Maintenance treatment after induction therapy in non-small cell lung cancer: latest evidence and clinical implications

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Abstract: Non-small cell lung cancer (NSCLC) is the leading cause of cancer death in the industrialized world. Despite significant progress in early stage disease, survival rates for advanced disease remain low. Maintenance therapy is a treatment strategy that has been investigated extensively in NSCLC. Therapies that have been studied in this setting in randomized trials to date include chemotherapy and molecularly targeted agents. Following the development of multiple new agents that show activity in NSCLC and have a tolerable side-effect profile, there has been increasing interest in utilizing them to maintain response to initial therapy after treatment with platinum-based doublets. Two effective strategies have evolved: continuation and switch maintenance. Despite improvements in progression-free survival and often overall survival on multiple clinical trials, there remains considerable controversy around this treatment paradigm. Here, we briefly outline the evolution of this treatment strategy and examine the available data, including recently updated data from the PARAMOUNT, AVAPERL, and PointBreak maintenance trials. Ultimately, the decision to use maintenance chemotherapy requires a nuanced discussion between the patient and physician that adequately assesses benefits of prolonged therapy and impact in terms of toxicity, quality of life, and financial cost.

Keywords: cost–benefit analysis, decision making, disease management, maintenance chemotherapy, metastatic, non-small cell lung cancer, quality of life

Introduction

In advanced non-small cell lung cancer (NSCLC), standard first-line chemotherapy (i.e. induction therapy) with four to six cycles of platinum-based doublet chemotherapy results in modest prolongation of survival and improvements in cancer-related symptoms. With chemotherapy, long-term survival for patients with advanced disease remains poor, with less than 5% of patients surviving 5 years. Certainly, integration of molecularly targeted therapy has resulted in prolongation of life for some patients with metastatic disease, but there is significant room for improvement for most patients. Over the past several years, the idea of prolongation of therapy for NSCLC has garnered clinical attention and academic debate. The concept of more therapy is intuitive when striving for goals of progression-free survival (PFS) and overall survival (OS), and many other common solid

tumor malignancies such as colon, prostate, and breast cancer are treated this way. Lung cancer, however, is often more aggressive and more resistant to chemotherapy than these other diseases, and patients with lung cancer are often older and have multiple tobacco-related comorbidities making treatment delivery more challenging. Many clinicians and researchers have been skeptical that more therapy could result in meaningful responses in these patients. Early trials investigating continuation maintenance therapy with a carboplatin-based doublet were largely negative because of excessive toxicity, deterioration in quality of life (QOL), and clinically insignificant survival gains [Gerber and Schiller, 2013]. However, a renewed interest in this concept began with the success of the ECOG 4599 study. Although not specifically designed as a maintenance trial, the study continued bevacizumab therapy beyond the standard

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four to six cycles of a platinum-based doublet for patients who had stable or responsive disease [Sandler *et al.* 2006].

Two effective single-agent maintenance strategies have since evolved: continuation maintenance and switch maintenance. Continuation maintenance is a continuation of one or more drugs used in the induction regimen. Switch maintenance introduces an additional agent immediately after completion of four to six cycles of platinum-based doublet induction chemotherapy and is viewed by many as an early second-line strategy. Both strategies have been shown to improve PFS and/or OS for patients with stable or responsive disease after completion of induction chemotherapy. Recent studies have also investigated use of multiple maintenance agents (combination maintenance). This review discusses recent data from trials investigating maintenance chemotherapy (Table 1) and the relevance of this data to the management of patients with advanced NSCLC.

Single-agent maintenance

Owing to the toxicity associated with carboplatin, single-agent maintenance seems to be a reasonable clinical approach. Multiple agents, such as docetaxel, gemcitabine, pemetrexed, and erlotinib, have been evaluated in several notable single-agent maintenance trials.

Continuation maintenance

The platinum component of platinum-based doublet therapy is responsible for the majority of reports of serious treatment-related toxicity. For this reason, most patients cannot tolerate prolonged administration of platinum-based doublets. However, this is not true for third-generation single-agent treatment and targeted therapies, in which some patients can get multiple cycles of second-line therapy with minimal toxicity [Hanna *et al.* 2004]. Because the tolerability of these newer drugs, specifically gemcitabine, docetaxel, pemetrexed, and erlotinib, is significantly better than many second-generation chemotherapeutics, a recent strategy has been to investigate the value of continued treatment of responding and stable patients with the nonplatinum component of their induction regimen, 'continuation maintenance' therapy.

The first study to use continuation maintenance with newer agents was ECOG 4599 [Sandler

et al. 2006]. In this study, 878 patients with advanced nonsquamous NSCLC were randomized to carboplatin, paclitaxel, and bevacizumab induction followed by bevacizumab maintenance or carboplatin and paclitaxel induction alone. There was a 2-month improvement in median OS for patients who received bevacizumab (12.3 months *versus* 10.3 months; hazard ratio [HR] 0.79, $p = 0.003$). Similar results were noted in FLEX, a randomized phase III trial that added cetuximab to induction chemotherapy and continued cetuximab maintenance for those with nonprogressive disease [Pirker *et al.* 2009]. In this study, the addition of cetuximab to cisplatin and vinorelbine chemotherapy improved OS from 10.1 to 11.3 months (HR 0.87, $p = 0.044$). Although these studies were not randomized maintenance studies to specifically evaluate the effect of continuation maintenance, they provided a proof-of-concept that additional therapy prolongs survival and that some of the benefit could be attributable to maintenance therapy after induction.

Two phase III European trials, CECOG [Brodowicz *et al.* 2006] and IFCT-GFPC 0502 [Perol *et al.* 2012], have investigated gemcitabine as a maintenance agent. These studies demonstrated improvements in PFS of 1.5 to 2 months with maintenance gemcitabine in patients without progression after induction with cisplatin and gemcitabine. A third study, presented only in abstract form, failed to show an improvement in PFS or OS with continuation maintenance gemcitabine after carboplatin and gemcitabine induction [Belani *et al.* 2010]. The difference between this study and the two European studies has been attributed to a patient population with worse performance status (PS). The majority, 64%, of patients had a PS of ≥ 2 at the time of randomization. However, it is worth noting that the median PFS was 3.8 and 3.9 months in the control and experimental groups, respectively, which was similar to median PFS in the experimental arms of the European studies. These two positive gemcitabine maintenance trials included patients with all NSCLC histologies, were all similarly sized with between approximately 120 and 150 patients per maintenance arm, and had primary endpoints of PFS. Neither achieved a statistically significant improvement in OS, although they were not powered to detect this difference.

PARAMOUNT [Paz-Ares *et al.* 2013] was a phase III study that evaluated pemetrexed as

Table 1. Summary of notable maintenance trials.

Study name	Patients (N)	Maintenance arms	PFS (months)	HR	p-value	OS (months)	HR	p-value	Reference
Continuation maintenance									
ECOG 4599	878*	(Carbo+Pac) Bev	6.2	0.66	<0.001	12.3	0.79	0.003	[Sandler <i>et al.</i> 2006]
FLEX	1125*	(Carbo+Pac)	4.5	0.94	0.39	10.3	0.871	0.004	[Pirker <i>et al.</i> 2009]
		(Cis+Vin) Cetux	4.8			11.3			
CECOG	352	(Cis+Vin)	4.8	<0.001		10.1		0.195	[Brodowicz <i>et al.</i> 2006]
		Gemcitabine BSC	3.6			13			
Belani	255		2.0			11	0.97	0.84	[Belani <i>et al.</i> 2010]
		Gemcitabine BSC	3.9			8.0			
IFCT-GFPC 0502	309		3.8	0.56	<0.001	9.3	0.89	0.3867	[Perol <i>et al.</i> 2012]
		Gemcitabine Observation	3.8			12.1			
PARAMOUNT	539		1.9	0.60	<0.001	10.8	0.78	0.0195	[Paz-Ares <i>et al.</i> 2013]
		Pemetrexed BSC	4.4			13.9			
			2.8			11.0			
Switch maintenance									
Fidias	309	Docetaxel	5.7		0.0001	12.3		0.0853	[Fidias <i>et al.</i> 2009]
		Second-line docetaxel	2.7			9.7			
JMEN	663	Pemetrexed	4.3	0.50	<0.0001	13.4	0.79	0.012	[Ciuleanu <i>et al.</i> 2009]
		Placebo	2.6			10.6			
SATURN	889	Erlotinib	3.0	0.71	<0.0001	12.0	0.81	0.0088	[Cappuzzo <i>et al.</i> 2010]
		Placebo	2.8			11.0			
IFCT-GFPC 0502	310	Erlotinib	2.9	0.69	0.003	11.4	0.87	0.3043	[Perol <i>et al.</i> 2012]
		Observation	1.9			10.8			
Combination maintenance									
ATLAS	768	Bev + Erlotinib	4.8	0.72	0.0012	15.9	0.90	0.2686	[Miller <i>et al.</i> 2009; Kabbinavar <i>et al.</i> 2010]
		Bevacizumab	3.7			13.9			
AVAPERL	253	Bev + Pem	10.2	0.58	<0.001	19.8	0.88	0.32	[Barlesi <i>et al.</i> 2013; Rittmeyer <i>et al.</i> 2013]
		Bevacizumab	6.6			15.9			
PointBreak	939*	(Carbo) Pem+Bev	12.6	1.00	0.949	6.0	0.83	0.012	[Patel <i>et al.</i> 2012]
		(Carbo+Pac) Bev	13.4			5.6			
PRONOUNCE	361*	(Carbo) Pem	4.4	1.06	0.610	10.5	1.07	0.616	[Zinner <i>et al.</i> 2013]
		(Carbo+Pac) Bev	5.5			11.7			
ECOG 5508	1282**	Bevacizumab Pemetrexed Bev + Pem	Currently enrolling patients [ClinicalTrials.gov identifier: NCT01107626]						

Bev, bevacizumab; BSC, best supportive care; Carbo, carboplatin; Cetux, cetuximab; Cis, cisplatin; HR, hazard ratio; NR, not reached; OS, overall survival; Pac, paclitaxel; Pem, pemetrexed; PFS, progression-free survival; Vin, vinorelbine.

*These studies were not randomized maintenance studies. Statistics reflect the comparison for the entire cohort of patients from time of enrollment prior to induction therapy. Chemotherapy in parentheses was used only during the induction phase of the trial.

**Projected accrual for ECOG 5508. This study is currently enrolling patients.

continuation maintenance therapy, having been used previously only as switch maintenance (see the description of the JMEN study in the following section). This study, the largest maintenance study conducted at the time, enrolled over 900 patients with nonsquamous NSCLC and randomized those with nonprogressive disease (539 patients) after four cycles of cisplatin and pemetrexed to maintenance pemetrexed *versus* best supportive care (BSC) in a 2:1 randomization in favor of pemetrexed. The final analysis confirmed that maintenance pemetrexed prolonged OS by 3 months compared with BSC (16.9 months *versus* 14 months; HR 0.78, $p = 0.019$).

Switch maintenance

The central premise of the switch maintenance strategy is the Goldie–Coldman hypothesis [Goldie and Coldman, 1979], which states that even small cancers harbor at least one drug-resistant clone. To overcome resistance, the use of different, non-cross-resistant chemotherapy regimens has been investigated. This hypothesis is the basis of maintenance trials in which patients with NSCLC are switched to a new, potentially non-cross-resistant agent if they respond or remain stable after initial chemotherapy. Many see this strategy as early second-line treatment, and this treatment paradigm is likely the most debated.

One of the first trials to demonstrate a benefit of maintenance with cytotoxic chemotherapy was a phase III study by Fidias and colleagues [Fidias *et al.* 2009] that randomized over 300 patients with advanced NSCLC to docetaxel immediately following four cycles of carboplatin and gemcitabine induction *versus* delayed docetaxel at the time of disease progression. Early docetaxel therapy resulted in a significant 3-month improvement in PFS ($p = 0.0001$). An OS improvement of approximately 2½ months did not reach statistical significance, possibly because the study was underpowered to detect an OS benefit shorter than 4 months. Toxicity and QOL were similar in both groups. Notably, approximately one-third of patients randomized to delayed docetaxel never received the intended second-line therapy due to disease progression, patient decision, or death. The patients who did receive docetaxel in the delayed treatment arm had similar OS as those treated in the immediate docetaxel arm.

Pemetrexed has been shown to be noninferior and better tolerated than docetaxel in the

second-line setting [Hanna *et al.* 2004]. Pemetrexed has also gained approval for the first-line setting of nonsquamous NSCLC based upon a phase III noninferiority study of cisplatin and pemetrexed *versus* cisplatin and gemcitabine (10.3 months OS in both arms) [Scagliotti *et al.* 2008]. However, in a preplanned subset analysis, survival in the 847 patients with adenocarcinoma was significantly prolonged with cisplatin plus pemetrexed compared to cisplatin plus gemcitabine (median 12.6 *versus* 10.9 months). Conversely, cisplatin plus gemcitabine was superior to cisplatin plus pemetrexed in the 473 patients with squamous cell carcinoma (SCC; median 10.8 *versus* 9.4 months).

JMEN, a landmark phase III study that evaluated maintenance pemetrexed and that began prior to the publication of the study by Scagliotti and colleagues, was the first to show an improvement in OS with maintenance therapy [Ciuleanu *et al.* 2009]. In this study, 663 patients with NSCLC who had completed induction chemotherapy with a platinum doublet without progression were enrolled and randomized to pemetrexed switch maintenance or BSC. No patients in this study received pemetrexed as part of their induction regimen because pemetrexed had not yet been shown to be effective in the first-line setting at the time of patient enrollment. These patients, approximately 25–30% of whom had SCC, were randomized in a 2:1 fashion to pemetrexed or BSC. OS was significantly longer in those receiving pemetrexed (13.4 *versus* 10.6 months; HR 0.79, $p = 0.012$). In subgroup analysis by histology, there was no difference in PFS or OS in those with SCC. The effect on those with nonsquamous NSCLC was even more dramatic, with an OS prolonged by nearly 5 months (15.5 *versus* 10.3 months; HR 0.70, $p = 0.002$). This study has been criticized because 82% of the patients on the BSC arm never received second-line pemetrexed, and many (33%) were not treated with any post-discontinuation therapy.

Erlotinib is appealing as a maintenance agent due to its oral administration and tolerability. Subsequent to the BR.21 study that identified an OS benefit for erlotinib in the second- or third-line setting for patients with NSCLC [Shepherd *et al.* 2005], two clinical trials have studied erlotinib as a single-agent maintenance strategy. SATURN was a phase III study that randomized 889 patients with nonprogressive disease after four cycles of chemotherapy to

maintenance erlotinib or placebo [Cappuzzo *et al.* 2010]. The use of erlotinib maintenance was associated with approximately 1-week and 1-month improvements in PFS and OS, respectively, and was well tolerated. These results were replicated in the IFCT-GFPC 0502 study, in which patients were randomized to maintenance gemcitabine (see the continuation maintenance section above), erlotinib, or placebo after four cycles of cisplatin and gemcitabine induction chemotherapy [Perol *et al.* 2012]. Those randomized to the erlotinib arm had a 1-month improvement in PFS when compared with placebo; an improved OS did not reach statistical significance. The erlotinib arm was approximately one-third the size of those receiving erlotinib in the SATURN trial, which could account for the reduced power to detect a statistically significant OS benefit.

Combination maintenance

The ATLAS trial studied the combination of bevacizumab and erlotinib as a maintenance strategy after the SATURN study had shown an improved PFS and OS with erlotinib alone [Miller *et al.* 2009; Kabbinar *et al.* 2010]. In ATLAS, patients received four cycles of platinum-based chemotherapy with bevacizumab and those with at least stable disease (SD) continued bevacizumab with or without erlotinib *versus* placebo. The trial enrolled 1160 patients and randomized 768 patients to maintenance therapy. The trial closed early after meeting its primary endpoint of improved PFS, which was prolonged by 1 month (4.8 *versus* 3.7 months, HR 0.72, $p = 0.0012$). A 1-month improvement in OS did not reach statistical significance. These results are consistent with SATURN results that show erlotinib improves PFS by approximately 1 month.

Given widespread adoption of bevacizumab for use as continuation maintenance, investigators were interested in combination with other tolerable agents. After Scagliotti and colleagues' study [Scagliotti *et al.* 2008], combination maintenance with pemetrexed became particularly intriguing. A phase II study proved the combination of pemetrexed and bevacizumab maintenance was safe and resulted in a 14.1 month median OS [Patel *et al.* 2009]. Combination maintenance with these two drugs was carried forward as a maintenance strategy in three important phase III studies, AVAPERL, PointBreak, and ECOG 5508.

AVAPERL was the first of these combination maintenance studies to report interim PFS results at ESMO 2011 [Barlesi *et al.* 2011, 2013]. This smaller European study enrolled 376 patients and randomized them to maintenance pemetrexed plus bevacizumab (Pem-Bev) or bevacizumab alone after platinum, pemetrexed, and bevacizumab (PPemBev) induction. Those receiving Pem-Bev maintenance had a significantly prolonged PFS of 3.6 months (10.2 *versus* 6.6 months, HR 0.58, $p < 0.001$), but OS results did not reach statistical significance (19.8 *versus* 15.9 months, HR 0.88, $p = 0.32$) [Rittmeyer *et al.* 2013].

PointBreak randomized patients to carboplatin, paclitaxel, and bevacizumab followed by bevacizumab maintenance (the ECOG 4599 regimen) *versus* PPemBev followed by Pem-Bev maintenance (the PointBreak regimen) [Patel *et al.* 2012]. OS was identical between the two arms (13.4 *versus* 12.6 months, HR 1.00, $p = 0.95$). PFS favored the PPemBev arm, but the improvement was less than 1 month. The important findings of this study were the notable differences in toxicity profile between the ECOG 4599 and PointBreak regimens. Those receiving ECOG 4599 experienced more neutropenia and peripheral neuropathy; those treated with PointBreak were found to have more anemia, thrombocytopenia, and fatigue. A preplanned analysis comparing the two maintenance strategies for those with nonprogressive disease demonstrated a 2-month improvement in OS (17.7 *versus* 15.7 months) for patients receiving maintenance in the PPemBev arm [Patel *et al.* 2013].

PRONOUNCE, a smaller study with a similar approach to PointBreak, enrolled 361 patients and randomized them to carboplatin and pemetrexed followed by maintenance pemetrexed *versus* carboplatin, paclitaxel, and bevacizumab followed by bevacizumab [Zinner *et al.* 2013]. The primary endpoint of this study was PFS without grade 4 toxicity (GFPFS). The study did not meet its primary endpoint and there were no differences in PFS or OS between the arms, although the study was underpowered to detect differences in PFS or OS.

ECOG 5508 [ClinicalTrials.gov identifier: NCT01107626] is the most important ongoing maintenance study at this time currently enrolling patients. This study plans to enroll 1282 patients with nonsquamous NSCLC with carboplatin,

paclitaxel, and bevacizumab induction followed by randomization into three maintenance arms: (1) pemetrexed alone, (2) bevacizumab alone, or (3) combined Pem-Bev. This study will effectively evaluate most previously successful maintenance methods: continuation bevacizumab, switch pemetrexed, and combination therapy.

Clinical implications

Although many of the trials discussed previously have proven maintenance chemotherapy is an effective strategy for patients with metastatic NSCLC, this is not applicable to all patients. In nearly every trial, a significant proportion of patients are not eligible for maintenance therapy. In general, this is due to progressive disease or death. For example, in the PARAMOUNT study [Paz-Ares *et al.* 2013] only 539 of 939 (57%) of patients enrolled continued to randomization for the maintenance phase. A total of 23% of patients had progressive disease during induction, 7% had adverse events, and 6% died. These results are consistent with other trials. In PointBreak [Patel *et al.* 2012] 349 of 939 patients (37%) did not receive maintenance. In this group of patients, there was no difference in PFS (2.53 months in each arm), but OS favored the ECOG4599 arm (6.1 *versus* 4.7 months) over the PPemBev arm. Patients with progressive disease should not be treated with maintenance therapy but should proceed to second-line chemotherapy, if applicable. Even when excluding patients with progressive disease, serious adverse events, or toxicity, other factors should be considered when trying to determine which patients would derive the most benefit from maintenance therapy. Some of the important factors include histology, molecular status, response to first-line therapy, QOL, and economic considerations [Gerber and Schiller, 2013].

Histology

Since the recognition that the benefit of pemetrexed is limited to nonsquamous NSCLC [Scagliotti *et al.* 2008], histology has become an important consideration in all patients with NSCLC. In JMEN, where unselected patients were treated with pemetrexed, patients with SCC had no benefit from maintenance therapy in subset analysis [Ciuleanu *et al.* 2009]. All subsequent pemetrexed maintenance trials have included only patients with nonsquamous NSCLC. Therefore, a pemetrexed maintenance

strategy, whether with continuation or switch maintenance, is only applicable to patients with nonsquamous NSCLC. The efficacy of maintenance with gemcitabine or erlotinib may be less contingent upon histology and have broader applicability.

In a meta-analysis of the three maintenance trials that studied erlotinib, SATURN, ATLAS, and IFCT-GFPC 0502, all subgroups of patients, including those with SCC, derive a benefit in PFS (all histology: HR 0.76, $p < 0.00001$; nonsquamous NSCLC: HR 0.71, $p < 0.00001$; SCC: HR 0.83, $p = 0.02$) [Petrelli *et al.* 2011]. However, data from SATURN and IFCT-GFPC 0502 suggest the benefit may be smaller in those with squamous histology. In SATURN, there was an OS benefit only in patients with adenocarcinoma, and the PFS benefit appears to have been more profound in those with nonsquamous NSCLC (HR 0.60; 95% confidence interval [CI] 0.48–0.75) compared with those with SCC (HR 0.76; 95% CI 0.60–0.95), although the study was not powered to compare these two groups [Cappuzzo *et al.* 2010]. The PFS difference between these two subgroups (HR 0.60 *versus* 0.76), however, is likely not clinically significant because a HR of 0.71 for the larger cohort correlated to a difference in PFS of only 1 week. Unlike the SATURN trial, in the IFCT-GFPC 0502 trial, subgroup univariate analysis demonstrated that patients with SCC did not have a significant benefit in PFS when treated with erlotinib maintenance compared to placebo (HR 0.79; 95% CI 0.53–1.19) [Perol *et al.* 2012]. Neither patients with adenocarcinoma nor SCC had improved OS in this analysis.

Molecular characteristics

Mutation status has been shown to impact effectiveness of epidermal growth factor receptor (EGFR)-targeted therapies, but erlotinib was initially studied and gained approval for second-line and maintenance treatment in unselected patients. The INTEREST and TITAN studies demonstrated no difference in outcomes between gefitinib or erlotinib and chemotherapy in the second-line setting [Kim *et al.* 2008; Ciuleanu *et al.* 2012]; however, these studies did not require EGFR mutation testing, which could have skewed results by having EGFR-mutated patients in the EGFR directed therapy arms. Similarly, the SATURN trial demonstrated that PFS and OS were prolonged for all patients receiving

maintenance erlotinib compared with placebo, regardless of the presence or absence of EGFR-activating mutations. However, it is worth noting that nearly 50% of the patients enrolled in SATURN had missing or indeterminate EGFR mutation testing, making the results difficult to interpret [Cappuzzo *et al.* 2010]. It is now recommended that all patients with nonsquamous NSCLC have their tumor tested for EGFR-activating mutations at the time of diagnosis, so treating patients with unknown EGFR mutation status is uncommon.

More recent studies have highlighted the lack of benefit of erlotinib for patients without EGFR mutations. The TAILOR trial, which was presented in abstract form at ASCO 2012, compared erlotinib and docetaxel as options for second-line therapy in EGFR-wild-type patients [Garassino *et al.* 2012]. In this study, those receiving erlotinib had a significantly lower response rate (RR) and PFS than those receiving docetaxel (RR, 2.2% *versus* 13.9%, $p = 0.004$; 6-month survival, 16% *versus* 28%, HR, 0.70, $p = 0.016$). Overall survival data have not been reported. This trial has been criticized because it showed unprecedented response rates to second-line docetaxel with 4% of patients achieving a complete response (CR), which suggests the results should not be generalized to other patient populations. A phase III non-inferiority trial, TORCH, evaluated the use of erlotinib in the first-line setting before cisplatin–gemcitabine in an unselected population and found that first-line erlotinib resulted in inferior median OS (11.6 *versus* 8.7 months; HR 1.24) to chemotherapy followed by erlotinib [Gridelli *et al.* 2012a].

Response to first-line therapy

Response to first-line therapy may be an indicator for how much benefit a patient will derive from maintenance therapy. In the SATURN trial, patients with SD after first-line chemotherapy had a significant improvement in OS with maintenance erlotinib, whereas those with partial response (PR) or CR did not [Cappuzzo *et al.* 2010]. Interestingly, data from a meta-analysis combining patients from SATURN and IFCT-GFPC 0502 show that both subsets of patients had improved PFS with erlotinib [Petrelli *et al.* 2011]. It is difficult to understand how patients with SD could have an improved OS without improved PFS without a confounding factor, such as a difference in disease characteristics or

second-line treatments. Exploratory subgroup analysis from the IFCT-GFPC 0502 trials suggested that there was no difference in PFS or OS based on disease response to first-line chemotherapy for those receiving erlotinib, but there may have been an OS advantage for patients receiving gemcitabine who had an objective response to first-line chemotherapy [Perol *et al.* 2012]. In PARAMOUNT, a similar subgroup analysis suggests there may be a larger benefit for patients with responsive disease after first-line chemotherapy [Paz-Ares *et al.* 2013]. Unfortunately, these subgroup analyses from SATURN, IFCT-GFPC 0502, and PARAMOUNT are simply exploratory, and the 95% CIs of the subgroups are overlapping in all cases. In AVAPERL, there were no differences based on response to first-line chemotherapy [Barlesi *et al.* 2013]. Complete data from PointBreak have not yet been reported, but the importance of response to first line chemotherapy is unlikely to be determined unless a maintenance trial is designed to answer this question. In keeping with these conflicting results, the United States Food and Drug Administration (FDA) has approved maintenance erlotinib for all patients who have not progressed after induction chemotherapy. In contrast, the European Medicines Agency (EMA) has only approved maintenance erlotinib for patients with SD.

Performance status

PS is a strong prognostic factor and is predictive of survival benefit and toxicity from chemotherapy [Schiller *et al.* 2002]. Several studies have evaluated the effect of PS on outcomes for maintenance therapy. In the CECOG trial, the improvement in OS with maintenance gemcitabine did not reach statistical significance, but subgroup analysis based on PS revealed that patients with a Karnofsky Performance Status (KPS) >80 had a significantly improved OS on the gemcitabine maintenance arm [Brodowicz *et al.* 2006]. In the trial from Fidias and colleagues [Fidias *et al.* 2009], patients with PS 2 were included, but made up only about 10% of the patients enrolled. One of the major reasons for failure to receive docetaxel in the delayed dose arm was clinical deterioration. Although there was no subgroup analysis reported, a higher proportion of patients with PS 2 (10.3% *versus* 5.9%) were in the delayed docetaxel arm, which may have contributed to differences between the two groups. Patients with PS 0 in the IFCT-GFPC 0502 trial had the greatest

benefit from gemcitabine or erlotinib maintenance [Perol *et al.* 2012]. Those with PS 1–3 did not have a statistically significant improvement in OS. Most other maintenance studies have excluded patients with PS 2. Based on the subgroup analyses of these studies, patients with worse PS appear to have less significant survival benefits, and those with PS 2 should not receive maintenance therapy.

Quality of life

Maintenance chemotherapy has been shown to improve PFS or OS in many clinical trials, but most studies have demonstrated improvements of only 1–3 months. Given only modest improvements in PFS or OS, QOL during this time becomes critical for evaluating the utility of maintenance therapy. On the one hand, giving continual therapy provides an opportunity for additional treatment exposure and prevention of a more rapid deterioration in health that could preclude some patients from receiving second-line therapy. On the other hand, tying patients to continual therapy, whether intravenous infusions every 3 weeks or daily oral medications, prevents patients from enjoying a chemotherapy holiday they might otherwise have had if they chose to forgo maintenance therapy.

Several maintenance trials have incorporated QOL analysis into their design, often using the Lung Cancer Symptoms Scale (LCSS), a validated instrument used to assess symptom burden and impact on QOL in patients with lung cancer [Hollen *et al.* 1994]. The Fidias and colleagues study compared LCSS scores and concluded that there was no difference in QOL between those receiving immediate docetaxel *versus* delayed docetaxel treatment [Fidias *et al.* 2009]. Patients treated on the JMEN study also completed a symptom assessment with each cycle of chemotherapy from the time of randomization. On this study, however, instead of comparing LCSS scores directly, the time to worsening symptoms, defined as a 15 mm decrease on the visual scale, was compared between the two arms [Belani *et al.* 2012]. For most symptoms, there were no differences in time to worsening of symptoms or overall QOL between the pemetrexed and placebo groups. However, those receiving maintenance pemetrexed had significantly longer time before worsening of pain and hemoptysis symptoms. Although there was no difference in time to developing loss of appetite, patients receiving

pemetrexed had a larger degree of loss of appetite while receiving chemotherapy.

The PARAMOUNT study reported QOL using the EQ-5D instrument, a two-part questionnaire that gauges a patient's health status with descriptive questions and a visual analog scale [Gridelli *et al.* 2012b]. The investigators found no statistical difference in EQ-5D scores between the maintenance pemetrexed and BSC groups.

Patients on the SATURN study were given Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaires, an instrument validated to assess physical function and well-being, every 6–12 weeks or until progression while on study [Juhasz *et al.* 2013]. There were no differences in time to symptom progression, deterioration, or time to deterioration in trial outcome index between the erlotinib and placebo maintenance groups. There was a significant delay in the time to pain and analgesic use in those receiving erlotinib maintenance.

Based on these multiple QOL analyses accompanying their respective trials, it appears that QOL is not significantly worse with maintenance therapy and may delay the time to pain or other disease-related symptoms. Unlike earlier studies that show an improvement in QOL with chemotherapy for metastatic NSCLC [Non-Small Cell Lung Cancer Collaborative Group, 1995; Cullen *et al.* 1999; Spiro *et al.* 2004], there is no evidence that additional maintenance therapy improves QOL. It is likely, however, that our QOL tools are crude at best, and subtle toxicities are not reflected as major deterioration.

Cost and healthcare utilization

Prior to the use of maintenance therapy in lung cancer, patients with SD after four to six cycles of chemotherapy were routinely observed until progression. The additional therapy during this period has been shown to have modest improvements in PFS and OS, but significantly increased financial cost. In the United States, US\$2.8 trillion per year is spent on healthcare, and growth of healthcare spending is expected to outpace the gross domestic product (GDP) and increase to as much as 40% of federal healthcare spending in the next 25 years [Emanuel *et al.* 2012]. There has been significant political focus on ways to contain healthcare spending, including increases in the transparency of cost and quality of care.

Several cost-effective analyses of maintenance pemetrexed have been conducted using the JMEN trial as a model in the United States, United Kingdom, Switzerland, and Japan. The US study used maximum Medicare reimbursement rates for pemetrexed in 2009 and other direct NSCLC costs from a claims database to calculate the cost of maintenance pemetrexed without dose reductions or delays [Klein *et al.* 2010]. The investigators concluded that for patients with nonsquamous NSCLC, the incremental cost-effectiveness ratio (ICER) per life-year gained of maintenance pemetrexed was US\$122,371, just below the accepted US standard of renal hemodialysis, which has an ICER of US\$129,090 [Lee *et al.* 2009]. A similar cost-effective analysis was conducted using the JMEN results and the Swiss healthcare system as a model and determined the ICER was €106,202 (approximately US\$139,000), above the nationally accepted willingness to pay (WTP) threshold in Switzerland of €72,000 [Matter-Walstra *et al.* 2012]. Interestingly, maintenance pemetrexed was approved by the United Kingdom's National Institute for Health and Clinical Excellence (NICE) based on an estimated ICER of £47,000 (approximately US\$72,000) [Learn and Bach, 2010]. Finally, a Japanese analysis concluded the ICER for maintenance pemetrexed was US\$150,115. This ratio was above the Japanese threshold of US\$43,478. The differences between the ICER in the UK and in other countries may be accounted for by the difference in the cost of pemetrexed in the UK. The Swiss cost-effectiveness study found the main driver of the high ratio was cost of the drug; using the cost of pemetrexed as available in the UK, they found the ICER was reduced to €68,886, which is below the Swiss WTP threshold of €72,000 [Matter-Walstra *et al.* 2012].

One cost-effective analysis has been conducted for continuation maintenance pemetrexed based on the PARAMOUNT results in a Chinese healthcare system model [Zeng *et al.* 2013]. This study found the ICER to be US\$124,793, similar to the US and Swiss studies for switch maintenance pemetrexed. The study concluded that the ICER was significantly higher than the World Health Organization's (WHO) recommendation for a threshold of three times the country's per-capita GDP, which ranges from approximately US\$7500 to US\$40,000, depending on geography. Therefore, maintenance pemetrexed was determined not to be cost effective for use in

China. In conclusion, the variance in ICER for maintenance pemetrexed between different countries is largely attributed to differences in drug costs. The threshold to determine cost-effectiveness may also vary from country to country depending on the national standards and relative wealth of its citizens.

Conclusion

Maintenance therapy has become a strategy that can lead to an improvement in PFS and OS in select patients with advanced NSCLC with non-progressive disease after four to six cycles of induction chemotherapy. Other patient populations, such as those with SCC, could also benefit from maintenance therapy. Maintenance strategies do not appear to have adverse effects on a patient's QOL and could delay disease-related symptoms. It is clear that maintenance therapy will not benefit all patients. However, there is a need to better identify subgroups of patients who will garner clinically meaningful benefit from this treatment strategy. Further studies should evaluate patient willingness to receive maintenance therapy, should focus on surveillance algorithms for those who decide not to have maintenance therapy, and also should continue to analyze cost. Ultimately, the decision to use maintenance chemotherapy requires a nuanced discussion between the patient and physician that adequately assesses benefits of prolonged therapy and impact in terms of toxicity, QOL, and financial cost.

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Conflict of interest statement

Dr Gentzler has no conflicts of interest to disclose. Dr Patel has no financial conflicts of interest to disclose, but was the principal investigator on a phase II trial [Patel *et al.* 2009] and the phase III PointBreak trial [Patel *et al.* 2012, 2013], which are discussed at length in this review.

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