

Resistance to epidermal growth factor receptor tyrosine kinase inhibitors, T790M, and clinical trials

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ABSTRACT

Tumours with sensitizing mutations in the *EGFR* gene constitute a distinct molecular subgroup of non-small-cell lung cancers (NSCLCs) that benefit from precision medicine. First- and second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are recommended as upfront therapy for *EGFR*-mutated advanced NSCLC and, compared with chemotherapy, have resulted in superior progression-free survival, improved tumour response rates, and improved quality of life. However, resistance inevitably develops, and the third-generation TKI osimertinib has been approved to target the gatekeeper *EGFR* mutation T790M, which is responsible for resistance in 60% of cases. Multiple drivers of TKI resistance have now been identified, and many new drugs are in development. With respect to this rapidly evolving field, our review highlights the current status of treatment options for patients with *EGFR*-mutated advanced NSCLC, focusing especially on identified causes of resistance, challenges, and clinical trials aiming to improve outcomes in this patient population.

Key Words Lung cancer, *EGFR*, resistance, T790M

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INTRODUCTION

Lung cancer continues to be a leading cause of cancer-related mortality worldwide. In 2017, estimates suggested that, in North America alone, 222,500 new cases of lung cancer and 155,870 deaths occurred¹. Non-small-cell lung cancer (NSCLC) constitutes 85% of lung cancers and has traditionally been classified as squamous cell carcinoma, adenocarcinoma, or large-cell carcinoma. Molecular profiling can now identify key subgroups of patients according to tumour genotype, notably *EGFR* mutations and *ALK* and *ROS1* rearrangements, to be reported routinely at diagnosis. Mutations in *EGFR* occur in advanced lung cancer in more than half of all Asian patients and in approximately 15% of white patients^{2,3}. The classical phenotype for patients with *EGFR* mutations is a female nonsmoker with adenocarcinoma^{4–6}.

The *EGFR* tyrosine kinase domain spans exons 18–24, with most mutations having been identified within exons 18–21. The “classical” sensitizing *EGFR* mutations include deletions in exon 19 and the point mutation L858R in exon 21. Non-classical or uncommon mutations account for approximately 15% of the remaining alterations, which consist of a large heterogeneous group of insertions, deletions, point mutations, and other complex aberrations⁷.

In the advanced setting, many trials have shown the superiority of first-line gefitinib, erlotinib, and afatinib in comparison with standard platinum doublet chemotherapy^{8–16}. A randomized phase II study failed to show a difference between gefitinib and erlotinib in pretreated patients¹⁷. Compared with gefitinib, first-line afatinib is associated with greater progression-free survival (PFS); however, no difference in overall survival (OS) is observed, and afatinib is associated with greater toxicity^{18,19}. Afatinib differs from gefitinib and erlotinib because of its irreversible binding and targeting of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptors 2–4 (HER2, HER3, HER4)²⁰. Recently, dacomitinib, another second-generation tyrosine kinase inhibitor (TKI), when compared with gefitinib, has also demonstrated an improvement by 5.5 months in PFS (14.7 months vs. 9.2 months), but again with increased toxicities²¹. Afatinib might have an important role in patients with uncommon mutations; however, reports of its activity have been inconsistent²².

Despite initial response rates of up to 70% in patients with the classical mutations, resistance to first- and second-generation TKIs will develop, on average, after 9–16 months of treatment^{8,10,13,14}. In this review, we focus on mechanisms of resistance and current clinical trials evaluating combination therapies to overcome resistance.

APPROACH TO TKI RESISTANCE AND T790M INHIBITORS

De novo resistance to EGFR TKIs in common *EGFR* mutations can occur in up to 10% of patients²³. Intrinsic resistance could be a result of the presence of a concurrent non-sensitizing mutation, including T790M.

Given variation in the detection methods, the reported baseline incidence of T790M mutations is variable, but is associated with inferior outcomes to first- and second-generation EGFR TKIs²⁴. The allele fraction of T790M might predict response, and clonal selection over time can influence the development of resistance²⁵. Pharmacogenomics might also affect sensitivity to the TKIs; deletion polymorphisms in *BIM*, which mediates EGFR TKI apoptosis, can reduce TKI efficacy²⁶. In-frame deletions in exons 2–7 of the extracellular domain of *EGFR* are another mechanism of intrinsic resistance²⁷. *In vivo* and *in vitro* modelling has demonstrated that the overexpression of CRIPTOL, a protein that is part of the *EGF-CFC* family can cause *de novo* resistance through activation of SRC and epithelial-to-mesenchymal transition²⁸. Targeting SRC concurrently with an EGFR TKI might delay time to drug failure.

Mechanisms of acquired EGFR TKI resistance can be broadly classified by the aberration of the EGFR pathway, including the T790M mutation in exon 20, alternative pathways, or by pathologic transformation. Repeat testing for *EGFR* T790M is required to guide treatment options after failure of first-line TKIs. The burden of disease progression and symptoms experienced by the patient are important considerations when deciding when to switch systemic therapies (Figure 1).

Oligometastatic Progression

In the setting of oligometastatic progression, adding a local therapy while continuing the initial TKI is appropriate²⁹. Alternatively, for low-burden asymptomatic progressive disease, continuation of the EGFR TKI beyond radiologic progression, with a switch at the time of development of symptoms or clinically significant progression, can prolong the time on first-line therapy. That approach is supported by data from the phase II ASPIRATION trial, which demonstrated that approximately half of all patients, after development of disease progression by RECIST (the Response Evaluation Criteria in Solid Tumors) at a median of 11.0 months, were able to continue on the same TKI therapy until a median of 14.1 months before developing clinically significant disease progression and switching therapies³⁰.

EGFR T790M-Positive Progression and Third-Generation TKIs

In approximately 60% of patients, the T790M mutation is responsible for resistance, and treatment with a third-generation TKI is indicated. The substitution of methionine for threonine at amino acid 790 induces steric hindrance and increased affinity of the receptor for adenosine triphosphate, limiting the efficacy of first- and second-generation TKIs.

Osimertinib is a third-generation TKI currently approved for the treatment of T790M-positive disease, and multiple other agents in this class are being investigated

(Table 1). Osimertinib is given orally at a dose of 80 mg daily³⁸. Third-generation TKIs limit wild-type inhibition, and therefore, compared with first- and second-generation agents, cause less rash and diarrhea^{31,38}. Their superiority compared with chemotherapy in T790M-positive NSCLC after failure of first-generation TKIs has now been reported, with the recent publication of the AURA3 phase III study³¹. The overall response rate was 71% compared with 31%, and the PFS was 10.1 months compared with 4.4 months in the osimertinib and chemotherapy arms respectively. Grade 3 or greater toxicity in the chemotherapy cohort was double that seen with osimertinib (47% vs. 23%). Osimertinib is now the standard of care in this subgroup of *EGFR*-mutated lung cancers after initial first-generation TKI failure. Very recently, the results of the FLAURA study comparing first-generation EGFR TKIs with osimertinib were presented, and an unprecedented superior PFS of 18.9 months was seen in patients receiving osimertinib compared with 10.2 months in those receiving erlotinib or gefitinib (hazard ratio: 0.46; 95% confidence interval: 0.37 to 0.57; $p < 0.0001$)³⁹.

At least 6 third-generation TKIs have been evaluated in clinical trials. Rociletinib was associated with a response rate of 59% in an early phase I/II trial involving *EGFR* T790M-positive patients³², but that high rate failed to be confirmed in the study expansion^{40,41}. Rociletinib becomes activated after amide hydrolysis to produce the metabolite M502, which can be converted to M460. M502 inhibits insulin-like growth factor receptor, and as a result, hyperglycemia occurred in 43% of patients³². The continued clinical development of rociletinib was terminated in 2016, and enrolment in studies was halted, including enrolment in the randomized phase III study of rociletinib compared with single-agent chemotherapy in patients for whom an EGFR TKI and a platinum doublet had failed. Olmutinib (HM61713) was approved in South Korea for T790M-positive NSCLC; however, safety concerns related to grades 3 and 4 skin-related adverse events were reported, and further development of the drug was stopped. In addition, ASP8273, which had demonstrated activity in early phase I results is no longer in clinical development after early results from the SOLAR study, in which it was compared head-to-head with gefitinib or erlotinib (see NCT02588261 at <http://ClinicalTrials.gov>). Table 1 shows data from studies of other third-generation TKIs in earlier phases of development.

T790M-Negative Progression and Other Mechanisms of Resistance to TKIs

In tumours that do not harbour an exon 20 T790M mutation, standard treatment after failure of initial first-generation TKI involves either cytotoxic chemotherapy or enrolment in a clinical trial. In a real-world study by Martin *et al.*, only 21% of patients received chemotherapy after TKI failure, despite 70% being seen to achieve disease control when platinum doublet chemotherapy was administered²⁵.

It is important to acknowledge that combining a TKI with chemotherapy does not result in improvement compared with chemotherapy alone, but it does increase toxicity rates. The large phase III IMPRESS study—which intercalated gefitinib and chemotherapy after patients

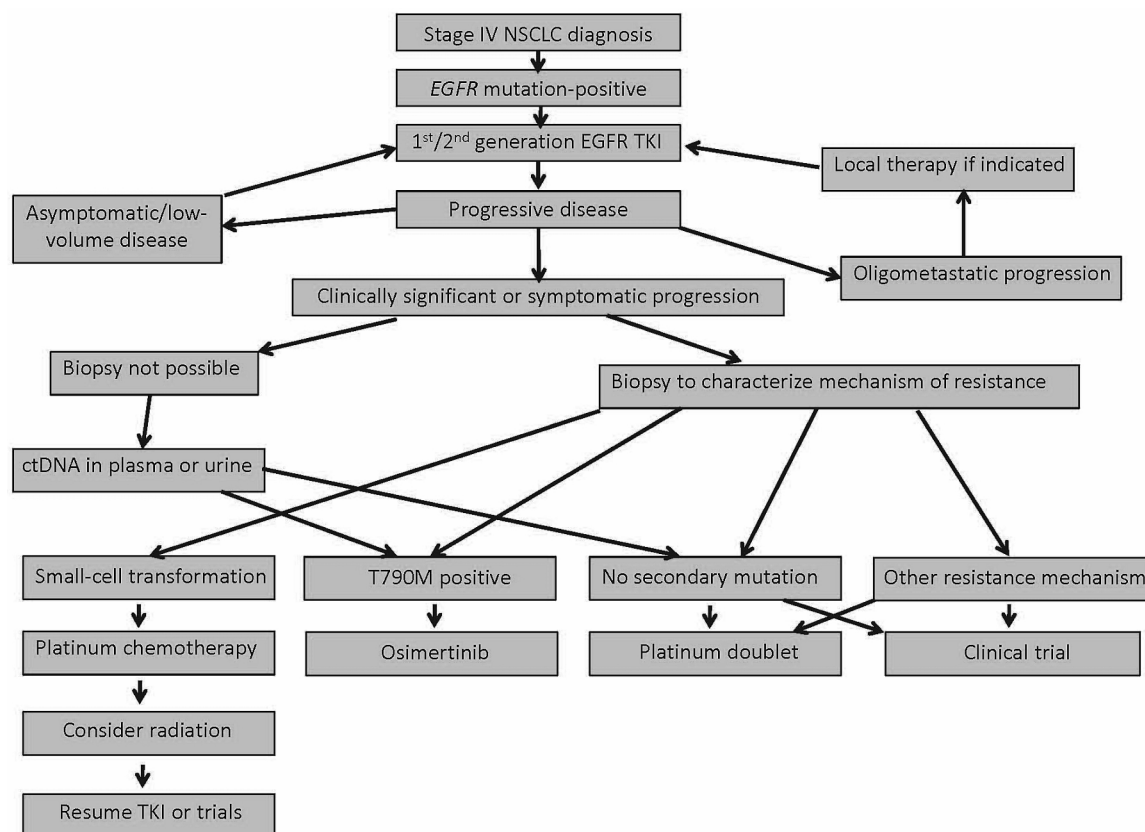


FIGURE 1 Clinical approach to the *EGFR* mutation-positive lung cancer patient. NSCLC = non-small-cell lung cancer; *EGFR* = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; ctDNA = circulating tumour-derived DNA.

progressed while receiving first-line gefitinib—failed to show a survival benefit. In fact, the combination appeared to have a deleterious effect⁴².

C797S and Other *EGFR*-Mediated Pathways

Excluding T790M, other point mutations in *EGFR* that have been reported to cause resistance include A761T, T854A, L747S, and L718Q^{43–46}. Chabon *et al.*⁴⁷ also detected resistance mutations L798I, L762V, and E709K in cell-free DNA. Amplification of *EGFR* can also promote resistance to *EGFR* TKIs^{48–50}. Afatinib inhibits T790M *in vitro*, but does not have major clinical activity in this population⁵¹. *In vivo* modelling has demonstrated that, compared with single-agent TKIs, combined afatinib–cetuximab might delay the time to resistance, and an ongoing phase II/III trial in TKI-naïve patients is being led by swog (see NCT02438722 at <http://ClinicalTrials.gov>)⁵².

The C797S point mutation, which changes cysteine to serine in exon 20, represents the most common resistance mutation in patients progressing on osimertinib and has been reported in patients progressing on olmutinib^{53–55}. Most third-generation TKIs use the cysteine site for covalent binding. Based on *in vitro* modelling, the combination of first- and third-generation TKIs has demonstrated efficacy when the C797S emergent allele develops in *trans* of T790M, but not in *cis*⁵⁶. In data recently presented, C797S detected in samples of circulating tumour DNA was in *cis* with T790M

in 82% of samples, in *trans* with T790M in 10% of samples, and present as an isolated mutation in 6% of samples⁵⁷. A potential fourth-generation *EGFR* TKI, EA1045, has shown promise in targeting T790M and C797S *in vivo*, but only when combined with cetuximab⁵⁸. The clinical utility of this compound is not yet known.

The combination of anti-*EGFR* antibodies and kinase inhibitors continues to be evaluated. Recent *in vivo* models have shown synergy for brigatinib–cetuximab in targeting C797S, T790M, and activating *EGFR*-mutant tumours⁵⁹. *Leu792* mutations have been reported to co-occur with C797S after osimertinib failure. Those mutations occurred in *cis* with T790M, but in *trans* with C797S, and might affect osimertinib binding⁶⁰.

How this complex and varied biology will affect continued drug development and translate into the clinical setting is unclear. As third-generation TKIs move to the frontline setting, resistance mechanisms are certainly likely to diversify. Oxnard *et al.*⁶¹ presented data from the results of next-generation sequencing analysis of 157 plasma samples prospectively collected from patients in the AURA trial at the time of progression on osimertinib. Those authors concluded that loss of T790M does not indicate re-sensitization to first-generation TKI, but often indicates overgrowth of a competing resistance mutation (for example, *KRAS* mutations, *RET* fusions, *FGFR* fusions). They also noted that the timing of osimertinib resistance

TABLE 1 Tyrosine kinase inhibitors (TKIs) approved or being investigated for the treatment of T790M-positive non-small-cell lung cancer

Variable	Osimertinib ³¹ (AZD9291)	Rociletinib ³² (CO1686)	Olmutinib ³³ (HM61713)	Nazartinib ³⁴ (EGF816)	ASP8273 ³⁵	PF-06747775 ³⁶
Most recently reported phase	Phase III (AURA 3)	Phase I/II (TIGER-X)	Phase I/II	Phase I	Phase I	Phase I
Population	Prior TKI failure	Prior TKI failure	Prior TKI failure, with or without prior chemotherapy	Prior TKI failure	Prior TKI failure	Prior TKI failure
Characteristics	T790M+ and T790M–	T790M+ and T790M–	T790M+ (phase I) T790M+ (phase II) 76 (phase II)	T790M+	T790M+ and T790M–	T790M+ and T790M–
Patients (n)	419	130	173 (phase I) 76 (phase II)	132	60	26
Objective response rate (%)	Osimertinib: 71 Platinum–pemetrexed: 31	T790M+: 59 (27/46) T790M–: 29 (5/17)	T790M+: 62 (43/69)	T790M+: 44 (56/127)	T790M+: 38 (15/40)	T790M+: 42 (11/26, all patients)
Disease control rate (%)	Not reported	T790M+: 93 T790M–: 59	91	91	65	65
Progression-free survival (months)	Osimertinib: 10.1 Platinum–pemetrexed: 4.4	T790M+: 13.1 T790M–: 5.6	Not reported	9.2	6.7	Not reported
Grade 3 or greater toxicities (TKI only)	<1% Diarrhea Nausea or vomiting Transaminitis Neutropenia	Up to 22% Hyperglycemia QTc prolongation Nausea or vomiting Fatigue Muscle spasms	Up to 5% Diarrhea Rash Skin exfoliation	Up to 14% Rash Anemia Diarrhea	Up to 23% ^a Diarrhea Hyponatremia	Up to 31% Diarrhea Skin toxicity
Approval	FDA-approved	No longer in development	Approval in South Korea ELUXA no longer accruing	Trials accruing	No longer in development	Trials accruing

^a Reported by Nishio *et al.*³⁷ in phase I/II early results in TKI-naïve patients.

FDA = U.S. Food and Drug Administration.

can offer insight into the related molecular mechanisms, such that early resistance tended to be associated with T790M loss and competing resistance mechanisms, and late resistance was associated with continued *EGFR* addiction, but secondary mutations such as C797S⁶¹.

ALTERNATIVE PATHWAY ACTIVATION

With increasing use of molecular profiling, the understanding of resistance mechanisms is deepening. In 10%–15% of patients, synchronous aberrations have been found^{48,62,63}.

HER2 and *MET* amplification

Amplification of the *MET* oncogene is thought to account for 5%–20% of resistance to EGFR TKIs, including osimertinib and other third-generation agents^{64,65}. *MET* overexpression leads to downstream activation of *AKT* and uncontrolled cell proliferation⁶⁶. Case reports of *MET* amplification have been documented, with reports of responses to crizotinib and other *MET* inhibitors^{64,67–69}. *MET* amplification was identified in more than one quarter of rociletinib-treated patients who developed resistance, and xenograft tumour models regressed with crizotinib⁷⁰. Amplification of *MET* generally occurs with loss of *EGFR* T790M. Pre-existing, co-occurring *MET* amplification has been associated with inferior responses to rociletinib⁴⁷. Cabozantinib, a dual inhibitor [*MET* and vascular endothelial growth factor (*VEGF*)], has demonstrated antitumour activity when combined with erlotinib after failure of EGFR TKI^{71,72}. The TATTON multi-arm study is evaluating the addition of a *MET* inhibitor (AZD6094) in combination with osimertinib (see NCT02143466 at <http://ClinicalTrials.gov>).

In vitro and *in vivo* models have shown that *HER2* amplification might be another important mechanism of resistance, mutually exclusive of T790M⁷³. Acquired *HER2* amplification has been described as a mechanism of osimertinib resistance as found by Oxnard *et al.*⁷⁴ in 2 of 40 patients with loss of T790M. Functional *in vitro* analyses performed by Ortiz-Cuaran *et al.*⁶⁸ suggest that *HER2* activation replaces EGFR signalling and reduces the efficacy of EGFR TKIs.

RAS Pathway

Mutations in *NRAS*, together with copy number gains, have been found to cause osimertinib resistance *in vitro*. Sensitivity to selumetinib (a MEK inhibitor) in the relevant cell lines was subsequently seen⁷⁵. In the study by Ortiz-Cuaran *et al.*⁶⁸, PC9 cell lines with the *KRAS* G12S mutation were inhibited by osimertinib and trametinib. The TATTON study (NCT02143466) includes a combination arm of osimertinib–selumetinib.

Vascular Endothelial Growth Factor Pathway

The *VEGF* and EGFR pathways are intimately related. Up-regulation of *VEGF* has been considered a mechanism of resistance to EGFR kinase inhibitors.

The BETA study, which enrolled more than 600 patients with recurrent or refractory NSCLC, allocated participants in a 1:1 ratio to receive erlotinib–bevacizumab or erlotinib–placebo, and did not identify a survival benefit. In a small subset analysis, a trend toward improved survival was

observed in the combination arm in patients with *EGFR*-mutated tumours⁷⁶. A phase II randomized study in Japanese patients who were treatment-naïve again demonstrated a superior PFS of 16 months with combination treatment compared with 9.7 months with erlotinib alone; as expected, more patients in the combination arm experienced hypertension (60% vs. 10%)⁷⁷. The BELIEF study, a single-arm study of bevacizumab–erlotinib in TKI-naïve patients, reported a median PFS of 13.2 months. Notably, the study population included patients with T790M-positive tumours that were confirmed before treatment. The median PFS was 16.0 months in the patients with a pre-existing T790M mutation ($n = 37$) and 10.5 months in the T790M-negative group ($n = 72$)⁷⁸. A PFS of 14.4 months has also been reported for gefitinib–bevacizumab⁷⁹. Clearly, the combination of an EGFR TKI and bevacizumab has demonstrated activity.

Ramucirumab is another monoclonal antibody targeting *VEGF2* that is being combined with erlotinib in untreated patients as part of the RELAY study (see NCT02411448 at <http://ClinicalTrials.gov>). The BOOSTER study (NCT03133546) will investigate osimertinib and bevacizumab in the second-line setting in patients with confirmed T790M.

Others

BRAF mutations and activating mutations in *PIK3CA* have also been identified as potential causes of resistance. The *PIK3CA* activating mutations are not mutually exclusive with *EGFR* mutations, and co-occurrence is associated with inferior outcomes⁸⁰. Loss of *PTEN*, and focal amplification of *FGFR1* have also been reported⁸¹.

Phenotypic Transformation

As repeat biopsy to elucidate resistance mechanisms becomes a standard of care, small-cell transformation is increasingly reported. The origins and mechanism for histologic transformation have recently been described. In this rare patient cohort, tumours tend to have shared clonality in the adenocarcinoma and small-cell components.

In the largest case series, transformation occurred in 21 patients with tumours harbouring completely inactivated *RBI* and *TP53*⁸². In a review of 18 reported cases in 2016, treatment had varied widely⁸³. The use of platinum–etoposide chemotherapy, sometimes incorporating additional radiation, is generally accepted, although the latter addition remains controversial. Given that the *EGFR* mutation persists, some authors advocate reintroduction of the EGFR TKI; however, evidence for that approach is lacking. In a review of 6 patients with reported outcomes to platinum–etoposide, 5 responded, but their OS was only 7.1 months⁸³.

The optimal management of these patients is not yet known. Induction of epithelial-to-mesenchymal transition has also been described in the setting of resistance, and that transformation has been successfully targeted using *AKT* inhibitors in preclinical models⁸⁴. A recent preclinical study further revealed aberrant activation of the Hedgehog pathway in resistant cell lines as a result of the induction of epithelial-to-mesenchymal transition and *ABCG2* upregulation, offering a putative biomarker for targeting resistance⁸⁵.

COMBINATION TREATMENT

Given the multiple potential resistance mechanisms that could emerge, combination therapy for this group of patients is drawing interest, and a number of clinical trials are ongoing. Broadly speaking, those trials are divided into four categories:

- Therapy combining an existing TKI with another class of molecularly targeted agent to overcome resistance
- Therapy combining a TKI with chemotherapy
- Therapy combining a checkpoint inhibitor with a TKI
- Therapy with novel TKIs

Role of Immune Checkpoint Inhibition in Treating Resistance

Immunotherapy has emerged as a new treatment paradigm, attracting significant enthusiasm from patients and providers alike. Nivolumab and atezolizumab have received approval for the treatment of unselected NSCLC in the second-line setting, and pembrolizumab has been approved in the first- and second-line settings in patients with PD-L1-positive tumours (score of 50% or greater by 22C3 assay).

Those agents have demonstrated superiority when compared with chemotherapy in terms of OS, response, and even quality of life, but their efficacy in patients with *EGFR*-mutated lung cancer is less clear. Expression of PD-L1 is less common in patients with *EGFR*-mutated lung cancer, but it is an independent negative prognostic factor^{86,87}. Notably, *EGFR*-mutated lung cancers have been shown to overexpress CD73 and the adenosine A2A receptor. CD73 represents a checkpoint in the adenosine pathway, and its interaction with the adenosine A2A receptor creates an immunosuppressive environment, suggesting a potential therapeutic target in *EGFR*-mutated NSCLC⁸⁸.

In a meta-analysis of checkpoint inhibitor trials, no survival benefit of immunotherapy compared with docetaxel was evident in the second-line setting in patients with whose tumours harboured *EGFR* mutations ($n = 186$)⁸⁹, but this approach remains under active investigation. The CAURAL trial of durvalumab–osimertinib, and the phase I TATTON study which is investigating the same combination, have been halted because of concerns about a high rate of interstitial lung disease seen in the combination arm⁹⁰. Similarly, a study of nivolumab–EGF816 was halted for toxic epidermal necrolysis (see NCT02323126 at <http://ClinicalTrials.gov>). Early reports about erlotinib–nivolumab have emerged from the CheckMate 012 study, with grade 3 toxicity being observed in 19% of patients (no grade 4 toxicities), the overall response rate being 19%, and the OS at 18 months being 64%. Early results from trials of durvalumab–gefitinib and atezolizumab–erlotinib have reported response rates of up to 80%. Elevation in liver transaminases was the most common reason for dose interruption^{91,92}. Although the combination of a TKI and an immune checkpoint inhibitor appears to be active, an understanding of who is susceptible to toxicity will be an ongoing area of investigation.

Liquid Biopsies to Detect T790M

Tumour heterogeneity and the limitations of biopsy in this advanced cancer population mean that using a “liquid”

biopsy to detect the T790M mutation in plasma or urine is an important option, with approval as companion diagnostics given by the U.S. Food and Drug Administration. Many real-time methods, including non-digital assays [Cobas (Roche Diagnostics, Basel, Switzerland), TheraScreen (Qiagen, Hilden, Germany)] and digital assays [digital droplet polymerase chain reaction (PCR), BEAMing (beads, emulsion, amplification, magnetics) digital PCR] are available to detect *EGFR* sensitizing and T790M mutations in plasma. Cross-comparisons between platforms demonstrated high sensitivity for Cobas and BEAMing in detecting T790M (73% and 81% respectively).

A prospective study by Sacher *et al.*⁹³ using digital droplet PCR to detect *EGFR* and *KRAS* mutations reported a detection sensitivity of 77% for T790M and 64% for *KRAS* mutations. In a *post hoc* analysis of the initial AURA study, patients with T790M detected in plasma achieved a response rate of 70% with osimertinib. Patients who were tissue-negative but plasma-positive for the mutation experienced outcomes similar to those achieved in the overall study population, with a response rate of 63% and a PFS of 9.7 months⁹⁴. Those results suggest that plasma genotyping could be an option as the first method of detecting T790M mutations and might spare patients from undergoing repeat tissue biopsy, reserving tissue biopsies for only those patients who are plasma T790M-negative. The phase IV ASTRIS study will prospectively investigate that possibility. Currently, plasma genotyping is recommended only for patients in whom a tumour biopsy cannot be obtained⁹⁵. Serial analyses of plasma when patients are receiving TKIs might reveal the emergence of resistance before radiologic or symptomatic progression is seen^{96,97}; whether such detection should prompt a change in treatment is currently unknown.

CENTRAL NERVOUS SYSTEM METASTASIS IN *EGFR*-MUTATED LUNG CANCER

In patients who progress intracranially in the presence of extracranial disease control, local therapy to the brain can be used while the *EGFR* TKI is continued. First- and second-generation TKIs are known to have only minor cerebrospinal fluid penetration, and central nervous system (CNS) progression can be the first site of uncontrolled disease in up to one third of patients. That progression might potentially be overcome by high-dose pulsed *EGFR* TKI; however, that approach does not tend to be used in clinical practice in Canada⁹⁸.

The mechanisms of CNS resistance can differ from those causing systemic progression. The Jackman criteria for acquired resistance note that relapse only in the CNS does not indicate systemic resistance⁹⁹. Autopsy studies have demonstrated heterogeneity in systemic compared with intracranial metastasis resistance mutations, with the novel D761Y mutation being detected in a brain metastasis⁴⁴. In continuing TKI alongside whole-brain radiation or stereotactic radiosurgery, a small retrospective study found an intracranial disease control rate of 76%¹⁰⁰.

With the longer duration of patient survival in the era of targeted therapies, the treatment of CNS metastases is gaining increasing attention. A recent comparison of stereotactic radiosurgery followed by TKI, whole-brain

radiation therapy followed by TKI, or TKI followed by local treatment showed that the median OS was superior when a local treatment was used first (46 months vs. 30 months vs. 25 months respectively, $p < 0.01$)¹⁰¹. Erlotinib was the TKI used in most patients.

A similar retrospective analysis reported superior time to intracranial progression when whole-brain radiation therapy was administered first for CNS control; however, no difference in survival was observed¹⁰². Newer-generation TKIs are showing promise in the treatment of intracranial disease, with better cerebrospinal fluid penetration. Osimertinib demonstrated activity in early clinical trials, later confirmed in the randomized AURA3 study¹⁰³. The highlight was a significant improvement in PFS for patients with CNS metastases in the osimertinib group (8.5 months vs. 4.2 months with chemotherapy; hazard ratio: 0.32; 95% confidence interval: 0.21 to 0.49)³¹.

The BLOOM study (see NCT02228369 at <http://ClinicalTrials.gov>) will evaluate osimertinib 160 mg daily in NSCLC patients with leptomeningeal disease. Early results have reported radiologic responses in 7 of 18 evaluable patients¹⁰⁴. The study is also evaluating AZD3579, a novel EGFR TKI designed to cross the blood–brain barrier. Recent results have been promising, achieving an intracranial response rate of 63% and an extracranial response rate of 50%. The drug was tolerable, with a spectrum of toxicities similar to that seen with other EGFR TKIs¹⁰⁵.

FUTURE DIRECTIONS

Third-generation TKIs are now being investigated in the adjuvant setting (ADAURA), and multiple studies are also evaluating their role in first-line treatment for advanced EGFR-mutated lung cancer (FLAURA). As the understanding of resistance mechanisms evolves, circulating DNA is likely to start to be used for the detection of mutations, with tissue biopsies held in reserve. Whether the early detection of resistance in blood should dictate a treatment change is unknown. The optimal sequencing of drugs to be used in EGFR-mutated lung cancer to extend survival and maintain quality of life is likely to emerge in the coming years. We expect that the time to chemotherapy start will continue to be delayed as the current treatment paradigm unravels and new drugs are approved.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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