Maintenance therapy in advanced non-small cell lung cancer: evolution, tolerability and outcomes

Linda E. Coate and Frances A. Shepherd

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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 and has been the subject of considerable recent debate. Options for maintenance include continuing the initial combination chemotherapy regimen, continuing only single agent chemotherapy ('continuation maintenance') or introducing a new agent ('switch' maintenance therapy). Therapies that have been studied in this setting in randomized trials to date include chemotherapy, molecularly targeted agents and immunotherapy approaches. 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. Despite considerable controversy, it has become an acceptable treatment paradigm. Here, we briefly outline the evolution of this treatment paradigm and examine which subgroups of patients are most likely to benefit.

Keywords: anti-angiogenic, cetuximab, chemotherapy, erlotinib, gefitinib, maintenance, non-small cell lung cancer, prolonged

Introduction

Four to six cycles of platinum-based doublet chemotherapy, the current standard of care for advanced non-small cell lung cancer (NSCLC), results in modest prolongation of survival and improvement in cancer-related symptoms. However, with <5% long-term survival at 5 years [Schiller *et al.* 2002], there is scope for improving the current treatment paradigm.

Maintenance therapy is one strategy that has been evaluated extensively in recent years. It has been the focus of considerable debate and many questions remain regarding optimal utilization of this strategy. Different approaches that might be classified as maintenance therapy in advanced NSCLC include: (1) continuing induction therapy until progression; (2) continuing only the *nonplatinum* or molecularly targeted component of the induction regimen, also known as 'continuation maintenance'; and (3) switching to a *different* cytotoxic or molecularly targeted agent, often called 'switch maintenance'.

The focus of this review is mainly on advanced NSCLC, and data presented are from large randomized phase III studies where possible.

Methods

An English language search of PubMed and Google Scholar was performed using the following keywords: non-small cell lung cancer, chemotherapy, maintenance, prolonged, erlotinib, gefitinib, cetuximab, and anti-angiogenic. The proceedings of American society of Clinical Oncology (ASCO) annual meetings and of World Conferences on Lung Cancer from 2003–2010 were searched using the same keywords. We also searched www.ClinicalTrials.gov for unreported, active maintenance trials.

Results

Continuation of first-line induction chemotherapy

The ASCO guideline for the treatment of advanced NSCLC recommends platinum-based

Correspondence to:
Frances A. Shepherd,
MD FRCPC

Department of Medical
Oncology, Princess
Margaret Hospital, Room
5-104, 610 University
Avenue, Toronto, Ontario,
Canada M5G 2M9
frances.shepherd@uhn.on.ca

Linda E. Coate,
MD, MRCPI

Department of Medical
Oncology and Hematology
of the University Health
Network, Princess
Margaret Hospital Site and
the University of Toronto,
Toronto, Ontario, Canada

chemotherapy be administered for no more than six cycles [Azzoli *et al.* 2009]. This recommendation was based on the results of randomized trials that compared shorter *versus* longer periods of administration of platinum-based chemotherapy [Park *et al.* 2007; von Plessen *et al.* 2006; Smith *et al.* 2001]. The recently published ESMO guidelines [D'Addario *et al.* 2010] state that the role of maintenance treatment is not definitively established and that the superiority of immediate maintenance therapy *versus* delayed therapy is not proven. The NCCN guidelines [NCCN, 2010] list the following options: continuation of current regimen until progression, continuation of bevacizumab, cetuximab or pemetrexed, or switch maintenance to pemetrexed, erlotinib or docetaxel.

The largest randomized trials that compared the administration of different numbers of cycles of initial chemotherapy regimen [Park *et al.* 2007; von Plessen *et al.* 2006; Socinski *et al.* 2002; Smith *et al.* 2001] varied with respect to the number of cycles in the 'standard' arm (three gave three and one four cycles) and three trials administered six cycles in the experimental arm. Only one trial employed a true 'maintenance' approach in the experimental arm with continuation of chemotherapy until progression [Socinski *et al.* 2002]. There are also several small studies, or studies reported only in abstract form, that use this trial design [Barata *et al.* 2007; Tourani *et al.* 1990; Buccheri *et al.* 1989], but we review here only the phase III, peer-reviewed reports.

Socinski and colleagues compared four cycles of carboplatin/paclitaxel *versus* carboplatin/paclitaxel until progression in 230 patients [Socinski *et al.* 2002]. All patients were scheduled to receive second-line weekly paclitaxel upon progression. Relatively poor performance status (PS) patients were allowed to participate, as patients were only required to have a Karnofsky PS ≥ 70 .

The median number of treatment cycles on *both* arms was four. Only 42% of patients on the investigational arm received more than four and 18% received eight or more cycles. Conversely, on the standard arm, only 57% received all four cycles of planned treatment, perhaps reflecting the inclusion of relatively poor PS patients. Median survivals were 6.6 and 8.5 months, with no

significant difference for those receiving chemotherapy until progression ($p = 0.63$).

Quality of life (QoL) data were available for 218/230 patients. There were no statistical differences between baseline and week 11 QoL scores between the arms, but by 25 weeks, there appeared to be significant QoL *deterioration*, particularly in the prolonged chemotherapy arm ($p = 0.002$). There was also significantly more grade 2–4 neurotoxicity in patients randomized to continue chemotherapy (27% *versus* 14%, $p = 0.02$). Thus, the deterioration in QoL is probably related to the toxicity of combination regimens.

Continuing first-line single-agent induction chemotherapy without the platinum analogue

The platinum component of platinum-based doublet therapy is responsible for the majority of serious treatment-related toxicity. For this reason, most patients cannot tolerate prolonged administration of platinum-based doublets. This is not true for third-generation single-agent treatment, a finding repeatedly demonstrated in the trials of second-line therapy in advanced NSCLC [Ramlau *et al.* 2006; Hanna *et al.* 2004; Fossella *et al.* 2000; Shepherd *et al.* 2000], in which some patients received up to 28 cycles of single-agent chemotherapy. As these drugs are so tolerable, 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. Trials of this design are summarized in Table 1.

In a North American study [Belani *et al.* 2003], 401 patients were treated with differing schedules of carboplatin/paclitaxel induction for 16 weeks. Responding and stable patients then were randomized to receive maintenance single-agent paclitaxel, 70 mg/m² weekly or best supportive care (BSC). Of the 130 patients randomized to the maintenance paclitaxel arm, 80% completed one cycle of paclitaxel, but only 23% completed four cycles. The most common reasons for discontinuing paclitaxel were disease progression and adverse events. Median time to progression (TTP) in the maintenance arm was 38 weeks *versus* 29 weeks for observation ($p = 0.124$), with median survival times of 75 and 60 weeks, respectively ($p = 0.243$). One-year survival rates were 72% and 60% with 2-year rates of 32% and 26% (p -value not reported).

Table 1. Continuing the nonplatinum compound following induction treatment for non-small cell lung cancer.

Trial	Induction therapy	Total patients	Response rate CR/PR Stable	Treatment arms	Number randomized	Progression-free survival Median HR	<i>p</i> -value	Overall survival Median HR	<i>p</i> -value
Brodowicz <i>et al.</i> [2006]	Four cycles of cisplatin/ gemcitabine	354	21.6% 54.4%	Maintenance gemcitabine <i>versus</i> BSC	138 Gemcitabine 68 BSC	6.6 months 5 months HR NR	<0.001	13 months 11 months HR NR	0.172
Belani <i>et al.</i> [2003]	Three differing regimens of carboplatin/ paclitaxel for 16 weeks	401	32% arm 1 24% arm 2 18% arm 3 (SD NR)	Maintenance paclitaxel <i>versus</i> observation	65 Paclitaxel 65 Observation	38 wks 29 wks HR NR	NR	75 weeks 60 weeks HR NR	NR
Belani <i>et al.</i> [2010]	Four cycles of carbo- platin/gemcitabine.	519	28% 37%	Maintenance gemcitabine <i>versus</i> BSC	128 Gemcitabine 127 BSC	7.4 months 7.7 months HR 1.09	0.575	8 months 9.3 months HR 0.97	0.838
IFCT study [Perol <i>et al.</i> 2010]	Four cycles of cis- platin/gemcitabine	NR	53% 47%	Maintenance gemcitabine <i>versus</i> BSC	154 Gemcitabine 155 BSC	3.8 months 1.9 months HR 0.55	<0.0001	Median not reported HR 0.91	NR

HR, hazard ratio; CR, complete response; PR, partial response; SD, stable disease; NR, not reported; MIC, mitomycin; ifosfamide and cisplatin; NS, not significant; IFCT, Intergroupe Francophone de Cancérologie Thoracique; BSC, Best supportive care.

During maintenance therapy, 86% of treated patients experienced at least one adverse event, and 45% reported at least one grade 3/4 adverse event. There was no subgroup analysis reported regarding the benefit of maintenance therapy in different patient subgroups. The authors of this study concluded that, although the results were provocative, the sample size was too small to draw definitive conclusions regarding the clinical utility of maintenance paclitaxel, although this study did introduce the concept of maintenance chemotherapy.

The Central European Cooperative Oncology Group (CECOG) conducted a 350-patient randomized study to evaluate the effect of gemcitabine maintenance following four cycles of gemcitabine/cisplatin induction. [Brodowicz *et al.* 2006] Responding and stable patients were randomized 2:1 to receive maintenance gemcitabine or BSC alone. Response or stable disease was seen in 257 patients (73%) but only 215 (61%) were randomized (138 maintenance gemcitabine, 68 BSC). Maintenance patients received a median of three gemcitabine cycles (range 0–38). Median TTP throughout the study was significantly longer on the maintenance arm, 6.6 *versus* 5.0 months on BSC ($p < 0.001$). After randomization, patients on maintenance also had significantly longer TTP (3.6 *versus* 2 months, $p < 0.001$). Patients of KPS ≥ 70 were allowed entry, but at baseline, 40.9% had a KPS > 80 . At the beginning of the maintenance phase 47.8% and 48.5% of patients had a KPS > 80 on the gemcitabine and BSC arms, respectively.

Median overall survival (OS) on the gemcitabine arm was 13 months *versus* 11 months for BSC ($p = 0.195$). Patients with a better PS had significantly longer survival, both throughout the study and during the maintenance period. Median survival throughout the study for patients with KPS > 80 was 25.3 months, compared with 10.0 months for those with KPS ≤ 80 . In the maintenance phase, median survivals were 22.9 and 7.0 months (p -value not reported). Regarding toxicity, the most notable difference between the gemcitabine and BSC arms during maintenance was the need for transfusion (20% *versus* 6.3%, $p = 0.018$). Maintenance gemcitabine was well tolerated and did *not* result in deterioration in QoL, compared with BSC. There also was a trend toward better control of cough, hemoptysis and pain on the gemcitabine arm.

A larger 519 patient study, designed to validate the CECOG trial, randomised patients responding to initial gemcitabine/carboplatin with carboplatin/gemcitabine to maintenance gemcitabine or BSC, and has been presented only in abstract form to date [Belani *et al.* 2010]. Only 255 patients were randomized after induction, and notably, nearly two thirds were PS ≥ 2 . The median OS for gemcitabine and BSC was 8 and 9.3 months, respectively (hazard ratio [HR] = 0.97, $p = 0.84$). Progression-free survival (PFS) rates were 7.4 and 7.7 months. Toxicity included 15% neutropenia and 9% anemia on the gemcitabine arm. What sets this trial apart from other trials of ‘continuation maintenance’ is the preponderance of PS 2/3 patients, and may explain the negative results. Furthermore, only 16% and 17% of patients received any form of further therapy, which may have been a function of their PS.

The Intergroupe Francophone de Cancérologie Thoracique (IFCT) [Perol *et al.* 2010] also examined the role of BSC *versus* maintenance gemcitabine in responding or stable patients following four cycles of cisplatin/gemcitabine. All patients were scheduled to receive pemetrexed at the time of progression. Among 834 patients initially enrolled, 155 and 154 were randomized to observation and gemcitabine maintenance, respectively. Patients were required to be ECOG PS 0–1, but were not selected by histology, even for pemetrexed. In the gemcitabine arm, the median number of cycles was 4 (range 1–19). Median PFS was significantly longer in the gemcitabine arm (3.8 *versus* 1.9 months, HR = 0.55, $p < 0.0001$). Upon relapse, 76% of observation and 60.4% of gemcitabine patients were able to receive pemetrexed. The overall response rate (ORR) to pemetrexed was 15.2% in the observation arm and 8.1% in the gemcitabine arm.

Switching to a new non-cross-resistant chemotherapy agent

Central to the evolution of this treatment strategy is the Goldie–Coldman hypothesis [Goldie and Coldman, 1979], which dictates that even the smallest detectable cancers contain at least one drug-resistant clone and that increasing numbers of resistant clones emerge as tumours grow and progress. To overcome this phenomenon, the use of different non-cross-resistant chemotherapy regimens in alternating or sequential fashion has been employed (Table 2). This same

Table 2. Trials of switch maintenance - cytotoxic chemotherapy agents.

Study	Induction therapy	Total patients	Response rate CR/PR stable	Treatment arms	Number randomized	Progression-free survival Median HR	p-value	Overall survival Median HR	p-value
Westeel <i>et al.</i> [2005]	Four cycles of MIC (stage wet IIIB/IV), or two cycles and (Stage III) induction therapy	573	51.9% 7.7% (IIIB) 31.7% 16.6% (IV)	Vinorelbine <i>versus</i> observation	91 vinorelbine 90 observation	5 months* 3 months* HR 0.77	0.32	12.3 months 12.3 months HR 1.08	0.65
Fidias <i>et al.</i> [2009]	Four cycles of induction carbo- platin/ gemcitabine	566	31% 43.3%	Docetaxel immedi- ately following induction <i>versus</i> Docetaxel adminis- tered at time of progression	153 immediate treatment 156 treatment at progression	5.7 months 2.7 months HR NR	0.0001	12.3 months 9.7 months HR NR	0.85
Ciuleanu <i>et al.</i> [2009]	Four cycles induction therapy with a platinum doublet	660	47% 52% (pemetrexed arm) 52% 48% (placebo arm)	Pemetrexed <i>versus</i> placebo	441 pemetrexed 222 placebo	4.3 months 2.6 months HR 0.60	<0.0001	13.4 months 10.6 months HR 0.79	<0.0001

*From date of randomization.

NR, not reported; HR, Hazard ratio; CR, complete response; PR, partial response; SD, stable disease.

hypothesis underpins the design of *maintenance* trials in which NSCLC patients are switched to a new, potentially non-cross-resistant agent if they respond to or remain stable on initial therapy. This 'switch maintenance' therapy is the most closely examined and has become the most debated [Stinchcombe, 2010].

A French study utilized this design in a trial of 573 patients who were treated initially with mitomycin, ifosfamide and cisplatin (MIC) [Westeel *et al.* 2005]. Stage IIIB patients received two cycles of chemotherapy followed by radiation (55–60 Gy in 30 fractions), and those with 'wet' IIIB and IV received four cycles of MIC. Although PS 2 patients were eligible, they constituted only 15.5% at registration. Only 181 of the 227 responding patients were randomized to receive weekly vinorelbine for 6 months or BSC. The mean duration of therapy was 13.8 weeks and only 23% of patients completed 6 months of vinorelbine. The most common reasons for stopping prematurely were progressive disease (38%) and toxicity (21%). Median survival in both groups was 12.3 months ($p=0.48$) with HRs for PFS and OS, after adjustment for stage, of 0.77 ($p=0.11$) and 1.08 ($p=0.65$), respectively. Median PFS from the date of randomization was 5 months for vinorelbine and 3 months for observation ($p=0.32$). There were no subgroup analyses reported.

A 566-patient study performed by Fidias and colleagues compared the administration of docetaxel immediately following completion of four cycles of carboplatin/gemcitabine induction to observation and docetaxel given *only at the time of documented progression* [Fidias *et al.* 2009]. Among 388 patients who completed four cycles of gemcitabine/carboplatin, 309 were randomized. Of the patients randomized to immediate docetaxel, 94.8% received at least one treatment cycle, whereas only 62.8% of patients randomized to delayed treatment ever received docetaxel. The most common reasons for not receiving docetaxel on the delayed arm were disease progression, patient or investigator decision, and death. The median number of cycles of docetaxel administered on both arms of the study was 4.4. PFS was significantly longer for patients treated immediately ($p=0.0001$). OS also favoured immediate docetaxel administration, (median 12.3 *versus* 9.7 months) although the difference was not significant ($p=0.0853$). The fact that the improved PFS did not translate into a significant

improvement in OS may simply be a result of the fact that the study was underpowered to detect a 2-month difference in OS at a significant level. At a clinical level, however, many clinicians would consider a 2-month prolongation of survival to be clinically meaningful.

There were no differences in toxicity or QoL between the two treatment groups. The marked discrepancy in the number of patients receiving the planned treatment in the delayed arm was thought by the authors to be due to declining PS at the time of progression that precluded further treatment. When the survival of the patients *who actually received docetaxel* in the delayed arm was compared with that of the treated patients in the immediate arm, no major differences were seen. This suggests that when patients stop first-line chemotherapy, they should be followed closely, in order to detect progression early and at a time when they remain fit for further treatment.

Pemetrexed has been shown to be noninferior to and better tolerated than docetaxel in the second-line treatment of NSCLC [Hanna *et al.* 2004]. Pemetrexed is also approved for the first-line treatment of nonsquamous NSCLC in combination with a platinum analogue [Scagliotti *et al.* 2008]. The JMEN study compared maintenance chemotherapy with pemetrexed with placebo in stable and responding patients treated initially with one of three platinum-based regimens [Ciuleanu *et al.* 2009]. Stable and responding patients were randomized 2:1 to receive pemetrexed or placebo. There were 660 patients randomized and an analysis by histology was a prespecified endpoint. Of the patients randomized to pemetrexed, 48% received ≥ 6 cycles and 23% ≥ 10 cycles. There was a significant PFS advantage seen in the group as a whole (HR 0.6, $p=0.00001$). Subgroup analysis revealed that patients with *nonsquamous* histology had a HR of 0.47 ($p=0.00001$, interaction p -value 0.036). When OS was examined, there remained a significant advantage in the entire treatment group (HR 0.79, $p=0.012$). Furthermore, patients with nonsquamous tumours had a median survival advantage of 5 months (15.5 *versus* 10.3 months) with a significant OS benefit (HR 0.7, $p=0.002$, interaction p -value 0.033). There were no significant differences in QoL and toxicity was modest. In the placebo arm only 19% patients received pemetrexed at any future point. This means that conclusions regarding earlier *versus* later

administration of pemetrexed cannot be drawn from this trial. However, the survival advantage in patients with nonsquamous tumours is compelling. Of particular note in this study is the fact that only patients with PS 0–1 were eligible.

Two drug regulatory bodies, the European Medicines Agency (EMA) and the Federal Drug Authority (FDA), have approved pemetrexed as maintenance chemotherapy in nonsquamous NSCLC. The FDA approval of maintenance pemetrexed in July 2009 prompted a caveat to be added to the ASCO guidelines for NSCLC as follows [Azzoli *et al.* 2009]: ‘*Special Announcement: The data supporting this change have been recently presented and were outside the scope of the comprehensive data review for this guideline. The recommendation on maintenance therapy in this guideline will be updated pending consideration of recently published relevant data.*’

Maintenance therapy with molecularly targeted agents

Several molecularly targeted agents are approved for the treatment of NSCLC, most notably, agents targeting angiogenesis [Wheatley-Price and Shepherd, 2008b] and the epidermal growth factor (EGF) pathway [Wheatley-Price and Shepherd, 2008a]. In the first-line setting, the monoclonal antibody bevacizumab that targets vascular endothelial growth factor (VEGF) and cetuximab, an antibody that targets the EGF receptor (EGFR) have been studied in large randomized trials. Modest improvements in ORR, PFS and OS have been demonstrated in most studies with the addition of these agents to platinum-based chemotherapy doublets [Pirker *et al.* 2009; Reck *et al.* 2009; Rosell *et al.* 2008; Sandler *et al.* 2006]. All studies were designed to continue maintenance antibody therapy in responding and stable patients following completion of a maximum of six cycles of chemotherapy. Whether this is necessary, or whether it simply adds to cost and the potential for toxicity, is unknown at this time as there have been no trials in which responding and stable patients were randomized either to stop or to continue treatment. The EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib have been shown to prolong survival when administered as second-line or third-line therapy in advanced NSCLC [Shepherd *et al.* 2005; Thatcher *et al.* 2005]. More recently, they have been evaluated as maintenance therapy in earlier stages of

NSCLC. The phase III studies of molecularly targeted maintenance therapy are summarized in Table 3.

EGFR inhibitors

The sequential Tarceva® in unresectable non-small cell lung cancer trial (SATURN) was a large international study in which 1949 patients were treated initially with four cycles of platinum-based chemotherapy [Cappuzzo *et al.* 2010]. Stable and responding patients ($n=889$) were randomized to receive maintenance erlotinib or placebo. The primary endpoint was PFS and patients were stratified by a number of clinical factors as well as by EGFR protein expression (assessed by immunohistochemistry [IHC]) and EGFR gene copy assessed by fluorescent *in-situ* hybridization (FISH). Both PFS and OS were significantly longer in the erlotinib arm (HR for PFS 0.71, $p<0.0001$; HR for OS 0.81, $p=0.0088$). Biomarker analysis showed that there was no significant interaction for EGFR protein expression or EGFR copy number. However, patients with EGFR sensitizing mutations in exons 19 or 21 derived significantly greater PFS benefit from maintenance erlotinib (HR 0.10, $p<0.0001$) compared with those with wild-type tumours (HR 0.780, $p=0.018$, treatment-by-mutation interaction $p<0.001$). In contrast, these biomarkers did *not* predict for a differential OS benefit, likely due to crossover to erlotinib treatment at progression.

Erlotinib maintenance has also been studied after induction therapy with paclitaxel/carboplatin and the VEGF monoclonal antibody bevacizumab in the the ATLAS (a phase IIIb trial comparing bevacizumab therapy with or without erlotinib after completion of chemotherapy with bevacizumab for first-line treatment of locally advanced, recurrent or metastatic NSCLC) trial [Kabbavar *et al.* 2010]. In this global study, 743 stable and responding patients remained on maintenance bevacizumab, and were randomized to receive oral erlotinib 150 mg daily or placebo. Patients were excluded if their PS was >1 . PFS was significantly longer in the erlotinib arm (HR 0.72, $p=0.001$), although the absolute difference in median PFS was only 1 month. PFS improvement was seen across multiple subgroups, including those defined by sex, histology, age and smoking status; molecular subgroup analyses have not been reported. There was no overall survival benefit (HR of 0.92, $p=0.56$) from the addition of erlotinib to bevacizumab. In addition,

Table 3. Phase III studies of maintenance therapy with molecularly targeted agents and immunotherapy for lung cancer.

Study	Patient population	Number	Treatment	Number randomized	Response rate	Progression-free survival	Overall survival	p-value
SATURN [Cappuzzo <i>et al.</i> 2009]	Four cycles of a platinum doublet	1949	Erlotinib <i>versus</i> placebo	438 erlotinib 451 placebo	11.9% 5.4%	Median not reported HR 0.79 CI 0.62–0.82	12 months 11 months	<0.0001 (PFS) 0.01 (OS)
ATLAS [Miller <i>et al.</i> 2009]	Four cycles of a platinum doublet and bevacizumab	1160	Bevacizumab plus erlotinib <i>versus</i> bevacizumab plus placebo	373 erlotinib 370 placebo	NR	4.76 months 3.75 months	14.4 months 13.3 months	0.0012 (PFS) 0.56 (OS)
SWOG 0023 [Kelly <i>et al.</i> 2008]	Two cycles cisplatin and etoposide + concurrent TRT followed by 3 cycles docetaxel	620	Gefitinib <i>versus</i> placebo	118 gefitinib 125 placebo	NR	8.3 months 11.7 months	23 months 35 months	0.17 (PFS) 0.013 (OS)
L-BLP25 [Nemunaitis <i>et al.</i> 2006]	Any first-line chemotherapy	171	L-BLP25 <i>versus</i> BSC	66 L-BLP25 68 BSC	NR	NR	17.4 months 13.0 months	0.11
Nemunaitis <i>et al.</i> [2006]	Completed or refused conventional therapy	75	Three dose levels** of belagen-pumatecel-L	20 cohort 1 (1.25 x 10 ⁷) 20 cohort 2 (2.5 x 10 ⁷) 21 cohort 3 (5 x 10 ⁷)	Cohort 1 11/16 Cohort 2 3/11 Cohort 3 2/13	NR	39% 1-year survival cohort 1 68% 1-year survival cohorts 2 and 3 combined	0.0069
IFCT [Perol <i>et al.</i> 2010]	Four cycles of cisplatin and gemcitabine	NR	Maintenance erlotinib <i>versus</i> BSC	155 155	53% 47%	2.9 months 1.9 months HR 0.82	Medians not reported HR 0.91	0.002 (PFS)
Takeda <i>et al.</i> [2010]	Three cycles of platinum doublet	604	Maintenance gefitinib <i>versus</i> platinum doublet x 3 cycles	302 302	34.2% 29.0%	4.3 months 4.6 months	12.9 months 13.7 months	<0.001 (PFS) 0.11 (OS)
*Includes response and stable disease. **Doses expressed as cells/injection NR, not reported; IHC+, EGFR protein expression positive; PR, partial response; SD, stable disease; PD, progression of disease; BSC, best supportive care; HR, hazard ratio; CI, confidence interval; TRT, thoracic radiation; PCI, prophylactic cranial irradiation.; PFS, progression-free survival; OS, overall survival; IFCT1, Intergroupe Francophone de Cancérologie Thoracique.								

this combination was associated with substantial toxicity which is not desirable for maintenance therapy.

In the French trial described above [Perol *et al.* 2010], which compared gemcitabine to BSC, there was a third arm in which 155 patients were randomized to receive maintenance erlotinib. The study was designed to compare erlotinib with BSC, *but not with gemcitabine maintenance*. In the erlotinib arm the median duration of treatment was 12.12 weeks, and the median PFS was 2.9 months *versus* 1.9 months for observation (HR 0.82, $p=0.002$). Of the 464 patients randomized, 204 tumour specimens were available for evaluation. In patients with EGFR positive tumours by IHC, the HR was 0.83 compared with 0.86 for those with IHC negative tumours (p -value not reported).

The EGFR inhibitor, gefitinib, also has been assessed as maintenance treatment in three randomized trials. The European Organization for the Research and Treatment of Cancer (EORTC) 08021 trial was similar in design to the SATURN study. Initially, all stable and responding patients were eligible for study, but the protocol was amended to require EGFR protein expression by IHC. This resulted in a slowing of recruitment, and ultimately led to study closure before its target accrual was reached. There was significant prolongation of PFS with a median PFS benefit of 1.2 months for maintenance gefitinib (HR 0.61, $p=0.002$). This did not translate into a statistically significant OS benefit (HR 0.81, $p=0.204$).

In the Southwest Oncology Group (SWOG) 0023 trial, good PS (0–1) patients with inoperable stage III NSCLC received induction etoposide/cisplatin administered concurrently with thoracic radiation, followed by consolidation single-agent docetaxel [Kelly *et al.* 2008]. Responding and stable patients were randomized to receive oral gefitinib (initially 500 mg and subsequently 250 mg daily) maintenance or placebo. This trial was stopped early by the data and safety monitoring committee when survival in the active treatment arm was found to be *inferior* to that of patients on placebo (median OS 23 *versus* 35 months, HR 0.63, $p=0.13$). The authors suggested three possible reasons for this: (1) there were no molecular correlates reported in this study and the authors suggested there may have been undetected imbalances in molecular

characteristics between the arms; (2) poststudy treatments may have been different between the two treatment arms but treatment at progression was not recorded; and (3) radiation was used in this study, which may change EGFR pathway signalling, resulting in the observed inferior survival seen in the gefitinib arm. Without the requisite information to draw these conclusions, it remains difficult to interpret the results of this study.

A Japanese study [Takeda *et al.* 2010] randomly assigned 604 patients to either platinum-doublet chemotherapy up to six cycles or platinum-doublet chemotherapy for three cycles followed by gefitinib 250 mg orally once daily, until progression. Despite a significant improvement in PFS (HR 0.68, $p<0.001$), the trial failed to meet its primary OS endpoint (HR 0.86, $p=0.11$). Exploratory subset analysis showed a survival advantage for patients with adenocarcinoma (HR 0.79, $p=0.03$). Molecular subset analyses were not reported.

Maintenance studies are underway investigating the role of differing doses of cetuximab and pemetrexed and cetuximab in the maintenance setting (Table 4). Also underway is a phase II trial investigating the addition of OSI 906, a small molecule, dual kinase inhibitor of both insulin-like growth factor-1 receptor and insulin receptor, administered with maintenance erlotinib.

Angiogenesis inhibitors

Two trials comparing chemotherapy alone with chemotherapy plus bevacizumab, a monoclonal antibody directed against VEGF, showed improvements in ORR and PFS [Reck *et al.* 2009; Sandler *et al.* 2006]. In both studies bevacizumab continued in responding and stable patients after chemotherapy. In the Eastern Cooperative Oncology Group (ECOG) 4599 trial [Sandler *et al.* 2006], of the 407 patients starting treatment with chemotherapy and bevacizumab, 215 (53%) continued bevacizumab monotherapy, and of these, 107 (50%) received more than five cycles in the maintenance phase. In the global bevacizumab trial [Reck *et al.* 2009], 351 patients were randomized to receive high-dose (15 mg/kg) and 345 to low-dose (7.5 mg/kg) bevacizumab. Of these, 42% and 41% of patients, respectively, continued single-agent bevacizumab as maintenance treatment after chemotherapy. In fact, 94% of patients eligible to

Table 4. Phase III maintenance trials currently accruing (from ClinicalTrials.gov).

Study	Patient population	Target accrual	Treatment	Number randomized	Primary endpoint
STOP [ClinicalTrials.gov identifier: NCT00676507]	Patients with advanced NSCLC who did not progress after up to six cycles of platinum-based chemotherapy	700	Belagenpumatucel-L <i>versus</i> placebo	Currently accruing	Overall survival
START [ClinicalTrials.gov identifier: NCT00409188]	Patients with Stage III NSCLC who do not progress after chemotherapy and TRT	1300	L-BLP 25 <i>versus</i> placebo	Currently accruing	Overall survival
CALGB 30607 [ClinicalTrials.gov identifier: NCT 00693992]	Patients with Stage IV NSCLC who do not progress after 4 cycles of platinum-based chemotherapy	244	Sunitinib <i>versus</i> placebo	Currently accruing	Progression-free survival
Paramount [ClinicalTrials.gov identifier: NCT00789373]	Patients with non-squamous stage IV NSCLC	900	Cisplatin and pemetrexed for four cycles followed by maintenance pemetrexed <i>versus</i> placebo (2:1 randomization)	Currently accruing	Progression-free survival
PointBreak [ClinicalTrials.gov identifier: NCT00762034]	Patients with non-squamous stage IV NSCLC	900	Carboplatin/pemetrexed/bevacizumab followed by maintenance pemetrexed and bevacizumab <i>versus</i> carboplatin/paclitaxel/bevacizumab followed by maintenance bevacizumab	Currently accruing	Overall survival
ClinicalTrials.gov identifier: NCT01107626]	Patients with non-squamous stage IV NSCLC	1282	Carboplatin/paclitaxel/bevacizumab followed by maintenance pemetrexed <i>versus</i> maintenance bevacizumab <i>versus</i> maintenance pemetrexed and bevacizumab	Currently accruing	Overall survival
AVAPERL 1	Patients with non-squamous stage IV NSCLC	362	Cisplatin/pemetrexed/bevacizumab followed by maintenance bevacizumab <i>versus</i> maintenance bevacizumab and pemetrexed	Currently accruing	Progression-free survival
ClinicalTrials.gov identifier: NCT00632203]	Patients with stage III/IV NSCLC	100	2-6 cycles of doublet systemic therapy, +/- radiation therapy, followed by maintenance temozolomide <i>versus</i> observation	Ongoing but not recruiting	Incidence of brain metastases

receive single-agent bevacizumab were still receiving maintenance therapy at cycle 7.

It is impossible to determine what proportion of the PFS benefit in the bevacizumab arms of these two trials might have come from maintenance treatment as neither trial was designed to answer this question. Indeed, the entire PFS and OS benefits of bevacizumab may have come from the higher response rates in the bevacizumab arms reported in *all* studies and may not have been a true maintenance effect at all. Considering the potential for toxicity and the cost of this drug, the issue of maintenance therapy with bevacizumab is one that deserves further attention. Trials testing the utility of bevacizumab administered in conjunction with pemetrexed and in conjunction with erlotinib in the maintenance setting are underway. In addition, a trial is underway testing carboplatin/paclitaxel/bevacizumab, followed by maintenance bevacizumab *versus* carboplatin/pemetrexed followed by maintenance pemetrexed and bevacizumab. All of these studies are restricted to patients with nonsquamous NSCLC (Table 4).

In addition to the monoclonal antibodies, there are a number of *oral* angiogenesis inhibitors directed against VEGF receptor tyrosine kinases, which have been investigated in combination with chemotherapy. All trials performed to date continued the oral angiogenesis inhibitor following chemotherapy in responding and stable patients. No study has demonstrated a significant PFS or OS benefit to date, and so, at this time, no conclusions can be drawn concerning the potential for benefit from maintenance therapy with these agents. However, the Cancer and Leukemia Group B (CALGB) 30607 trial is designed to address this question. In this phase III study, patients receive four cycles of platinum-based chemotherapy (bevacizumab is allowed in eligible patients), and responding and stable patients are randomized to receive sunitinib 37.5 mg daily or placebo. The primary endpoint is PFS and crossover to sunitinib is allowed at progression. This study does not administer sunitinib during the chemotherapy phase. Early stage trials investigating pazopanib and vandetinib are also underway.

Immunotherapy

Harnessing the immune response to improve the disease-free interval is a strategy that is being investigated in the maintenance setting in

NSCLC [Bradbury and Shepherd, 2008]. One agent of interest in this setting is L-BLP25 (Stimuvax; Biomira, Alberta, CA). This is a liposome vaccine targeted to the extracellular core peptide of mucin-1 (MUC1), a transmembrane protein expressed on epithelial cells. In a randomized phase 2B trial of L-BLP25, stable and responding patients with stage III/IV NSCLC who were randomized to receive vaccination weekly for 8 weeks followed by maintenance vaccination every 6 weeks or BSC [Butts *et al.* 2005]. All patients received a single infusion of cyclophosphamide 3 days before vaccine administration to reduce suppressor T-cell activity. There were 88 patients in the BSC arm and 83 in the vaccine arm. Median OS was 17.4 months for the vaccinated patients *versus* 13 months for BSC ($p=0.66$). An unplanned exploratory analysis revealed that patients with locoregional stage IIIB disease randomized to vaccine had improved survival compared with those randomized to BSC (HR 0.52, $p=0.69$). For this reason, a large international placebo-controlled trial of L-BLP25 vaccine in patients treated with chemoradiation for locally advanced stage III NSCLC is now underway: the Stimulating Targeted Antigenic Responses To NSCLC trial (START) [ClinicalTrials.gov identifier: NCT00409188]. However, it should be noted that this is maintenance of response to induction chemoradiation, a rationale that differs from the others discussed in this review.

Belagenpumatucel-L (Lucanix; NovaRx Corporation, San Diego, CA) is developed from allogeneic NSCLC cell lines that have been genetically modified to secrete antisense oligonucleotide to transforming growth factor- β 2 (TGF- β 2). A randomized phase II study of this drug recruited 75 patients with stage II–IV NSCLC, following induction therapy (or patient refusal of induction therapy) [Nemunaitis *et al.* 2006]. Patients were randomized to one of three dose levels. Patients receiving the highest dose had a median survival of 581 days, compared with 252 days for those on the lowest dose. This vaccine is now in phase III testing in the maintenance setting in patients with advanced disease who have not progressed on standard first-line induction chemotherapy as the Phase III LucanixTM Vaccine Therapy in Advanced Non-small Cell Lung Cancer (NSCLC) Following Front-line Chemotherapy (STOP) trial [ClinicalTrials.gov identifier: NCT00676507].

Predicting patients who benefit most from maintenance therapy

Response to initial therapy

As shown in Table 5, patients on the JMEN study [Ciuleanu *et al.* 2009] who demonstrated response to initial therapy (CR/PR) had a HR of 0.81 ($p=0.198$) compared with those who remained stable (HR 0.61, $p=0.0017$) (Table 5). Similarly, in the SATURN study [Cappuzzo *et al.* 2009], patients who exhibited stable disease also seemed to derive greater OS benefit from maintenance erlotinib than those who achieved CR or PR (HR 0.72, $p=0.0019$ for SD and 0.94, $p=0.618$ for CR/PR).

In contrast, in the IFCT [Perol *et al.* 2010] study the HR for PFS for patients treated with gemcitabine after CR/PR was 0.44, and for patients with stable disease it was 0.68 (p -values not reported). Similarly, in the same study, HRs for maintenance erlotinib according to CR/PR and SD showed no difference at 0.80 and 0.83, respectively.

Other trials did not report subgroup benefits by response to induction therapy. In view of these conflicting results, at this time, we feel that response cannot be recommended as a selection tool for maintenance therapy. In keeping with this, maintenance erlotinib has been approved for use by the FDA for patients *who have not progressed* following treatment with platinum therapy. In Europe, however, the EMEA has approved maintenance erlotinib only for patients who demonstrate *stable disease* and not response to induction therapy. In their summary for the public, they state clearly that ‘*stable means that the cancer had neither improved nor got worse during chemotherapy*’.

Performance status

PS is a strong prognostic factor and is predictive of survival benefit from chemotherapy in NSCLC. It is also a predictor of increased toxicity from chemotherapy [Blagden *et al.* 2003; Radzikowska *et al.* 2002]. In the trial by Socinski and colleagues discussed above, poor PS correlated with worse survival [Socinski *et al.* 2002]. Good PS patients treated with platinum-based therapy until progression exhibited a median survival of 9.1 months *versus* 6.2 months for patients with poor PS on the same treatment arm. Those patients treated with four cycles of platinum-based therapy who had good PS had a

Table 5. Survival according to response to initial therapy.

Trial	CR/PR		SD		p-value
	Median Survival	Hazard ratio	Median survival	Hazard ratio	
JMEN [Ciuleanu <i>et al.</i> 2009] OS (nonsquamous)	14.4 months pemetrexed 11.4 months placebo	0.81	16.6 months pemetrexed 8.6 months placebo	0.61	0.0017
IFCT 0502 [Perol <i>et al.</i> 2010] PFS (gemcitabine <i>versus</i> observation)	NR	0.44	NR	0.68	NR
SATURN [Cappuzzo <i>et al.</i>]	12.0 months erlotinib 12.5 months placebo	0.94	11.9 months erlotinib arm 9.6 months placebo arm	0.72	0.002
IFCT 0502 [Perol <i>et al.</i> 2010] PFS (erlotinib <i>versus</i> observation)	NR	.80	NR	NR	NR

CR, complete response; PR, partial response; SD, stable disease; IFCT, Intergroupe Francophone de Cancérologie Thoracique; SATURN, Sequential Tarceva in Unresectable NSCLC; NR, not reported.

median survival of 11.1 months compared with patients on the same treatment arm with poor PS who had a median survival of only 3.7 months. In the Cox model the hazard ratio for patients with a poor PS was 1.4 ($p=0.12$).

The CECOG trial of maintenance gemcitabine [Brodowicz *et al.* 2006] enrolled patients with $KPS \geq 70$. An analysis was performed comparing survival benefit from maintenance gemcitabine according to KPS score. OS from the time of randomization for patients with $KPS > 80$ on the maintenance gemcitabine arm was 22.9 months *versus* 8.3 months for those on observation. For patients with poor PS ($KPS 70-80$) patients derived no apparent survival benefit with median survivals of 7.0 and 7.7 months for gemcitabine maintenance and BSC, respectively. The interaction p -value was not reported.

In the negative gemcitabine maintenance study presented this year by Belani and colleagues, PS ≥ 2 was a highly significant prognostic variable for survival in the overall multivariate analysis (HR 1.5, $p=0.009$) [Belani *et al.* 2010]. Survival benefit from maintenance therapy was not presented separately, however, for patients with PS 0–1 and those with PS 2–3. The inclusion of so many poor PS patients (nearly two thirds were PS 2–3) may explain why this trial was negative, and it is hoped that more data with respect to PS will be presented in the final manuscript.

In the Fidias study of early *versus* late docetaxel [Fidias *et al.* 2009], ECOG PS 2 patients were eligible, but constituted only 10.8% of patients enrolled initially, and only 5.9% and 10.3% of patients randomized in the immediate and delayed docetaxel arms, respectively. Subgroup analysis was not reported, but in the discussion, the main reasons for patients not proceeding to delayed docetaxel were disease progression with resultant declining PS and patient decision.

In the JMEN and SATURN maintenance pemetrexed and erlotinib studies, patients with ECOG PS > 1 were not eligible. This is also true of the currently enrolling PARAMOUNT and PointBreak trials. The French study examining maintenance gemcitabine or erlotinib *versus* placebo [Perol *et al.* 2010] did allow patients with PS 2–3 on study, but their numbers were very small, constituting only 3%, 6% and 6% of the observation, gemcitabine and erlotinib arms, respectively.

Histological subtype

In the JMEN study [Ciuleanu *et al.* 2009], patients with nonsquamous histology experienced a 3.2-month survival advantage ($p < 0.0001$), mostly driven by the adenocarcinoma subgroup where the HR was 0.51 ($p < 0.0001$), with a median OS advantage of 5.3 months. In contrast, patients with squamous cell carcinoma derived no survival benefit from maintenance pemetrexed (HR 1.03, $p=0.896$) (Table 6).

In SATURN, the HR for OS for squamous cell carcinoma patients treated with erlotinib was 0.76 compared with 0.60 for patients with adenocarcinoma, but this apparent difference did not reach statistical significance. The Japanese study of maintenance gefitinib reported a HR for OS of 0.79 ($p=0.03$) in patients with adenocarcinoma and 1.24 ($p=0.25$) for nonadenocarcinoma (interaction p -value not reported). In the IFCT trial, there was no apparent difference in histologic subsets, and survival by histology was not reported for the EORTC trial.

Molecular subgroups

In SATURN [Cappuzzo *et al.* 2010], tumour samples were examined for *EGFR* copy and mutation status and *EGFR* protein expression by IHC. There were only 49 mutation positive patients and they had a HR for PFS of 0.10 ($p < 0.0001$); however, there was no significant OS benefit for this group, likely because of cross-over at progression. There was no significant interaction for either protein expression or *EGFR* copy number, although patients whose tumours were FISH or IHC positive derived numerically greater PFS and OS benefit compared with patients without these markers. Patients whose tumours expressed *EGFR* by IHC were found to have a HR for PFS of 0.69 ($p < 0.0001$) as well as significant prolongation of OS. OS was significantly prolonged with erlotinib *versus* placebo in the intention-to-treat population with a median survival of 12 *versus* 11 months (HR 0.81, $p=0.0088$). The HR for OS for patients with IHC positive tumours was only marginally better at 0.77 ($p=0.0063$).

In the IFCT study [Perol *et al.* 2010] PFS was reported according to *EGFR* IHC status. HRs for patients with *EGFR* IHC positive and negative tumours were 0.83 and 0.86, respectively (p -values not reported). The WOTG 0203 and

Table 6. Survival according to histology.

Trial	Histology	PFS			OS		
		Median	HR	p-value	Median	HR	p-value
JMEN [Ciuleanu <i>et al.</i> 2009] Pemetrexed versus placebo	Overall population	4 months	0.60	<0.0001	13.4 months	0.79	0.012
	Adenocarcinoma	2 months			10.6 months		
		4.6 months	0.51	<0.0001	15.5 months	0.73	0.026
	Nonsquamous cell carcinoma	2.7 months			10.3 months		
	Large cell carcinoma	4.4 months	0.47	<0.0001	16.8 months	0.70	0.002
	Other	1.8 months			11.5 months		
SATURN [Cappuzzo <i>et al.</i>] Erlotinib versus placebo		4.5 months	0.40	0.019	8.4 months	0.98	0.96
		1.5 months			7.9 months		
		4.1 months	0.44	0.0003	11.3 months	0.61	0.025
	Squamous cell carcinoma	1.6 months			7.7 months		
		2.4 months	1.03	0.896	9.9 months	1.07	0.68
		2.5 months			10.8 months		
WTOG [Takeda <i>et al.</i> 2010] Platinum-doublet x 3 followed by gefitinib versus Platinum-doublet x 6	Adenocarcinoma	NR	0.60	NS	NR	0.77	NS
	Squamous cell carcinoma	NR	0.76	NS	NR	0.86	NS
	Adenocarcinoma	5.1 months	0.60	<0.001	15.4 months	0.79	0.03
		4.4 months			14.3 months		
	Nonadenocarcinoma	3.4 months	1.14	0.47	7.7 months	1.24	0.25
IFCT 0502 [Perol <i>et al.</i> 2010] (Gemcitabine versus observation) IFCT 0502 [Perol <i>et al.</i> 2010] (Erlotinib versus observation)		3.6 months			9.2 months		
	Adenocarcinoma	NR	0.53	NR	NR	NR	NR
	Other		0.56				
	Adenocarcinoma	NR	0.79	NR	NR	NR	NR
	Other		0.88				
HR, hazard ratio; OS, overall survival; PFS, progression-free survival; NR, not reported.							

EORTC studies of maintenance gefitinib, did not report outcomes according to EGFR biomarkers.

Given these findings, erlotinib approval for maintenance therapy has not been linked to any EGFR marker in either the United States or Europe.

Discussion

Despite over a year of vigorous debate, and further emerging prospective evidence, there still are unanswered questions surrounding the issue of maintenance therapy in NSCLC.

In reality, when the survival benefit derived by *unselected* patients for both maintenance chemotherapy and molecular therapy is examined critically, the benefits must be considered modest at best, particularly when offset against the cost, toxicity and inconvenience for patients. However, the data become somewhat more compelling when the results are examined in specific patient subsets. For example, in the maintenance pemetrexed trial [Ciuleanu *et al.* 2009], the median survival benefit was only 2.8 months in the study overall (HR 0.79), but in patients with nonsquamous histology, the median survival advantage was 5.2 months (HR 0.70, $p < 0.0001$). This magnitude of benefit is larger than any that has been reported to date for any chemotherapeutic or molecularly targeted agent even in the first-line treatment of NSCLC, and so it cannot be ignored. Similarly, the Brodowicz and colleagues study demonstrated a remarkable survival benefit in good PS patients [Brodowicz *et al.* 2006]. The subsequent validation study suggests strongly that patients with poor PS should not be selected for maintenance chemotherapy, although the effect of PS does not seem to be as marked in the maintenance studies of EGFR TKIs, which, generally, are accepted to be tolerated better than cytotoxic chemotherapy.

Before its widespread acceptance, further study of the cost implications of maintenance therapy with either chemotherapy or molecularly targeted agents must be undertaken. One study has been published [Klein *et al.* 2010] and a National Institute for Health and Clinical Excellence (NICE) guideline has been made public [NICE, 2010] relating to the cost-effectiveness of pemetrexed. The study, costed from a US payer perspective, used a semi-Markov model comparing the cost-effectiveness of maintenance pemetrexed with erlotinib. It is important to

distinguish that this study was not designed as a head-to-head comparison, and perhaps more importantly was entirely conducted by Eli Lilly, the manufacturer of pemetrexed. This study found pemetrexed to have an acceptable incremental cost ratio (ICER) per life year gained (LYG) at US\$122,371.00 in patients with nonsquamous histology. Interestingly, the NICE approval was achieved with an ICER per quality adjusted life year gained of £43,000 per QALY (approximately US\$71,000.00). The sole reason for the difference in these two reports is drug acquisition cost since patients in the UK pay roughly half as much as patients in the US for the same drug administered for the same indication. The issue of cost, particularly in these times of global financial crisis and constant political debate in many jurisdictions over healthcare reform, is one that is crucial in any discussion of prolonged, potentially costly treatment. The 'one-size-fits-all' approach of treating all *unselected* patients with expensive chemotherapy or molecularly targeted therapies is arguably the approach that is most likely to result in *unfavourable* pharmacoeconomic profiles. To date, most cost-effective analyses (CEAs) have been performed retrospectively and frequently detailed data have been abstracted from chart review for only a subset of trial patients. The most robust data for any type of analysis come from *prospective studies*, and so, just as with QoL information, health resource utilization data that will allow meaningful CEAs should be collected *prospectively* in all future maintenance trials. However, a word of caution is necessary when interpreting costs in clinically or molecularly selected subsets of patients, as the cost-effective ratio may not always be that which is expected. A retrospective CEA by Bradbury and colleagues reported differing and favourable economic profiles in patients who demonstrated known clinical and molecular markers of response to treatment with erlotinib [Bradbury *et al.* 2008]. Unexpectedly, however, the cost per year of life gained was not the most favourable in patients with sensitizing mutations in the *EGFR* gene. This was because these patients derived relatively greater benefit and stayed on treatment *longer*, thereby incurring considerably higher drug acquisition costs. Similarly, the CEA of maintenance chemotherapy for good PS patients may also be higher since these patients are expected to derive greater benefit from maintenance chemotherapy and also are likely to stay on treatment longer. In view of this, a CEA of the SATURN and IFCT studies

would be of considerable interest. Therefore, although the way forward almost undoubtedly lies in personalizing medicine, both to benefit the patients most likely to respond and also to spend our health dollar wisely, the true cost savings may arise from *not* treating those patients who derive no benefit or only marginal benefit from treatment.

The mode of treatment delivery is always a consideration and this is especially true when treatment is prolonged. Patients may prefer oral agents rather than the inconvenience of adhering to an intravenous administration schedule [Liu *et al.* 1997] and utilization of oral agents may also mean cost savings from allied costs associated with intravenous regimens.

'*Primum non nocere*' is a fundamental ethos underpinning the practice of medicine, and nowhere is this more important than in oncology where the therapeutic index is the narrowest of all medical specialties. The way in which toxicity from oncology therapy is graded is borne from experience of adverse events endured as part of a relatively intense, but finite, course of treatment. In the maintenance setting, our willingness as clinicians to risk patient exposure to adverse events, and patients' willingness to accept toxicity, may be less, particularly if toxicity may last for months or even years. This is particularly true when the goal of treatment is not cure. What may be acceptable for a number of days as a grade 2/3 adverse event, experienced a total of six times on a cytotoxic chemotherapy regimen may not be viewed as acceptable if experienced on an ongoing seemingly endless basis. The degree of toxicity is captured in most trials in a dispassionate objective format. What is often not collected or reported is the effect that toxicity has on patient QoL. Many clinicians not in favour of maintenance therapy in NSCLC perceive a deleterious effect from continuous administration of chemotherapy or targeted agents. When we examine the evidence, however, this is not the case. Although QoL is not reported in every trial of maintenance therapy, only one study has suggested a negative effect on QoL, and this was the study that utilized platinum-based therapy until progression: a maintenance approach no longer utilized. More recent studies of maintenance therapy have found no association between prolonged therapy and deterioration in QoL. Furthermore, the PFS advantage seen in nearly all maintenance studies has been associated with a significantly longer

period without symptom deterioration, which is clearly a clinically meaningful endpoint.

Conclusion

What constitutes the optimal maintenance treatment strategy in unselected patients is yet to be determined as the maintenance trials performed to date are relatively heterogeneous in design and are difficult to compare and contrast fairly. The trials of pemetrexed and erlotinib show that benefit is derived most in specific subgroups of patients, and approvals have, in some jurisdictions, been based on these subgroups.

Clearly, maintenance therapy will not benefit all patients, and there is a pressing need to continue to identify patient subgroups most likely to benefit from this treatment strategy. There is also a need for studies to evaluate patient willingness to receive maintenance therapy, studies to evaluate surveillance algorithms for those who decide not to have maintenance therapy, and last, but far from least, independent cost analyses are urgently needed for both maintenance chemotherapy and molecularly targeted therapy.

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