CHAPTER 6

Challenges in the management of EGFR-mutated non-small cell lung cancer patients with acquired resistance to tyrosine kinase inhibitors

J.L. Kuiper, E.F. Smit

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Chapter 6

ABSTRACT

Non-small cell lung cancer (NSCLC) patients with an epidermal growth factor receptor (EGFR) mutation have a median progression-free survival of 12 months on treatment with tyrosine kinase inhibitors (TKIs). Clearly, the introduction of these agents had major implications for the treatment of NSCLC, but new questions and challenges arise as well. Traditionally, response assessments of anti-cancer treatment are conducted according to the RECIST criteria. Progressive disease is usually indicative of a change of therapy. In the current era of targeted therapies, it has become clear that different patterns of progressive disease are observed with TKI treatment in EGFR-mutated NSCLC patients, with potential consequences for therapeutic decision-making. In this review, we will discuss whether the RECIST criteria are still optimal for response evaluation. Rebiopsy studies have provided more insight into different resistance mechanisms at the time of acquired resistance to TKIs. These mechanisms, as well as the role of rebiopsy in daily clinical practice, will subsequently be covered. Finally, treatment strategies for different types of progressive disease will be discussed.
Challenges in the management of EGFR-mutated NSCLC patients with acquired resistance to TKIs

INTRODUCTION

The epidermal growth factor receptor (EGFR) gene is one of the druggable oncogenes in non-small cell lung cancer (NSCLC). Mutations in this gene occur in approximately 9.4% of non-squamous NSCLC patients in a Western population (1) and in up to 47.9% of Asian NSCLC patients (2). The majority of all EGFR kinase mutations include exon 19 deletions (45%) and point mutations in exon 21 (L858R; 40%) (3). These mutations convert the cell without the presence of a ligand (growth factor) to provide for continuous proliferation, resulting in unrestrained cellular proliferation (4). EGFR-mutated NSCLC patients were found to have excellent response rates to the tyrosine kinase inhibitors (TKIs) erlotinib, gefitinib and afatinib (5-7). However, resistance to these TKIs is inevitable after a median of 12 months (8).

This review will discuss some important issues in the current field of TKI resistance in EGFR-mutated NSCLC patients. First, the definition of ‘progression’ in the setting of TKI resistance is a matter of ongoing debate with consequences for therapeutic decision-making. Second, repeated biopsies (hereafter called ‘rebiopsies’) in EGFR-mutated NSCLC patients with acquired TKI resistance have been crucial for a better understanding of the different mechanisms of resistance. The role of rebiopsy in EGFR-mutated NSCLC will subsequently be covered. Finally, potential therapeutic strategies and promising agents for TKI-resistant, EGFR-mutated NSCLC will be discussed.

PROGRESSIVE DISEASE WITH TKI TREATMENT IN EGFR-MUTATED NSCLC PATIENTS

Historical and Current Tumour Response Assessment Criteria

In 1981, the World Health Organization (WHO) criteria were the first criteria introduced to uniformly assess the response to anti-cancer treatments (9). These criteria prescribed bidimensional tumour measurement but provided no definition of a particular imaging modality and no minimal size of measurable lesions.

There was an urgent need for new criteria in order to improve tumour assessment in traditional cytotoxic therapies. Therefore, in 2000, the Response Evaluation Criteria in Solid Tumours (RECIST) criteria were proposed in order to be able to compare results from clinical trials uniformly (9). In 2009, the RECIST criteria were revised (RECIST 1.1), reducing the number of target lesions, defining the assessment of pathologic lymph nodes, including PET scanning in response assessment and adjusting the criteria for ‘progressive disease’ (10). In this version, progressive disease is defined as an increase in size of the target lesions of at least 20% or a development of new lesions. Up until today, the RECIST criteria are the most widely used criteria for response assessment. Virtually every clinical trial that evaluates anti-
cancer agents incorporates the RECIST criteria in its endpoints. Also in clinical practice, the RECIST criteria often serve as a guidance for therapeutic decision-making.

Radiological progressive disease is interpreted as an indication of drug failure, and, consequently, cessation or switch of therapy is recommended. In this way, radiological progressive disease is supposed to represent the clinical status of acquired resistance.

**Patterns of Progressive Disease in EGFR-Mutated NSCLC Patients at the Time of Acquired Resistance to TKI Treatment**

The term ‘acquired resistance’ implies a period of previous sensitivity (tumour shrinkage or stabilization) to a drug, followed by insensitivity (tumour growth) while still on that drug. Clinical criteria for acquired resistance during TKI treatment in *EGFR*-mutated NSCLC patients were first proposed by Jackman et al. (11). These criteria apply regardless of different molecular mechanisms of resistance and are described in Table 1.

**Table 1: Clinical criteria for acquired TKI-resistance in *EGFR*-mutated NSCLC patients proposed by Jackman et al (11)**

<table>
<thead>
<tr>
<th>Criterion</th>
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<tr>
<td>1. Treatment with single-agent EGFR-TKI</td>
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<tr>
<td>2. Confirmed <em>EGFR</em>-mutation or partial response according to RECIST or prolonged stable disease according to RECIST (&gt;6 months) to TKI</td>
</tr>
<tr>
<td>3. Progressive disease according to RECIST within 30 days of continuous EGFR-TKI therapy</td>
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<tr>
<td>4. No intervening therapy</td>
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At that time, there was an urgent need for clinical criteria for the development of acquired resistance to EGFR-TKIs in order to be able to uniformly assess clinical trials. However, physicians treating patients with targeted therapies experience the third criterion to be very heterogeneous. The patterns of clinical and radiological progression of disease vary widely in terms of the growth rate, number and location of progressive lesions. Several years of experience with these therapies have raised the question of whether traditional response criteria are still applicable to the measurement of the anti-tumour effects of these agents.

Considering the growth rate and number of growing tumour lesions, three clinically heterogeneous patterns can be distinguished [H. West, pers. commun.]. In the first pattern, the disease is under perfect control except for one single growing lesion. The second pattern shows several growing lesions, but their growth rate is low and indolent. The third pattern comprises a progressive disease that is rapid and multifocal. In the first two patterns, the tumour load is typically still smaller than in the pre-treatment setting, while in the third pattern, the tumour load usually has increased.

The location of the progressive lesions may distinguish different types of progression also in terms of the molecular characteristics of these lesions. Patients solely having progressive lesions in the central nervous system (CNS), with control of the disease elsewhere, may
represent a distinct subgroup within the group of EGFR-mutated NSCLC patients on TKI treatment with progressive disease as per the RECIST. The T790M mutation is a mechanism of resistance that is commonly detected in systemic lesions in progressive disease (discussed later in this review); however, in CNS lesions, it is detected less frequently (12). The blood-brain barrier keeps most agents from penetrating into the CNS, creating a pharmacological sanctuary site. Lesions developing in the CNS are believed to have escaped pharmacological inhibition and may therefore represent a type of progression different from systemic progression.

**Considerations in Evaluating Response in Oncogene-Driven NSCLC**

There is increasing evidence for a role of tumour heterogeneity in the development of resistance to a targeted therapy. Although it is hypothesized that all cancer cells in an individual are derived from a single common ancestor cell (13), advanced-stage tumours usually consist of heterogeneous populations of cancer cells. Tumour cells are subject to a greater genetic instability than normal cells and have a higher mutation rate (14). According to historical evolution theories (15), tumour heterogeneity is the result of a selection process in which the ‘fittest’ cancer cell populations survive. It has been described both in NSCLC (16) and in other fields of oncology (17).

The cancer cells best adapted to the environment of the tumour will have the highest chance of survival. This tumour microenvironment is subject to changing physiological and iatrogenic conditions (e.g. caused by cancer treatment). Targeted therapies are directed against specific molecular targets, the mutated oncogenes, which are termed the ‘Achilles heel’ of a tumour cell. For this reason, these agents have the potential to efficiently eliminate certain sensitive cancer cell populations. Pre-existent resistant clones, however, get the opportunity to outgrow the other cells, eventually becoming the dominant clone (18). According to this theory, the term ‘acquired resistance’ is actually misleading; the resistant clones are present at baseline and become the dominant clones through selective pressure. Once these clones have proliferated to tumour sizes that have considerably increased since previous scans, progressive disease can radiologically be detected. However, the sensitive clones are still adequately suppressed. According to this theory, it is plausible that minor tumour cell populations in a radiologically progressive tumour will still be sensitive to the previous treatment.

**Alternative Response Assessment Criteria in Other Fields of Oncology**

Alternative tumour response assessment criteria have emerged in other fields of oncology in which treatment with targeted therapies for selected patients has become the standard of care. PET uses the uptake of 2-deoxy-2-[¹⁸F]fluoro-α-D-glucopyranose (FDG) to measure tumour metabolism. It is a valid method of measuring the anti-tumour activity of a treatment, in particular of treatments that are more likely to induce a decrease in tumour metabolism but
not necessarily a change in tumour size. PET is increasingly used in the diagnosis and follow-up of cancer, and in 2009 the PERCIST criteria were proposed (19). These quantitative criteria measure the percentage change in standard uptake volume (SUV) or in SUV normalized to the lean body mass (SUL). In the PERCIST, partial response is defined as a 30% decline in SUL peak and progressive disease as a 30% increase or confirmed new lesions.

The criteria by Choi et al. (20) were the first to have been developed to assess tumour response to a specific therapy in patients with gastrointestinal stromal tumours (GIST) who are treated with imatinib. In these patients, tumour response is usually most evident in the centre of the tumour, which becomes homogeneous and dense on CT, whereas the border of the tumour is usually not involved in the response. As a result, the RECIST criteria fail to measure a response, even though the tumour burden has decreased. The Choi criteria incorporate tumour density and the number of intratumoural vessels into the response assessment. Subsequently, the Choi criteria became the standard response evaluation system for imatinib-treated metastatic GIST patients.

Vascular EGFR inhibitors and multitargeted TKIs are known to induce central tumour necrosis, which is undetectable with the RECIST criteria. Crabb et al. (21) proposed a method incorporating tumour cavitation into the tumour response assessment. MASS (morphology, attenuation, size and structure) criteria were evaluated in metastatic renal cell carcinoma (22). A significant association with progression-free survival was detected, but further prospective validation of these criteria is awaited.

The introduction of ipilimumab (23), a fully human monoclonal antibody that promotes anti-tumour immunity, in the treatment of metastatic melanoma prompted oncologists to develop a novel set of criteria known as the ‘immune-related response criteria’ (24). Immunotherapeutic agents are known to induce a response only after an increase in tumour burden that would be assessed as progressive disease according to the RECIST criteria. The immune-related response criteria allow for partial response or stable disease even in the presence of new lesions. Further evaluation of these criteria in prospective trials is warranted.

**Alternative Response Assessment Criteria in Oncogene-Addicted NSCLC**

The different patterns of progressive disease in oncogene-addicted NSCLC are evident, and several groups evaluated potential complementary or alternative response assessment criteria for response evaluation in EGFR-mutated NSCLC. The change in tumour burden and the growth rate of the tumour lesions are important indicators of the efficacy of a treatment and may complement the RECIST criteria in the response assessment of TKI treatment in EGFR-mutated NSCLC patients (25).

The measurement of volumetric tumour change during the treatment of NSCLC with US Food and Drug Administration (FDA)-approved software has been found to be feasible and reproducible (26). Nishino et al. (27) analysed the volumetric growth rate in EGFR-mutated
NSCLC patients after the volume of the tumours had reached its nadir during EGFR-TKI therapy, with the ultimate goal of being able to identify slowly progressing patients who can safely remain on TKI therapy. The occurrence of 2 consecutive events of a growth rate of >0.15/month was determined as a threshold. Despite the retrospective design of the study by Nishino et al. (27) and the small number of patients included, this was a first attempt to develop criteria that may complement the RECIST, thereby optimizing the response assessment of TKI treatment in EGFR-mutated NSCLC patients and maximizing the beneficial effects of this targeted therapy. Further development of these volumetric assessment criteria in a larger group of patients is planned for.

Different patterns of EGFR-TKI failure in EGFR-mutated NSCLC patients were described by Yang et al. (28). The patients were categorized into three groups based on the duration of disease control on previous TKI treatment, the evolution of tumour burden and clinical symptoms. They were subsequently categorized into a ‘dramatic progression’ group, a ‘gradual progression’ group and a ‘local progression’ group. Progression-free survival, post-progression survival and overall survival were significantly different between the groups, and the best prognosis was established for the gradual progression group. The patients in this category had the longest disease control on previous TKI treatment, the longest volume doubling time for the target lesions, a moderate progressive involvement and a persistent symptom benefit. Although some of these criteria are RECIST based (previous disease control and progression of target lesions), the clinical condition of the patient is incorporated into these criteria, which is an important parameter in decision-making for physicians.

Lee et al. (29) proposed new CT response criteria for EGFR-TKI treatment that incorporated changes in tumour attenuation values on CT, morphologic changes such as tumour cavitation within the target lesions and the change in tumour constituents (like ground-glass opacity components). Of 80 NSCLC patients treated with TKI, 16 non-responders according to the RECIST 1.1 would have been classified as responders according to the newly developed CT response criteria. According to these criteria, patients categorized as responders had better overall survival than non-responders ($P = 0.06$), whereas this difference was less obvious with the assessment by RECIST ($P = 0.24$). However, this was a retrospective study, performed on unselected NSCLC patients. A prospective evaluation of these criteria in molecularly selected patients is still necessary.

Although the RECIST criteria provide easily applicable, standardized tumour response evaluation criteria, there is an unmet demand for additional response assessment criteria for the treatment of oncogene-driven NSCLC. In other fields of personalized treatment in oncology, successful efforts have been made to obtain criteria for tumour response assessment. Also for NSCLC, several groups have attempted to develop additional criteria, but prospective evaluations and validations are still necessary.
REBIOPSY IN EGFR-MUTATED NSCLC PATIENTS WITH TKI RESISTANCE

Before the era of targeted therapies, treatment was based on a single baseline biopsy, and this is still the case for the majority of cancers. With the concept of ‘oncogene-driven cancers’ and the introduction of therapies specifically directed against these oncogenes, it was hypothesized that molecularly defined tumours may have dynamic characteristics enabling them to ‘adapt’ to a certain environment in order to escape elimination. Rebiopsies have been crucial for a better understanding of this phenomenon. Several groups have reported on rebiopsy at the time of progressive disease during TKI treatment (Table 2) (12, 30-33).

Resistance Mechanisms Detected at Rebiopsy

Extensive preclinical and clinical investigation has increased our knowledge about the resistance mechanisms in acquired TKI resistance. The most important mechanisms of resistance will be discussed.

**T790M Mutation**

The T790M mutation is detected in 49 – 68% of EGFR-mutated NSCLC patients with acquired TKI resistance (Table 2). This secondary mutation occurs at exon 20 and is most often observed in the cis isoform (34). It enhances the ATP-binding affinity of EGFR-mutated cells, and since EGFR-TKIs are competitive ATP inhibitors, their efficacy is decreased by this mutation (35). Previously, it was thought that pre-treatment detection of T790M was rare, but by using more sensitive detection methods, T790M can be detected in a substantial part of TKI-naïve patients (36). The survival of patients exhibiting the T790M mutation at progression is reported to be better than that of patients who do not develop this resistance mutation (12), although not all authors confirm this finding (32). Follow-up rebiopsies in EGFR-mutated NSCLC patients revealed that the T790M mutation can be a dynamic phenomenon; although it is detected in most patients after acquiring resistance to TKI, it can become undetectable in rebiopsies after subsequent lines of treatment in some of these patients (31).

**Transformation to SCLC**

Transformation to SCLC is another mechanism of resistance that can be detected at time of acquired resistance (31, 33). It is still unknown whether it occurs in association with the development of resistance or is a causative factor itself. Initially, it was described in 14% of patients; however, more recent studies reported 1 – 3% of the NSCLC tumours to transform to SCLC after TKI treatment (31, 33). Patients with a transformation to SCLC seem to respond favourably to traditional chemotherapeutic SCLC regimens (31).
### Table 2: In vivo studies reporting on rebiopsy in EGFR-mutated NSCLC patients with acquired TKI-resistance

<table>
<thead>
<tr>
<th>Group</th>
<th>Year</th>
<th>Patients</th>
<th>Prospective / retrospective</th>
<th>Incidence of most prevalent resistance mechanisms?</th>
<th>Other findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequist et al (31)</td>
<td>2011</td>
<td>39</td>
<td>Retrospective</td>
<td>T790M = 49% MET = 5% SCLC-transformation = 14% PIK3CA = 5%</td>
<td>Changing T790M-status at longitudinal biopsies</td>
</tr>
<tr>
<td>Arcila et al (30)</td>
<td>2011</td>
<td>99</td>
<td>Prospective</td>
<td>T790M = 68% MET-amplification = 11%</td>
<td></td>
</tr>
<tr>
<td>Yu et al (33)</td>
<td>2013</td>
<td>155</td>
<td>Prospective</td>
<td>T790M = 63% MET = 5% SCLC-transformation = 3%</td>
<td>No mutations in PIK3CA, AKT1, BRAF, ERBB2, KRAS, MEK1 or NRAS were detected at acquired resistance</td>
</tr>
<tr>
<td>Hata et al (12, 33)</td>
<td>2013</td>
<td>78</td>
<td>Retrospective</td>
<td>T790M: CNS lesions 1.7%, Non-CNS lesions 41%</td>
<td>Emergence of T790M in CNS lesions is rare. T790M-positive patients have better prognosis than T790M-negative patients</td>
</tr>
<tr>
<td>Sun et al (32)</td>
<td>2013</td>
<td>70</td>
<td>Prospective</td>
<td>T790M = 51% SCLC-transformation = 1%</td>
<td>No prognostic or predictive role for T790M mutation</td>
</tr>
</tbody>
</table>
MET Amplification
An association between an acquired amplification of MET and EGFR-TKI resistance has been described (37). MET is a proto-oncogene encoding for the hepatocyte growth factor receptor that possesses tyrosine kinase activity. In order to maintain the downstream signalling paths of EGFR (PI3K pathway), signalling occurs through MET, thereby bypassing EGFR (37). MET amplification is rare in untreated EGFR-mutated NSCLC patients (38). In TKI-resistant patients, its prevalence was originally described as being 22.0% (31), but a recent study reported a lower incidence of 3.0% (33). Moreover, in the latter trial (33), MET amplification was detected only concurrently with other mechanisms of resistance. It may therefore be questioned whether it can be considered a mechanism of resistance in itself.

Infrequently Detected Mechanisms of Resistance
Other clinically detected mechanisms of resistance concern the D761Y, T854A and L747S mutations and epithelial-to-mesenchymal transition. The incidence of these mechanisms is low and is beyond the scope of this review.

Rebiopsy
Whether certain biomarkers are present and/or absent in a tumour has major consequences with regard to the choice of therapy. Since surgical treatment is not often an option for patients with advanced-stage tumours, biopsy is the most important method of obtaining tumour tissue for analysis. However, several considerations should be made when performing a rebiopsy.

Complications
Like with any other invasive medical procedure, there is a risk of complications when performing a rebiopsy. Yoon et al. (39) reported on the adequacy and complication rate of rebiopsy in 94 patients with NSCLC who had previously been treated with chemotherapy. All biopsies were technically successful and 80% of the biopsies yielded sufficient tumour tissue for mutational analysis. The complication rate was acceptable at 14% and comprised mainly pneumothorax.

Another study evaluated 745 research biopsies in 576 patients (40). The overall and major complication rates were 5.2% and 0.8%, respectively, although the rate was higher for intrathoracic biopsies (17.1%). The rebiopsy study by Yu et al. (33) showed a complication rate of 0.01%; 1 of 155 patients developed pneumothorax.

Tumour Heterogeneity
Apart from its previously discussed role in the development of resistance, tumour heterogeneity may also cause a misinterpretation of biopsy results. Most mutations are
heterogeneously present in different tumour lesions, especially after targeted treatment (41), and, therefore, results from a single-site rebiopsy may not be representative for all tumour lesions.

The role of tumour heterogeneity in the development of resistance to targeted therapies has only recently been elucidated. The consequences for interpreting results of rebiopsies should still be determined. Further research on this topic is necessary, and, in this light, the TRACERx trial (www.ClinicalTrials.gov: NCT01888601) has been initiated, which will evaluate the evolutionary genomic landscape between primary and metastatic NSCLC sites and the dynamics of intratumoral heterogeneity over time.

Alternative Ways of Obtaining Information on Tumour Characteristics

Over time, scientists have attempted to obtain information on tumour characteristics via other, less invasive ways than by biopsy. The potential of malignant tumours to metastasize, one of the hallmarks of cancer (42), led to speculation on the existence of circulating tumour cells (CTCs) already centuries ago. The potential of these CTCs to act as prognostic markers has been described for several cancers. Moreover, monitoring CTCs during the course of treatment offers the possibility of detecting changes in the molecular profile of the tumour (43). Besides the use of CTCs, the use of circulating tumour DNA has recently been described as well (44). Both are promising techniques, but whether these ‘liquid biopsies’ are going to replace traditional tumour tissue rebiopsies in clinical practice remains to be seen.

Clinical Implications of Rebiopsy

Performing rebiopsies in EGFR-mutated NSCLC patients with acquired TKI resistance has provided important information on resistance mechanisms, and, therefore, the scientific value of rebiopsy is evident. Also, rebiopsy is imperative for the selection of patients for clinical trials. Its value and necessity for clinical practice, however, remain a matter of debate. Currently, as will subsequently be discussed, there are no registered treatments for EGFR-mutated NSCLC patients with TKI resistance. Moreover, transformation to SCLC as a mechanism of acquired TKI resistance occurs less frequently than previously thought. Still, it may have important consequences for the choice of a subsequent line of treatment, because several patients have been reported to respond to SCLC chemotherapy regimens. However, at this moment, as long as no other strategies have been proven effective or agents have been registered, it is debatable whether the low incidence of transformation to SCLC justifies rebiopsies. In our opinion, outside clinical trials, a rebiopsy should only be performed after thorough explanation of the risks and benefits to a patient.
Chapter 6

TREATMENT OPTIONS FOR DIFFERENT PATTERNS OF PROGRESSIVE DISEASE

Different patterns of progressive disease may represent different biological molecular phenomena. It is therefore important to distinguish between these patterns as different therapeutic strategies may apply. In the ongoing search for new treatment strategies for acquired TKI resistance in EGFR-mutated NSCLC patients, several options have emerged.

In accordance with the previously explained theory of tumour heterogeneity, it may be reasonable to continue targeted treatment beyond progression, as minor tumour cell populations will still be sensitive to the previous therapy. Moreover, cessation of TKI treatment in EGFR-mutated NSCLC may result in a ‘disease flare’ (45, 46). This has been reported in up to 23% of patients and usually develops quickly after TKI discontinuation (median: 7 – 8 days) (45, 46). Disease flare predicts poorer survival in EGFR-mutated NSCLC patients after the cessation of TKI treatment (46).

Continuation of a targeted treatment beyond progression is also common practice in other molecularly defined tumours, such as the continued use of imatinib in GIST, of ipilimumab in melanoma and of trastuzumab in HER2-amplified breast cancer (47-49). For EGFR-mutated NSCLC, there is increasing evidence as well that it may be beneficial to continue TKI treatment beyond progression according to the RECIST criteria (50). A recent study reported that 88% of EGFR-positive NSCLC patients who underwent first-line treatment with a TKI continued TKI treatment beyond progressive disease according to the RECIST criteria (51). Results from a prospective trial (ASPIRATION) allowing physicians to continue erlotinib beyond progression according to the RECIST criteria in cases of slowly progressive disease, asymptomatic minimally progressive disease or locally controlled brain metastasis are expected late 2014 (52).

Patients with oligoprogressive disease or progressive CNS disease can be efficiently treated with a local therapy (e.g. radiotherapy or sometimes surgery) while TKI treatment is continued (53). Weickhardt et al. (54) proposed a schema of therapy based on the nature of progression: local therapy in oligoprogressive disease with continuation of TKI treatment versus a change in therapy for patients with widespread progression. This treatment strategy will be evaluated prospectively in a phase II trial (www.ClinicalTrials.gov: NCT01573702).

Another strategy at the time of progressive disease is to switch to another therapy (e.g. chemotherapy) or to withhold a targeted therapy for a period of time followed by re-initiation of the previous treatment. Regaining of TKI sensitivity after a ‘drug holiday’ has been described (55). The patients either had a treatment-free interval or were treated with chemotherapy after having acquired a resistance to TKIs. When the TKIs were restarted, they re-responded or showed prolonged stable disease. This strategy will also be evaluated prospectively (www.ClinicalTrials.gov: NCT02025218).
Next-generation TKIs (like afatinib) had shown promising preclinical results in targeting T790M-mutated NSCLC cells (56), but clinical trials evaluating afatinib monotherapy were disappointing (57). The combination of afatinib with cetuximab, however, showed evident clinical activity in these patients (58). Also, promising phase I trial results for two new agents, CO-1686 and AZD9291, were recently presented (59, 60).

Despite intensive investigation, there is currently no registered subsequent line of treatment or therapeutic strategy registered for EGFR-mutated NSCLC patients with acquired TKI resistance. The results of the abovementioned prospective trials are eagerly awaited. It is hoped that these results lead to new developments in the area of TKI resistance in EGFR-mutated NSCLC.

**CONCLUSION AND FUTURE DIRECTIONS**

The discovery of EGFR as a targetable oncogene and the introduction of TKIs have been a major, if not the most important, breakthrough in the treatment of NSCLC. However, as is usual in science, most answers lead to new questions. Obtaining tumour tissue for mutation analysis is crucial with NSCLC patients in order to assure that they receive optimal treatment. With the introduction of targeted treatments, it became clear that tumour characteristics are dynamic and may alter during the course of targeted treatment. Until the present day, the only way of being informed on these characteristics is by pathological analysis of tumour tissue obtained via biopsy. Several innovative procedures, e.g. monitoring CTCs and DNA, are being investigated but have as yet not found their way into clinical practice. The clinical significance of different types of progressive disease in TKI treatment of EGFR-mutated NSCLC patients has to be determined. There is a tendency to continue TKI treatment and to locally treat slow-growing, oligoprogressive lesions. However, patients with fulminant, multifocal progressive disease on TKI treatment should preferably switch to chemotherapy or a clinical trial. Results from prospective trials in this field are eagerly awaited.

Although there is a long road ahead, it is to be expected that the progress that has been made in cancer treatment in recent years will continue, ultimately leading to the transformation of oncogene-driven cancer from a once fatal to a chronic disease.
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