VOLUME 31 · NUMBER 8 · MARCH 10 2013

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Maintenance Chemotherapy for Advanced Non–Small-Cell Lung Cancer: New Life for an Old Idea

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Published online ahead of print at www.jco.org on February 11, 2013.

Supported by a National Institutes of Health Clinical and Translational Science Award North and Central Texas Clinical and Translational Science Initiative (No. KL2RR024983) and National Cancer Institute Clinical Investigator Team Leadership Award (No. 1P30 CA142543-01 supplement; D.E.G.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/13/3108-1009/$20.00

DOI: 10.1200/JCO.2012.43.7459

ABSTRACT

Although well established for the treatment of certain hematologic malignancies, maintenance therapy has only recently become a treatment paradigm for advanced non–small-cell lung cancer. Maintenance therapy, which is designed to prolong a clinically favorable state after completion of a predefined number of induction chemotherapy cycles, has two principal paradigms. Continuation maintenance therapy entails the ongoing administration of a component of the initial chemotherapy regimen, generally the nonplatinum cytotoxic drug or a molecular targeted agent. With switch maintenance (also known as sequential therapy), a new and potentially non–cross-resistant agent is introduced immediately on completion of first-line chemotherapy. Potential rationales for maintenance therapy include increased exposure to effective therapies, decreasing chemotherapy resistance, optimizing efficacy of chemotherapeutic agents, antiangiogenic effects, and altering antitumor immunity. To date, switch maintenance therapy strategies with pemetrexed and erlotinib have demonstrated improved overall survival, resulting in US Food and Drug Administration approval for this indication. Recently, continuation maintenance with pemetrexed was found to prolong overall survival as well. Factors predicting benefit from maintenance chemotherapy include the degree of response to first-line therapy, performance status, the likelihood of receiving further therapy at the time of progression, and tumor histology and molecular characteristics. Several aspects of maintenance therapy have raised considerable debate in the thoracic oncology community, including clinical trial end points, the prevalence of second-line chemotherapy administration, the role of treatment-free intervals, quality of life, economic considerations, and whether progression-free survival is a worthy therapeutic goal in this disease setting.

J Clin Oncol 31:1009-1020. © 2013 by American Society of Clinical Oncology

INTRODUCTION

Although only recently accepted as a treatment strategy for advanced non–small-cell lung cancer (NSCLC), maintenance chemotherapy has been used in the treatment of other cancers, particularly hematologic malignancies, for years. In both adult and pediatric acute lymphocytic leukemia, for instance, a 2-year regimen of weekly methotrexate, daily mercaptopurine, and vincristine and prednisone pulses every 3 months after induction and consolidation therapy seems to increase cure rates.[1,2] Maintenance rituximab has been studied extensively in follicular non-Hodgkin lymphoma, where it increases 2-year complete response rates from 52% to 72% when given after first-line induction therapy and increases overall survival (OS) when administered in the setting of relapsed or refractory disease.[3,4] In multiple myeloma, maintenance lenalidomide after autologous stem-cell transplantation increases progression-free survival (PFS) and OS.[5]

Historically, evaluation and uptake of maintenance chemotherapy have been less widespread for solid tumors. In breast cancer, maintenance chemotherapy improves PFS but not OS.[6] In metastatic colorectal cancer—a disease for which chemotherapy typically yields radiographic response rates, PFS, and OS approximately twice those achieved in advanced NSCLC—a strategy of stopping treatment after 12 weeks of first-line chemotherapy and resuming the same regimen at the time of progression is associated with similar OS and less toxicity than continuous treatment.[7,8] In advanced ovarian cancer, maintenance paclitaxel and maintenance bevacizumab increase PFS.[9-11] Among thoracic malignancies, small-cell lung cancer, a more chemotherapy-sensitive disease than NSCLC, has been the setting for several clinical trials of maintenance chemotherapy over the last three decades. Two systematic reviews of this strategy have been performed.[12,13] One concluded the individual trials lacked sufficient quality for quantitative analysis.[12] The other, a meta-analysis of 14 trials encompassing 2,550 individual patients, reported a significant improvement in 1-year OS (odds ratio, 0.67; 95% CI, 0.56 to 0.78; $P < .001$; corresponding to an increase in 1-year OS from 30% to 39%) and 2-year OS (odds ratio, 0.67; 95% CI,

0.53 to 0.86; $P < .001$; corresponding to an increase in 2-year OS from 10% to 14%).[13] A maintenance therapy strategy has also been applied to locally advanced NSCLC. For unclear reasons, the administration of the epidermal growth factor receptor (EGFR) inhibitor gefitinib after concurrent chemoradiotherapy with cisplatin-etoposide and consolidation docetaxel was associated with substantially inferior OS (median OS, 23 months *v* 35 months for maintenance placebo; $P = .013$).[14]

In advanced NSCLC, the goal of maintenance therapy is to prolong a favorable clinical state after delivery of first-line platinum-based combination chemotherapy. Clinical trials have demonstrated that administration of platinum doublet regimens until disease progression is associated with increased toxicity but no improvement in OS compared with administration of a prespecified number (generally four or six) of treatment cycles.[15] Thus, until recently, the standard approach to this disease included attaining maximal tumor shrinkage with four to six cycles of first-line platinum-based chemotherapy and then discontinuing therapy until evidence of disease progression. To maintain quality of life and permit prolonged treatment administration, contemporary studies of maintenance therapy generally use well-tolerated, single-agent regimens. The following two treatment paradigms have emerged: continuation maintenance and switch maintenance. Continuation maintenance therapy entails the ongoing administration of a component of the initial chemotherapy regimen, either the nonplatinum cytotoxic drug or a molecular targeted agent. With switch maintenance, a new and potentially non–cross-resistant agent is introduced immediately after completion of first-line chemotherapy. Although maintenance therapy for advanced NSCLC is now US Food and Drug Administration approved and widely practiced, several aspects of this strategy have raised considerable debate in the thoracic oncology community, including clinical trial end points and design, the prevalence of second-line chemotherapy administration, the role of treatment-free intervals, quality of life, economic considerations, and whether PFS is a worthy therapeutic goal in this disease setting.

RATIONALE FOR MAINTENANCE THERAPY

Table 1 lists selected clinical and biologic rationales for maintenance therapy. A switch maintenance therapy paradigm increases exposure to effective, non–cross-resistant therapies. Although sometimes called early second-line therapy, this is not entirely accurate, because second-line therapy implies that the patient has experienced progression after first-line therapy. Despite the fact that second-line chemotherapy is proven to extend OS in advanced NSCLC,[27-29] only approximately 20% to 80% of patients who achieve disease control after four cycles of first-line chemotherapy ever receive second-line therapy at the time of progression.[16,30-33] The wide-ranging and, in some instances, low rates of second-line therapy administration have been attributed to variations in performance status, the frequency and nature of clinical and radiographic follow-up, local practice patterns, and the possibility of rapid clinical decline precluding further treatment. With switch maintenance, effective drugs are delivered to a substantially higher proportion of patients, generally more than 90%.[16,17] Switch maintenance therapy may also decrease chemotherapy resistance. The Goldie and Coldman hypothesis states that resistant clones emerge and increase in number as tumors grow.[18] It follows that cancers would be more sensitive to a new agent at the time of maximum tumor shrinkage than they would at the time of subsequent progression. The Norton-Simon hypothesis states that solid tumors are composed of distinct populations of faster growing cells, which are sensitive to therapy, and slower growing, more resistant cells.[19,20,34] Thus, the administration of sequential, non–cross-resistant regimens is required to achieve maximum antitumor effect. Antiangiogenic effects may be seen not only with agents targeting vascular endothelial growth factor (VEGF) or the VEGF receptor, but also with metronomic chemotherapy.[21-23] In a metronomic schedule, cytotoxic agents are administered at lower doses and more frequent intervals (eg, weekly paclitaxel). Metronomic chemotherapy may also augment antitumor responses via effects on regulatory T cells.[25]

CLINICAL EXPERIENCE WITH MAINTENANCE THERAPY IN ADVANCED NSCLC

Continuation of Platinum-Based Doublet Therapy

Initial studies examining treatment duration in advanced NSCLC examined the role of prolonging administration of first-line platinum-based combination chemotherapy (Table 2). These trials differ with regard to the regimen under study, as well as the number of cycles in the standard and prolonged administration arms. Most of the

Table 1. Clinical and Biologic Rationales for Maintenance Chemotherapy

Rationale	Explanation
Increase exposure to effective therapies	At time of disease progression, only 20%–80% of patients with advanced NSCLC receive potentially effective second-line therapies. With a switch maintenance (ie, sequential or early second-line) strategy, > 90% of eligible patients receive the intended therapy.[16,17]
Decrease chemotherapy resistance	Because resistance depends on spontaneous mutations and therefore increases with time (Goldie and Coldman hypothesis), early use of non–cross-resistant therapies may increase the likelihood of killing more cancer cells before resistance develops.[18]
Maximize antitumor efficacy of therapy	Solid tumors are composed of faster growing cells, which are sensitive to therapy, and slower growing, more resistant cells (Norton-Simon hypothesis). Maximum antitumor effect is therefore achieved with sequential, non–cross-resistant regimens.[19,20]
Antiangiogenic effects	Metronomic (ie, low-dose, continuous) chemotherapy reduces tumor blood vessel formation via direct cytotoxic effects on endothelial cells; altering the balance of angiogenic growth factors and inhibitors; and effects on recruitment of bone marrow–derived endothelial progenitor cells. Cytotoxic agents with antiangiogenic effects in preclinical models include cyclophosphamide, doxorubicin, taxanes, and vinca alkaloids, among others.[21-24]
Alter antitumor immunity	Metronomic (ie, low-dose, continuous) chemotherapy decreases $CD4^+CD25^+$ regulatory T cells, in turn augmenting antitumor immune responses. Immunomodulatory effects have been seen with prolonged, low-dose administration of alkylating agents such as cyclophosphamide and temozolomide.[25,26]

Abbreviation: NSCLC, non–small-cell lung cancer.

Table 2. Selected Phase III Trials of Platinum-Based Combination Chemotherapy Duration

Trial	Year	Treatment	No. of Patients	% of Patients Completing Treatment	Second-Line Therapy (% of patients)	PFS		OS	
						Median	*P*	Median	*P*
Smith et al[35]	2001	MVP × 3 cycles	155	72	NR	5 months	.4	6 months	.2
		MVP × 6 cycles	153	31	NR	5 months		7 months	
Socinski et al[15]	2002	CP × 4 cycles	114	57	42 (single-agent paclitaxel)	NR	—	6.6 months	.63
		CP until PD	116	—	47 (single-agent paclitaxel)	NR		8.5 months	
von Plessen et al[36]	2006	Carboplatin AUC 5 on day 1 and vinorelbine 25 mg/m^2 on days 1 and 8 every 21 days × 3 cycles	150	78	12	16 weeks	.21	28 weeks	.75
		Carboplatin AUC 5 on day 1 and vinorelbine 25 mg/m^2 on days 1 and 8 every 21 days × 6 cycles	147	54	10	21 weeks		32 weeks	
Park et al[37]	2007	Third-generation platinum doublet* × 4 cycles	156	92	74	4.6 months	.001	15.9 months	.46
		Third-generation platinum doublet* × 6 cycles	158	68	63	6.2 months		14.9 months	
Barata et al[38]	2007	Carboplatin-gemcitabine × 4 cycles	110	Median No. of cycles = 3.5	14 (docetaxel)	4 months	.08	7 months	.05
		Carboplatin-gemcitabine × 6 cycles	110	Median No. of cycles = 4.8	15 (docetaxel)	5 months		12 months	

Abbreviations: AUC, area under the curve; CP, carboplatin AUC 6 and paclitaxel 200 mg/m^2 every 21 days; MVP, mitomycin 8 mg/m^2 (courses 1, 2, 4, and 6), vinblastine 6 mg/m^2, and cisplatin 50 mg/m^2 every 21 days; NR, not reported; OS, overall survival; PD, progressive disease; PFS, progression-free survival.
*Cisplatin 70 mg/m^2 on day 1 plus either paclitaxel 175 mg/m^2 on day 1 or docetaxel 75 mg/m^2 on day 1 or gemcitabine 1,000 mg/m^2 on days 1 and 8 every 21 days.

studies compared either three or four cycles of first-line chemotherapy with six cycles of first-line chemotherapy, with only one trial evaluating the continuation of therapy until progression.[15] With the exception of a recent study presented in abstract form,[38] these studies have demonstrated similar OS between both treatment arms, less toxicity with shorter duration chemotherapy, and either equivalent or superior quality of life with shorter duration chemotherapy.[15,35-37] Across studies, because of toxicity or disease progression, only 31% to 68% of patients in the longer duration treatment arms received the full number of intended chemotherapy cycles. In the trial comparing a maximum of four cycles of carboplatin-paclitaxel with the same regimen until progression, up to 19 cycles of chemotherapy were administered in the indefinite therapy arm, but the median number of cycles was four in both arms.[15] The rate of grade 2 to 4 neuropathy increased from 20% after four cycles to 43% after eight cycles, and by 25 weeks, quality of life deteriorated among patients assigned to indefinite therapy ($P = .02$).

Continuation Maintenance Therapy

Continuation maintenance strategies have been conducted using nonplatinum cytotoxic agents or molecular targeted therapies such as VEGF and EGFR inhibitors. Table 3 lists selected phase III clinical trials of continuation maintenance with cytotoxic agents, including paclitaxel, gemcitabine, and pemetrexed. In these studies, between 34% and 65% of enrolled patients were ultimately randomly assigned to maintenance therapy,[39,43] suggesting that toxicities, decline in functional status, and/or disease progression preclude consideration of maintenance therapy in a substantial proportion of patients who initiate first-line platinum-based chemotherapy. The proportion of randomly assigned patients receiving subsequent therapy at the time of progression ranged from 16% to 76%.[30,33] This wide variation reflects study design (with some trials mandating and specifying subsequent therapy and others leaving the decision to the individual investigator) and differences in population performance status. For example, in a phase III trial of continuation maintenance gemcitabine after completion of four cycles carboplatin-gemcitabine, 56% of patients in the gemcitabine arm and 58% of patients in the best supportive care arm had an Eastern Cooperative Oncology Group (ECOG) performance status of ≥ 2.[30] On the basis of histology-restricted efficacy in subset analysis of first-line, switch maintenance and second-line clinical trials of pemetrexed,[17,29,44] enrollment onto the three studies of continuation maintenance pemetrexed (PARAMOUNT, Point Break, and AVAPERL) was restricted to patients with nonsquamous tumors. To date, only the PARAMOUNT study (cisplatin-pemetrexed for four cycles followed by pemetrexed monotherapy) has demonstrated an OS benefit. The lack of OS benefit seen thus far in other continuation maintenance trials may arise from enrollment of patients with poor functional status and from aspects of trial design. With PFS as the primary end point, these studies may be underpowered to detect differences in OS.

In advanced NSCLC, no clinical trial provides direct evidence of the effect of continuation maintenance therapy with targeted agents. In first-line studies of bevacizumab, cetuximab, erlotinib, or gefitinib combined with chemotherapy, these drugs were continued as monotherapy after completion of six cycles of combination therapy in all patients without unacceptable toxicity or disease progression.[45-53] Because the comparator arm was doublet chemotherapy without any maintenance therapy (rather than a three-drug induction arm without the maintenance targeted agent), it is not possible to determine the extent to which maintenance therapy contributed to clinical benefit. On the basis of experience in numerous clinical trials, it does seem that this approach is feasible

Table 3. Selected Phase III Trials of Continuation Maintenance Therapy

Trial	Year	Induction Therapy: Regimen	Induction Therapy: No. of Patients	Maintenance Therapy: Regimen	Maintenance Therapy: No. of Patients	Therapy at Progression (poststudy therapy; % of patients)	PFS: Median	PFS: *P*	OS: Median	OS: *P*
Belani et al[39]	2003	CP regimens* for 16 weeks	401	Paclitaxel 70 mg/m^2 weekly, 3 of 4 weeks	65	47 (not specified by arm)	38 weeks	NR	75 weeks	NR
				Observation	65		29 weeks		60 weeks	
CECOG[40]	2006	Cisplatin 80 mg/m^2 on day 1 plus gemcitabine 1,250 mg/m^2 on days 1 and 8 every 21 days × 4 cycles		Gemcitabine 1,250 mg/m^2 on days 1 and 8 every 21 days + BSC	138	57	6.6 months (3.6 months†)	< .001	13.0 months (10.2 months†)	.195
				BSC	68	57	5.0 months (2.0 months†)		11.0 months (8.1 months†)	
Belani et al[30]	2010	Carboplatin AUC 5 on day 1 plus gemcitabine 1,000 mg/m^2 on days 1 and 8 every 21 days × 4 cycles	519	Gemcitabine 1,000 mg/m^2 on days 1 and 8 every 21 days + BSC	128	16	3.9 months† (7.4 months)	.58	8.0 months	.84
				BSC	127	17	3.8 months† (7.7 months; HR, 1.09)		9.3 months (HR, 1.97)	
IFCT-GFPC 0502[33]‡	2010	Cisplatin 80 mg/m^2 on day 1 plus gemcitabine 1,250 mg/m^2 on days 1 and 8 every 3 weeks × 4 cycles	834	Gemcitabine 1,250 mg/m^2 on days 1 and 8 every 3 weeks	154	68 (60% pemetrexed [8% RR])	3.8 months	< .001	Median not reported (HR, 0.91)	NR
				Observation	155	82 (76% pemetrexed [15% RR])	1.9 months (HR, 0.58)			
PARAMOUNT[42]§	2012	Cisplatin 75 mg/m^2 plus pemetrexed 75 mg/m^2 every 21 days × 4 cycles	939	Pemetrexed 500 mg/m^2 every 21 days + BSC	359	64 (various)	4.1 months†	< .001	16.9 months	.019
				Placebo + BSC	180	72 (various)	2.8 months† (HR, 0.62; 95% CI, 0.49 to 0.79)		14.0 months (HR, 0.78; 95% CI, 0.64 to 0.96)	
AVAPERL[43]§	2011	Cisplatin 75 mg/m^2 and pemetrexed 500 mg/m^2 + bevacizumab 7.5 mg/kg × 4 cycles	376	Pemetrexed 500 mg/m^2 plus bevacizumab 7.5 mg/kg every 3 weeks	125	NR	10.2 months	< .001	NR	.23
				Bevacizumab 7.5 mg/kg every 3 weeks	120	NR	6.6 months (HR, 0.5)		15.7 months (HR, 0.75)	
Point Break (JHMD)[43a]§	Ongoing	Carboplatin AUC 6 and paclitaxel 200 mg/m^2 + bevacizumab 15 mg/kg × 4 cycles	900	Bevacizumab 15 mg/kg every 3 weeks	467		5.6 months	.012	13.4 months	.95
		Carboplatin-pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg × 4 cycles		Pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg every 3 weeks	472		6.0 months (HR, 0.83; 95% CI, 0.70 to 0.96)		12.6 months (HR, 1.00; 95% CI, 0.86 to 1.16)	

Abbreviations: AUC, area under the curve; BSC, best supportive care; CECOG, Central European Cooperative Oncology Group; CP, carboplatin and paclitaxel; HR, hazard ratio; IFCT-GFPC, Intergroupe Francophone de Cancerologie Thoracique–Groupe Francais de Pneumo-Cancerologie; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, response rate.

*Random assignment to carboplatin AUC 6 on day 1 plus paclitaxel 100 mg/m^2 weekly for 3 of 4 weeks (arm 1); carboplatin AUC 2 plus paclitaxel 100 mg/m^2 weekly for 3 of 4 weeks (arm 2); or carboplatin AUC 2 plus paclitaxel 150 mg/m^2 (cycle 1) or 100 mg/m^2 (cycle 2) weekly for 6 of 8 weeks (arm 3).

†Measured from random assignment.

‡IFCT-GFPC 0502 was a three-arm trial randomly assigning patients to maintenance gemcitabine, maintenance erlotinib, or observation. The active maintenance therapy arms were individually compared with observation. Results from the maintenance erlotinib arm are shown in Table 5.

§Nonsquamous non–small-cell lung cancer only.

in advanced NSCLC. In the ECOG 4599 trial of carboplatin-paclitaxel ± bevacizumab, 53% of patients who initiated therapy in the bevacizumab arm continued bevacizumab monotherapy. Of those who started bevacizumab maintenance therapy, 50% received five or more cycles.[45] Further insight into the potential benefit of continuation maintenance bevacizumab is available from clinical experience in ovarian cancer. In a three-arm phase III trial, patients with incompletely resectable stage III or stage IV epithelial ovarian cancer were randomly assigned to carboplatin-paclitaxel, carboplatin-paclitaxel plus concurrent bevacizumab, or carboplatin-paclitaxel plus concurrent bevacizumab followed by up to 10 months of maintenance bevacizumab monotherapy.[10] Median PFS was 10.3 months with carboplatin-paclitaxel, 11.2 months with carboplatin-paclitaxel plus concurrent bevacizumab (hazard ratio [HR], 0.91; 95% CI, 0.80 to 1.05; $P = .16$), and 14.1 months with carboplatin-paclitaxel plus concurrent bevacizumab followed by maintenance bevacizumab (HR, 0.72; 95% CI, 0.62 to 0.82; $P < .001$).

Switch Maintenance Therapy

The cytotoxic agents vinorelbine, paclitaxel, docetaxel, and pemetrexed have been evaluated in phase III clinical trials incorporating a switch maintenance paradigm (Table 4).[16,17,54,55] These trials differ by patient population (one study enrolled patients with locally advanced NSCLC treated initially with chemoradiotherapy as well as metastatic NSCLC treated initially with chemotherapy[54]), eligibility for random assignment (one study mandated responding disease,[54] whereas others required only nonprogression after first-line therapy), the post–random assignment control arm (one study continued first-line combination chemotherapy until disease progression[55]), and restrictions and recommendations regarding treatment at the time of progression. The switch maintenance studies of vinorelbine and paclitaxel demonstrated no improvement in PFS or OS.[54,55] The negative results seen in the vinorelbine trial may reflect the inclusion of locally advanced stage III disease (a context in which consolidative or maintenance chemotherapy after chemoradiotherapy has not been demonstrated to improve outcomes[14,56]), the relatively small number of randomly assigned patients, or the modest activity of single-agent vinorelbine.[54,57] The continuation of first-line combination chemotherapy (gemcitabine, ifosfamide, cisplatin) in the control arm of the trial incorporating maintenance paclitaxel may have obscured clinical effects of this approach.[55]

By contrast, more recent switch maintenance trials with docetaxel and pemetrexed have shown promising outcomes. The docetaxel study by Fidias et al[16] is, to our knowledge, the only trial published to date that truly examines the impact of the timing of therapy. In this trial, patients with stable or responding disease after four cycles of carboplatin-gemcitabine were randomly assigned to immediate docetaxel 75 mg/m^2 every 3 weeks for up to six cycles or delayed docetaxel initiated at the time of disease progression. Immediate docetaxel was associated with a clinically and statistically significant 3-month improvement in PFS. Additionally, immediate docetaxel increased median OS by 2.6 months, but this effect did not reach statistical significance ($P = .09$) in this trial powered to detect a survival difference of 4 months.[16] Sixty-three percent of patients assigned to delayed docetaxel received the intended therapy at the time of progression. Notably, median OS was identical (12.5 months) between patients who received immediate docetaxel and patients assigned to delayed docetaxel who ultimately received it, suggesting that the ability to receive treatment—rather than its timing—drives clinical benefit.

In a randomized, double-blind, phase III trial (JMEN),[17] switch maintenance therapy with pemetrexed extended PFS (median PFS, 4.0 months *v* 2.0 months in the control arm; $P < .001$) and OS (median OS, 13.4 months *v* 10.6 months in the control arm; $P = .01$), resulting in US and European regulatory approval for this indication. The trial design was less stringent than that used in the maintenance docetaxel trial, with various first-line chemotherapy regimens administered and the selection of chemotherapy at the time of progression left to investigator discretion. As a result, although 67% of patients in the control arm received further treatment at the time of disease progression, only 19% received pemetrexed at any future point. Additionally, in contrast to maintenance docetaxel delivery, pemetrexed was administered until progression or intolerable toxicities. As previously shown,[29] the regimen was well tolerated, with 48% of patients receiving six or more cycles and 23% receiving 10 or more cycles. Similar to studies of pemetrexed in other treatment settings, clinical benefit was limited to patients with nonsquamous tumors (see Predicting Benefit From Maintenance Therapy and Table 6).

The strategy of switch maintenance therapy with targeted agents has been evaluated in a number of phase III trials (Table 5). Three studies have used the EGFR inhibitor erlotinib,[33,58,59] and three have used the EGFR inhibitor gefitinib.[61-63] In the Sequential Tarceva in Unresectable NSCLC (SATURN) trial, maintenance erlotinib after four cycles of platinum doublet chemotherapy yielded a clinically modest but statistically significant improvement in OS (median OS, 12.0 months *v* 11.0 months for placebo; $P = .01$), resulting in regulatory approval for this indication. By contrast, none of the gefitinib trials has demonstrated an OS benefit, possibly because of small patient numbers and high rates of EGFR tyrosine kinase inhibitor (TKI) use after disease progression in the control arms. Consistent with EGFR TKI use in first- and second-line therapy contexts, the greatest benefit from maintenance EGFR TKI use was observed in patients with tumors harboring activating *EGFR* mutations (see Predicting Benefit From Maintenance Therapy and Table 6).

Ongoing clinical trials of maintenance therapy are investigating new technologies as well as the optimal means to deliver existing agents. Immunotherapy may be particularly suited to the postinduction chemotherapy setting. Promising data from early-phase studies of liposomal BLP-25 (vaccine targeting the extracellular core peptide of mucin-1) and belagenpumatucel-L (a drug derived from NSCLC cell lines genetically modified to secrete antisense oligonucleotide to transforming growth factor $\beta 2$) have led to phase III clinical trials (NCT00409188 and NCT00676507).[65,66] The Point Break trial (NCT00762034) directly compares carboplatin-paclitaxel plus bevacizumab followed by maintenance bevacizumab with carboplatin-pemetrexed plus bevacizumab followed by maintenance pemetrexed plus bevacizumab. ECOG 5508 (NCT01107626) is comparing maintenance pemetrexed versus maintenance bevacizumab versus maintenance pemetrexed and bevacizumab after induction therapy with carboplatin-paclitaxel plus bevacizumab. Cancer and Leukemia Group B 30607 (NCT00693992) is comparing maintenance sunitinib with placebo after four cycles of platinum-based chemotherapy.

META-ANALYSES OF MAINTENANCE THERAPY IN ADVANCED NSCLC

Given the overall modest survival benefit from maintenance chemotherapy observed in individual clinical trials, numerous meta-analyses

Table 4. Selected Phase III Trials of Switch Maintenance Therapy With Cytotoxic Chemotherapy Agents

		Induction Therapy		Maintenance Therapy			PFS		OS	
Trial	Year	Regimen	No. of Patients	Regimen	No. of Patients	Therapy at Progression (% of patients)	Median (months)	*P*	Median (months)	*P*
Westeel et al[54]	2005	MIC × 4 cycles (wet IIIB or stage IV) or MIC × 2 cycles followed by RT to 55-60 Gy (stage IIIB)	573	Vinorelbine 25 mg/m^2 weekly for up to 6 months	91	NR (cisplatin-etoposide advised)	5 (from random assignment)	.11	12.3	.65
				Observation	90	NR (cisplatin-etoposide advised; vinorelbine prohibited)	3 (HR, 0.77)		12.3 (HR, 1.08)	
Sculier et al[55]	2007	GIP × 3 cycles	485	GIP until progression	140	61 (paclitaxel 225 mg/m^2 every 3 weeks until progression in 49% [12% RR]; GIP in 6% [12% RR])	4.4	.56	11.9	.17
				Paclitaxel 225 mg/m^2 every 3 weeks until progression	141	47 (GIP until progression in 33% [17% RR])	4		9.7	
Fidias et al[16]	2009	Carboplatin AUC 5 day 1 + gemcitabine 1,000 mg/m^2 on days 1 and 8 every 3 weeks × 4 cycles	566	Docetaxel 75 mg/m^2 every 3 weeks for up to 6 cycles	153	NR	5.7	< .001	12.3	.09
				Observation	156	63 (docetaxel 75 mg/m^2 every 3 weeks up to 6 cycles)	2.7		9.7	
JMEN (Ciuelanu et al[17])	2009	Platinum-based doublet* × 4 cycles	745	Pemetrexed 500 mg/m^2 every 3 weeks + BSC	441	51	4.0	< .001	13.4	.01
				Placebo + BSC	222	67 (19% pemetrexed)	2.0 (HR, 0.6)		10.6 (HR, 0.79)	
ECOG 5508†	Ongoing	Carboplatin AUC 6 and paclitaxel 200 mg/m^2 + bevacizumab 15 mg/kg	1,282	Bevacizumab 15 mg/kg every 3 weeks Pemetrexed 500 mg/m^2 every 3 weeks Bevacizumab 15 mg/kg + pemetrexed 500 mg/m^2 every 3 weeks						

Abbreviations: AUC, area under the curve; BSC, best supportive care; ECOG, Eastern Cooperative Oncology Group; GIP, gemcitabine 1,000 mg/m^2 on days 1 and 8 plus ifosfamide 3 g/m^2 on day 1 plus cisplatin 50 mg/m^2 on day 1; HR, hazard ratio; MIC, mitomycin 6 mg/m^2 on day 1 plus ifosfamide 1.5 g/m^2 per day on days 1 to 3 plus cisplatin 30 mg/m^2 per day on days 1 to 3; NR, not reported; OS, overall survival; PFS, progression-free survival; RR, response rate; RT, radiotherapy.

*Cisplatin or carboplatin plus gemcitabine, docetaxel, or paclitaxel.

†Nonsquamous non–small-cell lung cancer only.

Table 5. Selected Phase III Trials of Maintenance Therapy With Molecularly Targeted Agents

Trial	Year	Induction Therapy		Maintenance Therapy		Therapy at Progression (% of patients)	PFS		OS	
		Regimen	No. of Patients	Regimen	No. of Patients		Median	*P*	Median (months)	*P*
SATURN[58]	2010	Platinum-based doublet × 4 cycles	1,949	Erlotinib 150 mg PO daily	438	55	12.3 weeks	< .001	12.0	.01
				Placebo	451	64 (16% EGFR TKI [67% of patients with *EGFR* mutations received EGFR TKI])	11.1 weeks (HR, 0.71)		11.0 (HR, 0.81)	
ATLAS[59,60]	2009	Platinum-based doublet plus bevacizumab 15 mg/kg × 4 cycles	1,160	Bevacizumab 15 mg/kg every 3 weeks plus erlotinib 150 mg PO daily	743 randomly assigned	NR	4.8 months	.001	15.9	.27 (or .56?)
				Bevacizumab 15 mg/kg every 3 weeks plus placebo		56 (40% EGFR TKI)	3.7 months (HR, 0.72)		13.9 (HR, 0.9)	
IFCT-GFPC 0502[33*]	2010	Cisplatin 80 mg/m^2 on day 1 plus gemcitabine 1,250 mg/m^2 on days 1 and 8 every 3 weeks × 4 cycles	834	Erlotinib 150 mg PO daily	155	63 (pemetrexed)	2.9 months	.002	11.8	
				Observation	155	82 (76% pemetrexed [15% RR])	1.9 months (HR, 0.82)		10.7 (HR, 0.91)	
WJTOG 0203[61]	2010	Platinum-based doublet chemotherapy × 3 cycles	302	Gefitinib	172	65	4.6 months	< .001	13.7	.11
		Platinum-based doublet chemotherapy for up to 6 cycles	301	Observation		73 (54% EGFR TKI)	4.3 months (HR, 0.68)		12.9 (HR, 0.86)	
EORTC 08021–ILCP 01/03[62]	2010	Platinum-based doublet × 4 cycles	173	Gefitinib 250 mg PO daily	86	NR	4.1 months	.002	10.9	.20
				Placebo	87	NR	2.9 months (HR, 0.61)		9.4 (HR, 0.81)	
INFORM (C-TONG 0804)[63]	2011	Platinum-based doublet × 4 cycles	298	Gefitinib 250 mg PO daily	148	NR	4.8 months	< .001	18.7	.26
				Placebo	148	32 (EGFR TKI)	2.6 months (HR, 0.42)		16.9 (HR, 0.84)	
CALGB 30607	Ongoing	Platinum-based chemotherapy × 4 cycles	244	Sunitinib 37.5 mg PO daily						
				Placebo						

Abbreviations: CALGB, Cancer and Leukemia Group B; C-TONG, Chinese Thoracic Oncology Group; EGFR, epidermal growth factor receptor; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; IFCT-GFPC, Intergroupe Francophone de Cancerologie Thoracique–Groupe Francais de Pneumo-Cancerologie; ILCP, Italian Lung Cancer Project; NR, not reported; OS, overall survival; PFS, progression-free survival; PO, oral; RR, response rate; TKI, tyrosine kinase inhibitor; SATURN, Sequential Tarceva in Unresectable Non–Small-Cell Lung Cancer; WJTOG, West Japan Thoracic Oncology Group.
*IFCT-GFPC 0502 was a three-arm trial randomly assigning patients to maintenance gemcitabine, maintenance erlotinib, or observation. The active maintenance therapy arms were individually compared with observation. Results from the maintenance gemcitabine arm are listed in Table 3.

have been performed in recent years.[67-70] A 2009 meta-analysis of prolonged first-line and continuation maintenance cytotoxic chemotherapy studies (seven trials; 1,559 patients) found that treatment with more than four cycles of chemotherapy was associated with improved PFS (HR, 0.75; 95% CI, 0.65 to 0.85; $P < .001$) without significant OS benefit (HR, 0.97; 95% CI, 0.84 to 1.11; $P = .65$).[67] Another 2009 meta-analysis of 13 trials (3,027 patients) included studies with varying duration of combination first-line chemotherapy, continuation maintenance, and switch maintenance strategies with cytotoxic agents.[68] It too found a substantial improvement in PFS with extended chemotherapy (HR, 0.92; 95% CI, 0.69 to 0.81; $P < .001$), as well as a modest OS benefit (HR, 0.92; 95% CI, 0.86 to 0.99; $P = .03$). The PFS effect was greater for trials incorporating third-generation agents compared with older drugs and for trials with a switch maintenance design. A third meta-analysis, published in 2011, examined eight trials (3,736 patients) incorporating a continuous or switch maintenance strategy with cytotoxic agents or TKIs.[69] PFS improvement was statistically significant for both switch maintenance (HR, 0.67; 95% CI, 0.57 to 0.78) and continuation maintenance (HR, 0.53; 95% CI, 0.43 to 0.65) strategies. OS improvement reached statistical significance for switch maintenance trials (HR, 0.85; 95% CI, 0.79 to 0.92; $P < .001$) and demonstrated a similar trend for continuation maintenance trials (HR, 0.88; 95% CI, 0.74 to 1.04; $P = .12$). There were no significant differences in OS or PFS between switch maintenance therapy with cytotoxic agents and with EGFR TKIs. Similar conclusions were reached in a fourth meta-analysis, incorporating 10 randomized trials (3,451 patients), published in 2012.[70]

PREDICTING BENEFIT FROM MAINTENANCE CHEMOTHERAPY

Over recent years, the concept of maintenance chemotherapy has come under debate because of modest survival benefits, added toxicity, economic considerations, and quality-of-life concerns. As a result, interest in identifying patients likely to derive greatest benefit from this evolving treatment paradigm has emerged. Table 6 lists patient, treat-

Table 6. Factors Predicting Benefit From Maintenance Chemotherapy

Factor	Examples
Response to first-line therapy	In clinical trials of switch maintenance therapy with pemetrexed (JMEN) and erlotinib (SATURN), the survival benefit of maintenance therapy was limited to patients who had stable disease (in contrast to responding disease) after induction chemotherapy. In JMEN, the OS HR was 0.68 for patients with stable disease *v* 0.90 for patients with responding disease. In SATURN, the OS HR was 0.72 for patients with stable disease *v* 0.94 for patients with responding disease. In contrast, in the clinical trial of switch maintenance therapy with docetaxel, the survival benefit of maintenance therapy was limited to patients who had responding disease (HR, 0.61 *v* 1.02 for patients with stable disease).[16,17,58]
Performance status	In the CECOG trial of continuation maintenance with gemcitabine, a survival benefit for maintenance therapy was observed only in patients with good performance status. For KPS > 80 (n = 99), median OS was 8.3 months with BSC and 22.9 months with gemcitabine (HR, 2.1; 95% CI, 1.2 to 3.8). For KPS ≤ 80 (n = 120), median OS was 7.7 months with BSC and 7.0 months with gemcitabine (HR, 0.8; 95% CI, 0.5 to 1.3).[40]
Likelihood of therapy at progression	The clinical trial of switch maintenance therapy with docetaxel demonstrated that OS is similar between patients who received immediate docetaxel after completion of four cycles of carboplatin-gemcitabine and patients who received delayed docetaxel at time of progression. Therefore, factors associated with lower likelihood of receipt of second-line chemotherapy may predict patients most likely to benefit from maintenance therapy. Two single-center retrospective studies have evaluated factors predicting receipt of second-line chemotherapy among patients with advanced NSCLC. In a US study, these factors included socioeconomic status (by insurance type) and a surrogate marker of disease burden (prechemotherapy palliative radiation therapy). Second-line chemotherapy administration was not associated with age, sex, race, histology, or year of diagnosis. In a Korean study, poor performance status, larger initial target lesions, and smaller decrease in target lesions after first-line therapy were associated with a lower likelihood of second-line chemotherapy administration.[16,31,32]
Histology	In certain clinical trials of switch maintenance therapy with EGFR inhibitors, clinical benefit seems greater in patients with adenocarcinoma histology. In SATURN, the OS benefit from erlotinib was significant in patients with adenocarcinoma (HR, 0.77; 95% CI, 0.61 to 0.97) but not in patients with squamous cell histology (HR, 0.86; 95% CI, 0.68 to 1.10). In WJTOG 0203, which did not demonstrate a significant survival advantage with gefitinib in the overall study population, a subset analysis of patients with adenocarcinoma demonstrated a significant OS difference (HR, 0.79; $P = .03$). However, there was no treatment-histology interaction in the IFCT-GFCP-052 trial of switch maintenance therapy with erlotinib. As noted in other clinical trials of pemetrexed, the clinical benefit of switch maintenance therapy with pemetrexed is limited to patients with nonsquamous histology. In the JMEN trial, for nonsquamous histology in the pemetrexed and placebo arms, PFS was 4.4 *v* 1.8 months, respectively (HR, 0.47; $P < .001$), and OS was 15.5 *v* 10.3 months, respectively (HR, 0.7; $P = .002$); for squamous histology, PFS was 2.2 *v* 2.5 months, respectively (HR, 1.03), and OS was 9.9 *v* 10.8 months, respectively (HR, 1.07). Subsequent maintenance therapy trials incorporating pemetrexed have restricted enrollment to patients with nonsquamous tumors.[17,33,43,58,61,71,72]
Molecular characteristics	As noted in other clinical trials of EGFR inhibitors, the clinical benefit of maintenance therapy with erlotinib or gefitinib is greatest for patients with tumors harboring activating *EGFR* mutations. In SATURN, for *EGFR* mutant tumors, the PFS HR was 0.10 (95% CI, 0.04 to 0.25; $P < .001$); for *EGFR* wild-type tumors, the PFS HR was 0.78 (95% CI, 0.63 to 0.96; $P = .0185$). In WJTOG 0203, patients with *EGFR* mutant tumors had a median PFS of 16.6 months with gefitinib *v* 2.8 months with placebo (HR, 0.17; 95% CI, 0.07 to 0.42); patients with *EGFR* wild-type tumors had a median PFS of 2.7 months with gefitinib *v* 1.5 months with placebo (HR, 0.86; 95% CI, 0.48 to 1.51). Also consistent with clinical trials of EGFR inhibitors in other settings, *KRAS* mutations seem to be associated with lack of benefit from maintenance therapy with EGFR inhibitors. In the ATLAS trial, the PFS HR was 0.67 (95% CI, 0.49 to 0.9) for *KRAS* wild-type tumors. For *KRAS* mutant tumors, the PFS HR was 0.93 (95% CI, 0.55 to 1.56).[58,59,63,71]

Abbreviations: BSC, best supportive care; CECOG, Central European Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HR, hazard ratio; IFCT-GFPC, Intergroupe Francophone de Cancerologie Thoracique–Groupe Francais de Pneumo-Cancerologie; KPS, Karnofsky performance score; NSCLC, non–small-cell lung cancer; OS, overall survival; PFS, progression-free survival; SATURN, Sequential Tarceva in Unresectable NSCLC; WJTOG, West Japan Thoracic Oncology Group.

ment, and disease characteristics associated with maintenance therapy outcomes. The impact of response to first-line therapy on the effects of maintenance therapy varies among trials, with OS benefits observed among patients with stable but not responding disease in switch maintenance trials with pemetrexed (JMEN) and erlotinib (SATURN).[17,58] Given these findings, the European Medicines Agency approval for maintenance erlotinib is formally limited to patients demonstrating stable disease (and not radiographic response) after induction therapy, whereas the broader US Food and Drug Administration approval includes all patients with nonprogressive disease after induction. In the docetaxel switch maintenance trial, the converse was observed, with OS benefit limited to patients with responding disease after induction therapy.[16] Performance status has also been associated with benefit from maintenance chemotherapy. As an example, in the Central European Cooperative Oncology Group randomized trial of continuation gemcitabine maintenance therapy versus best supportive care after four cycles of cisplatin-gemcitabine first-line therapy, a subset analysis demonstrated clear differences according to performance status, with a clinically meaningful and statistically significant increase in OS among patients with a Karnofsky performance score of greater than 80 and no survival difference among patients with a Karnofsky performance score of ≤ 80.[40] Given the observation in some studies that the survival differences achieved with maintenance chemotherapy may be limited to patients who do not receive second-line therapy at the time of progression,[16] some investigators have suggested that patient and disease characteristics associated with receipt of second-line therapy might guide selection of patients for a maintenance strategy.[31,32] Finally, as noted in clinical trials of these agents in other contexts, tumor histology and molecular characteristics predict benefit from maintenance therapy with pemetrexed and EGFR inhibitors.

QUALITY-OF-LIFE CONSIDERATIONS IN MAINTENANCE CHEMOTHERAPY

Evaluating effects on quality of life in maintenance chemotherapy trials requires placing these studies in the overall context of advanced NSCLC treatment. Given the natural history of untreated or progressive disease, it has been shown that both first-line chemotherapy at the time of diagnosis and second-line chemotherapy at the time of progression reduce symptoms and improve quality of life compared with supportive care alone.[73,74] By contrast, stable or responding advanced NSCLC after first-line chemotherapy may represent a period of disease-related symptom control and recovery from prior treatment. With close clinical and radiographic surveillance, disease progression is often detected and addressed before clinical deterioration. Although this period off therapy until disease progression lasts less than 4 months on average, it persists for more than 6 months in 10% to 20% of patients.[16,17,58]

To date, no clinical trial has demonstrated significant improvement in global quality of life with maintenance therapy compared with observation alone. Nevertheless, several have shown that global quality of life does not deteriorate, indicating the favorable toxicity profile of prolonged administration of single-agent cytotoxic or biologic agents compared with extended treatment with combination chemotherapy regimens.[15,35,37,68] In the immediate versus delayed docetaxel trial, 18% of patients in the delayed docetaxel arm had a worsened Average Symptom Burden Index compared with 11% of patients in the immediate docetaxel arm ($P = .76$).[16] In the SATURN trial of maintenance erlotinib, there was no significant difference in time to deterioration of quality of life based on the Functional Assessment of Cancer Therapy–Lung (HR, 0.96; 95% CI, 0.79 to 1.16).[58] In the JMEN trial of maintenance pemetrexed, overall quality of life was similar between the pemetrexed and placebo arms, with the exception of increased loss of appetite and delayed worsening of pain and hemoptysis among patients receiving maintenance pemetrexed.[75]

ECONOMIC CONSIDERATIONS IN MAINTENANCE CHEMOTHERAPY

With increasing medical costs receiving ever greater public and political scrutiny, the economic impact of maintenance chemotherapy for advanced NSCLC has spawned numerous cost-effectiveness analyses. For maintenance pemetrexed, as used in the JMEN trial, it is estimated that the incremental cost-effectiveness ratio (ICER) per life-year gained is $205,597.[76] Limiting the use of maintenance pemetrexed to nonsquamous histology reduces the ICER to $122,371. Renal hemodialysis, often considered a benchmark threshold for health care cost effectiveness in the United States, has an ICER of $129,090.[77] A cross-market cost comparison performed in France, Germany, Italy, and Spain of erlotinib versus pemetrexed for maintenance therapy found maintenance erlotinib to have lower overall costs.[78] Yet, in the United Kingdom, maintenance pemetrexed—but not maintenance erlotinib—falls below the National Institute for Health and Clinical Excellence willingness-to-pay threshold, because of the fact that pemetrexed is sold for approximately half the cost there than it is in the United States.[79] The influence of drug costs on maintenance therapy is particularly apparent in an economic evaluation of maintenance paclitaxel and maintenance bevacizumab in ovarian cancer, a setting where both drugs have been shown to improve PFS substantially.[80] Compared with carboplatin-paclitaxel alone, carboplatin-paclitaxel plus maintenance paclitaxel had an ICER of $13,402 per quality-adjusted life-year. The addition of bevacizumab concurrent with carboplatin-paclitaxel and then as maintenance monotherapy had an ICER of $326,530 per quality-adjusted life-year.

THE PATIENT PERSPECTIVE ON MAINTENANCE CHEMOTHERAPY

Although the thoracic oncology community has seen considerable debate over maintenance chemotherapy in recent years, there is little insight into patient perceptions of this evolving paradigm. Some guidance may be provided by a descriptive interview-based study of 81 patients previously treated with cisplatin-based chemotherapy for advanced NSCLC.[81] The median survival threshold for accepting chemotherapy was 4.5 months for a regimen with mild toxicity and 9 months for a regimen with severe toxicity. Approximately one fifth of patients chose chemotherapy over supportive care for a survival benefit of 3 months, whereas nearly 70% chose chemotherapy for a substantial reduction in symptoms without survival prolongation. A recently published analysis of patient preferences demonstrated that PFS benefits were viewed as most beneficial when disease symptoms were mild but were viewed as detrimental when disease symptoms were severe.[82] Among characteristics of therapy, the potential for fatigue was considered the greatest risk, followed by diarrhea, which was followed by rash, nausea/vomiting, fever, and infection. Mode of administration was the least important attribute of therapy, with a preference for oral versus intravenous delivery. In focus groups of patients with advanced NSCLC

who had initiated but not yet completed first-line chemotherapy, the following themes related to maintenance therapy emerged: survival benefit, disease control, and buying time (including the notion of stabilizing disease until further advances in disease management are available); quality-of-life concerns; the role of health care provider opinion/preference; and the importance of logistics.[83] In a study of 30 patients with advanced NSCLC surveyed before chemotherapy and after two cycles and four cycles of chemotherapy, at baseline, 83% considered maintenance chemotherapy worthwhile for a survival benefit of 6 months, 67% considered it worthwhile for a 3-month benefit, and 43% considered it worthwhile for a 1-month benefit. These proportions decreased somewhat over time.[84]

ONGOING QUESTIONS AND CONCLUSIONS

Given the associated costs and toxicities, should one administer maintenance therapy to patients with advanced NSCLC, particularly in clinical scenarios where only a benefit in PFS is observed, but not a survival benefit? Presumably, an improvement in PFS without an improvement in OS suggests that it does not matter when the additional treatment is given—as long as the patient receives it.[85] In the absence of a clear-cut survival advantage or differential improvement in symptoms, it may be difficult to justify extending therapy instead of delaying it, thus denying the patient a chemotherapy holiday. Nevertheless, many patients planned for further chemotherapy at progression never receive it. Thus, there remains an ongoing need for better ways to identify patients most likely to benefit.

Why do some switch maintenance trials show both a PFS and a survival benefit, when others show only a PFS benefit? This observation may reflect a modest effect of the maintenance drug in some settings, which is insufficient to translate into a survival benefit.[85] Other explanations include the possibility that a detected PFS benefit may be a false-positive one (as a result of evaluation bias or attrition bias) or that some agents may lead to changes in tumors resulting in a more aggressive behavior, which offsets the earlier delay in progression.[85] These considerations may be even more applicable to continuation maintenance paradigms.

The recently presented PARAMOUNT trial, in which patients were randomly assigned to pemetrexed or placebo after four cycles of cisplatin-pemetrexed, is the first study of continuation maintenance therapy to demonstrate an OS benefit. Nevertheless, questions remain about this approach. Among patients in the control arm (all of whom had initially sustained disease regression or stabilization on a pemetrexed-based regimen), only 4% received pemetrexed at the time of disease progression.[42] Thus, it is not known whether rechallenge with this agent after a treatment-free interval might also provide clinical benefit, while reducing the costs and toxicities of continuous therapy. Such an approach has shown promise with the EGFR inhibitors gefitinib and erlotinib.[86,87]

Maintenance chemotherapy is clearly not applicable to all patient subsets. Unfortunately, because of disease progression or treatment-associated toxicities, a substantial proportion of patients (ranging from 35% to 65% in clinical trials) who initiate first-line chemotherapy are not candidates for maintenance therapy. Some of the more promising agents for maintenance therapy, such as pemetrexed and bevacizumab, are not available to the 30% of patients with NSCLC with squamous histology. In addition, pemetrexed cannot be administered in the setting of renal dysfunction (creatinine clearance < 45 mL/min), a clinical scenario that develops in approximately 10% of patients with advanced NSCLC (20% of those age ≥ 65 years) treated with chemotherapy.[88] Importantly, clinical trials of maintenance therapy have also brought to attention the varying and at times substantial proportions of patients with disease control after first-line chemotherapy who never receive second-line treatment. Modifying the clinical and radiographic surveillance of these patients to increase the likelihood of second-line therapy administration may represent another means to improve clinical outcomes in advanced NSCLC.

In conclusion, both continuation and switch maintenance chemotherapy have demonstrated favorable toxicity profiles, prolongation of PFS, and—in some instances—an OS benefit. Nevertheless, in an era of increasing focus on the cost and quality of care, economic considerations and quality of life remain critical questions. For maintenance therapy to be broadly acceptable to patients, clinicians, and payors, it will need to be convenient, well tolerated, cost effective, and able to prolong OS.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.
Employment or Leadership Position: None **Consultant or Advisory Role:** None **Stock Ownership:** None **Honoraria:** None **Research Funding:** Joan H. Schiller, Genentech **Expert Testimony:** None **Other Remuneration:** None

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Collection and assembly of data: David E. Gerber
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors

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