to EGFR TKIs is beyond the scope of this review.

Multiple mechanisms of acquired resistance to first- and second-generation EGFR TKIs have been reported, including secondary EGFR mutations, bypass track signaling pathway activation (e.g., MET amplification) and histologic transformation (e.g., small-cell lung cancer or epithelial-to-mesenchymal transition) (25,26). Importantly in the context of third-generation EGFR TKIs, acquired resistance to gefitinib, erlotinib and afatinib has been associated with selection for a second EGFR mutation, the p.Thr790Met (T790M) point mutation in exon 20 (also in the kinase domain), detectable in 50–63% of tissue biopsy samples taken after disease progression (25,27-31). The substitution of threonine for methionine at amino acid position 790 (T790M) in exon20 of EGF translates to reduced binding of first-generation EGFR TKIs due to steric hindrance, which concomitantly restores ATP binding affinity similar to that of WT EGFR (32). First-generation EGFR TKIs have the disadvantage of being reversible inhibitors and are ineffective against the T790M mutation; while EGFR T790M only modestly affects gefitinib binding, gefitinib is outcompeted by ATP (32,33). On the other hand, the second-generation afatinib has reasonable potency against dual L858R/T790M mutations, but cannot be delivered to patients in concentrations necessary to overcome T790M resistance, as seen in vitro (33,34). The IC$_{50}$ values of each agent from independent studies are summarized in Table 1. EGFR TKI specificity for mutant conformations is necessary for efficacy and to reduce toxicity caused by off-target activity against WT EGFR.

In summary, erlotinib, gefitinib and afatinib are considered ineffective against T790M-mutant EGFR NSCLC. Consequently, “third-generation” EGFR TKIs were developed specifically to target the EGFR T790M mutation as the primary mechanism of acquired resistance to first- and second-generation EGFR inhibitors. In this review, we present the clinical context leading to the development of third-generation EGFR TKIs, the mode of action of these inhibitors and the clinical data to date supporting their use. We review the third-generation TKI agents that are
Table 1  Summary of reported pre-clinical half maximal inhibitory concentrations (IC\textsubscript{50}) of third-generation EGFR TKIs for common EGFR mutations

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<th>Comments</th>
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</table>

\*, reported apparent IC\textsubscript{50}, due to time-dependent changes to enzyme activity with irreversible inhibitors; \textsuperscript{a}, assessed by kinase assay (see methods and supplemental methods from; (32,37,38); \textsuperscript{b}, evaluated in Ba/F3 cells transduced with either mutated or wild-type EGFR, see (35,36,38); \textsuperscript{c}, Exon 19 deletion evaluated in PC-9 cells (\textsuperscript{31}) and HCC827 cells (\textsuperscript{b}); \textsuperscript{d}, L858R mutation evaluated in H3255 cells (\textsuperscript{31}); \textsuperscript{e}, L858R/T790M mutation evaluated in H1975 cells (\textsuperscript{b}) and NIH/3T3_TC32T8 cells (\textsuperscript{b}); \textsuperscript{f}, Ex19del/T790M evaluated in PC9-DRH cells (\textsuperscript{b}) and PC9-ER cells (\textsuperscript{b}); \textsuperscript{g}, WT EGFR evaluated in A549 cells (\textsuperscript{b}), H358 cells (\textsuperscript{b}) and A431 (\textsuperscript{b}). EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; WT, wild-type.
approved, in development, and those that failed in clinical trials. Finally, we will touch upon combination treatment strategies currently being explored to improve the efficacy of treatment with third-generation EGFR TKIs.

**Third-generation EGFR TKIs—targeting the T790M mutation**

The development of the third-generation EGFR TKIs focused on three key aspects namely; the inhibition of T790M isoform-specific kinase activity, maintaining efficacy against exon 19 and 21 mutations, and sparing the inhibition of WT EGFR (33). The first third-generation EGFR TKI to be developed was WZ4002 (41), which did not progress into clinical trials, followed by rociletinib (CO-1686) (42) and osimertinib (AZD9291) (33). All three are reported to be potent inhibitors of T790M-mutant EGFR, while exhibiting minimal activity against the WT receptor. A common feature of these inhibitors is the covalent bond they form with the C797 residue within the EGFR ATP-binding pocket (33,42). A selected summary of ongoing clinical trials with third-generation EGFR inhibitors is found in Table 2. Multiple third-generation agents have now been developed but, to date the only one with regulatory approval is osimertinib. Therefore, the majority of this review focuses on osimertinib, though others will be mentioned. Figure 1 illustrates the clinical development status of third-generation EGFR TKIs under investigation in NSCLC.

**Osimertinib (AZD9291)**

Osimertinib (AZD9291) is an irreversible EGFR TKI selective for both EGFR-TKI sensitizing and T790M resistance mutations (33) and has a nearly 200× greater potency against L858R/T790M than against WT-EGFR. Osimertinib was the first third-generation EGFR TKI to receive FDA and EMA approval for the treatment of metastatic *EGFR*-mutant and acquired *EGFR* T790M mutation-positive NSCLC progressing on or after EGFR TKI therapy (50,51).

**Osimertinib in EGFR-TKI (first- and second-generation) resistant NSCLC**

The initial phase I/II AURA (NCT01802632) study was the first to report use of osimertinib in patients with *EGFR*-mutant (either ex19del, L858R or T790M) advanced lung cancer who had radiological disease progression after previous treatment with an EGFR TKI (52). This 253-patient study documented a favourable adverse event (AE) profile and encouraging clinical benefit. Jänne and colleagues initially reported an overall objective tumour response of 51%. However, in the 127 patients with a centrally confirmed *EGFR* T790M tumour mutation who could be evaluated for response, the objective response was 61% (95% CI, 52% to 70%), compared to a response of 21% (95% CI, 12% to 34%) in the 61 patients without a detectable T790M mutation. The median PFS was also higher in *EGFR* T790M-mutant patients compared to those without a detected tumour mutation, 9.6 months (95% CI, 8.3 to not reached) vs. 2.8 months (95% CI, 2.1 to 4.3) respectively. The most common AEs were diarrhea (47%), skin toxicity ( rash/ acne, 40%), nausea (22%) and decreased appetite (21%). The 80 mg daily dose was selected as the recommended phase II dose (RP2D). In an updated analysis of phase I data from the 61 response-evaluable patients harbouring the T790M tumour mutation treated at the RP2D of 80 mg daily of osimertinib, the objective response was 71% (95% CI, 57% to 82%) and median PFS was 9.7 months (95% CI, 8.3 to 13.6) (53).

Based on these encouraging results, the phase II portion of the AURA study was extended to include an additional 201 T790M-positive advanced NSCLC patients, dosed at 80 mg daily (54). In 198 evaluable patients, the primary endpoint of overall response was 62% (95% CI, 54% to 68%) with a disease control rate of 90% (95% CI, 85% to 94%) and a median PFS of 12.3 months (95% CI, 9.5 to 13.8). These results confirmed initial observations of clinical efficacy. Diarrhea and rash were the most common possibly causally related AEs. Interstitial lung disease (ILD) was reported in eight patients of 201, and was fatal in three cases.

 Whilst enrolling to AURA extension the AURA 2 study was initiated. The AURA2 study, an open-label, single arm, phase II study (NCT02094261), enrolled patients with confirmed *EGFR* T790M-positive mutations, locally advanced or metastatic (stage IIIB/IV) NSCLC who progressed on previous EGFR TKI therapy to receive osimertinib 80 mg orally once daily (55). The primary endpoint was the objective response rate, and at data cut-off, objective response was seen in 140 (70%; 95% CI, 64% to 77%) of the 199 evaluable patients by blinded independent central review. Confirmed complete responses were achieved in 6 (3%) patients and partial responses were achieved in 134 (67%) patients. In the context of EGFR TKI-resistant disease, this was an impressive and exciting response.
Table 2 Selected ongoing clinical trials with third-generation (T790M-targeting) EGFR TKIs* in NSCLC

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase/Alt. study name</th>
<th>Monotherapy or combination</th>
<th>Clinical conditions (line, mutation status etc.)</th>
<th>Clinical trial ID/reference</th>
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<td>Phase 3 ADAURA</td>
<td>Osimertinib</td>
<td>Stage IB-IIIA EGFRm+ (Ex19Del, L858R) NSCLC, following complete tumour resection ± adjuvant chemotherapy</td>
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<td>Phase 1/2</td>
<td>Osimertinib and gefitinib</td>
<td>EGFR TKI-naïve advanced EGFRm+ NSCLC</td>
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<td>Phase 1</td>
<td>Osimertinib and dacomitinib</td>
<td>TKI-naïve metastatic EGFRm+ NSCLC</td>
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<td>Phase 1 TATTON</td>
<td>Osimertinib and AZD6094 (savolitinib) or selumetinib</td>
<td>EGFRm+ Advanced NSCLC with progression following EGFR TKI therapy</td>
<td>NCT02143466/(44)</td>
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Table 2 (continued)
Table 2 (continued)

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<tr>
<td>PF-</td>
<td>Phase 2 YH25448</td>
<td>EGFRm+ (T790M) advanced NSCLC with or without asymptomatic brain metastasis who progressed after prior therapy with EGFR TKIs</td>
<td></td>
<td>NCT03046992</td>
<td>Recruiting</td>
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</table>

*, CO-1686, HM61713 and ASP8273 excluded due to halted drug development. Clinicaltrials.gov search terms included: “AZD9291” (86 studies), “AC0010” (4 studies), “avitinib” (1 study), “EGF816” (7 studies), “nazarinib” (0 studies), “PF-06747775” (1 study), “mavelertinib” (0 studies), “YH25448” (1 study), “GNS-1480” (0 studies) in combination with “NSCLC” that were “not yet recruiting”, “recruiting” or “active, not recruiting”. Data current as of 10-Apr-2019. Alt., alternative; EGFRm+, EGFR mutation-positive; NSCLC, non-small cell lung cancer; CNS, central nervous system; RP2D, recommended phase II dose.

A pre-planned pooled analysis of T790M-positive patients from the AURA extension and AURA2 studies enabled evaluation of 411 patients previously treated with EGFR inhibitors (first- or second-generation) (56). In the evaluable for response set, the pooled objective response was 66% (95% CI, 61% to 70%) and the median PFS (full analysis set), 9.9 months (95% CI, 9.5 to 12.3). The pooled median overall survival (OS) was 26.8 months (95% CI, 24.2 to not calculable (NC)); median OS in the second-line and third-line (or greater) cohorts was 25.8 months (95% CI, 24.0 to NC) and NC (95% CI, 22.1 to NC), respectively. The 12- and 24-month survival rates were 80% and 56%, respectively. The AEs were consistent with previous reports.

This led to AURA3 (NCT02151981), the confirmatory phase III study of osimertinib compared to platinum-based chemotherapy plus pemetrexed, published in 2017 (57). This was a randomized (2:1, 419 patients), open-label trial in the second-line setting for patients with centrally-confirmed EGFR T790M mutation-positive advanced NSCLC who progressed while on first-line EGFR TKI therapy. The primary endpoint of median PFS was met, with a significantly longer median PFS with osimertinib than with chemotherapy [10.1 vs. 4.4 months; hazard ratio
(HR), 0.30; 95% CI, 0.23 to 0.41; P<0.001]. The objective response was also significantly better with osimertinib (71%; 95% CI, 65% to 76%) than with chemotherapy (31%; 95% CI, 24% to 40%). Importantly, the toxicity profile was more favourable in the osimertinib arm than in the platinum–pemetrexed arm. These trial results solidified osimertinib’s place as standard treatment in EGFR T790M-positive NSCLC patients after disease progression on a first- or second-generation EGFR TKI. Data on OS are not yet mature, but are eagerly anticipated.

**Osimertinib as a first-line therapy**

Given the known activity of osimertinib against ex19del and L858R alterations (33), the next step was to examine its efficacy in the first-line setting testing two hypotheses; firstly, whether the activity of osimertinib against the common sensitizing mutations was as robust as the first- and second-generation EGFR TKIs and secondly, whether treating with a T790M inhibitor could delay the development of T790M mutations. In the FLAURA study (NCT02296125), osimertinib was compared to standard EGFR-TKIs in previously untreated, EGFR mutation–positive advanced NSCLC (58). This was a double-blind, randomized phase III trial, enrolling 556 patients with EGFR mutation-positive (ex19del or L858R) advanced NSCLC to either gefitinib or erlotinib vs. osimertinib at a 1:1 ratio. The primary endpoint was investigator-
assessed PFS. Median PFS was significantly longer with osimertinib than with standard EGFR-TKIs (18.9 vs. 10.2 months; HR for disease progression or death, 0.46; 95% CI, 0.37 to 0.57; P<0.001). The objective response was similar in both groups: 80% with osimertinib and 76% with standard EGFR-TKIs but the median duration of response was longer with osimertinib versus standard EGFR-TKIs [17.2 months (95% CI, 13.8 to 22.0) and 8.5 months (95% CI, 7.3 to 9.8), respectively]. A doubling of the duration of response with osimertinib suggests it is effective at delaying the onset of acquired resistance in comparison to erlotinib or gefitinib. Furthermore, the osimertinib arm had less frequent AEs of grade 3 or higher. Though survival data is not yet mature, the FDA granted osimertinib approval for first-line treatment of metastatic NSCLC with exon 19 deletions or exon 21 L858R mutations based on the FLAURA data (59).

**Adjuvant therapy with osimertinib**

Adjuvant therapy with EGFR TKIs versus placebo was originally examined with first-generation EGFR TKIs in the BR19 (gefitinib) and RADIANT (erlotinib) studies (60,61), which were conducted in unselected NSCLC populations, as these trials were initiated when the importance of EGFR mutations was not thoroughly understood. Both studies had small numbers of EGFR tumour mutation-positive patients (BR19 n=15, RADIANT n=161). In RADIANT, EGFR mutation-positive patients receiving erlotinib trended towards improved disease-free survival, however this did not reach statistical significance. In the BR19 study the EGFR mutation-positive sample size precluded meaningful benefit analysis, neither disease-free survival or OS were improved in this population. More recently in EGFR-mutant (Ex19del/L858R) NSCLC, a Chinese study of gefitinib versus vinorelbine plus cisplatin in the adjuvant setting reported a significantly longer median disease-free survival with gefitinib [28.7 months (95% CI, 24.9 to 32.5)] than with vinorelbine plus cisplatin [18.0 months (95% CI, 13.6 to 22.3); HR 0.60; 95% CI, 0.42 to 0.87; P=0.0054] (62).

With this as background, the ongoing ADAURA (NCT02511106) is currently investigating the implementation of osimertinib therapy in the adjuvant setting (see Table 2) (43). ADAURA is a phase III, double-blind, randomized study of osimertinib versus placebo in primary non-squamous stage IB–IIIA NSCLC, following complete tumour resection, with or without adjuvant chemotherapy. Patients are required to have central confirmation of an EGFR ex19del or L858R mutation and are randomized 1:1 to receive osimertinib 80 mg once daily or placebo once daily. The primary endpoint of this study is disease-free survival and results are expected in 2021.

**Osimertinib in lung cancer central nervous system (CNS) metastases**

CNS metastases are more common in EGFR-mutant NSCLC than in EGFR WT patients (63) and a number of small prospective trials, subgroup analyses and case studies have documented limited CNS efficacy with EGFR TKIs. Response rates in patients with brain metastases are 0–33% with gefitinib, 58.3–83% with erlotinib and 35–82% with afatinib (64-69). Improvements in overall PFS with afatinib from the LUX-lung 3 and 6 studies were detected even in patients with brain metastases (64). With this background, we discuss below the role of osimertinib in EGFR mutation-positive NSCLC with CNS metastases.

The first indications of intra-cranial osimertinib activity were detected in the AURA extension study which included 25 patients in a CNS response analysis set. Encouraging systemic PFS with osimertinib in patients with CNS metastases and a high CNS response (64%; 95% CI, 43% to 82%) in those with measurable CNS lesions (n=25) was reported. Four patients experienced a complete response, 12 patients a partial response and tumour shrinkage was seen in the majority of patients (54). Similarly, the high proportion of objective responses observed with osimertinib in patients with CNS metastases from the AURA2 study (n=84) was consistent across pre-defined subgroups, and in a post-hoc analysis of PFS in sub-groups (55).

In 2018, Goss et al. published a pre-specified sub-group analysis of pooled data from the AURA extension and AURA2 studies (70). Of 128 patients with CNS metastases on baseline brain scans, 50 were included in the evaluable CNS response set. Confirmed CNS objective response and disease control rates were 54% (27/50; 95% CI, 39% to 68%) and 92% (46/50; 95% CI, 81% to 98%), respectively and CNS response was observed regardless of prior brain radiotherapy. The safety profile observed in the evaluable CNS response set was consistent with the overall patient population.

Due to encouraging signal in the phase II studies, the AURA3 study pre-planned a CNS disease subgroup analysis (71), finding that of the 116 patients with measurable or non-measurable CNS metastases, the CNS overall response in patients with ≥1 measurable CNS lesions...
(n=46) was 70% (21 of 30; 95% CI, 51% to 85%) with osimertinib and 31% (5 of 16; 95% CI, 11% to 59%) with platinum-pemetrexed (odds ratio, 5.13; 95% CI, 1.44 to 20.64; P=0.015) and the response was 40% (30 of 75; 95% CI, 29% to 52%) and 17% (7 of 41; 95% CI, 7% to 32%), respectively, in the full analysis set (n=116) (odds ratio, 3.24; 95% CI, 1.33 to 8.81; P=0.014).

Along with preclinical data supporting the ability of osimertinib to cross the blood-brain barrier and penetrate the CNS (72), phase II observations led to a pre-planned sub-group analysis, with CNS PFS as the primary objective, in patients with CNS metastases evaluable-for-response in the FLAURA study (n=41, osimertinib n=22, standard EGFR TKI n=19) (73). Median CNS PFS in patients with measurable and/or non-measurable CNS lesions was not reached with osimertinib (95% CI, 16.5 months to NC) and 13.9 months (95% CI, 8.3 months to NC) with standard EGFR-TKIs (HR, 0.48; 95% CI, 0.26 to 0.86; P=0.014). This analysis confirmed the probability of experiencing a CNS progression event was consistently lower with osimertinib versus standard EGFR-TKIs, thus confirming that osimertinib has CNS efficacy in patients with untreated EGFR-mutated NSCLC.

### Other third-generation EGFR TKIs

**Rociletinib (CO-1686)**

Rociletinib is an oral, targeted covalent (irreversible) mutant-selective EGFR TKI for the treatment of EGFR-mutant (activating and T790M) NSCLC (42) that was granted breakthrough therapy designation by the FDA in 2014 (74). This decision was based on the initial results of the phase I/II dose-finding trial of rociletinib (CO-1686-008 (TIGER-X), NCT01526928) which had promising and durable antitumour activity in patient with T790M-positive NSCLC following progression on a EGFR TKI (75). The response rate among 46 patients with centrally confirmed T790M-positive tumours was 59% (95% CI, 45% to 73%) and 29% (95% CI, 8% to 51%) among the 17 patients whose tumours were T790M-negative by central testing. The maximum tolerated dose (MTD) was not reached, hyperglycemia was the only dose-limiting toxicity and a RP2D of 625 mg BID was chosen for future trials (75,76). Two phase II expansion cohorts (NCT01526928) enrolled patients with T790M-positive disease either after progression on their first and only TKI therapy, or after progression on their second or later TKI therapy or chemotherapy. TIGER-X expansion cohorts, combined with data from TIGER-2, were expected to serve as the basis for regulatory approval (77). However, in 2016, following the FDAs decision to not approve the New Drug Application the sponsor announced termination of all ongoing sponsored studies of rociletinib, thus discontinuing rociletinib’s development (78).

**Nazartinib (EGF816)**

Nazartinib is another irreversible mutant-selective (L858R, Ex19del, and T790M) EGFR inhibitor that specifically targets EGFR-activating mutations arising de novo and upon acquired resistance, while sparing WT EGFR (79). Nazartinib is currently in phase I/II testing in a multicenter, open-label study of EGF816, administered orally in patients with EGFR-mutant NSCLC (NCT02108964) (CEGF816X2101). This study established the RP2D (Phase I portion) for nazartinib at 150 mg daily in 2018 (47), and preliminary results of the phase II portion in treatment-naive NSCLC patients with activating EGFR mutations (ex19del, L858R) were also presented (80). At cut-off, 45 patients were considered evaluable and among these patients, the overall response was 64% (29/45; 95% CI, 49% to 78%) and the disease control rate, 93%. Nazartinib was considered to have tolerable safety profile, frequent AEs (>25%) regardless of causality were diarrhea (38%) and maculopapular rash (31%), with the latter representing 9% of grade 3/4 events. Of 17 patients with baseline brain metastases, 9 pts (53%) showed resolution of these (80).

In a “strategic decision by the company”, a phase III study of Nazartinib versus erlotinib/gefinitib (NCT03529084) was withdrawn in 2018, however combination trials with nazartinib are underway (Table 2).

**Mavelertinib (PF-06747775)**

Mavelertinib is a selective, third-generation irreversible EGFR TKI being studied in patients with mutated EGFRex19del or L858R with or without T790M mutation (35). In 2017, the first reports from the ongoing, phase I, first in human study (NCT02349633) in patients with metastatic EGFR mutation-positive NSCLC became available (49,81). Dose escalation with 6 dose levels (25 to 600 mg) and two expansion cohorts (200 and 300 mg) was conducted in 44 patients. The RP2D was 200 mg (81). The most common all grade AEs (≥25%) were: diarrhea (57%), rash (59%), paronychia (52%), dermatitis acneiform (34%), stomatitis.
(32%), pruritus (27%), dry skin (25%), and rhinorrhea (25%). There were no grade 4 AEs and preliminary clinical efficacy data is pending (81).

**Avitinib (AC0010)**

Avinitinib (AC0010) is a third-generation pyrrolopyrimidine-based irreversible EGFR inhibitor which potently inhibits T790M EGFR, but spares EGFR WT (38). The first-in-human dose escalation study of AC0010 in EGFR-TKIs resistant (T790M-positive) NSCLC patients (NCT02274337) was published in 2018 (82). Fifty-two patients (45 T790M-positive and 7 T790M-negative) were treated with escalating doses without reaching the MTD. When all evaluated doses and patients (including n=7, T790M-negative) were included, the overall response was 36.5%, but in patients treated with daily doses of 350 mg or higher, the overall response was 50.0%. Common treatment-emergent AEs were diarrhea (75%), skin rash (48%), and increased alanine transaminase level (44%); AEs of grade ≥3 or higher were increased transaminase level (12%) and skin rash (4%). The RP2D was determined to be 300 mg twice daily.

More recently, avitinib was evaluated for blood-brain-barrier penetrability, which was weak (48) (NCT02330367). Sixteen NSCLC patients were included, half (8/16) had brain metastases. The median intracranial PFS of evaluable patients with brain metastases (n=7) was 142 days compared to an overall median PFS of 247 days (95% CI, 154.8 to 339.2). The cerebrospinal fluid concentration of avitinib was determined to be lower than its IC50 in approximately half of patients, and consequently the calculated blood brain barrier penetration rate was 0.046–0.146%.

An ongoing phase II, single-arm, open-label trial (NCT03300115) in EGFR T790M mutation-positive advanced NSCLC is currently recruiting. This study aims to expand the sample size of patients treated with the RP2D in order to further evaluate the study drug’s efficacy (objective response) and safety. This trial is recruiting exclusively in China (see Table 2).

**Lazertinib (YH25448/GNS-1480)**

Lazertinib is an oral, potent, irreversible third-generation EGFR TKI that is highly selective for activating EGFR and T790M resistance mutations. In pre-clinical studies, lazertinib induced profound tumour regression in a brain metastasis model with favourable brain/plasma and tumour/brain area under the concentration-time curve values (39).

An ongoing Korean phase I/II clinical trial for advanced EGFR T790M mutated NSCLC (NCT03046992 n=118), lazertinib demonstrated potent systemic and intracranial activity (83). The dose escalation cohort included 38 patients administered with 20 to 240 mg once daily across 7 dose levels, and 80 patients in the dose expansion cohort were administered 40 to 240 mg (5 dose levels). Of the evaluable patients (n=110) at data cut-off, the objective response was 61% (95% CI, 51.8% to 70.0%). The objective response for the T790M-positive patients (n=76) was 66% (95% CI, 56.6% to 76.0%), and for the T790M-negative patients (n=15) was 33%. In patients with brain metastases (n=11), the intracranial response was 55% (95% CI, 25.1% to 84.0%). The most common treatment emergent AEs were pruritus (24%), rash (19%) and decreased appetite (17%). Recruitment to the dose extension phase is ongoing (Table 2).

**Olmutinib (HM61713/BI 1482694)**

Olmutinib was designed as an irreversible third-generation kinase inhibitor active against mutant EGFR, including T790M, while sparing WT EGFR (84). NCT01588145 is a phase I/II trial of olmutinib in NSCLC patients with an EGFR mutation. In the phase II part of this trial; 76 patients with T790M-mutant tumours received olmutinib and 71 were evaluable for response (85). Of these, 40 (56%) had an objective response by investigator review [31 (44%) confirmed] with a median duration of response of 8.3 months (range 5.6 to NC), the disease control rate was 90% and the median PFS by investigator review was 7.0 months. Olmutinib received breakthrough therapy designation in the United States in 2015 and was approved for use in Korea in 2016 (86). However, our understanding is that in September 2016, South Korea’s Ministry of Food and Drug Safety issued a safety letter following two cases of toxic epidermal necrolysis, one of them fatal, and one case of Stevens-Johnson-Syndrome (non-fatal) during the phase II trial of olmutinib, thus halting ongoing studies.

**Naquotinib (ASP8273)**

Naquotinib is a third-generation EGFR TKI that targets mutant EGFR, including T790M (87). In a phase I dose-escalation study (NCT02113813), naquotinib was administered to NSCLC patients with disease progression after prior treatment with an EGFR TKI. In total, 110
patients were treated with naquotinib. Across all doses, in patients with \textit{EGFR} T790M, the response rate was 30.7\% (n=27/88; 95\% CI, 19.5\% to 44.5\%), and median PFS was 6.8 months (95\% CI, 5.5 to 10.1 months). Naquotinib was concluded to be well tolerated with demonstrated antitumour activity (87). In the randomized phase III SOLAR trial (NCT02588261), the clinical efficacy and safety of naquotinib was being evaluated compared to erlotinib or gefitinib for the first-line treatment of patients with advanced \textit{EGFR}-mutant NSCLC; however this trial was terminated upon recommendation by the SOLAR study iDMC, and development of naquotinib was stopped in 2017 (88).

**Present and future directions of third-generation EGFR inhibition: combination therapy**

As with other TKIs, patient’s tumours inevitably progress whilst on a third-generation EGFR TKI. However, the strategy of combining third-generation EGFR TKI with potentially synergistic agents is being evaluated to overcome resistance and improve efficacy.

**Third-generation EGFR TKI in combination with first- and second-generation EGFR TKIs**

Third-generation EGFR TKI inhibitors covalently bind the C797 residue in the kinase binding site of EGFR, and a mutation at this site (C797S, detected in 20–50\% of cases of acquired resistance to osimertinib) dramatically reduces their potency (89-91). No EGFR TKI to date overcomes triple-mutant (activating mutation/T790M/ C797S) \textit{EGFR} NSCLC and efforts are underway to prevent the development of this mutation. Pre-clinical studies demonstrated that T790M and C797S mutations occurring in \textit{trans} retain sensitivity to a combination of first- and third-generation EGFR TKIs (89). C797S, developing in the absence of the T790M mutation, confers resistance to third-generation EGFR TKI while retaining sensitivity to first-generation inhibitors (89,92,93). Thus, erlotinib, and to some extent gefitinib, retain activity against the activating \textit{EGFR} mutations (ex19del and L858R) and the C797S mutation (91,94). Since osimertinib has demonstrated efficacy in the first-line setting for \textit{EGFR} activating mutation-positive NSCLC (58), it has been hypothesized that combining first- and third-generation EGFR TKIs may delay the onset of the C797S and T790M resistance mutations, given the efficacy of each agent against these respective mutations. Consequently, combination therapy trials of osimertinib with gefitinib (NCT03122717) and dacomitinib (NCT03810807), and of EGF816 with gefitinib (NCT0329213, NCT03333343) are currently underway (Table 2).

**In combination with immunotherapy**

Contrary to work demonstrating improved OS in mouse models of \textit{EGFR}-driven NSCLC (95), clinical trials examining immune checkpoint inhibitors (ICIs) in NSCLC have consistently failed to show superiority in the ICI arms in \textit{EGFR} mutation-positive subgroup analyses. A recent review and meta-analysis comparing ICI versus docetaxel in advanced NSCLC (second line setting) involving 3025 patients, confirmed there was no OS advantage in favour of the ICIs for \textit{EGFR}-mutant patients (HR, 1.11; 95\% CI, 0.80 to 1.53; P=0.54; interaction, P=0.005), whereas there was reduction in the risk for death in the \textit{EGFR} WT subgroup (HR, 0.67; 95\% CI, 0.60 to 0.75; P<0.001) (96).

Durvalumab (anti-PD-L1) was tested in patients with \textit{EGFR} mutations or \textit{ALK} rearrangements to establish clinical benefit in the phase II ATLANTIC study (97). The study concluded that a higher proportion of \textit{EGFR}/-\textit{ALK}-NSCLC patients achieved a response than \textit{EGFR}+/\textit{ALK}+ NSCLC, although the activity in patients with \textit{EGFR}+ NSCLC with \textgeq25\% of tumour cells expressing PD-L1 was encouraging and warranted further investigation.

In a planned paired-biopsy biomarker study from the AURA1 study (98), patients with \textit{EGFR} mutation-positive NSCLC receiving the \textit{EGFR} inhibitor osimertinib, had reduced PD-L1 expression and a trend towards increased CD8+ TIL infiltration after therapy, consistent with proinflammatory changes (98). These findings provided the rationale to examine EGFR TKI in combination with ICI (specifically those targeting the PD-1/PD-L1 signaling axis).

The phase Ib TATTON study (NCT02143466) tested osimertinib in combination with durvalumab, savolitinib or selumetinib. The trial included patients with advanced NSCLC who had progressed on prior \textit{EGFR}-TKI therapy and \textit{EGFR}-TKI naïve patients with confirmed T790M mutation status. In the durvalumab combination arm, all patients received osimertinib (80 mg daily) and durvalumab (3 or 10 mg/kg IV q2w). The primary objective was safety and tolerability; secondary objectives included clinical activity. Preliminary data showed that in patients with prior \textit{EGFR}-TKI therapy, investigator-assessed objective response was 67\% and 21\% in those with T790M-positive and T790M-negative tumours, respectively, and 70\% in...
EGFR-mutant treatment-naive patients (44). However, this encouraging clinical data was overshadowed by the increased occurrence of ILD events reported with the combination of osimertinib and durvalumab, compared to what would be expected with either drug alone. The combined ILD rate of 38% [6/23 (26%) in pre-treated patients, 7/11 (64%) in TKI-naïve patients], with 5 cases of grades 3/4 reported for the combination, was greater than either sole agent. There was no apparent increase in the severity of the ILD.

The CAURAL study (NCT02454933) was a phase III study investigating osimertinib with durvalumab vs. osimertinib monotherapy in patients with EGFR mutation-positive (activating and T790M) advanced NSCLC and disease progression after EGFR-TKI therapy. As with the TATTON trial, it was terminated early due to increased incidence of ILD (99). At termination, 15 patients had been randomly assigned to osimertinib monotherapy and 14 to the combination arm. The most common AEs were diarrhea [53% (grade 3 in 6% of patients)] in the osimertinib arm and rash [67% (grade ≥3 in 0 patients)] in the combination arm. One patient randomized to the combination arm reported grade 2 ILD while receiving osimertinib monotherapy (after discontinuing durvalumab therapy after one dose). The objective responses were 80% in the osimertinib arm and 64% in the combination arm.

Currently, there are two active phase II clinical trials examining dual-inhibition of ICI and EGFR TKI in EGFR mutation-positive (Ex19del or L858R +/- T790M) NSCLC. PF-06747775 is being combined with avelumab, and in previously treated T790M mutation-positive NSCLC, EGF816 is being combined with nivolumab (Table 2).

**In combination with other targeted TKIs or biological agents**

In first-generation TKI-resistant tumors, MET amplification is a frequent (5–20%) mechanism of acquired resistance in pre-clinical and clinical specimens (25,79,100,101). Thus, the study of combined EGFR and MET inhibition in cases of cMET-driven acquired resistance to EGFR TKI is a logical line of inquiry. Savolitinib (c-MET inhibitor) was investigated in combination with osimertinib in the phase Ib TATTON trial with encouraging antitumor activity in patients with NSCLC and MET-driven EGFR-TKI resistance. At data cut-off (n=45), confirmed partial responses were reported in 20% (5/25) of patients previously treated with a third-generation EGFR TKI, and 42% (5/12) and 43% (3/7) in T790M-negative and T790M-positive patients, respectively, without prior third-generation EGFR-TKI exposure (102). Savolitinib is being carried forward into phase II testing with the ongoing SAVANNAH trial (NCT03778229) exploring the combination of savolitinib and osimertinib to overcome MET-driven EGFR TKI resistance following treatment with osimertinib (Table 2). The combination of EGF816 with cMET inhibitor, INC280, is now in phase I/II clinical investigation in patients with advanced EGFR-mutant NSCLC (NCT02335944).

The phase III NEJ026 study combined erlotinib with vascular endothelial growth factor (VEGF) monoclonal antibody inhibitor, bevacizumab, in EGFR-mutated chemotherapy-naïve advanced NSCLC (103). The combination arm demonstrated statistically significant improved PFS and objective response over erlotinib monotherapy, thus supporting the hypothesis of synergism with dual inhibition of EGFR and VEGF pathways. The combination of osimertinib with bevacizumab is being investigated and the first phase I results were reported in 2017, showing that the combination is tolerable (45). Three phase II studies with this drug combination in various lines of treatment are currently ongoing (NCT02803203, NCT03133546, NCT02971501, see Table 2). In addition, a phase II study of osimertinib in combination with the monoclonal antibody VEGF receptor 2 inhibitor, ramucirumab, is expected to begin recruitment in April 2019 (NCT03909334).

Other targeted inhibitors being evaluated in early phase studies in combination with osimertinib include MEK/ MAPK/ERK inhibitor, selumetinib (NCT03392246); AXL inhibitor, DS-1205c (NCT03255083); CDK4/6 inhibitor, G1T38 (NCT03455829); HER-2-targeting antibody–drug conjugate, JAK1 inhibitor (NCT02917993), T-DM1 (NCT03784599); BCL-2 inhibitor, navitoclax (NCT02520778) and anti-EGFR monoclonal antibody, necitumumab (NCT02496663). Combination therapy studies with other third-generation EGFR TKI are also underway and include: MEK1/2 (trametinib with EGF816) (NCT03516214, NCT03333343), CDK4/6 (ribociclib with EGF816, palbociclib with PF-06747775) (NCT03333343, NCT02349633), and RAF pathways (LXH254 with...
EGF816) (NCT03333343) (Table 2).

In combination with other treatments

Osimertinib is being evaluated in combination with chemotherapy. A phase 1 study of osimertinib with platinum (carboplatin or cisplatin) and etoposide is currently recruiting (NCT03567642), and an ongoing Japanese phase II trial of osimertinib with carboplatin/pemetrexed recently reported safety data (46).

Osimertinib has demonstrated activity in EGFR-mutated NSCLC with brain and leptomeningeal disease (71,72). Stereotactic radiosurgery (SRS) is one of the standard local treatments for patients with brain metastases. However, it is unclear whether adding SRS to osimertinib will improve intracranial disease control in patients with EGFR-mutated NSCLC and brain metastases. Osimertinib will therefore be tested alone or in combination with SRS in EGFR-mutated NSCLC with brain metastases, diagnosed de novo or developed while on first-line EGFR TKIs, to assess intracranial disease control (NCT03497767). Osimertinib is also being tested as maintenance therapy following definitive chemo-radiation in locally advanced unresectable EGFR mutation-positive NSCLC (stage III) (NCT03521154).

Conclusions

The ongoing attempts to identify and target resistance mechanisms to EGFR TKIs in EGFR mutation-positive NSCLC has proved to be a successful strategy, impacting patient efficacy outcomes and quality of life. This is particularly true for the third-generation EGFR TKIs, exemplified by osimertinib which has demonstrated both increased efficacy and less toxicity than the first- and second-generation agents. Osimertinib’s impressive efficacy in the CNS has added another treatment modality to radiation for the control of CNS EGFR mutation-positive NSCLC and the oncology community eagerly awaits the OS data from the FLAURA and AURA3 trials. EGFR activating mutation-positive NSCLC is rapidly becoming, for the majority of patients, a chronic disease and the third-generation EGFR TKIs have contributed significantly to this end. Nevertheless, we know that on their own, these agents are not curative and that combination therapy with other agents is a necessary next step in striving for better cancer control. Therefore, there remains much to do!

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Footnote

Conflicts of Interest: GD Goss has received research funding from AstraZeneca. Honoraria from Bristol-Myers Squibb, AstraZeneca, Pfizer and Boehringer Ingelheim. Consulting IO Biotech. NM Andrews Wright has no conflicts of interest to declare.

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