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Issues Surrounding Clinical Trial Endpoints in Solid Malignancies With a Focus on Metastatic Non-Small Cell Lung Cancer

Edward B Garon, MD

David Geffen School of Medicine at the University of California, Los Angeles, CA

Summary

Relative to best supportive care alone, cytotoxic chemotherapy has an established role in prolonging overall survival (OS) in patients with or without previous treatment for metastatic non-small cell lung cancer (NSCLC). OS has been the principal endpoint influencing regulatory decisions regarding targeted therapies for metastatic NSCLC, including the vascular endothelial growth factor monoclonal antibody bevacizumab in the frontline setting and the epidermal growth factor receptor tyrosine kinase inhibitors gefitinib and erlotinib in patients after prior treatment. Progression-free survival (PFS), another common endpoint in oncology clinical trials, has been discussed as a potential surrogate for OS in metastatic NSCLC. A number of phase III clinical trials of investigational targeted agents for treatment of metastatic NSCLC are ongoing, with OS designated as the primary endpoint in some cases and PFS in others. Both endpoints have been developed largely to evaluate outcomes in unselected populations in which a fraction of patients are anticipated to derive significant benefit. New approaches are being considered for the evaluation of targeted agents. Recent high profile trials have been designed to assess PFS using a randomized discontinuation design and disease control rate after 8 weeks of treatment. With a series of recent advances towards increasingly personalized biomarker-directed anticancer therapies, the appropriateness of the traditional regulatory approach has been questioned.

Keywords

lung cancer; progression-free survival; overall survival; surrogate endpoint; disease control rate; clinical research

Introduction

Lung cancer represents a debilitating disease that leads to as many deaths as the next four most common malignancies combined [1]. One reason for the high mortality is that non-small cell lung cancer (NSCLC) usually presents in an advanced, unresectable stage [2]. For

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Contact information for corresponding author and for page proofs: Edward B Garon, MD, Assistant Professor of Medicine, Hematology-Oncology, UCLA Translational Oncology Research Laboratory, 2825 Santa Monica Blvd., Suite 200, Santa Monica, CA 90404, Tel: 310-586-2098, Fax: 310-586-0841, EGaron@mednet.ucla.edu.

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Conflicts of Interest

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metastatic NSCLC, it is well established that the addition of chemotherapy to best supportive care, as both initial therapy and therapy after an initial relapse, improves overall survival (OS) [3–6]. In addition to enhancing survival, chemotherapy can reduce disease burden, often translating into improvement in symptoms, including pain and dyspnea. Despite the benefits of chemotherapy, clinical data indicate that advances based on selecting one chemotherapy regimen over others in unselected populations are limited [7]. Based on aggressive attempts to elucidate the molecular events leading to NSCLC [8], the disease has served as a major platform for the development of targeted agents as a supplement or alternative to conventional chemotherapy.

The US Food and Drug Administration (FDA) has two mechanisms for approval of drugs and biologics—regular and accelerated approval [9]. Regular approval is granted as a result of demonstrated clinical benefit in terms of a longer life, better life, or a favorable effect on an established surrogate for clinical benefit. Accelerated approval, introduced into regulations in 1992 exclusively for new drugs or biologics for the treatment of serious or life-threatening illness, allows for approval based on a surrogate endpoint that is deemed “reasonably likely to predict clinical benefit.” Accelerated approval requires confirmation of clinical benefit in subsequent trials. Accelerated approval is a critical mechanism for providing patients with earlier access to treatments that are “better than available therapy,” but an option for which there is inherent uncertainty surrounding the choice of surrogate endpoint and the feasibility of ultimately achieving full approval.

As development of targeted approaches to malignancy take on an increasing role in drug development, topics related to the appropriate endpoints correlating with benefit in targeted patient populations have garnered increased interest. This review discusses different clinical trial endpoints in oncology with a focus on OS and progression-free survival (PFS) in metastatic NSCLC but also includes key developments relevant to this topic in other malignancies (ie, metastatic breast cancer [MBC] and metastatic melanoma) and other potential surrogate endpoints of interest (eg, response rate [RR], disease control at 8 weeks).

The History of PFS as a Clinical Trial Endpoint in Oncology

PFS was first accepted as an endpoint suitable for regulatory approval in 1991 for the approval of carboplatin in ovarian cancer. It was recommended by the Oncologic Drugs Advisory Committee (ODAC) as an endpoint for advanced NSCLC clinical trials in 2003 [10]. Whereas a PFS benefit without OS benefit may be deemed sufficient for regulatory approval in settings where effective therapies are unavailable, there may be limited applicability in settings with alternative treatment(s) that provide an OS benefit [9]. In recent years, PFS has been instrumental in supporting regulatory approval of certain anticancer drugs, including a monoclonal antibody (bevacizumab) and several multitargeted tyrosine kinase inhibitors (TKIs) directed against vascular endothelial growth factor (VEGF) and its receptors for advanced renal cell carcinoma (RCC), a poorprognosis and chemotherapy-insensitive malignancy [10]. However, the PFS endpoint with bevacizumab without an accompanying OS benefit was not considered adequate for regulatory approval in the setting of breast cancer, as discussed later in this article [11].

OS and PFS

OS is regarded as the “gold standard” clinical trial endpoint in oncology trials, supplanting improved RR as the main prerequisite for anticancer drug approval during the 1980s. OS is favored as an endpoint because it is not influenced by investigator bias and is a useful parameter for informing clinical practice decisions regarding the potential risk and benefit of a given therapy [10]. A major issue with OS as a study endpoint is the large study population and long follow-up required [10,12,13]. Additional issues with OS measurement

include the confounding impact of subsequent therapies (including cross-over treatments) and cancer-unrelated deaths [12,14].

PFS as a measure of clinical benefit and a surrogate for OS in cancer trials is a controversial topic and a source of continued discussion and debate [12,15]. PFS, based on more accurate reflection of stable disease (SD) and time to progression (TTP), is viewed as a more favorable endpoint than objective RR by the US FDA, although several oncology drugs were approved based on RR, primarily in breast cancer (including anastrozole, letrozole, exemestane, and capecitabine) [10]. However, the relationship of PFS with OS requires assessment and validation for each individual type of cancer [14], and analysis of PFS data poses interpretative challenges [9]. Specific limitations of designating PFS as a primary endpoint of a clinical trial include the need for frequent and ongoing disease status assessment, variable definitions related to progression, and propensity for bias [10,13,14].

Meta-analyses have addressed whether PFS constitutes an appropriate surrogate for OS [16–19]. In advanced colorectal cancer, PFS has been shown to be an acceptable surrogate for OS, as supported by several meta-analyses [15,20–22]. Conversely, on the basis of a meta-analysis of 66 randomized studies conducted across various metastatic tumor types, it was concluded that PFS reflects the effect of a drug on tumor growth during the time period of administration and is not a surrogate for OS [23]. Numerous anticancer agents have demonstrated a PFS benefit without an accompanying OS benefit in phase III clinical trials, with potential explanations including availability of effective subsequent therapies, confounding influence of cancer-unrelated deaths, lack of sufficient statistical power, and a PFS benefit too small to impact OS [12].

Median OS data from registration trials of FDA-approved chemotherapeutic and targeted agents for the treatment of metastatic NSCLC and indications for first-line or subsequent therapies are summarized in Table I. The primary endpoints of several ongoing phase III trials of targeted agents for metastatic NSCLC are summarized in Table II. Improved OS supported the regulatory approval of bevacizumab for advanced non-squamous NSCLC [10] in combination with carboplatin and paclitaxel (Table II), the FDA-approved chemotherapy backbone for bevacizumab therapy in NSCLC [24]. However, no gain in OS was achieved when bevacizumab was added to cisplatin and gemcitabine in a subsequent phase III trial [25]. Erlotinib is approved in patients after prior chemotherapy, based on a trial showing superiority in OS as compared with best supportive care [26]. However, neither the epidermal growth factor receptor (EGFR) TKI gefitinib nor erlotinib has offered consistent OS benefit with first-line chemotherapy for unselected patients with advanced NSCLC [9,27]. Erlotinib is recommended as first-line therapy in a molecularly selected patient population based on clinical trial data [2], but this indication is not approved by the FDA.

Interestingly, OS benefit has been difficult to demonstrate for EGFR TKIs in patients whose tumors harbor *EGFR* mutations [28]. In this molecularly selected population, EGFR-TKI therapy is clearly effective; however, it is likely that in an era in which EGFR TKIs are available, patients often receive these agents as subsequent therapies, preventing a survival benefit. It is also possible that the time after progression is long enough to obscure improvements based on short-term interventions. OS is anticipated to closely mirror PFS in settings in which additional therapy is unavailable or ineffective. However, the strength of the relationship is less clear when effective subsequent therapies are available.

Bevacizumab in MBC

Designing studies with sufficient power to detect differences in OS is a recognized issue in MBC [22]. Accelerated FDA approval of bevacizumab for frontline MBC therapy was granted in 2008, with the E2100 study demonstrating that paclitaxel plus bevacizumab

significantly prolongs median PFS over paclitaxel alone, while also improving 1-year OS. However, median OS was not improved [29]. Subsequent results of placebocontrolled RIBBON-1 (bevacizumab plus capecitabine or taxane/anthracycline) [30] and AVADO (bevacizumab plus docetaxel in human epidermal growth factor receptor 2 [HER2]-negative MBC) [31] supported improvements in median PFS (primary endpoint) but not median OS among the bevacizumab recipients. In a pooled analysis of E2100, AVADO, and RIBBON-1, the PFS benefit of bevacizumab plus chemotherapy versus chemotherapy alone was apparent (9.2 vs 6.7 months; hazard ratio [HR], 0.64; $P < 0.0001$), with no OS benefit based on median durations (26.7 vs 26.4 months; HR, 0.97; 95% confidence interval [CI], 0.86–1.08; $P = 0.56$) but a significantly higher 1-year OS rate (81.6% vs 76.5%; $P = 0.003$) [32]. In mid-2010, ODAC voted against regular approval of bevacizumab in MBC based on a lack of OS benefit (despite no clear direction from the FDA that approval would rely on an OS benefit) [33], and the FDA revoked the MBC indication in November 2011.

Response and/or SD for Predicting Long-Term Outcomes

Several response evaluation criteria are available for assessing disease status during anticancer therapy (World Health Organization, Southwest Oncology Group, Response Evaluation Criteria in Solid Tumors [RECIST]), each with their own limitations [34,35]. Although RECIST is generally used, there is ongoing reevaluation of how response is defined and assessed in the contemporary era of clinical trial design [36–38].

In a literature review of tumor responses in phase I and II studies in various malignancies (including NSCLC), RR in early-phase studies was found to be predictive of future regulatory approval, with notable exceptions being melanoma and RCC [39]. The correlation between RR and OS in advanced NSCLC has been the topic of several systematic literature reviews and meta-analyses. In a meta-analysis of randomized trials of first-line cancer therapy including advanced NSCLC, RR was found to correlate with improved OS ($P < 0.0001$) but large differences in RR were required for the detection of an OS benefit (differences of 18% for 750 patients, 21% for 500 patients, and 30% for 250 patients) [40]. In a systematic review of phase II and III trials of single-agent gefitinib or erlotinib for advanced NSCLC, a strong correlation between RR and median OS was identified ($P < 0.0001$), with a positive albeit weaker correlation between disease control rate (DCR) and median OS ($P = 0.003$); it was concluded that RR may be a surrogate for OS in EGFR-TKI monotherapy-treated populations [41]. Interestingly, despite these results, RR formed the basis of accelerated approval of gefitinib in chemotherapy-pretreated advanced NSCLC, but it received a greatly restricted indication after subsequent trials showed no OS benefit [9,27].

This evaluation of EGFR TKIs is particularly illustrative in this era of targeted therapeutics. It is now recognized that the great majority of objective responses with EGFR-TKI therapy are observed in patients with *EGFR* mutations [2,28,42], the same patients in whom a survival benefit would be most strongly anticipated. Therefore, in this instance, both RR and PFS were associated with *EGFR* mutation rate and likely acted as surrogates for *EGFR* mutations. Thus, it is not surprising that RR was a better surrogate for OS than DCR, as DCR would be anticipated to include both patients with *EGFR* mutations as well as those with indolent disease, while RR would be expected to include almost exclusively patients with *EGFR* mutations in whom the greatest benefit would be anticipated.

Alternate Endpoints With a Focus on Sorafenib

SD has emerged as an important endpoint in early clinical trials of targeted agents, with disease stabilization appearing to contribute to long-term benefit [43]. SD as an endpoint, however, requires an understanding of the patient population and anticipated progression.

For instance, phase I trials often have a high degree of SD, but many patients are often afflicted with traditionally indolent tumors. Randomized discontinuation studies provide the opportunity to address SD as an endpoint for targeted treatments [44]. In a placebo-controlled randomized phase II discontinuation trial in pretreated metastatic NSCLC, sorafenib monotherapy was associated with significant PFS benefit and a significantly higher SD rate [45].

DCR at 8 weeks is being evaluated for its potential to provide an early readout of drug efficacy, as demonstrated in the M.D. Anderson Cancer Center BATTLE clinical trial program focused on biomarker discovery [46]. In the prospective biopsy-driven BATTLE-1 study in pretreated metastatic NSCLC, patients were initially enrolled into an umbrella study in which core biopsy specimens were obtained and tested for biomarkers across several molecular pathways, and then were assigned to one of four targeted treatments (erlotinib, sorafenib, vandetanib, or erlotinib/bexarotene) [46]. The primary endpoint was 8-week DCR (complete response, partial response, or SD by RECIST), with OS, PFS, RR, and toxicity as secondary endpoints. Advantages of this approach include, but are not limited to, shorter duration of required follow-up for the primary endpoint. This was of particular importance in a study of oral agents in which many patients needed to travel a distance to the study center. DCR at 8 weeks was found to be predictive of OS, with median OS of 11.3 months in the 104 patients with disease control at 8 weeks versus 7.5 months in patients without disease control at 8 weeks ($P = 0.002$). Of course, the relative importance of disease-related features (aggressive vs indolent) as opposed to therapeutic efficacy in this correlation is difficult to determine. The next study in the BATTLE program (BATTLE-2; NCT01248247) is also designed to evaluate 8-week DCR as the primary endpoint.

There is little data that these trials evaluating novel endpoints will help lead to regulatory approval, but they could serve as useful “signal-finding” experiments. In BATTLE-1, sorafenib performed favorably, particularly in a group of *Kirsten rat sarcoma viral oncogene homolog* (*KRAS*) mutant tumors [47], a subset that has traditionally not responded to targeted agents. The randomized discontinuation study of sorafenib was also a positive study [45]. However, a phase III trial of frontline chemotherapy with or without sorafenib did not demonstrate benefit [48]. Thus, the prospects for regulatory approval of sorafenib in NSCLC are murky at best, with no clear path for its regulatory approval.

Highly Targeted Agents in Other Malignancies

Metastatic melanoma is among the malignancies for which treatment-associated gain in OS have remained an elusive goal. Vemurafenib (Zelboraf[®]) is a small molecule v-raf murine sarcoma viral oncogene homolog B1 (BRAF) inhibitor. Interim phase III data (BRIM3) in *BRAF*^{V600} mutation-positive metastatic melanoma recently showed significant improvement in both OS and PFS compared with dacarbazine [49]. Based on the positive findings of BRIM3 as well as the BRIM2 [50] phase II trial, vemurafenib was approved in August 2011 for patients with unresectable or metastatic melanoma with a *BRAF*^{V600E} mutation [51].

Crizotinib (formerly PF-02341066) is a unique anticancer agent in terms of speed of clinical development. It targets an aberration not recognized until 2007, namely the *echinoderm microtubule-associated protein like-4/anaplastic lymphoma kinase* (*EML4-ALK*) fusion protein (implicated in up to 7% of patients with advanced NSCLC [mainly adenocarcinomas and non-smokers]) [52]. It received orphan drug status in the United States in September 2010 and was approved by the FDA in August 2011 [53]. Activity in this biomarker-defined treatment setting was identified during the dose-escalation component of a phase I trial, which then enrolled patients with prospectively identified *ALK*-positive NSCLC [54,55].

Considering all 116 evaluable patients with *ALK*-positive advanced NSCLC, there were high RR and clinical benefit rates (61% and 88%, respectively) and median OS had not been reached [55]. To address the lack of randomized controlled data for crizotinib in this population, an earlier analysis was conducted comparing outcomes of 82 patients relative to historical controls with crizotinib-untreated/*ALK*-positive disease or *ALK*-negative/*EGFR*-negative disease [56]. In patients with *ALK*-positive disease, a significant OS benefit was reported for crizotinib as second- or third-line treatment. However, even in the setting of an ineffective therapy, it would be anticipated that patients eligible to enroll in a clinical trial would have superior outcomes to patients who may have more aberrant laboratory tests or more substantial comorbidities. These phase I results and those from a phase II trial [57] of crizotinib in advanced *ALK*-positive disease led to its approval with a companion diagnostic test for expression of *ALK* [53].

The approval of crizotinib differs from current convention for anticancer agents, as it was based on RR rather than PFS or OS benefit. The results of a phase III trial comparing crizotinib to docetaxel or pemetrexed in the second-line setting (NCT00932893) are awaited to further elucidate the OS impact of this targeted agent over conventional chemotherapy in *ALK*-positive advanced NSCLC, although OS is designated as a secondary endpoint in this trial (PFS is the primary endpoint). Of note, this trial of crizotinib allows patients randomized to cytotoxic chemotherapy to enroll in a phase II trial of open-label crizotinib at the time of progression (NCT00932451). This contrasts with the aforementioned vemurafenib versus dacarbazine melanoma trial, for which crossover was not allowed until superior outcomes were shown in the vemurafenib arm. Undoubtedly, allowing crossover in the setting of an effective intervention can dilute an OS benefit, as patients may receive more effective interventions after the study than during their original treatment allocation. A second phase III trial (PROFILE 1014; NCT01154140) will evaluate first-line crizotinib versus chemotherapy, again with PFS as the primary endpoint.

Conclusions

OS and PFS represent the main endpoints for clinical trials. Although other endpoints, such as DCR, are being used to evaluate targeted agents and can generate interesting data, these endpoints have not yet led to a clear path to regulatory approval as demonstrated by the experience with sorafenib in NSCLC. While pending data from further studies, the approval of crizotinib without an OS benefit is an informative experience, and has the potential to change the approach to drug development in this era of targeted agents. Allowing crossover in trials can confound OS data, but withholding it in highly targeted patient populations, such as *BRAF*^{V600E} mutants or *ALK*-translocated patients, generates ethical dilemmas.

For regulatory approval of anticancer drugs, although OS is the traditional “gold standard” endpoint in oncology trials, it is recognized that demonstrating an OS benefit may pose insurmountable challenges in the targeted therapy era (given the confounding impact of subsequent therapies, including cross-over treatments). At the same time, however, it is increasingly apparent that the magnitude of prolonged PFS must not only be statistically significant but also clinically meaningful. In this regard, the experience with bevacizumab in MBC leads to some degree of caution when choosing PFS as a primary endpoint for regulatory approval. In advanced NSCLC, the extent to which PFS serves as a surrogate for OS remains to be elucidated. This is particularly important in the setting of *EGFR*-directed agents in patients whose tumors harbor *EGFR* mutations. Since patients with *EGFR* mutations may have a better prognosis compared with NSCLC patients overall and there are approved *EGFR* inhibitors to which a patient can “cross over,” this is a particularly difficult population in which to show a survival advantage.

Molecularly-targeted cancer therapeutics are presenting challenges to the current regulatory approach, and the appropriateness of that approach is being questioned and even modified in the evaluation of molecularly selected patient populations. Although OS will remain the gold standard for evaluation of clinical trial data, other endpoints will likely continue to be considered. In studies employing endpoints such as PFS, the impact of the intervention on quality of life is important. If OS is not prolonged but growth of a painful bone metastasis is delayed, the patient derives clear benefit. However, the benefit is less clear if growth of a painless liver metastasis is delayed without accompanying increased survival. Clinical trials using endpoints other than OS may be well served by including rigorous evaluation of quality of life in order to make the case that the numerical benefits seen are associated with tangible benefits for patients.

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Table ISummary of Median OS for Approved First-line or Subsequent Treatments for Advanced NSCLC^a

Agent	Approved indication for first-line or subsequent therapy in the United States ^a	Median OS (as stated in approved product labeling)	Primary references ^b
Chemotherapeutic agents			
Paclitaxel [58]	First-line combination use with cisplatin	9.3 mo ^c (vs 7.4 mo for etoposide/cisplatin; $P = 0.12$)	[59]
Docetaxel [60]	First-line combination use with cisplatin	10.9 mo (vs 10.0 mo for vinorelbine/cisplatin; HR, 0.88; 95% CI, 0.74–1.06; $P = 0.122$)	[61]
	Monotherapy after platinum failure	7.5 mo (vs 4.6 mo for BSC; HR, 0.56; 95% CI, 0.35–0.88; $P = 0.01$)	[4]
		5.7 mo (vs 5.6 mo for vinorelbine/ifosfamide; HR, 0.82; 95% CI, 0.63–1.06; $P = 0.13$)	[62]
Vinorelbine [63]	First-line monotherapy	30 wk (vs 22 wk for 5-FU/LV; $P = 0.06$)	[64]
	First-line combination use with cisplatin	7.8 mo (vs 6.2 mo for cisplatin; $P = 0.01$)	[65]
		9.2 mo (vs 7.4 mo for vindesine/cisplatin; $P = 0.09$; vs 7.2 mo for vinorelbine alone; $P = 0.05$)	[66]
Gemcitabine [67]	First-line combination use with cisplatin	9.0 mo (vs 7.6 mo for cisplatin; $P = 0.008$)	[68]
		8.7 mo (vs 7.0 mo for etoposide/cisplatin; $P = 0.18$)	[69]
Pemetrexed [70]	First-line combination use with cisplatin for non-squamous tumors	11.0 mo (vs 10.1 mo for gemcitabine/cisplatin; HR, 0.84; 95% CI, 0.74–0.96)	[71]
	Monotherapy for chemotherapy-pretreated non-squamous tumors	9.3 mo (vs 8.0 mo for docetaxel; HR, 0.78; 95% CI, 0.61–1.00)	[72]
Targeted agents			
Bevacizumab [73]	First-line combination use with carboplatin/paclitaxel for non-squamous tumors	12.3 mo (vs 10.3 mo for carboplatin/paclitaxel alone; HR, 0.80; 95% CI, 0.68–0.94; $P = 0.013$)	[24]
Gefitinib [74]	Monotherapy for continued treatment of advanced NSCLC after failure of both platinum-based and docetaxel chemotherapy for patients who have or are benefitting from gefitinib ^d	5.6 mo (vs 5.1 mo for placebo; HR, 0.89; $P = 0.11$)	[75]
Erlotinib [76]	Monotherapy after failure of at least 1 chemotherapy regimen	6.7 mo (vs 4.7 mo with placebo; HR, 0.73; 95% CI, 0.61–0.86; $P < 0.001$)	[26]
Crizotinib [53]	Monotherapy with companion FDA-approved diagnostic test for <i>ALK</i> abnormality	No survival data available ^e	[55,57]

5-FU/LV, 5-Fluorouracil/leucovorin; BSC, best supportive care; CI, confidence interval; FDA, Food and Drug Administration; HR, hazard ratio; NSCLC, non-small cell lung cancer; OS, overall survival; RR, response rate.

^aNot including maintenance therapy, for which erlotinib and pemetrexed have approved indications; methotrexate has an indication that mentions its use as monotherapy or in combination with other agents for lung cancer (particularly squamous cell and small cell types) but does not cover clinical trials or provide dosing recommendations specific to advanced NSCLC.

^bSeveral registration trials have been published, but results in some cases differ slightly from those in the approved product labeling.

^cFor paclitaxel dosed at 135 mg/m² dose in combination with cisplatin.

^dWithdrawal of application for approval planned [27].

^ePrescribing information states that the approval indication is based on RR and that no data are available demonstrating improvement in patient-reported outcomes or survival.

Table II

Investigational Antibodies and Small Molecule Inhibitors in Phase III Development for Advanced NSCLC^a

Agent	Active phase III trial(s)	Treatment setting	Primary endpoint
Antibody-based therapies			
Ramucirumab (anti-VEGFR-2 human monoclonal antibody)	NCT01168973	Second-line combination therapy with docetaxel	OS
Small molecule inhibitors			
Sorafenib (multitargeted TKI)	MISSION/NCT00863746	Third- or fourth-line monotherapy	OS
Sunitinib (multitargeted TKI)	CALGB 30607/NCT00693992	Maintenance monotherapy after first-line chemotherapy	PFS
Nintedanib (BIBF 1120; multitargeted TKI)	LUME-Lung 1/NCT00805194	Second-line combination therapy with docetaxel	PFS
	LUME-Lung 2/NCT00806819	Second-line combination therapy with pemetrexed	PFS
Cediranib (multitargeted TKI)	BR29/NCT00795340 [77] ^c	First-line combination therapy with paclitaxel/carboplatin	OS
Motesanib (multitargeted TKI)	MONET1/NCT00460317 [78] ^b	First-line combination therapy with paclitaxel/carboplatin	OS
Afatinib	LUX-Lung-3/NCT00949650	First-line monotherapy in <i>EGFR</i> mutation-positive disease	PFS
(BIBW 2992; irreversible Erb family TKI)	LUX-Lung-6/NCT01121393	First-line monotherapy in <i>EGFR</i> mutation-positive disease	PFS
	LUX-Lung-5/NCT01085136	Second-line ^d monotherapy; those with clinical benefit 12 weeks eligible to receive combination afatinib/paclitaxel or investigator's choice of chemotherapy	PFS
Dacomitinib (PF00299804; irreversible pan-HER TKI)	ARCHER 1009/NCT01360554	First-line monotherapy	PFS
	BR26/NCT01000025	Second-line or subsequent monotherapy ^e	OS

ALK, anaplastic lymphoma kinase; NCIC, National Cancer Institute of Canada; NSCLC, non-small cell lung cancer; PFS, progression-free survival; OS, overall survival; TKI, tyrosine kinase inhibitor; VEGF[R], vascular endothelial growth factor [receptor].

^aAs of May 2012, not including agents for which phase III clinical trials are active on clinicaltrials.gov but for which clinical development is no longer being pursued in advanced NSCLC.

^bPer abstract presentation, the primary endpoint was not met; information regarding plans for future development in advanced NSCLC is not available.

^cPer NCIC Web site, trial has been closed; information regarding plans for future development in advanced NSCLC is not available.

^dFailing prior erlotinib or gefitinib and 1 prior chemotherapy regimen.

^ePatients must have been pretreated with 1 to 2 prior chemotherapy regimens and must have failed erlotinib or gefitinib for advanced disease.