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REVIEW

Epidermal Growth Factor Receptor (EGFR) Kinase Inhibitors and Non-Small Cell Lung Cancer (NSCLC) – Advances in Molecular Diagnostic Techniques to Facilitate Targeted Therapy

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Abstract
A subset of patients with non-small cell lung cancer (NSCLC) respond well to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs), due to the presence of sensitising mutations in the gene encoding EGFR. Mutations associated with resistance to first generation EGFR TKIs have also been identified, which lead to therapeutic failure and the requirement for new drugs. Three generations of EGFR TKIs have been developed and either have been, or are being, evaluated as first and/or second line therapeutic agents. In this review, we consider the advances in molecular diagnostic techniques that are used, or are in development, to facilitate the targeted EGFR TKI therapy of patients with NSCLC. A literature search was conducted in May 2017 using PubMed, and spanning the period September 2005 (EU approval date of erlotinib) to May 2017. Search terms used were: EGFR TKI, NSCLC, clinical trial, erlotinib, gefitinib, afatinib, EGFR mutations, Exon 19 deletion, and Leu858Arg. The use of molecular data, in conjunction with other clinical and diagnostic information, will assist physicians to make the best therapeutic choice for each patient with advanced NSCLC. Personalized medicine and a rapidly developing therapy landscape will enable these patients to achieve optimal responses to EGFR TKIs.

Keywords Non-small cell lung cancer · NSCLC · Epidermal growth factor receptor tyrosine kinase inhibitors · EGFR TKIs · Molecular diagnostic techniques

Introduction

A subset of patients with non-small cell lung cancer (NSCLC) respond well to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs), due to the presence of sensitising mutations in the gene encoding EGFR [1–3]. Given the poor prognosis of patients with NSCLC [4], the observation that up to 17% of Caucasian patients and 47% of Asian patients, mainly never smokers or those with adenocarcinomas, have tumours that carry EGFR mutations is encouraging because it means that these patients are likely to derive benefit, in terms of significantly improved progression free survival (PFS), from EGFR TKI therapy [4–6].

We review the advances in molecular diagnostic techniques that are used, or are in development, to facilitate the targeted therapy of patients with NSCLC with EGFR TKIs.

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EGFR TKIs – an Overview

In 2005, erlotinib was the first reversible EGFR TKI to be approved in the European Union for the treatment of patients with locally advanced or metastatic NSCLC [7]. Gefitinib was approved in 2009 [8] and the irreversible EGFR TKI, afatinib, was approved in 2014 [9] for patients with locally advanced or metastatic NSCLC that carries activating EGFR mutation(s). Data from phase III trials comparing the efficacy of erlotinib or gefitinib with that of platinum doublet chemotherapy in

patients with NSCLC that carry EGFR mutations have demonstrated significant improvements in overall response rates (ORR) and PFS, but not in overall survival (OS) [10–12]. Unfortunately, resistance to erlotinib and gefitinib develops after protracted administration and so second generation EGFR TKIs were developed.

The LUX-Lung 3, 6 and 7 studies of the second generation EGFR TKI afatinib, which is an irreversible ErbB family inhibitor, are the largest phase III trials of first line EGFR TKIs conducted to date [13–19]. Patients with tumours carrying common (L858R and Exon 19 deletions) or uncommon mutations were enrolled in these studies. The results of LUX-Lung 3 and 6 demonstrated significant improvements in PFS and OS compared to chemotherapy [13, 14, 16, 17]. LUX-Lung 7 compared the safety and efficacy of afatinib and gefitinib head to head in patients with EGFR mutation positive NSCLC: patients taking afatinib experienced better ORRs, time to treatment failure (TTF) and PFS than those taking gefitinib [18, 19]. These studies yielded useful information on the response to therapy in patients with NSCLC that carries rare mutations.

Dacomitinib is another second generation, irreversible inhibitor that has pan-HER TKI activity: it exhibited potent EGFR signalling inhibition against first generation EGFR TKI resistant cell lines in vitro [20–22]. An analysis of pooled data from the ARCHER 1009 and 1028 trials, which compared dacomitinib and erlotinib in chemotherapy pre-treated, EGFR TKI naïve patients, demonstrated a trend towards extended PFS in dacomitinib-treated patients but statistical significance was not achieved. Very encouraging results have been reported, however, from the phase III ARCHER 1050 trial (NCT01774721) of first line EGFR TKI therapy in 452 patients with advanced, EGFR mutation positive NSCLC, which compared the safety and efficacy of dacomitinib with that of gefitinib [23]. The most frequently reported grade 3 adverse events were dermatitis acneiform (13.7%) and diarrhoea (8.4%) in the dacomitinib arm; and ALT elevations (8.5%) in the gefitinib arm. No unexpected adverse events were reported. The efficacy of dacomitinib was superior to that of gefitinib; the differences, in terms of PFS and duration of response (DR) in responders, were statistically significant ($p < 0.0001$) and clinically meaningful. It is possible that dacomitinib will become a first line option for previously untreated patients with advanced NSCLC that carries activating EGFR mutations.

Several third generation irreversible EGFR TKIs, such as osimertinib, rociletinib, olmutinib, and ASP8273, have been identified: they exhibit preferential activity against T790 M mutant tumours [24–26]. Osimertinib was approved in Europe in 2016 for the treatment of adult patients with locally advanced or metastatic EGFR T790 M mutation-positive NSCLC, based on the results of the AURA trials that demonstrated the superior efficacy of osimertinib over platinum chemotherapy plus pemetrexed in this patient group [27, 28]. Confirmatory data have been provided by updated analyses of phase I and II studies of pre-treated [26, 29] and untreated [30] patients with T790 M positive advanced NSCLC. Development of rociletinib has been halted [10]. Olmutinib has been approved in South Korea on the basis of phase I/II data; results are awaited from the ELUXA2 phase II trial (NCT02485652) [10]. Astellas is developing ASP8273: studies of this drug's efficacy and safety in patients with advanced NSCLC that harbours the T790 M mutation are ongoing (www.clinicaltrials.gov).

Impact of Genetic Alterations on the Response to EGFR TKI Therapy

The EGFR is a glycoprotein composed of an extracellular ligand binding domain, a transmembrane domain and an intracellular tyrosine kinase (TK) domain [31]. Binding of the ligand stimulates the intracellular kinase domain and tyrosine phosphorylation, which function as recruitment sites for downstream signalling molecules that regulate key aspects of cell growth, differentiation and migration.

Activating tumour mutations in the genes encoding EGFR intracellular and extracellular regions have been identified (Fig. 1 and Table 1) [32]. In patients with NSCLC, activating mutations in exons 18–21, that encode the EGFR kinase domain, were associated with an enhanced response to EGFR TKIs, possibly due to inhibition of oncogenic signalling by EGFR in the tumours [24, 31, 34]. These mutations increase EGFR's affinity for TKIs, which compete with ATP for access to the TK domain and thus inhibit the functioning of the receptor. Associations between EGFR activating mutations and the following patient characteristics have been identified: female gender, Asian ethnicity, non-smoking history, and tumour type (adenocarcinoma, adenosquamous) [2, 6, 38, 39]. The presence of sensitising mutations in NSCLC is the best predictor of a positive response to EGFR TKI therapy [10].

Most activating mutations in patients with NSCLC adenocarcinomas are deletions in exon 19 (del19) and a missense mutation in exon 21 (leucine replaced by arginine, L858R) [32, 34]. Other sensitising mutations have been detected in exon 18 (G719C, G719S, G719A) and exon 21 (L861Q, L861R) but they are less common than del19 and L858R [24, 32, 35]. The presence of activating mutations is required for EGFR TKI therapy. [40].

However, as was shown in the IPASS trial, 20–30% of these patients do not experience tumour regression during therapy, and are considered to exhibit intrinsic or primary resistance to EGFR TKIs (Table 1). Acquired resistance emerges in the tumours of patients who initially respond after a median PFS period of 10–16 months [40]. There are many molecular factors underlying secondary resistance, very few

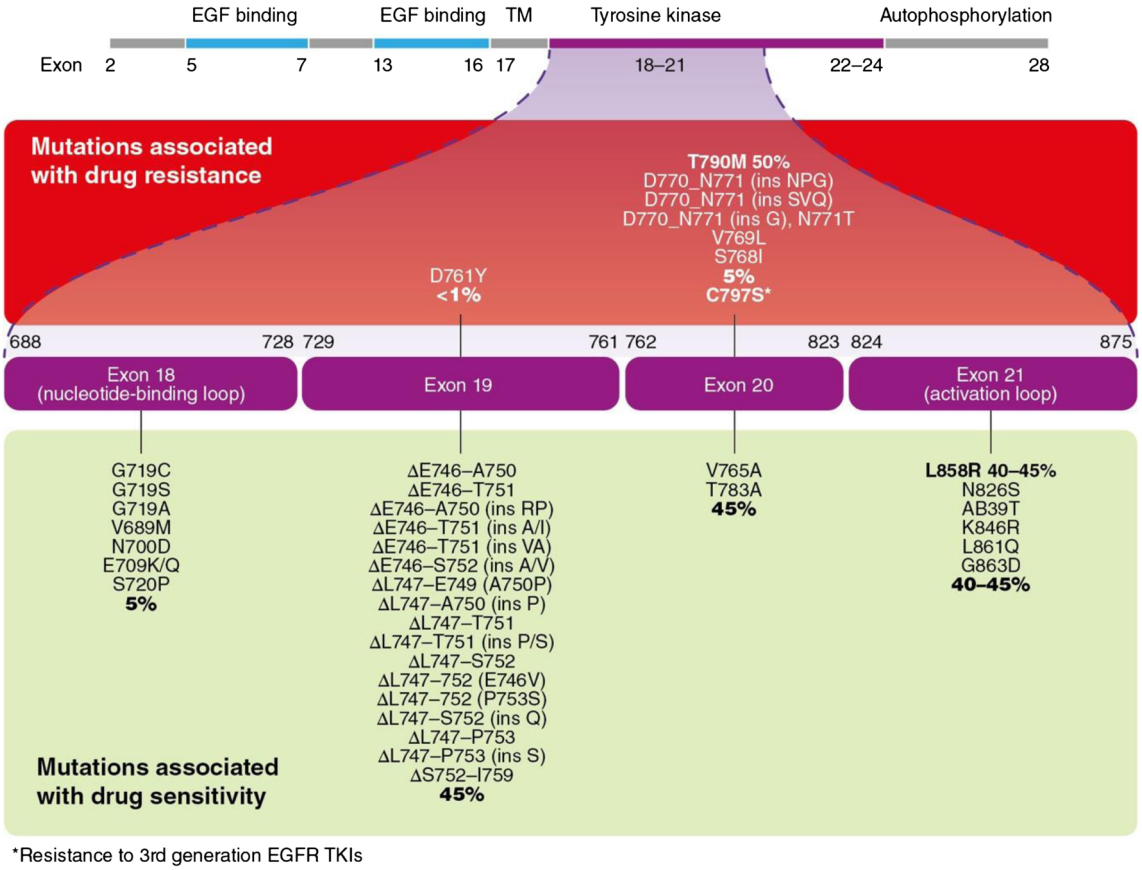

Fig. 1 Screening the EGFR1 gene, adapted from [32, 33]

of which are understood; however, in 60% of cases, this is related to the selection of a particular mutation occurring at codon 790 within exon 20 (T790 M) [24, 31, 36, 37]. Third generation EGFR TKIs inhibit the proliferation of cells harbouring a T790 M mutation [24, 40]. The presence of the acquired EGFR C797S mutation mediates resistance to osimertinib in vitro and in patients (Fig. 1) [33]. Amplification of MET and HER2 proto-oncogenes, and transformation to a small cell lung cancer (SCLC) phenotype have also been shown to confer resistance to EGFR TKIs in a minority of cases [36, 40–43].

In a series of 17,047 tumour samples (Evans and Taniere, submitted), 10.2% had an EGFR mutation; of these, 15.9% were 'rare' sensitising mutations (G719X, L861Q, S768I, Ins 20, T790 M), suggesting that these mutations are not as rare as initially reported [35]. This finding has implications for the choice of testing techniques by testing laboratories: assays should cover all the relevant mutations including rarer ones.

Table 1 Summary of key mutations in EGFR1 gene [24, 31, 32, 34–37]

Activating mutations	Resistance mutations
del19 (exon 19)	T790 M
L858R (exon 21)	Ins 20 (exon 20 insertions)
G719C, G719S, G719A (exon 18)	D761Y
L861Q, L861R (exon 21)	S768I
	V769 L

It is now good practice to test any advanced non-small cell carcinoma for EGFR mutations in order to choose the most appropriate first line therapy. Testing is feasible using a range of routine formalin fixed paraffin embedded samples, including fine needle aspirations, and is achievable within a few working days. Genetic evolution of tumours can occur during therapy and monitoring the emergence of mutations will assist optimisation of the patient's therapy [44, 45]. This is best illustrated by the need to test tumours progressing during EGFR TKI therapy to screen for the presence of T790 M mutation, which will determine suitability for third generation EGFR TKI therapy (osimertinib). Repeat testing can be undertaken using either a tissue sample of the progressing tumour or plasma. It would be beneficial to relate the presence of specific mutations to patient outcome, but confidentiality concerns may restrict access patient records. Testing should be offered to all patients with NSCLC since key EGFR mutations have been identified in a minority of patients with tumours other than adenocarcinomas or who were heavy smokers [1].

EGFR TKIs are licensed for use in patients with NSCLC that harbours EGFR mutations. The mutation rate in squamous cell carcinoma varies considerably between series, but

is considerably lower than in adenocarcinomas [1, 2]. Furthermore, it remains controversial whether patients with mutated squamous cell carcinomas respond as well to EGFR TKI therapy as those with adenocarcinomas. It is for this reason that practice varies between centres with respect to testing squamous cell carcinomas. However, it should be borne in mind that diagnosis is usually made on the basis of a very small sample of the whole tumour, and it is sometimes difficult to determine whether a tumour is a pure squamous cell carcinoma or an adenosquamous carcinoma showing focal squamous differentiation.

Overview of Molecular Techniques – Advantages and Disadvantages of each Approach

Molecular analyses of lung cancer specimens are challenging because of their limited size and low quality following formalin fixation [44–46]. Molecular profiling is performed on the remainder of the diagnostic samples that are initially used for morphology assessment and immunoprofiling. Any advanced lung carcinoma should be routinely tested for two to three molecular targets in addition to EGFR. This implies careful management of the samples in order to be able to carry out all of the required tests. The other mandatory tests that predict potential responses to licensed and approved targeted drugs are ALK translocation and PDL1 expression. ROS1 translocation evaluation is often requested nowadays.

Tissue biopsies are the gold standard for specimens to detect molecular alterations [44, 47]. However, many patients with NSCLC are elderly, diagnosed with advanced disease and/or in poor health; therefore, surgical biopsies may incur unacceptable risks and provide insufficient tissue [44–48]. Alternative tissue sampling methods are needed for these patient groups. In an analysis of 57 clinical trials in which biopsies were obtained, the complication rate for thoracic biopsies was 17.1% (36/211) [47]. At Queen Elizabeth Hospital, Birmingham, UK, 20,000 tissue samples underwent testing for EGFR mutations May 2009–September 2016: mutations were identified in 10.5% of samples and the failure rate was 5.2% (personal communication, Dr. Taniere). Lack of tissue, poor specimen processing and decalcification were responsible for testing failures.

Given the limitations of biopsy specimens, less invasive sampling techniques have been explored for diagnostic and monitoring purposes [25, 44–46, 48, 49]. Cytology samples can provide information on mutational status if they have been processed correctly [46]. In practice, nowadays, the advent of new procedures such as endoscopic ultrasound (including transbronchial aspiration, EBUS), combined with changes in practice in pathology departments, i.e. embedding cytological specimens in paraffin blocks following formalin fixation, has fulfilled the needs of molecular testing.

A surrogate for, or an add on to, tissue testing is analysis of circulating tumour DNA (ctDNA) in plasma. Plasma and serum samples can yield circulating tumour cells (ctCs), circulating ctDNA, ctRNA, ctmiRNA, and platelet markers for analysis [25, 44]. The source of ctDNA and the mechanism(s) by which it is released into the bloodstream are not fully elucidated, although apoptosis and necrosis of primary tumours and metastases are assumed to release ctDNA [44, 48]. Plasma testing is hindered by the fragmented state of ctDNA, the small quantity available and the potential for contamination with cellular DNA. Blood samples should preferably be collected in tubes containing preservatives that prevent cell lysis for up to five days (i.e. not EDTA) to facilitate the extraction of quality ctDNA: healthcare professionals must be educated about this key issue. If EDTA tubes are used, logistics must be put in place to ensure that samples are processed quickly. As with tissue sampling, there are various techniques in use in routine practice; none currently represent a gold-standard for analysis. The choice of the spectrum of mutations targeted and the sensitivity of the technique have not yet been conclusively established. More data are needed to correlate the sensitivity of the technique to its clinical specificity.

ctDNA analysis can provide useful information about the heterogeneity of a tumour. An exploratory analysis of EGFR mutations in 238 matched tissue and blood samples, obtained from patients who had participated in the FASTACT-2 study, demonstrated that the agreement between the samples was 88%. The sensitivity of the ctDNA test was 75% and its specificity was 96%. Five patients had EGFR mutation positive blood samples but EGFR mutation negative tissue samples, suggesting that the tissue samples had not provided a complete picture of the heterogeneity of the tumours'.

The most common technology in use at present for EGFR mutation detection is real-time PCR (RT PCR), for which there are several commercial kits available, e.g. Therascreen (QIAGEN), Cobas (Roche) and Idylla (Biocartis), etc. These have been used in trials assessing the clinical value of first, second and third generation TKIs in EGFR-mutated NSCLC. However, there are multiple other technologies that can be used, such as next generation sequencing (NGS), digital PCR (dPCR), etc. All techniques have their own relative advantages and limitations in relation to the amount of DNA needed; the spectrum of mutations screened; turnaround time; validation and cost. In practice, several – if not all techniques – are running in parallel in larger testing laboratories.

dPCR is a refinement of RT PCR: the DNA sample is dispersed into compartments where individual, parallel PCR reactions, each involving one or zero DNA molecule, take place [44, 45]. Sequence specific targets are detected by fluorescent-labelled probes. The absolute concentration of the target can be determined at the end of the PCR process

in the positive compartments. dPCR provides highly sensitive detection of mutated ctDNA (0.01–0.1%), even in the presence of high levels of cell free DNA. It can be implemented in clinical settings due to its simple workflow. The drawback is that it can only screen for known mutations.

The first step of the BEAMing technique is a conventional PCR, using primers that detect the targeted sequence, that is performed on an emulsion in the presence of tagged magnetic beads [44, 45]. Flow cytometric analysis detects and quantifies mutant alleles. BEAMing has been used to detect EGFR activating mutations and T790 M from plasma DNA samples [48, 50]. BEAMing is a targeted approach; has a complex workflow; and its high cost per sample makes it impractical for routine clinical use at present [44].

Both dPCR and BEAMing PCR provides an absolute quantification of mutated alleles, which may facilitate monitoring treatment outcomes, disease progression and the detection of early treatment failure [45]. However, validation of EGFR mutation levels in relation to clinical endpoints is required to determine clinical cut off values.

A comparison of four EGFR targeted plasma assays has been reported [48]. There was a high level of concordance between the Cobas and BEAMing results: the sensitivity of detecting EGFR sensitising mutations was 82% and 87%, respectively and the specificity was 97%. The sensitivity of T790 M detection with these technologies was 73% and 81%, and the specificity was 67% and 58%, respectively. The concordance was 90%. For T790 M, the digital platforms (dPCR, BEAMing PCR) were superior to the non-digital platforms (Cobas EGFR mutation test, Therascreen EGFR ARMS PCR).

Impact of Molecular Data on Choice of EGFR TKIs

Data from numerous clinical studies have confirmed that EGFR sensitising mutations (del19, L858R) are associated with a good response to first line EGFR TKIs [24]. For example, in the French study mentioned previously, identification of a genetic alteration influenced first line therapy for 4176 (51%) patients and was associated with a significantly better ORRs and PFS to first line therapy in these patients compared to those without a genetic alteration (ORR: 37% [95% CI 34.7–38.2] vs 33% [29.5–35.6] $p = 0.03$; PFS: 10.0 months [95% CI 9.2–10.7] vs 7.1 months [6.1–7.9]; $p < 0.0001$) [51]. The choice of first line EGFR TKI is dictated by the balance between efficacy and toxicity. The LUX-Lung 3, 6 and 7 studies of afatinib are the largest phase III trials of first line EGFR TKIs conducted to date [13–19]. In LUX-Lung 3, afatinib was compared with cisplatin/pemetrexed in both Asian and non-Asian patients [11]. The first head to head study of first line EGFR TKIs was LUX-Lung 7: the efficacy and safety of afatinib and gefitinib in treatment naïve patients with NSCLC were compared [18, 19]. Afatinib exhibited superior efficacy to gefitinib and had a manageable tolerability profile in this study. There was a numerical difference of 3.4 months in terms of OS between the two groups in favour of afatinib, but this did not reach statistical significance [19]. Most patients whose disease progressed while taking study drug crossed over to another systematic anti-cancer therapy: this could have confounded the OS results.

In the ARCHER 1050 trial, patients were enrolled who had untreated stage IIIB/IV/ recurrent NSCLC carrying an EGFR activating mutation (exon 19 del or exon 21 L858R mu +/− exon 20 T790 M mu) [23].

The emergence of resistance to first line EGFR TKIs or the presence of intrinsic resistance allows disease progression to occur. The development of third generation EGFR TKIs has provided second line drugs for patients with locally advanced or metastatic NSCLC [24–26]. If resistance to first line EGFR TKIs is due to the presence of T790 M, then, based on the results of the AURA trial, patients should be offered osimertinib since its administration is associated with a high ORR (62%, 95% CI 54–68%), a median PFS of 12.3 months (95% CI 9.5–13.8 months) and a durable response (median duration: 15.2 months, 95% CI 11.3 months -not calculable) [26].

It is unclear whether therapeutic responses to EGFR TKIs differ if either del19 or L858R is present: conflicting data have been reported [15, 52–56]. The only studies that have demonstrated a statistically significant difference in OS between patients with del19 positive tumours and those with L858R are the LUX-Lung 3 and 6 trials [57]. Although data from LUX-Lung 7 provided data that NSCLC carrying del19 is a distinct disease from L858R positive NSCLC [18], there is insufficient evidence to select afatinib or gefitinib based on whether del19 or L858R is present.

Initial data from 60 patients with advanced or metastatic EGFR mutated NSCLC who were treated with osmertinib in phase I expansion cohorts of the AURA trial suggested that patients who experienced disease progression did not develop drug resistance due to the T790 M mutation [30]. Prolongation of PFS during first line therapy with osmertinib is particularly encouraging. Data from the ongoing phase III trial are needed before this approach to delay or prevent the emergence of T790 M can be recommended [30]. It should be noted that this strategy may pre-select for resistance mutations such as C797S and this would have an impact on future treatment options.

FLAURA is a phase III study of the efficacy and safety of osimertinib as first line therapy for patients with advanced NSCLC that carried EGFR common mutations. The comparators are gefitinib and erlotinib (https://clinicaltrials.gov/ct2/show/NCT02296125) [24]. A press release from AstraZeneca in July 2017 described the results of FLAURA as

demonstrating that osimertinib therapy conferred a statistically significant and clinically meaningful PFS improvement compared to that achieved with current standard of care treatment [58]. Full details will be presented at an unspecified date.

A combined post hoc analysis of data from LUX-Lung 2, 3 and 6 demonstrated that 75/600 (12%) afatinib-treated patients had tumours carrying uncommon mutations [59]. They responded well to afatinib (both OR and PFS). Objective responses were observed in patients with tumours bearing the most frequent, uncommon mutations: 14 (77.8%, 95% CI 52.4–93.6) cases with G719X; nine (56.3%, 95% CI 29.9–80.2) with L861Q; and eight (100.0%, 95% CI 63.1–100.0) with S768I. Patients with tumours carrying de novo T790 M and exon 20 insertion mutations responded less well to afatinib. Similar data have not been obtained with other EGFR TKIs, suggesting that afatinib is unique in being effective against tumours carrying uncommon mutations [24].

Using increasingly sensitive techniques to identify low levels of less common mutations, e.g. in small, subclinical clones of cells, is appealing in principle, but it is debatable whether this approach will improve clinical outcomes [45]. It is not known if the overall level of mutated DNA within a tumour reflects the presence of specific mutations that drive tumour proliferation. The results of prospective studies are needed to determine whether such detailed molecular data will affect treatment choices and patient responses.

Conclusions

The use of molecular data, in conjunction with other clinical and diagnostic information, will assist physicians to make the best therapeutic choice for each patient with advanced NSCLC. Even poor performance patients can respond well to afatinib and so should not be denied the benefits of EGFR TKI therapy [24, 60, 61]. Personalized medicine and a rapidly developing therapy landscape will enable patients with advanced NSCLC to achieve optimal responses to EGFR TKIs.

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Compliance with Ethical Standards

Conflicts of Interest QG consultancy for AstraZeneca, Roche, Boehringer Ingelheim and Chugai.

SB consultancy for AstraZeneca, Roche and Pfizer.

PT consultancy for AstraZeneca, Roche, Boehringer Ingelheim and Qiagen.

BO'S consultancy for Roche.

ME has no conflicts of interest.

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