

Second-Line Therapy for Advanced NSCLC

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ABSTRACT

Most patients with lung cancer have non-small cell lung cancer (NSCLC) subtype and have advanced disease at the time of diagnosis. Improvements in both first-line and subsequent therapies are allowing longer survival and enhanced quality of life for these patients. The median overall survival observed in many second-line trials is approximately 9 months, and many patients receive further therapy after second-line therapy. The cytotoxic agents pemetrexed and docetaxel and the epidermal growth factor receptor (EGFR) tyrosine kinase inhibi-

tors (TKIs) erlotinib and gefitinib are standard second-line therapies. For patients with EGFR mutation, a TKI is the favored second-line therapy if not already used in first-line therapy. For patients without the EGFR mutation, TKIs are an option, but many oncologists favor cytotoxic therapy. The inhibitor of the EML4/ALK fusion protein, crizotinib, has recently become a standard second-line treatment for patients with the gene rearrangement and has promise for patients with the ROS1 rearrangement. *The Oncologist* 2013;18:947–953

Implications for Practice: The landscape of first-line treatment has generated challenges for clinical decisions in second-line therapy. For the patient treated with standard chemotherapy in the first line who has a treatable molecular change, this change should be targeted. More specifically, the patient with an epidermal growth factor receptor (EGFR) mutation should be treated with an EGFR tyrosine kinase inhibitor, and the patient with EML4/ALK rearrangement should be treated with crizotinib. However, these agents are increasingly being used in the first line, and most patients do not have these molecular changes. This leaves the clinician with many challenging questions regarding second-line therapy. How should the patient without treatable mutations be treated? Which clinical trials are most promising? How should the patient treated with a targeted agent in the first line be treated in the second line? This review addresses these issues, exploring the key existing data available to help guide informed clinical decisions.

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality in the United States and in the world [1, 2]. Most patients have the non-small cell lung cancer (NSCLC) subtype and have advanced-stage disease at the time of diagnosis. The standard first-line therapy for advanced disease (defined as stage IIIb or IV) is a platinum doublet alone or with a targeted agent such as bevacizumab for four to six cycles [3]. Chemotherapy extends overall survival (OS), reduces disease-related symptoms, and improves quality of life (QoL). Historically, after completion of four to six cycles of platinum-based therapy, patients were observed, and at the time of radiographic or clinical evidence of disease progression, therapy was re-initiated. Approximately 30% of patients experience disease progression during first-line chemotherapy, and all patients with initial disease control will eventually experience disease progression and require subsequent therapy. The use of anticancer agents in these clinical situations is referred to as “second-line therapy.” Currently, there are two cytotoxic agents, pemetrexed and docetaxel, and two epidermal growth factor receptor (EGFR)

tyrosine kinase inhibitors (TKI), erlotinib and gefitinib, that are established agents in the second-line setting [4–8].

Several trials have challenged the standard of care of observation for the management of patients without progression after four cycles of platinum-based doublet first-line chemotherapy. This strategy, referred to as “maintenance therapy,” involves the administration of established second-line agents immediately after successful first-line therapy, instead of waiting for disease progression. Phase III trials of erlotinib compared with placebo and pemetrexed compared with placebo have demonstrated an improvement in progression-free survival (PFS) and OS with maintenance therapy [9, 10]. Maintenance therapy with pemetrexed is beneficial only for patients with nonsquamous histology. When a maintenance strategy is used as part of first-line therapy, the agent used is typically not considered an option for second-line or later treatment. The use of maintenance therapy has led to reconsideration of the traditional definition of second-line therapy.

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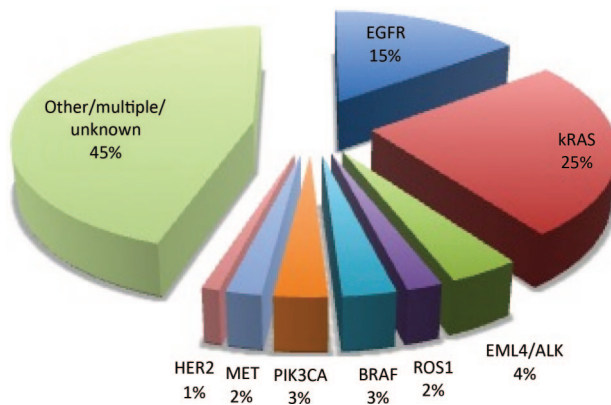


Figure 1. Approximate incidence of common mutations in adenocarcinoma. Numbers should be considered approximate to illustrate the relative frequency of these changes as they have never been all reported in the same series and estimates vary. References: *EGFR* [11, 12], *Kirsten rat sarcoma viral oncogene homolog (KRAS)* [12], *Echinoderm microtubule-associated protein-like 4/anaplastic lymphoma kinase (EML4/ALK)* [13], *ROS1* [14, 15], *BRAF* [12], *Phosphatidylinositol-4,5-Bisphosphate 3-Kinase (PIK3CA)* [12], *hepatocyte growth factor receptor (MET)* [12] (note: this rate refers to *MET* mutation; overexpression is more common), *Human Epidermal Growth Factor Receptor 2 (HER2)* [12], Other/unknown [12].

The use of a molecularly targeted agent in first-line therapy can also increase the challenge of second-line therapy selection. With complete testing, a driver mutation can now be found for more than half of adenocarcinomas of the lung [11–14] (Fig. 1). Both *EGFR* TKIs and crizotinib have been specifically studied in second-line therapy, but both are also approved for first-line use in patients with the relevant molecular changes (*EGFR* mutation and *ALK* rearrangement, respectively). We will explore therapeutic options for second-line therapy for patients treated with targeted therapy in the first-line setting.

Docetaxel

The first agent approved for use in the second-line setting was docetaxel, and its approval was based on the results of two phase III trials (Table 1) [4, 6]. In the trial by Shepherd et al., patients were required to have a performance status of 0–2 and to have received one or more platinum-based chemotherapy regimens [4]. Patients were randomly assigned to docetaxel 100 mg/m² every 3 weeks or best supportive care (BSC). The trial was amended because of excessive toxicity in the docetaxel arm, and the dose of docetaxel was reduced to 75 mg/m² every three weeks. The time to disease progression and OS were statistically significantly longer in the docetaxel arm compared with the BSC arm in the intent-to-treat (ITT) patient population. These differences were more significant in the cohort of patients treated with 75 mg/m² every 3 weeks. The QoL assessments were significantly better in the docetaxel arm as well, with significant differences in the pain and fatigue scales [15].

A second trial compared docetaxel 100 mg/m² or 75 mg/m² every three weeks versus vinorelbine or ifosfamide (selection of the agent was at the investigator's discretion) [6]. Patients assigned to the docetaxel arm experienced a longer PFS at 26 weeks ($p = .005$), but OS did not differ among the

three arms. The one-year OS rate was significantly higher in the docetaxel 75 mg/m² arm compared with the control arm. These two trials established docetaxel 75 mg/m² as the standard second-line therapy. The clinically significant toxicities were neutropenia and febrile neutropenia. To reduce the rate of these toxicities, several trials investigated a weekly compared with the standard schedule of docetaxel every three weeks. A meta-analysis using individual patient data compared weekly with every three weeks docetaxel and revealed similar OS with both schedules [16]. Patients treated with docetaxel weekly compared with docetaxel every three weeks experienced a lower rate of neutropenia (5% vs. 18%; $p < .00001$) and febrile neutropenia (<1% vs. 6%; $p < .00001$); no significant differences were observed for anemia, thrombocytopenia, and nonhematologic toxicities. In clinical practice, both schedules are frequently used.

Clinicians are increasing their use of pemetrexed in combination with a platinum agent in the first-line setting or as single-agent maintenance therapy in patients with nonsquamous histology. The restriction to nonsquamous histology and the use of pemetrexed earlier in the disease course have reduced the availability of pemetrexed in the second-line setting.

Pemetrexed

A subsequent phase III trial compared pemetrexed 500 mg/m² every three weeks with docetaxel 75 mg/m² every three weeks (Table 1) [7]. The trial was designed to demonstrate the non-inferiority of pemetrexed compared with docetaxel in OS. A statistically significant difference in PFS and OS was not observed. In the docetaxel arm compared with the pemetrexed arm, a higher rate of grade 3 or 4 neutropenia (40.2% vs. 5.3%; $p < .001$) and febrile neutropenia (13.4% vs. 1.9%; $p < .001$) was observed. The rate of nonhematologic toxicities was similar. This trial established pemetrexed as an alternative to docetaxel in the second-line setting.

After completion of this trial, an interaction between pemetrexed efficacy and histology (squamous vs. nonsquamous) was detected. In a retrospective subset analysis, it was found that patients with nonsquamous histology ($n = 399$) experienced a superior OS with pemetrexed compared with docetaxel [17]. In contrast, patients with squamous histology ($n = 172$) experienced a statistically significantly inferior OS with pemetrexed. This trial and other phase III trials demonstrated that the efficacy of pemetrexed is limited to patients with nonsquamous histology tumors [10, 17]. Clinicians are increasing their use of pemetrexed in combination with a platinum agent in the first-line setting or as single-agent maintenance therapy in patients with nonsquamous histology. The restriction to nonsquamous histology and the use of pemetrexed earlier in the disease course have reduced the availability of pemetrexed in the second-line setting.

EGFR TKIs

The National Cancer Institute of Canada Clinical Trials Group performed a phase III trial (BR.21) that compared erlotinib with placebo in patients who had disease progression during

Table 1. Select second-line phase III trials of cytotoxic agents

Authors	Patients (n)	Treatment arms	Median PFS or TTP	Median OS (months)	1-year OS rate
Shepherd et al. [4]	204	Docetaxel 100 mg/m ²		5.9	19%
		Docetaxel 75 mg/m ²	10.6 weeks	7.5	37%
		BSC	6.7 weeks	4.6	19%
			$p \leq .001^a$	$p = .047^a$	
Fossella et al. [6]	373	Docetaxel 100 mg/m ²	8.4 weeks	5.5	21%
		Docetaxel 75 mg/m ²	8.5 weeks	5.7	32%
		Vinorelbine or ifosfamide	7.9 weeks	5.6	19%
			$p = .046$	NS	NS (0.025) ^b
Hanna et al. [7]	571	Docetaxel 75 mg/m ²	2.9 months	7.9	29.7%
		Pemetrexed 500 mg/m ²	2.9 months	8.3	29.7%
			HR = 0.71; $p = .759$	HR = 0.99; $p = .226$	

^aDocetaxel groups combined in reported TTP, p values represent docetaxel compared with BSC.

^bFor 1-year OS rate, comparison with docetaxel 100 mg/m² was NS, but with docetaxel 75 mg/m², $p = .025$.

Abbreviations: BSC, best supportive care; CI, confidence interval; HR, hazard ratio; NS, not significant; OS, overall survival; PFS, progression-free survival; TTP: time to tumor progression.

Table 2. Select second-line phase III trials of EGFR TKIs

Authors	Patients (n)	Treatment arms	Median PFS or TTP (months)	Median OS (months)	1-year OS rate
Shepherd et al. [5]	731	Erlotinib 150 mg daily	2.2	6.7	30%
		Placebo	1.8	4.7	21%
			HR = 0.61; $p < .001$	HR = 0.70; $p < .001$	
Thatcher et al. [22]	1,692	Gefitinib 250 mg daily	3.0 ^a	5.6	1.7%
		Placebo	2.6	5.1	2.1%
			HR = 0.82; $p = .0006$	HR = 0.89; $p = .087$	
Kim et al. [8]	1,433	Gefitinib 250 mg daily	2.2	7.6	32%
		Docetaxel 75 mg/m ²	2.7	8.0	34%
			HR = 1.04; $p = .47$	HR = 1.02; 96% CI: 0.905–1.15	
Vamvakas et al. [23]	297	Erlotinib 150 mg daily	3.6	7.7	35.7%
		Pemetrexed 500 mg/m ²	2.7	8.9	38.5%
			$p = .434$	HR = 1.02; 96% CI: 0.905–1.15	
Ciuleanu et al. [24]	424	Erlotinib 150 mg daily	1.6	5.3	26%
		Chemotherapy (choice of pemetrexed or docetaxel)	2.2	5.5	24%
			HR = 1.19; $p = .089$	HR = .96; $p = .73$	
Garassino et al. [25]	229	Erlotinib	2.4	Not yet reported	Not yet reported
		Docetaxel	3.4		
			HR = 0.69; $p = .014$		

^aNumbers (3.0 and 2.6) represent the time to treatment failure, defined as the time from randomization to the date the patient discontinued therapy because of an unacceptable adverse event, lack of clinical benefit, patient choice, or death.

Abbreviations: BSC, best supportive care; CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; TTP, time to tumor progression.

one or two lines of chemotherapy and who were not eligible for further chemotherapy (Table 2). Patients assigned to the erlotinib arm experienced a statistically significantly longer PFS and OS than those in the BSC group [5]. Patients assigned to the erlotinib arm also experienced a statistically significantly longer median time to deterioration in cough, dyspnea, and pain, and improvement in physical function and global QoL [18].

Gefitinib was granted accelerated approval in the United States based on an improvement in response rate in two phase II trials [19, 20]. A phase III trial compared gefitinib with placebo in patients who were refractory or intolerant to their

previous chemotherapy (Table 2). However, a statistically significant difference in the primary endpoint of OS was ultimately not observed [21]. Based on these data, the U.S. Food and Drug Administration withdrew approval for gefitinib, and it is not commercially available in the United States. Following these results, a phase III trial comparing gefitinib 250 mg daily with docetaxel continued to enroll patients who had already received at least one platinum-based regimen. The co-primary endpoint of the study, non-inferiority of gefitinib compared with docetaxel in OS, was observed [8]. Key trials comparing TKIs to placebo [5, 22] and to chemotherapy [8, 23–25] are summarized in Table 2.

Second-Line Therapy for Patients With *EGFR* Wild-Type Disease

The use of *EGFR* mutation testing and first-line therapy has resulted in two subpopulations of patients who are eligible for second-line therapy: patients with *EGFR*-mutated NSCLC after *EGFR* TKI therapy, and patients with *EGFR* wild-type tumors. In contrast to the impressive results of *EGFR* TKI treatment for patients with *EGFR*-mutated NSCLC, the results in *EGFR* wild-type tumors are far more modest. Patients with *EGFR* wild-type NSCLC have a response rate to *EGFR* TKI therapy of 1%–7%, a median PFS of approximately 2 months, and a median OS of 6–8 months in retrospective subset analyses of second-line trials [24–26]. Two recent prospective trials have demonstrated that in the second-line setting, PFS is inferior for patients with *EGFR* wild-type tumors treated with erlotinib compared with those treated with cytotoxic chemotherapy [25, 27]. In one study, OS data are not yet available, and in the other trial, the results were similar between erlotinib and cytotoxic chemotherapy. These results left a clinical need to identify which patients with *EGFR* wild-type tumors will benefit from *EGFR* TKI therapy. A recent trial, PROSE, compared chemotherapy with erlotinib for the second-line treatment of unselected patients with NSCLC [28]. Overall, survival was similar in the ITT patient population. More importantly, patients were stratified based on VeriStrat (Biodesix, Boulder, CO, <http://www.biodesix.com/products/veristrat/>) status, a serum proteomics assay, and the trial prospectively assessed the predictive capacity of VeriStrat. Among patients with a VeriStrat “good” signature, survival was similar between chemotherapy and erlotinib. Among patients with a VeriStrat “poor” signature, survival was better with chemotherapy than with erlotinib. Findings were similar when the analysis was restricted to those with *EGFR* wild-type or with unknown-type disease, suggesting that VeriStrat may be able to identify patients with *EGFR* wild-type tumors who should preferentially be treated with cytotoxic therapy or who are unlikely to benefit from *EGFR* TKI therapy in the second line.

Second-Line Therapy for Patients With an *EGFR* Mutation After *EGFR* TKI

For those patients with an *EGFR* mutation who have disease progression on an *EGFR* TKI, chemotherapy remains the most often used second-line option, but a host of alternative treatments seek to challenge this standard. The simplest alternative to chemotherapy alone is the addition of an *EGFR* TKI to chemotherapy. This approach was initiated because it was observed that a portion of patients with *EGFR* mutation had “flare” of their disease when *EGFR* TKI therapy was withdrawn at the time of disease progression [29]. Researchers hypothesized that whereas some cells were resistant to the *EGFR* TKI,

In clinical practice, patients with *EGFR* mutation who have disease progression while taking a TKI often have progression in one or several locations, so called “oligoprogression.” Small retrospective case series have demonstrated the efficacy of local radiation therapy to the site(s) of progression followed by re-initiation of *EGFR* TKI therapy.

leading to progression, other cells remained sensitive, and that their growth was disinhibited by withdrawal of TKI. Although the combination of chemotherapy and an *EGFR* TKI has not improved treatment results in unselected populations, [30–34] prevention of flare and ongoing suppression of resistant clones might improve disease control over chemotherapy alone in a population selected for *EGFR* mutation. The treatment strategy of re-treating with a TKI after an interval with no TKI treatment has been evaluated in two retrospective series, both of which reported clinical activity of repeat *EGFR* TKI [35, 36]. In clinical practice, patients with *EGFR* mutation who have disease progression while taking a TKI often have progression in one or several locations, so called “oligoprogression.” Small retrospective case series have demonstrated the efficacy of local radiation therapy to the site(s) of progression followed by re-initiation of *EGFR* TKI therapy [37, 38]. The combination of afatinib with cetuximab, a monoclonal antibody against *EGFR*, seems promising in preliminary data. In the first 90 evaluable patients treated in this ongoing trial (NCT01090011), the disease control rate was 94%, the probability of being progression-free at six months was 42%, and the confirmed response rate was 40% (95% CI: 17–59) [39]. Final results from this study are eagerly awaited.

EML4/ALK Rearrangements

In approximately 4% of adenocarcinomas, a gene fusion between the echinoderm microtubule-associated protein-like 4 (*EML4*) and the anaplastic lymphoma kinase (*ALK*) gene leads to a fusion gene (*EML4/ALK*), which contributes to carcinogenesis [40]. Crizotinib has been compared with chemotherapy for second-line treatment of patients with the *EML4/ALK* rearrangement. In 347 such patients randomly assigned to crizotinib or chemotherapy (either docetaxel or pemetrexed), overall response rate was superior with crizotinib (65% vs. 20%) as was PFS (7.7 months vs. 3 months; hazard ratio = 0.49; $p < .0001$) [41]. Crizotinib was approved by the U.S Food and Drug Administration in August 2011 and may be considered a standard second-line treatment for patients with *EML4/ALK* who are treated with chemotherapy in the first line.

Although targeted therapy with crizotinib for patients with *EML4/ALK* rearrangements certainly represents a clinical advance, the maximum PFS thus far reported is approximately 10 months, generating a need to define optimal subsequent therapy [42]. For patients whose first anticancer treatment is crizotinib, the only standard subsequent therapy is chemotherapy, which is typically given in the first-line setting, namely a platinum doublet, with consideration of the addition of bevacizumab in eligible patients. Two retrospective series suggest superior treatment outcomes with pemetrexed for patients with the *EML4/ALK* rearrangement [43, 44]. Heat shock protein (HSP) inhibitors and more potent and selective *EML4/ALK* inhibitors have also shown promise as additional molecularly directed treatment options for patients with the *EML4/ALK* rearrangement [45–48]. Finally, as in patients with the *EGFR* mutation who have oligoprogression on erlotinib, retrospective data suggest the efficacy of local ablation followed by re-treatment. In the case of *EML4/ALK*, this approach may be particularly promising for those with intracranial-only progression [37].

Investigational Agents

There are substantial flaws with the existing standard second-line agents, thus increasing the interest in experimental agents. Docetaxel has significant toxicities and is difficult to tolerate even as a weekly dose, pemetrexed is active only in patients with nonsquamous histology and is frequently used as first-line therapy, crizotinib is approved only for patients with *EML4/ALK* rearrangements, and the EGFR TKIs have limited activity in patients whose tumors do not have the mutation. Fewer than 20% of patients will have the actionable changes *EGFR* and *EML4/ALK*. In contrast, *KRAS* is the most common known driver gene mutation, present in approximately 25% of adenocarcinomas [49]. Recently, two treatments have emerged as promising for the patient with *KRAS*. MAP kinase/ERK kinase (MEK) is downstream to signaling from RAS, and selumetinib is an MEK inhibitor. A multicenter international phase II trial compared treatment with docetaxel and placebo with treatment using docetaxel plus selumetinib for patients with *KRAS* mutation [50]. Patients randomly assigned to selumetinib and docetaxel experienced a numerically longer OS, a statistically significantly longer PFS, and higher overall response rate than those treated with docetaxel and placebo. The rate of febrile neutropenia in the docetaxel plus selumetinib arm was 18.2% and in the docetaxel plus placebo arms was 0%. Results with HSP-90 inhibitors also look promising for patients with *KRAS*. A study of single-agent ganetespib, an inhibitor of HSP-90 protein, included a molecularly defined cohort of patients in whom NSCLC included a *KRAS* mutation [48]. These results were followed by a randomized phase IIB/III study of docetaxel and ganetespib compared with docetaxel alone, known as the Ganetespib Assessment in Lung cAncer with docetaxel (GALAXY) study (NCT: 01348126) [51]. The co-primary endpoints were PFS in patients with elevated lactate dehydrogenase levels and mutant *KRAS* NSCLC. An interim safety analysis revealed no evidence of benefit and possible safety concerns in patients with non-adenocarcinoma histology, and consequently, eligibility was restricted to patients with adenocarcinoma histology. Preliminary results revealed benefit from the combination therapy in patients with adenocarcinoma histology, *KRAS* mutation, and an elevated lactate dehydrogenase level. These results are only preliminary, and a phase III trial is required.

MET is a receptor tyrosine kinase that is activated by hepatocyte growth factor. MET expression is associated with adverse prognosis and has been implicated in resistance to EGFR TKIs [52]. A randomized phase II study compared second-line or third-line erlotinib with erlotinib plus onartuzumab, a monoclonal antibody against the MET receptor [53]. Patients were required to provide tissue, and a companion diagnostic test was included in the trial design that determined whether MET expression was present in tumors. The co-primary endpoints were PFS in the ITT patient population and in MET-positive patients. Patients who were MET diagnostic positive and assigned to erlotinib and onartuzumab therapy experienced a significant improvement in PFS and OS with the addition of onartuzumab compared with those treated with erlotinib and placebo. A phase III study comparing erlotinib with erlotinib plus onartuzumab in patients who are *MET* diagnostic positive is underway (NCT01456325) [54].

Programmed death 1 (PD-1) protein is a T-cell co-inhibitory receptor, and PD-L1 is one of its ligands; disruption of this pathway allows tumor cells to evade the host immune system. A phase I trial of the anti-PD-L1 antibody (BMS-936559) enrolled 207 patients with advanced cancer; 75 patients had advanced NSCLC [55]. Of patients with advanced NSCLC, 49 were assessable for response, and of these, 5 had response. Another phase I trial of an anti-PD-1 antibody (BMS-936558) included 76 assessable patients with NSCLC of whom 14 experienced an objective response. In an exploratory analysis of 25 patients from this study with NSCLC and PD-L1-positive tumors, 9 responded to the drug [56]. Phase III trials with BMS-936558 in the second-line setting are ongoing.

CONCLUSION

This article has summarized the current key clinical data needed to inform clinical decision-making in second-line treatment of NSCLC. In practice, clinical decisions are personalized to the individual patient—their priorities, strengths, comorbidities, and prior therapies. The goals of care in the second-line setting are similar to those in the first-line setting: to maximize duration of life, minimize toxicity, and improve QoL.

When a targeted molecular option is available, the authors strongly prefer that it be used. Therefore, for the patient with *EGFR* mutation who has not yet been treated with erlotinib or gefitinib, or the patient with *EML4/ALK* who has not yet been treated with crizotinib, the clinical decision is easy. When an experimental target such as *KRAS* or *ROS1* is present, the authors recommend participation in a clinical trial with an agent that targets the relevant molecular pathway. Even when a specific trial drug–target match is not available, clinical trials for unselected patients should be strongly considered when available. Trials incorporating agents targeting PD-1 and PD-L1 are particularly promising.

Although targeted therapy is preferred when a target is present, most patients are still treated with cytotoxic chemotherapy in the first line and lack a drug-treatable target for second-line therapy. For the patient with nonsquamous histology who is treated with a non-pemetrexed doublet in the first line, pemetrexed is recommended for second-line therapy because of its favorable side effect profile and data indicating superior efficacy. For the patient with squamous histology or the patient treated with pemetrexed in the first line (whether as part of an initial cytotoxic doublet, as maintenance, or both), docetaxel and erlotinib are the standard options. In the absence of known *EGFR* mutation, existing data are not sufficient to define one of these medicines as superior to the other. In our practice, we favor docetaxel for healthy, fit, motivated patients based on superior PFS. However, we consider legitimate the choice of erlotinib or gefitinib (where available) for patients who are less fit, less healthy, or less tolerant of side effects.

Cytotoxic therapy is the most often used standard second-line therapy for patients with *EGFR* mutation who are treated with erlotinib as first-line therapy or for patients with *EML4/ALK* rearrangement treated with crizotinib as first-line therapy. Therapy consists of whatever drugs would have been otherwise used in the first line (typically carboplatin and paclitaxel with consideration of bevacizumab or carboplatin and pemetrexed with consideration of bevacizumab). The authors favor enrollment in a promising second-line clinical trial that

targets the mutation present prior to resorting to cytotoxic therapy, if such a trial is available. In patients with oligoprogression on erlotinib or crizotinib, the authors consider ablation of progressive sites followed by re-initiation of the relevant targeted agent when possible.

AUTHOR CONTRIBUTIONS

Conception/Design: Jared M. Weiss, Thomas E. Stinchcombe

Collection and/or assembly of data: Jared M. Weiss, Thomas E. Stinchcombe

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