Should progression-free survival be the primary measure of efficacy for advanced NSCLC therapy?

J. C. Soria*, C. Massard & T. Le Chevalier

Department of Medicine, Institut Gustave Roussy, Villejuif, France

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Non-small-cell lung cancer (NSCLC) is a leading cause of malignancy-related mortality in the Western world. Despite advances in early detection and standard treatment, NSCLC is frequently diagnosed at an advanced stage and therefore patients have a poor prognosis. However, its heterogeneity provides ample opportunity for multiple treatment approaches and target pathways. Considerable progress has been made in identifying novel targets, leading to a growing number of treatment options. Overall survival (OS) may not always be the most appropriate primary end point for assessment of efficacy, as it is likely that patients with NSCLC will receive multiple lines of therapy during their treatment. Additionally, crossover appears as an ethical necessity to many investigators if molecular targeted agents display outstanding early efficacy. While improving OS remains the goal for clinicians, progression-free survival (PFS) is increasingly being utilised as an alternative end point. In this article, we will evaluate the value of PFS as a primary measure of efficacy for advanced NSCLC, compare the clinical situation with that in other solid malignancies and review the growing number of treatment options for NSCLC.

Key words: clinical trials, end point determination, non-small-cell lung cancer, NSCLC, overall survival, progression-free survival

introduction

Non-small-cell lung cancer (NSCLC) accounts for ~80% of all cases of lung cancer [1]. Despite advances in early detection and standard treatment, NSCLC is frequently diagnosed at an advanced stage and therefore patients have a poor prognosis. NSCLC demonstrates great molecular heterogeneity in which several pathways are simultaneously active, leading to tumourigenesis. Several molecular alterations have recently been discovered that affect cell proliferation and homeostasis, such as alterations in angiogenesis, signal transduction, apoptosis, immortalisation and invasion [2]. Additionally, molecular characterisation of lung cancer leads to the identification of different molecular alterations [such as PI3K and epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase (ALK) translocation] [3–5] and subsets of lung cancer disease with a distinct natural history, sensitivity and resistance to treatment. Future clinical trials in the adjuvant and metastatic settings will need to consider the stratification of patients by molecular subtype [6, 7]. As a result, considerable progress has been made in identifying novel targets, leading to a growing number of treatment options [8–12]. Most of these large phase III trials demonstrated a clinical benefit for lung cancer patients with an increase in overall survival (OS) or progression-free survival (PFS). In order to improve the treatment of patients with NSCLC, it is important that clinical trials provide information which is immediately useful for clinicians’ treatment decisions and patient care. The method of assessing the activity of a drug [OS, PFS, response rate (RR), tolerance etc.] should neither penalise the patient population nor slow down the progress of evaluating the drug for approval.

Therefore, it is important that trials have a suitable primary end point. Here, we will evaluate the value of PFS as a primary measure of efficacy in advanced NSCLC and compare the clinical situation with that in other solid malignancies. We will also briefly review the growing number of treatment options for NSCLC.

choice of end point for clinical trials

progression-free survival

PFS is defined by the US Food and Drug Administration (FDA) as the time elapsed between treatment initiation and tumour progression or death from any cause, with censoring of patients who are lost to follow-up [13, 14]. Although the FDA has guidelines regarding the use of PFS as a clinical end point, it has recently revisited the appropriate use of end points used in oncology by convening an advisory committee following increasing discussions around this topic [15]. The European Medicines Agency (EMEA) defines PFS as the time from...
randomisation (or registration, in nonrandomised trials) to objective tumour progression or death from any cause, whichever occurs first [16, 17]. Including death as part of the composite end point differentiates PFS from other progression-based end points. For example, time to progression (TTP) is defined by the FDA as the time from randomisation until documented tumour progression (death is censored), and time to treatment failure (TTF) is a composite end point defined as the time from randomisation until the patient stops the trial treatment for any reason including progression, toxicity, or preference (death is censored). PFS assumes that patient deaths are randomly related to tumour progression and by including death, PFS is differentiated from other progression-based end points. Compared with TTP, PFS is the preferred regulatory end point of the FDA and the EMEA [13, 14, 16, 17]. However, in situations where the majority of deaths are unrelated to cancer, TTP is an acceptable end point. TTF is not recommended as a regulatory end point as it does not clearly distinguish the efficacy of the drug from toxicity, patient or physician withdrawal, or patient intolerance [14].

PFS is a good choice of end point where multiple therapy options exist as it measures only the effect of the study drug. PFS is less sensitive to subsequent therapy than OS because most patients who go on to receive second- or third-line therapy will have already experienced a progression event. Since disease progression is a consequence of tumour growth, using PFS as a surrogate end point is also likely to predict clinical benefit. In contrast to RR, PFS has the advantage of assessing the duration of tumour control. This characteristic is perhaps the most significant difference between PFS and OS, in that the activity of an investigational therapy and duration of benefit are demonstrated irrespective of subsequent treatment. By definition, PFS events occur more quickly and more frequently than OS events, and therefore PFS data mature more quickly than OS data [18, 19], and fewer patients may be required to show a statistical difference between treatment arms [20, 21]. Furthermore, PFS is a direct measure of the effect of treatment on tumour burden and captures both tumour shrinkage and tumour stabilisation, effects associated with most new target drugs. It is clear that as more active drugs enter the clinic, PFS will become an essential and clinically informative end point in advanced cancer.

limitations of PFS as an end point in clinical trials

PFS as an end point has clear and appealing characteristics but it suffers from several limitations in common with all progression-based end points. Firstly, it is vital that the relationship between PFS and OS be assessed thoroughly; there is uncertainty in some tumour types as to whether an improvement in PFS represents clinical benefit for patients [22]. The use of TTP or disease-free survival (DFS), interchangeably with PFS, can lead to puzzling interpretation of results because TTP and DFS are themselves different measures with different definitions [14]. Also, a concise definition of disease progression is required in each tumour type. No standard regulatory criteria for defining progression exist [14]; definitions of progression typically rely on criteria such as RECIST [23]. The precise definition of tumour progression therefore has to be carefully detailed in the study protocol [13, 14, 24–26].

Frequent radiological assessments are required, raising the potential for measurement error and bias [27]. Both the FDA and EMEA recommend blinded independent adjudication of assessments [13, 14, 16, 17]. PFS can vary depending on evaluation time bias (i.e. differences in evaluation times according to treatment arms) [27], and thus, appropriate time points for measuring progression must be established. RECIST and World Health Organization criteria, as well as other sets of criteria, do not specify time intervals for tumour assessment. Examinations may be taken at every 8, 12, or 24 weeks, but the actual points of disease progression will rarely occur at exactly the time of a scheduled follow-up. PFS may also be sensitive to nonprotocol scheduled assessments and variations in censoring [28]. To enable informative results to be generated, it may be pertinent to standardise disease assessments by the type of cancer studied and the cancer stage. Given these issues, the magnitude of the difference in PFS between study arms must be sufficient to confidently ascribe clinically meaningful benefit to the investigational therapy, requiring a median difference greater than the planned interval between two assessments (in general 2 months). Double-blinded studies are the most appropriate to accept PFS as a main objective in order to avoid bias that may lead the investigator to discontinue the treatment.

overall survival

OS is defined as the time from subject randomisation to the time of death from any cause [14] and is the definitive end point where life expectancy and treatment options are limited. Provided that quality of life is not compromised, OS represents the greatest clinical benefit for the patient. The EMEA regards OS and PFS as acceptable primary end points [16, 17] and the FDA considers OS benefit as the foundation for the approval of new anticancer drugs in the United States [13, 14].

OS has numerous advantages as an end point. Firstly, its value can be assessed easily and accurately, with 100% accuracy for the event and nearly 100% accuracy for the time of the event. Survival can be assessed on a daily basis, rather than at predetermined intervals, and is easily documented through direct contact and confirmed through registries. Secondly, statistically significant improvements in OS are considered clinically significant, provided the drug does not have unacceptable toxicity [14]. Additionally, because it is not measured in a subset but rather in the intent-to-treat population, it includes all randomised subjects in a clinical trial independent of their treatment outcome. For these reasons, OS is accepted as the gold standard for efficacy evaluation in clinical trials of oncology agents.

limitations of OS as an end point in clinical trials

Although OS is the traditional gold standard end point, with the advantage of being unambiguously defined and important to the patient, some of its limitations are increasingly problematic. Firstly, as a result of the development of more effective agents, OS has improved in many types of cancer and its measurement now requires increasingly longer follow-up.
periods. In order to avoid this problem, phase II studies often concentrate on overall response rate and differentiate the extent of treatment benefit into complete response (CR) and partial response. However, in phase III studies, a better appreciation of the duration of such responses is necessary in order to assess the benefits of individual therapies. If regulatory approval of a new agent is on the basis of a demonstrated improvement in OS, patients will be required to wait a long time, longer than in previous years, for access to treatments that are more effective than those currently available.

Secondly, large patient populations are required to show statistically significant differences among treatments. As comparator treatments continue to improve, statistical rules demand that the sample size required to show significant differences among treatments must increase. Recruitment may then be problematic for clinical trials in some cancer types due to the difficulty in obtaining study populations large enough to show significant differences. Long survival durations can also lead to subjects becoming lost to follow-up, impacting on statistical analyses.

The measurement of OS can also be skewed by the effects of subsequent therapies. This situation is particularly relevant in cancers for which several active anticancer drugs are available, such as colon cancer, breast cancer, renal cancer and more recently, lung cancer. The growing number of treatment options for NSCLC complicates the clinical evaluation of novel agents as multiple efficacious lines of therapy are available upon disease progression. Subsequent treatments may be received after the subject completes the trial or within the confines of the trial itself. Figure 1 illustrates the growing use of second-line therapy in NSCLC when considering trials using the cisplatin–gemcitabine backbone. Clinical trials with a crossover design enable patients who are receiving less effective therapy to switch to more effective therapy on disease progression. Most phase III randomised trials are not controlled for subsequent treatments and more trials are adopting a crossover design or allow crossover at the time that the trial result for PFS is positive.

Furthermore, if molecular targeted agents with very high response rates are identified in early clinical trials (i.e. phase I and Ib trials), then in molecularly selected NSCLC patients, crossover will become an ethical necessity thus completely skewing the OS readout. In such a case, the median OS of both arms may not differ but can still be indicative of the efficacy of the new compound if it goes beyond certain classical boundaries (i.e. 15 months).

The validation of surrogate end points for OS
The FDA considers PFS to be a valid end point for regular or accelerated licence approvals provided it has been statistically validated as a marker for OS in the specific tumour type. While there is some debate about the optimal approach for validating surrogate end points [29, 30], one option is to evaluate performance at the trial level [21]. It may also be relevant to consider other factors, such as RR and treatment tolerance/toxicity, in conjunction with PFS to precisely establish treatment benefit for patients.

This issue has been addressed by Prentice [31], who proposed a definition and validation criteria for surrogate end points. Two conditions are necessary for an intermediate end point to be an acceptable surrogate for the primary clinical end point: there must be a strong association between the surrogate end point and the true end point, and there must be a strong association between the effect of treatment on the surrogate and the true end point [32]. For example, the analysis of several trials in advanced colon cancer demonstrated a strong correlation between PFS and OS [33].

Sensitivity analysis in assessing PFS
Sensitivity analysis is a statistical technique used to assess whether the results of phase III trials are robust or likely to be oversimplified. Until recently, sensitivity analyses were rarely carried out, and there remains a poor understanding of them among oncologists. The influence of errors in protocol design, unintentional bias, deviations from assumptions fundamental
to statistical models, and any unforeseen treatment delivery or practice patterns on trial results are examined. Sensitivity analysis allows for an appreciation of the extent to which a positive outcome is caused by a single, possibly subjective, and therefore biased, aspect of an end point. A recent paper [34] examined the three types of bias that can occur when evaluating the PFS end point: assessment time bias, bias due to symptomatic (nonradiologic) disease progression, and bias due to missing data. As stated previously, PFS assessment inherently includes some degree of subjectivity and error in assessing disease progression, regardless of the use of an independent review. For these reasons, sensitivity analyses for evaluating the strength of PFS as an end point in oncology clinical trials have been recommended by the FDA [14] and the EMEA [17].

**comparable therapy areas**

**breast cancer**

Breast cancer therapy is a very well-established field and numerous treatment options exist. There are several second-line and subsequent therapies available as well as combination regimens for advanced breast cancer, and it is not unusual for patients to receive multiple lines of treatment which stretch into double figures [35–37]. In assessing new therapies and approaches, recent phase III studies have focused on PFS [37] and TTP [38, 39] with OS as a secondary end point. A recent paper [34, 40] assessed the frequency of use of efficacy end points in advanced breast cancer trials published from 2000 to 2007. In a total of 58 studies, the most frequently used primary end points were RR and TTP (n = 21 each), followed by PFS (n = 14), although some confusion around the definition of TTP was noted (the investigators frequently used PFS and TTP interchangeably in advanced breast cancer, indicating that uniform definition of these terms appears to be required). Only one trial used OS as the primary end point. Several reviews [18, 21, 41] have analysed trial results in an attempt to evaluate PFS as a surrogate for OS in breast cancer. However, none of these were definitive and the prediction of OS on the basis of PFS is still uncertain.

**colorectal cancer**

The field of colorectal cancer (CRC), although extensively studied, is less well developed than that of breast cancer. The primary end point for assessing the efficacy of first-line therapy in CRC was traditionally OS, but this end point was clearly confounded by the effect of second-line therapies [42]. As research interest in CRC has escalated, so has the number of treatment options, such as oxaliplatin, irinotecan, cetuximab, bevacizumab, and panitumumab. While older studies [43] used OS as a primary end point, more recent studies have utilised progression-based end points, relapse-free survival, OS [44], TTP [45], and PFS [46]. In addition, Di Leo has shown that the choice of OS as a primary end point in advanced CRC trials can lead to the underestimation of drug efficacy [47]. PFS has been shown to correlate with OS in the first-line setting for metastatic CRC [48]. Buyse et al. [33] demonstrated that PFS is an acceptable surrogate for OS in advanced CRC after a meta-analysis of 10 trials. PFS has recently been accepted by the US FDA as an acceptable end point for first-line approval in advanced CRC [49]. Pragmatic trials that mimic clinical practice may become more frequent; for example, in advanced colon cancer studies, all patients receive the experimental agent but in different sequences with standard therapy. These trials therefore provide data on the efficacy of the new drug as well as on the appropriate treatment sequence.

**other diseases**

Renal cell carcinoma (RCC) is highly resistant to chemotherapy but clear success has been seen with new treatments that inhibit vascular endothelial growth factor (VEGF). Recent phase III studies have used OS [50] and PFS [51] as primary end points, and FDA approval has previously been granted for the treatment of advanced RCC on the basis of the persuasive magnitude of improvement in PFS [52]. Malignant gliomas are uncommon but remain associated with high morbidity and mortality. Bevacizumab has shown clinical benefit in relapsed glioblastoma [53] and was approved by the FDA on the basis of the result of a large randomised phase II study which demonstrated increased PFS [54].

The advances in knowledge of the tumour biology of advanced prostate cancer have lead to the identification of promising new molecular targets in this disease [55]. Several molecular targeted therapies are currently being evaluated in phase II or III trials. At the moment, OS remains the primary end point for FDA approval. However, several retrospective studies have attempted to validate other end points to shorten the treatment development process in metastatic prostate cancer. Halabi et al. [56] demonstrated that PFS could be a helpful tool to predict OS in patients with hormone-sensitive and castrate-resistant prostate cancer (CRPC). In addition, a recent large phase III trial compared a new hormone therapy, abiraterone [37], with placebo in patients with CRPC who had experienced treatment failure with docetaxel. The primary end point of this trial was OS, but this study also attempted to validate circulating tumour cells as a surrogate end point for OS.

Given the increased use of progression-based end points with expanded treatment options, it is therefore reasonable to expect that research in NSCLC would follow the same pattern.

**emerging therapies and current use of end points in NSCLC**

Currently, there is a large amount of phase II and III research activity on the basis of therapies which target the EGFR and VEGF receptor and their ligands in NSCLC. mAb therapies for EGFR include panitumumab and cetuximab [58, 59], while bevacizumab is a mAb treatment which targets VEGF [58–63]. Table 1 shows a summary of each therapy and a description of its clinical use. Various small-molecule inhibitors of EGFR tyrosine kinase have been licensed (Table 2), including erlotinib and gefitinib [58–61]. Combination regimens which target both the EGF and VEGF pathways are under investigation, as are combined mAb–chemotherapy regimens [58, 59]. Broad tyrosine kinase inhibitors are being evaluated for NSCLC, such as sorafenib, sunitinib, and vandetanib [58, 85]. These inhibitors target multiple tyrosine kinases and therefore target...
Effective drug therapies for NSCLC include maintenance therapy, neoadjuvant therapy, vaccination, and combinations of biological and chemotherapies [94–97]. Alternative treatment strategies for NSCLC include molecular subset of patients with distinct clinical and therapeutic characteristics and the potential for high sensitivity to the ALK tyrosine kinase inhibitor PF-02341066 [5].

Table 1. mAb therapies for EGFR and VEGFR

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<th>Drug</th>
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<th>Conclusion</th>
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<td>Bevacizumab</td>
<td>Phase II trial evaluating panitumumab in combination with carboplatin and paclitaxel in patients with advanced or recurrent NSCLC [72]</td>
<td>No increase in RR or TTP. The development of panitumumab in NSCLC is proceeding in combination with antiangiogenic agents.</td>
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<td>Cetuximab</td>
<td>Phase I/Ia studies of combination therapy with platinum-based chemotherapy in first-line therapy of patients with NSCLC [65, 66]</td>
<td>Median TTP and OS results were similar to pemetrexed, docetaxel and erlotinib in comparable patients.</td>
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<td>Phase II study of platinum-based chemotherapy with or without cetuximab in first-line therapy of patients with NSCLC [67, 68]</td>
<td>Cetuximab in combination with chemotherapy was well tolerated and showed RR, TTP, and median OS slightly superior to historical controls.</td>
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<td>Phase III study comparing chemotherapy (cisplatin and vinorelbine) plus cetuximab with chemotherapy alone as first-line treatment in patients with advanced EGFR-positive NSCLC (FLEX trial) [69, 70]</td>
<td>Significant improvements in RR, PFS, and OS were seen compared with chemotherapy alone. There was some indication of potential synergistic activity of cetuximab plus chemotherapy. Patients given chemotherapy plus cetuximab survived longer than those in the chemotherapy-alone group.</td>
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<td>Panitumumab</td>
<td>Phase II trial evaluating panitumumab in combination with carboplatin and paclitaxel in patients with advanced NSCLC [71]</td>
<td>PFS and ORR were significantly better in the combination arm than the placebo. No OS benefit was observed.</td>
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<td>Phase III trial evaluating chemotherapy with paclitaxel and carboplatin alone or paclitaxel and carboplatin plus bevacizumab (CBP) in first-line therapy of patients with NSCLC [73]</td>
<td>Compared with the control arm, treatment with carboplatin and paclitaxel plus bevacizumab resulted in a higher RR, longer median TTP, and a modest OS increase in patients with advanced or recurrent NSCLC.</td>
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<td>Phase III study comparing two doses of bevacizumab plus cisplatin/ gemcitabine versus chemotherapy plus placebo in first-line therapy of patients with NSCLC [74].</td>
<td>The addition of bevacizumab to chemotherapy had a significant survival benefit. CBP was the first treatment regimen to show an OS of &gt;1 year in NSCLC.</td>
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<td>An open-label phase II study investigating cetuximab monotherapy in previously treated patients with NSCLC [64]</td>
<td>EGFR, epidermal growth factor receptor; VEGFR, vascular endothelial growth factor receptor; NSCLC, non-small-cell lung cancer; TTP, time to progression; OS, overall survival; RR, response rate; PFS, progression-free survival; ORR, overall response rate.</td>
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multiple pathways which may be important for tumour development (Table 3).

Other areas of investigation include proteosome inhibitors [58], mammalian target of rapamycin inhibitors [58], tubulin inhibitors [91], and microtubule-targeting agents [92].

Recently, the identification of the EML4-ALK fusion oncogene represents a novel molecular target in a small subset of NSCLC patients [93]. This alteration identifies a new molecular subset of patients with distinct clinical and therapeutic characteristics and the potential for high sensitivity to the ALK tyrosine kinase inhibitor PF-02341066 [5].

Alternative treatment strategies for NSCLC include maintenance therapy, neoadjuvant therapy, vaccination, and combinations of biological and chemotherapies [94–97].

In current clinical trials of NSCLC, an increasing number of studies are using PFS as a primary end point. A search of clinical trial registry databases reveal that currently >150 clinical trials are reported as using PFS as the primary end point in stage III/IV NSCLC studies. For example, four phase III clinical trials in NSCLC are exploring the efficacy of vandetanib [98]. Of these, three are using PFS as the primary end point. Two phase III studies with cetuximab have been conducted with different primary end points: OS in the First Line in lung cancer with Erbitux (FLEX) trial and PFS in the supportive BMS-099 trial [69]. Numerous phase III trials are currently evaluating bevacizumab in NSCLC [99]. Many of these trials are using PFS as the primary end point. One congress proceedings has been reported which compared PFS with best response or confirmed response as surrogate markers for OS in 343 NSCLC patients included in phase II trials. The authors concluded that PFS was more predictive of OS than best or confirmed response for phase II trials in advanced NSCLC. Discordant patients had relatively low tumour burden, relatively long TTP after first-line treatment and received several lines of treatment [100]. However, unlike other tumour types, no systematic assessment of PFS as a surrogate end point in NSCLC has been reported to date.

conclusions

NSCLC is a leading cause of malignancy-related mortality in the Western world. However, its heterogeneity provides ample opportunity for multiple treatment approaches and target pathways. As a consequence, a plethora of current and promising therapies and combinations are emerging which should considerably improve the prognosis for patients with NSCLC. It is vital that the efficacy of new therapies is assessed appropriately in order to establish how to best utilise these new treatment options. One concern with OS as the primary end point in advanced lung cancer is the prolonged period of observation required before analysis is complete. A second issue is the effect of second- and third-line therapies on OS, which has the potential to underestimate the efficacy of an
Table 2. Small-molecule inhibitors of EGFR

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<th>Drug</th>
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<th>Conclusion</th>
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<td>Erlotinib</td>
<td>Phase III study comparing erlotinib with placebo in patients with NSCLC after failure of first- or second-line treatment [75]</td>
<td>Erlotinib demonstrated prolonged survival and on the basis of these results, erlotinib was approved as a second- or third-line treatment of NSCLC.</td>
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<td>Two phase III trials [76, 77] evaluating the combination of erlotinib with conventional chemotherapy in first-line therapy in patients with NSCLC</td>
<td>Erlotinib with concurrent platinum-based doublet chemotherapy showed no survival benefit compared with chemotherapy alone in patients with untreated NSCLC.</td>
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<td>Phase I/Ii trial [61, 78] evaluating bevacizumab in combination with erlotinib for patients with recurrent NSCLC</td>
<td>Encouraging antitumour activity, OS, and PFS data support further development of this combination for patients with advanced NSCLC.</td>
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<tr>
<td>Gefitinib</td>
<td>Initially promising phase II trial results [79, 80] were obtained in previously treated patients with advanced NSCLC. Phase III trials [81] were then carried out.</td>
<td>Gefitinib received accelerated approval on the basis of improvements in quality of life from phase II results. A later phase III trial demonstrated no statistically significant OS benefit over placebo. FDA approval was then withdrawn.</td>
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<td>Phase III trials investigating addition of gefitinib to standard first-line platinum-based chemotherapies versus chemotherapy alone [82, 83]</td>
<td>There was no statistically significant improvement in OS, TTP, or RR between treatment groups in either of the two studies.</td>
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<td>Phase III trial investigating gefitinib versus docetaxel in patients with locally advanced or metastatic recurrent NSCLC who had previously received platinum-based chemotherapy [84]</td>
<td>The trial established noninferior survival of gefitinib compared with docetaxel, indicating that gefitinib is a valid treatment of pretreated patients with advanced NSCLC.</td>
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Table 3. Multiple tyrosine kinase inhibitors

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<td>Sorafenib</td>
<td>Phase II trial using single-agent sorafenib in patients with NSCLC who have had one prior chemotherapy regimen [86]</td>
<td>Sorafenib appeared to be well tolerated and active against relapsed NSCLC (preliminary evidence of objective response).</td>
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<td></td>
<td>Phase II trial of single-agent sorafenib in patients with advanced NSCLC [87]</td>
<td>Sorafenib was generally well tolerated and showed promising efficacy in patients with advanced progressive NSCLC, with ~60% of patients achieving disease stabilisation.</td>
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<tr>
<td>Sunitinib</td>
<td>Phase II trial investigating sunitinib monotherapy in previously treated patients with NSCLC [88]</td>
<td>Stable disease was experienced by 28.6% of patients. ORR was comparable with approved agents. Further evaluation is warranted.</td>
</tr>
<tr>
<td>Vandetanib</td>
<td>Phase II study comparing efficacy of vandetanib with that of gefitinib in previously treated patients with NSCLC [89]</td>
<td>Vandetanib prolonged PFS compared with gefitinib. OS was not statistically different between the two treatment groups.</td>
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<tr>
<td></td>
<td>Phase II study comparing different doses of vandetanib and docetaxel with docetaxel alone in patients with failure of first-line platinum-based chemotherapy with NSCLC [90].</td>
<td>Median PFS favoured the vandetanib arms; no statistically significant benefit in OS was observed between the three treatment arms.</td>
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NSCLC, non-small-cell lung cancer; ORR, overall response rate; PFS, progression-free survival; OS, overall survival.

EGFR, epidermal growth factor receptor; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression-free survival; FDA, Food and Drug Administration; TTP, time to progression; RR, response rate.

The trial established noninferior survival of gefitinib compared with docetaxel, indicating that gefitinib is a valid treatment of pretreated patients with advanced NSCLC.

While improving OS remains the goal for clinicians, PFS is increasingly being utilised as an alternative end point. PFS can be measured rapidly and can also be set in the context of first-line and pretreated patients. This observation is perhaps the most important difference between PFS and OS; however, PFS brings with it the limitations outlined earlier with progression-based end points. Further analysis of trials exploring the same question in NSCLC should be carried out to demonstrate the utility of alternative end points such as PFS in NSCLC.

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disclosure

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