

Maintenance therapies in advanced non-small-cell lung cancer

Advanced non-small-cell lung cancer is treated with upfront platinum doublet chemotherapy, which produces moderate survival improvements. Unfortunately, many patients quickly progress after first-line therapy and become unable or ineligible for additional therapies. In the past, treatment beyond four to six cycles of cytotoxic therapy was not recommended owing to lack of benefit and increased toxicity. The purpose of maintenance therapy is to provide an acceptably well-tolerated therapy, allowing patients to maintain a high quality of life with an improved survival. Maintenance therapy with cytotoxic agents such as gemcitabine or docetaxel has provided an advantage in progression-free survival but at the expense of increased cumulative toxicity. However, newer cytotoxic agents, such as pemetrexed, and biologics, such as erlotinib, bevacizumab and cetuximab, have resulted in improved patient overall survival and have offered patients manageable toxicity profiles.

KEYWORDS: bevacizumab = continuation maintenance = erlotinib = pemetrexed = quality of life = switch maintenance = toxicity

Non-small-cell lung cancer (NSCLC) has the second highest incidence of any newly diagnosed cancer and also has the highest mortality of any cancer type [1]. The majority of patients present with late-stage disease, by which time systemic therapy (chemotherapy) has become the primary treatment and platinum doublet chemotherapy is the first-line choice among patients with advanced disease (stage IIIB/IV). These treatments have produced modest but clinically significant gains in overall survival (OS) [2]. Attempts to improve on these survival benefits, utilizing longer treatment durations or continuation of chemotherapy with a different agent, such as docetaxel or gemcitabine, beyond four to six cycles or until disease progression, have resulted in no significant gains [3-5]. In fact, continuation of these therapies has only provided improvements in progression-free survival (PFS), with increased toxicity and no improvement in OS. Until recently, the American Society of Clinical Oncology (ASCO) guidelines recommended that all patients with good performance status (PS) discontinue first-line cytotoxic chemotherapy at disease progression, after four cycles in nonresponders and, regardless of ongoing response, patients discontinue cytotoxic therapy after a total of six cycles [6]. To date, with the accummulation of more data, patients can be considered for maintenance therapy, which is initiated following a platinumbased treatment in the setting of no evidence of progression [7-11].

There are two types of maintenance therapy, both adapted from the National Comprehensive Cancer Network [101]: continuation maintenance, which refers to the ongoing administration of at least one of the agents used in the first-line, and switch maintenance, which refers to the initiation of a different agent not included in the first-line regimen, continued in the absence of progression after four to six cycles of initial therapy [12]. The major goals of maintenance therapy are to improve the survival benefit of first-line therapy without significant increases in toxicity or decreases in quality of life (QOL). This article will focus on the most recent data presented on continuation and switch maintenance therapy, with a focus on both cytotoxic and biological agents, including docetaxel, gemcitabine, pemetrexed, erlotinib, bevacizumab and cetuximab.

Continuation maintenance: cytotoxic agents

Gemcitabine maintenance

Belani *et al.* recently presented, in abstract form, the results from a randomized Phase III trial in advanced NSCLC with four cycles of upfront gemcitabine/carboplatin followed by randomization to maintenance gemcitabine or best supportive care (BSC) (TABLE 1) [13]. BSC consisted of pain control and treatment of infections, palliative management of pleural effusions and transfusion/nutritional support. The study was closed early owing to slow accrual, but a total of

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Future

erapy of advan	iced lung cancer.				
otal number f patients	PFS	OS (months)	Second-line or poststudy therapy received	Second-line or poststudy therapy toxicity	Ref.
nmediate ocetaxel: 309 elayed ocetaxel: 309	5.7 (immediate) versus 2.7 (delayed) months; p = 0.001	12.3 versus 9.7 (p > 0.05)	63% of patients in delayed arm received docetaxel	1	[22]
iemcitabine naintanence: 128 SC: 127	7.7 versus 7.4 months; p = not significant	8.0 versus 9.3 (p > 0.05)	~20% patients in both arms received any second-line therapy	Increased toxicity in gemcitabine arm	[13]
bservation: 155 emcitabine: 154 rlotinib: 155	3.8 (gemcitabine) versus 1.9 months; p < 0.0001 2.9 (erlotinib) versus 1.9 months; p = 0.002	Gemcitabine versus observation: HR = 0.86 (95% CI: 0.66–1.12) erlotinib versus observation: HR = 0.91; not significant	Second-line therapy: observation: 76%, gemcitabine: 60% and erlotinib: 63%	Increased PRBC and ESA use in gemcitabine arm; increased rash in erlotinib arm	[14]
lotinib: 438 lacebo: 451	12.3 (erlotinib) versus 11.1 (placebo) weeks; p < 0.0001	12.0 (erlotinib) versus 11.0 (placebo); p = 0.0088	21% of patients ($n = 95$) in the placebo arm received second-line erlotinib; 71% in the erlotinib arm and 72% in the placebo arm received further therapies	1	[18]
68 subgroup not specified)	 4.8 (bevacizumab plus erlotinib) versus 3.7 (bevacizumab plus placebo) months; p = 0.0012 	1	1	1	[19]
emetrexed: 441 SC: 222	4.3 (pemetrexed) versus2.6 (BSC) months;p < 0.0001	13.4 (pemetrexed) versus 10.6 (BSC); $p < 0.012$ Adeno: 16.8 (pemetrexed) versus 11.5; $p < 0.0001$	Second-line therapy: 51% (pemetrexed) and 67% (BSC); 18% (n = 41) in the placebo arm received second-line pemetrexed	Increased fatigue, myelosuppression and gastrointestinal toxicity in pemetrexed arm	[10]

[6]

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61% (cetuximab) versus

Second-line therapy:

11.3 (cetuximab) versus 10.1; p = 0.044

Not significant

chemotherapy: 557

cetuximab maintenance

plus cetuximab to

versus cisplatin plus

vinorelbine alone

Chemotherapy

alone: 568

Cetuximab plus

Total: 1125

Cisplatin plus vinorelbine

Pirker *et al.*

(FLEX)

Platinum doublet to 2:1

Ciuleanu *et al.*

bevacizumab alone

oevacizumab or

randomization to pemetrexed or BSC

until POD

Platinum doublet plus

bevacizumab to

et al. (ATLAS)

Kabbinavar

erlotinib plus

(chemotherapy alone)

66% of patients

8

L

15 treatment-related deaths in the chemotherapy plus

12.3 (carboplatin, paclitaxel and bevacizumab) versus bevacizumab group

10.3; p < 0.001

bevacizumab) versus 4.5

6.2 (carboplatin,

paclitaxel and

paclitaxel) months;

p < 0.001

paclitaxel: 444

maintenance versus six

cycles of carboplatin

and paclitaxel

(carboplatin and

bevacizumab: 434 Carboplatin and

paclitaxel and

bevacizumab to

bevacizumab

paclitaxel and

Carboplatin,

Total: 878

Six cycles of carboplatin,

Sandler *et al.*

<u>able 1. Key trials in maintenance therapy of</u>

Regimen

Author

gemcitabine/carboplatin

Four cycles of

Fidias et al.

to immediate versus

delayed docetaxel

Gemcitabine/carboplatin

Belani *et al.*

maintenance versus BSC

to gemcitabine

gemcitabine/cisplatin to

Four cycles of

Perol *et al.*

gemcitabine versus

observation, or erlotinib

versus observation

Four cycles of platinum

Cappuzzo

et al. (SATURN) doublet to erlotinib

or placebo

Therapy (2011) 8(1)

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ATLAS: Adjuvant Tamoxifen Longer Against Shorter; BSC: Best supportive care; ESA: Erythropoiesis-stimulating agent; FLEX: First-line Erbitux in Lung Cancer; OS: Overall survival; PFS: Progression-free survival; POD: Progression of disease; PRBC: Packed red blood cell; SATURN: Sequential Tarceva in Unresectable non-small-cell lung cancer.

519 participants were still enrolled. The median patient age was 67 years, 86% had stage IV disease and 25% had Eastern Cooperative Oncology Group (ECOG) PS 2.

In the Belani study, the median PFS and OS were 3.9 versus 3.8 months and 8.0 versus 9.3 months for the gemcitabine versus BSC arms, respectively (p > 0.05). Grade 3/4 myelo-suppression and fatigue were higher in the gemcitabine maintenance arm. It is important to note that less than 20% of patients in both groups went on to receive any second-line therapy. This was believed to be partly because, at the time of eligibility for second-line therapy, 64% of all patients had a poor PS (ECOG \geq 2). Owing to this trial being terminated early, significant conclusions regarding the role of gemcitabine as maintenance therapy are impossible.

Another trial, published recently in abstract form, provided more favorable results. Perol et al. conducted a trial designed to evaluate the role of maintenance therapy with either gemcitabine or erlotinib compared with observation in patients with advanced NSCLC who were first treated with induction gemcitabine/cisplatin for four cycles (TABLE 1) [14]. The primary end point was PFS, with OS as a secondary end point. The trial was not designed to determine superiority among maintenance therapy arms. A total of 834 subjects (>90% with ECOG PS 0/1), including 63-67% with adenocarcinoma and 91-93% with stage IV disease, were enrolled. In all three groups (gemcitabine, erlotinib and observation), the induction therapy disease control rate (stable disease plus partial response plus complete response) was 53%. The recommended second- and third-line therapy choices for this trial were pemetrexed, and docetaxel or erlotinib (if not already received), respectively. The PFS rates for gemcitabine versus observation were 3.8 versus 1.9 months (p < 0.0001), and the PFS for erlotinib versus observation were 2.9 versus 1.9 months (p = 0.002). OS results have not yet reached maturity. Subgroup analysis demonstrated a PFS benefit in patients with EGFRpositive (by immunohistochemistry), wild-type EGFR tumors, adenocarcinoma and squamous cell carcinoma, with the most impressive results seen in the EGFR mutation-positive tumors (HR of 0.10; 95% CI: 0.04–0.25, p < 0.0001). In contrast to the trial of Belani et al., more than 60% of patients in all groups went on to receive additional second- or third-line therapies. The authors concluded that maintenance therapy involving gemcitabine and erlotinib delayed progression of disease regardless of histology,

especially in patients who achieved a minimum of stable disease after induction therapy, with predictable yet manageable increased toxicity. However, without mature or convincing survival data maintenance gemcitabine should only be used under the guidance of a clinical trial or under very select circumstances.

Continuation maintenance: biological agents

The first landmark trial to demonstrate a survival benefit with maintenance therapy was ECOG 4599 (TABLE 1). In this trial, 878 patients with advanced NSCLC and nonsquamous histology were randomized to chemotherapy with paclitaxel and carboplatin (PC) or PC plus bevacizumab (PCB), with the latter continued until disease progression after six cycles of PC [8]. In the study 44% were treated with PCB and 42% were treated with PC; patients who were 65 years old or above, and 88% of patients in both arms had either adenocarcinoma or an otherwise nonspecified histology. The ECOG PS was identically balanced between arms with PS 0 (40%) and PS 1 (60%). Patients in the PCB combination group demonstrated significantly improved OS versus those in the PC group (12.3 vs 10.3 months; p = 0.003) and significantly improved PFS and response rates (PFS: 6.2 vs 4.5 months, p < 0.001; response rate: 35 vs 15%, p < 0.001), suggesting a potentially important and beneficial role for bevacizumab as a maintenance therapy.

The First-Line Erbitux in Lung Cancer (FLEX) trial published by Pirker et al. was a multicenter, international trial of treatment-naive advanced-stage patients randomized to either chemotherapy alone (cisplatin 80 mg/m² on day 1 plus vinorelbine 25 mg/m² on days 1 and 8) every 21 days, given for up to six cycles, or the same chemotherapy plus cetuximab, administered weekly, beyond chemotherapy, until disease progression (TABLE 1) [9]. Approximately a third of subjects in each arm had squamous histology, while approximately 50% had adenocarcinomas. In both arms, patients had a median number of four chemotherapy cycles. Cetuximab was given for a median duration of 18 weeks (range 1-135 weeks). Response rates were higher with the addition of cetuximab (36 vs 29%; p = 0.01), and patients who received chemotherapy plus cetuximab demonstrated an improved median OS (11.3 vs 10.1 months; p = 0.044). PFS improvement was not significant. The main cetuximab-related toxicity was an acne-like rash (57/548 or 10% grade 3). More

patients in the chemotherapy-alone arm received second-line therapy at progression than in the cetuximab arm (66 vs 61%, respectively).

A separate multicenter Phase III trial (Bristol-Myers Squibb [BMS]099) evaluated the combination of carboplatin and paclitaxel with or without cetuximab plus maintenance (continued until progression) [15]. All histology subtypes were included and no EGF receptor (EGFR) testing for enrollment was carried out. Patient characteristics included more than 98% with ECOG PS 0/1, 8% in the cetuximab group and 7% in the chemotherapy group who never smoked, and 88% in the cetuximab group and 86% in the chemotherapy group had stage IV disease. Neither the primary end point of PFS nor the secondary end point of OS reached statistical significance (PFS: 4.40 vs 4.24 months, p = 0.2358; OS: 9.69 vs 8.38 months, p = 0.1685). Toxicity was acceptable in both arms, with 10.5% of patients in the cetuximab arm versus 0% in the chemotherapy arm showing an acne-like rash. In a retrospective analysis of this study, which evaluated the potential predictive role of K-Ras or EGFR mutations (i.e., response rate, PFS or OS) to cetuximab, no significant association was shown for either biomarker [16].

Overall, the FLEX trial demonstrated a modest improvement in OS, whereas the BMS099 trial did not yield significant survival gains. Both demonstrated increased toxicity with the addition of cetuximab to chemotherapy. Without a trial randomizing patients to upfront combination chemotherapy plus cetuximab or placebo followed by maintenance cetuximab or placebo, it is difficult to assign the survival benefit to upfront or maintenance cetuximab therapy. The FLEX trial regimen remains a viable choice for patients with advanced NSCLC and can be considered, in particular, for patients with squamous histology who cannot be offered pemetrexed or bevacizumab.

Switch maintenance: targeted therapy Erlotinib maintenance

Erlotinib is an attractive consideration for maintenance therapy owing to its oral formulation and its favorable safety profile (primarily manageable rash and diarrhea, which usually diminish over time) [7.17]. This article will review the results of two recently reported large trials [18,19]. The Sequential Tarceva in Unresectable NSCLC (SATURN) trial is a placebo-controlled Phase III study that tested erlotinib as a maintenance therapy in patients with advanced-stage NSCLC who did not experience progression after four cycles of the physicians' choice platinum doublet (TABLE 1) [18]. Bevacizumab or pemetrexed were not allowed as first-line therapies. The trial enrolled 1949 participants, with 889 achieving stable disease or better after induction. The study population included 438 versus 451 patients with stage IIIB/IV NSCLC in the erlotinib versus placebo arms, with the following breakdown: 14% erlotinib versus 15% placebo with Asian ethnicity, 18% erlotinib versus 17% placebo who never smoked, and 27% erlotinib versus 25% placebo who were women. EGFR immunohistochemistry status was determined $(\geq 10\%$ positive result) for all patients. Primary end points were PFS for all patients and PFS for patients with EGFR-positive tumors.

At 6 months, only 83 patients still remained on the erlotinib arm and 53 patients remained on placebo. The median PFS was 12.3 weeks versus 11.1 weeks (p < 0.0001) in favor of erlotinib. Subgroup analysis showed a PFS benefit in patients with EGFR-positive tumors and by immunohistochemistry, those with wild-type EGFR, adenocarcinoma and squamous cell carcinoma, with the most impressive results seen in the EGFR mutation-positive tumors (hazard ratio [HR] of 0.10; 95% CI: 0.04-0.25; p < 0.0001). The OS (secondary end point) was significantly in favor of erlotinib (12.0 vs 11.0 months; p = 0.0088), and the benefit persisted regardless of EGFR status (EGFRpositive by immunohistochemistry: HR of 0.77, 0.64-0.93, p = 0.0063; wild-type EGFR: HR of 0.77, 95% CI: 0.61-0.97, p = 0.0243), and was more pronounced in those who had stable disease (median: 11.9 vs 9.6 months, HR of 0.72, 95% CI: 0.59–0.89, p = 0.0019) versus those who had complete or partial response (median 12.5 vs 12.0 months, HR 0.94, 95% CI: 0.74-1.20, p = 0.618) following chemotherapy. Toxicity was predictable, with 60% of patients experiencing rash and 18% experiencing diarrhea within the treatment group compared with 0% in the placebo arm. In the placebo group, 21% of patients (n = 95) received second- or third-line erlotinib. No differences in QOL were found between the two arms. The trial reached its primary end point of demonstrating a PFS benefit with maintenance erlotinib (improvement in OS was also obtained); however, these improvements were only modest. Therefore, the question of whether maintenance erlotinib is superior to second-line therapy remains unanswered since only a small subset of the placebo arm patients received erlotinib.

A second study evaluating the role of erlotinib maintenance after platinum doublet plus bevacizumab induction has recently been presented. In this study, 1160 patients with advanced NSCLC were treated with first-line platinumbased therapy plus bevacizumab, followed by 743 patients continuing on bevacizumab and randomized to receive bevacizumab plus placebo (bevacizumab + placebo) or maintenance erlotinib (bevacizumab + erlotinib) [19]. The median PFS was 4.8 months for bevacizumab + erlotinib versus 3.7 months for bevacizumab + placebo (HR = 0.72, 95% CI: 0.59–0.88, p = 0.0012). The median OS data revealed a statistically nonsignificant difference between bevacizumab + erlotinib and bevacizumab + placebo (14.4 vs 13.6 months). In addition, erlotinib has begun to be evaluated in unresectable stage III patients treated with concurrent chemoradiotherapy, followed by erlotinib maintenance in a Phase II single-arm study, and we await the long-term results on these data [20].

With the advent of newer biological agents, one has to balance the cost of these maintenance therapies with the gains in PFS and OS, all the while considering the additional toxicities of the regimens. Whether this would translate into futile spending or whether money would be saved is certainly a hot topic in the future of lung cancer oncology. This was recently addressed by Klein *et al.*, who evaluated the cost per life-year gained using pemetrexed or erlotinib maintenance compared with BSC [21]. Maintenance therapy with either drug resulted in over \$200,000 cost per lifeyear saved compared with observation alone. A full discussion of the financial aspects of maintenance therapy is beyond the scope of this article.

Switch maintenance: cytotoxic therapy Docetaxel maintenance

Fidias et al. performed a study evaluating the role of immediate compared with delayed docetaxel after front-line therapy with four cycles of gemcitabine and carboplatin for advanced-stage (IIIB/IV) NSCLC (TABLE 1) [22]. Of the 536 participants who enrolled, 398 completed gemcitabine/carboplatin and 309 were randomized. A total of 254 patients were excluded owing to progression while on firstline therapy. Participants randomized had stable disease or better. The median age of the entire cohort was 65 years, 85% were stage IV and 89% of the patients had ECOG PS 0 or 1. The immediate treatment arm received docetaxel every 21 days for up to six cycles, starting at the time of progression with response evaluation every 6 weeks versus every 3 months in the delayed treatment group.

A total of 145 out of 153 patients in the immediate treatment group received at least one cycle of docetaxel maintenance, compared with 98 out of the 156 patients allocated to the delayed docetaxel arm. Toxicity was similar between the groups, with myelosuppression being the most common reason for dose adjustments or discontinuation.

In the Fidias et al. trial, the median PFS was significantly greater in the immediate docetaxel arm (5.7 vs 2.7 months; p = 0.0001). The median OS in the immediate docetaxel arm (n = 153 patients)was 12.3 months compared with 9.7 months in the delayed arm (n = 156); however, this was not significant (p = 0.0853). The OS was identical at 12.5 months among patients in both arms who actually received at minimum of one cycle of maintenance docetaxel. A total of 63% of patients randomized to delayed therapy received docetaxel. QOL was not different between the groups. Overall, the authors concluded that there was a statistically significant PFS benefit and that OS in the delayed arm could be improved to the same level as immediately treated patients upon initiation of treatment. One potential design flaw of the study was that the surveillance in the delayed arm was every 3 months, rather than every 6 weeks, which could have overlooked early progression. Therefore, since we do not know whether outcomes would have been different if the surveillance CT scans had been performed at the same frequency, it is not possible to determine which patients should receive delayed therapy.

Pemetrexed maintenance

In the pivotal trial by Ciuleanu and colleagues (TABLE 1), which led to FDA approval of pemetrexed as a maintenance therapy, 663 patients with stage IIIB/IV NSCLC were enrolled from 20 countries [10]. This was a double-blind, placebo-controlled study that included nonprogressors (n = 663) following four cycles of platinum doublet therapy. Patients were randomized in a 2:1 ratio to either pemetrexed maintenance (n = 441) every 21 days until progression or placebo and BSC (n = 222). The doublets included six choices: gemcitabine-carboplatin, gemcitabine-cisplatin, paclitaxel-carboplatin, paclitaxel-cisplatin, docetaxel-carboplatin or docetaxel-cisplatin. The study arms (pemetrexed vs BSC) were well balanced, with all patients having ECOG PS 0 or 1. Approximately 50 versus 48% had adenocarcinomas, 26% versus 28% were nonsmokers, and 30 versus 32% were of East/West Asian descent for pemetrexed versus BSC, respectively. Response evaluations were obtained every two cycles (every 6 weeks) via CT

scan or MRI after initial baseline scan following initial doublet therapy. After disease progression, patients were unmasked to study treatment and followed every 90 days until death. Subsequent therapy was allowed off-trial. The primary end point, PFS, was significantly improved in the pemetrexed arm compared with BSC (4.3 vs 2.6 months; p < 0.0001). OS was also improved in the pemetrexed arm (13.4 months vs 10.6 months; p < 0.012). The median OS was most impressive in those with adenocarcinoma receiving maintenance pemetrexed (16.8 vs 11.5 months; p < 0.0001). Differential toxicities (all grades) were worse with maintenance and primarily consisted of fatigue (24 vs 10%), nausea (19 vs 5%) and anemia (15 vs 5%). The median number of pemetrexed cycles administered was 5.0 (1-55) compared with 3.5 (1-46) in the BSC arm. In addition, 51% (227/441) of patients on the pemetrexed arm received postmaintenance second-line therapy, whereas 67% (149/222) in the placebo arm received any second-line therapy. One important concern of the trial was that only 18% of patients in the placebo arm crossed over to receive pemetrexed therapy. Therefore, whether patients could have benefited equally from delayed pemetrexed at disease progression still remains unanswered. Overall, it was a well-done trial that adds credence to the use of pemetrexed maintenance in nonsquamous histology; however, future questions remain regarding whether pemetrexed should be included as an upfront platinum doublet and continued as maintenance or whether switch maintenance, as studied previously, is the best strategy.

Conclusion

A major problem that exists in advanced NSCLC is that, despite the fact that patients will inevitably progress after front-line platinum doublet therapy, less than 50% of patients ever proceed to receive a second-line agent [23]. The reasons for not receiving a second-line agent include, but are not limited to, death of the patient, residual grade 3 toxicity or patient/family preference. In addition, over time, patients' PS and QOL tend to decrease [4]. These declines are seen regardless of whether or not the patient receives maintenance therapy and may occur to the point that patient is then rendered ineligible to receive second-line therapy. Maintenance therapy allows for more frequent surveillance of disease and clinical status, which may improve survival.

We evaluated the maintenance data of the cytotoxic agents, docetaxel and gemcitabine (TABLE 1). Docetaxel maintenance, either immediate or delayed, produced a 3-month improvement in PFS with a trend toward an OS advantage. Gemcitabine was highly toxic as maintenance with only one study demonstrating a 1.9 PFS benefit compared with observation. Cytotoxic maintenance therapy with these agents cannot be recommended outside of the clinical trial setting. We have discussed several trials that randomized patients to four to six cycles upfront of platinum doublet therapy with or without a biological agent, followed by a biological or targeted maintenance therapy. Overall, pemetrexed maintenance provided the most significant OS and PFS benefit (TABLE 1), especially when evaluating patients with adenocarcinoma histology. Bevacizumab, cetuximab and erlotinib offered more modest gains in OS and PFS. These therapies remain viable options for patients and physicians who choose to offer maintenance therapy. Despite these findings, several questions remain regarding the optimal timing of biological therapy. For example, does the survival advantage result from combination upfront therapy, or could the same survival be achieved by providing cetuximab or bevacizumab as maintenance without upfront therapy? Outside of a clinical trial, this question remains unanswered.

The benefits of maintenance therapy need to be balanced with the negative aspects of ongoing treatment for patients. Patients must be willing to stay on continued therapy after enduring four to six cycles of potentially toxic treatment. Toxicity can be increased with prolonged therapy and can be potentially cumulative over time. The out-of-pocket costs will be another ongoing issue for patients, and whether insurance carriers or national healthcare plans will pick up the costs for maintenance therapies. The decision to administer maintenance therapy or simply observe patients should only be made after an informed discussion between the physician and patient to help the decision-making process. The patient should be of adequate PS and have little residual toxicity to allow endurance of maintenance therapy, but this must be balanced with the patient's lifestyle and QOL preferences. Given the inconvenience and potential toxicity, a high bar must be met prior to the consideration of maintenance therapy for all patients.

Future perspective

The area of maintenance therapy remains a hot topic regarding clinical trials. A search for 'advanced non-small-cell lung cancer and maintenance' under the clinicaltrials.gov website generates 43 results [102]. Some notable trials include vaccine-based therapies, novel targeted agents, such

as human endostatin inhibitors combined with conventional chemotherapies, and numerous trials that involve gefitinib, erlotinib, cetuximab, bevacuzimab and pemetrexed, or combinations. One trial of interest is Study of Avastin[®] (bevacizumab) With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous NSCLC (AVAPERL1). This open-label study will assess the efficacy and safety of bevacizumab with or without pemetrexed as maintenance therapy in patients with advanced, metastatic or recurrent NSCLC. In the first phase of the study, patients will receive four cycles of treatment with bevacizumab (7.5 mg/kg intravenously) plus cisplatin (75 mg/m² intravenously) and pemetrexed (500 mg/m² intravenously) on day 1 of each 3-week cycle. In the maintenance phase of the trial, patients who respond to treatment will be randomized to receive maintenance therapy with or without pemetrexed until progression [103]. A similarly anticipated trial is being carried out by Patel *et al.*: this is a randomized Phase III trial comparing carboplatin/pemetrexed and bevacizumab for six cycles, followed by combined pemetrexed and bevacizumab maintenance versus the ECOG 4599 regimen of carboplatin–taxol–bevacizumab followed by bevacizumab maintenance until progression or toxicity [24]. Both of these trials should provide clinicians with answers regarding how to best

Executive summary

Background

- Advanced non-small-cell lung cancer (NSCLC) is treated with upfront platinum doublet chemotherapy.
- Many patients quickly progress after first-line therapy and become ineligible for additional therapies.
- The goal of maintenance therapy is to provide a relatively well-tolerated treatment regimen, which also maintains a high quality of life and results in improved survival.
- There are two types of maintenance therapy, continuation and switch maintenance.

Cytotoxic agents

- Docetaxel maintenance, either immediate or delayed, produced a 3-month improvement in progression-free survival (PFS) with a trend toward an overall survival (OS) advantage.
- Gemcitabine is highly toxic as a maintenance therapy, with only one study demonstrating a 1.9-month PFS benefit compared with observation.
- Cytotoxic maintenance therapy with these agents cannot be recommended outside of the clinical trial setting.

Continuation maintenance: biological agents

- Eastern Cooperative Oncology Group (ECOG) 4599 randomized patients with advanced NSCLC with nonsquamous histology to chemotherapy with paclitaxel and carboplatin alone or paclitaxel and carboplatin plus bevacizumab followed by maintenance bevacizumab. The paclitaxel and carboplatin plus bevacizumab arm resulted in an OS difference of 12.3 months (paclitaxel and carboplatin plus bevacizumab) versus 10.3 months (paclitaxel and carboplatin).
- The First-Line Erbitux in Lung Cancer (FLEX) trial randomized patients 1:1 to either chemotherapy alone, cisplatin plus vinorelbine or chemotherapy plus cetuximab. Response rates and OS reached significance, favoring the cetuximab maintenance arm: response rates of 36 versus 29% and OS of 11.3 versus 10.1 months, respectively.
- A retrospective analysis of the FLEX trial was published, which evaluated whether K-Ras or EGF receptor mutations could predict responsiveness, PFS or OS for cetuximab, but there were no significant associations found.

Switch maintenance: erlotinib & bevacizumab

- The Sequential Tarceva in Unresectable NSCLC (SATURN) trial was a placebo-controlled Phase III study to test erlotinib as a maintenance therapy in advanced-stage NSCLC patients who did not experience progression after four cycles of physicians' choice platinum doublet. The median PFS was 12.3 versus 11.1 weeks (p < 0.0001) in favor of erlotinib maintenance.</p>
- A second study, the Adjuvant Tamoxifen Longer Against Shorter (ATLAS) trial, evaluated the role of erlotinib maintenance after a platinum doublet plus bevacizumab induction. The median PFS was 4.8 months for bevacizumab plus erlotinib versus 3.7 months for bevacizumab plus placebo.

Switch maintenance: pemetrexed

Pemetrexed was studied in a large multicenter trial that enrolled nonprogressing patients with advanced-stage disease following four cycles of platinum doublet therapy, which did not include pemetrexed induction. The primary end point, PFS, was significantly improved in the pemetrexed arm compared with best supportive care (4.3 vs 2.6 months; p < 0.0001). OS was also improved in the pemetrexed arm (13.4 months vs 10.6 months; p < 0.012). The median OS in patients with adenocarcinoma treated with pemetrexed maintenance was 16.8 versus 11.5 months.</p>

Conclusion

- Maintenance therapy allows patients to continue or switch therapies after induction treatment, with the cost of increased toxicity, and benefit of increased surveillance and modest improvements in PFS and OS.
- As trials move forward, we will have to answer whether the survival advantage from maintenance therapy results from combination upfront therapy, or whether the same survival could be achieved by providing upfront targeted agents combined with platinum doublets.
 The benefits of maintenance therapy need to be balanced with the negative aspects of ongoing treatment for patients.

combine targeted agents in the maintenance setting. The next decade is likely to include multiple immunological or vaccine-based therapies and further targeted or molecular-based therapies, which can offer patients hope of improved survival and maintenance of QOL.

The ideal trial design would incorporate molecular analyses and develop further methods to predict which patients would be at risk of rapid progression and, thus, identify ideal candidates for maintenance therapy.

Financial & competing interests disclosure

A Chiappori has received honoraria for speaking engagements from Genentech and Eli Lilly. J Gray has received honoraria for speaking engagements and advisory services from Eli Lilly. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as: • of interest

- of considerable interest
- Jemal A, Siegel R, Xu J, Ward E: Cancer statistics, 2010. CA Cancer J. Clin. 60(5), 277–300 (2010).
- 2 Schiller JH, Harrington D, Belani CP *et al.*: Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N. Engl. J. Med.* 346(2), 92–98 (2002).
- Belani CP, Barstis J, Perry MC et al.: Multicenter, randomized trial for stage IIIb or IV non-small-cell lung cancer using weekly paclitaxel and carboplatin followed by maintenance weekly paclitaxel or observation. J. Clin. Oncol. 21(15), 2933–2939 (2003).
- 4 Socinski MA, Schell MJ, Peterman A et al.: Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIb/IV non-small-cell lung cancer. J. Clin. Oncol. 20(5), 1335–1343 (2002).
- 5 Brodowicz T, Krzakowski M, Zwitter M et al.: Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a Phase III trial. Lung Cancer 52(2), 155–163 (2006).
- 6 Azzoli CG, Baker S Jr, Temin S *et al.*: American society of clinical oncology clinical practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J. Clin. Oncol.* 27(36), 6251–6266 (2009).
- 7 Shepherd FA, Rodrigues Pereira J, Ciuleanu T et al.: Erlotinib in previously treated non-small-cell lung cancer. N Engl. J. Med. 353(2), 123–132 (2005).
- 8 Sandler A, Gray R, Perry MC *et al.*: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.* 355(24), 2542–2550 (2006).
- The Eastern Cooperative Oncology Group (ECOG) 4599 trial found that carboplatin/taxol plus bevacizumab followed

by bevacizumab maintenance is superior to carboplatin/taxol alone in advanced non-small-cell lung cancer (NSCLC).

- 9 Pirker R, Pereira JR, Szczesna A et al.: Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised Phase III trial. *Lancet* 373(9674), 1525–1531 (2009).
- Results from the First-Line Erbitux in Lung Cancer (FLEX) trial demonstrated that cisplatin/vinorelbine plus cetuximab followed by cetuximab maintenance is superior to cisplatin/vinorelbine alone in advanced NSCLC.
- 10 Ciuleanu T, Brodowicz T, Zielinski C et al.: Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, Phase 3 study. Lancet 374(9699), 1432–1440 (2009).
- Results from the JMEN trial demonstrated that pemetrexed maintenance in patients with disease control following a platinum doublet is superior to best supportive care in advanced NSCLC.
- 11 Hanna N, Shepherd FA, Fossella FV et al.: Randomized Phase III trial of pemetrexed versus docetaxel in patients with non-smallcell lung cancer previously treated with chemotherapy. J. Clin. Oncol. 22(9), 1589–1597 (2004).
- 12 Eaton KD, Martins RG: Maintenance chemotherapy in non-small cell lung cancer. J. Natl Compr. Canc. Netw. 8(7), 815–821 (2010).
- 13 Belani CP, Waterhouse DM, Ghazal H et al.: Phase III study of maintenance gemcitabine (G) and best supportive care (BSC) versus BSC, following standard combination therapy with gemcitabine-carboplatin (G-CB) for patients with advanced non-small cell lung cancer (NSCLC). J. Clin. Oncol. (Meeting Abstracts) 28(Suppl. 15), 7506 (2010).
- 14 Perol M, Chouaid C, Milleron BJ et al.: Maintenance with either gemcitabine or erlotinib versus observation with predefined

second-line treatment after cisplatingemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 Phase III study. J. Clin. Oncol. (Meeting Abstracts) 28(Suppl. 15), 7507 (2010).

- 15 Lynch TJ, Patel T, Dreisbach L *et al.*: Cetuximab and first-line taxane/carboplatin chemotherapy in advanced non-small-cell lung cancer: results of the randomized multicenter Phase III trial BMS099. *J. Clin. Oncol.* 28(6), 911–917 (2010).
- The Bristol-Myers Squibb (BMS)-099 trial demonstrated that, in patients with advanced NSCLC, carboplatin/paclitaxel/cetuximab followed by cetuximab maintenance was not superior to carboplatin/paclitaxel alone.
- 16 Khambata-Ford S, Harbison CT, Hart LL et al.: Analysis of potential predictive markers of cetuximab benefit in BMS099, a Phase III study of cetuximab and first-line taxane/carboplatin in advanced non-small-cell lung cancer. J. Clin. Oncol. 28(6), 918–927 (2010).
- 17 Reck M, Van Zandwijk N, Gridelli C et al.: Erlotinib in advanced non-small cell lung cancer: efficacy and safety findings of the global Phase IV tarceva lung cancer survival treatment study. J. Thorac. Oncol. 5(10), 1616–1622 (2010).
- 18 Cappuzzo F, Ciuleanu T, Stelmakh L et al.: Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled Phase 3 study. *Lancet Oncol.* 11(6), 521–529 (2010).
- Erlotinib maintenance following a platinum doublet extended overall survival by 1 month compared with placebo in patients with advanced NSCLC.
- 19 Kabbinavar FF, Miller VA, Johnson BE, O'connor PG, Soh C; Atlas Investigators: Overall survival (OS) in ATLAS, a Phase IIIb trial comparing bevacizumab (B) therapy with or without erlotinib (E) after completion of chemotherapy (chemo) with B for first-line treatment of locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC). *J. Clin. Oncol. (Meeting Abstracts)* 28(Suppl. 15), 7526 (2010).

- 20 Vazquez S, Firvida J, Lazaro M *et al.*: A Galician lung cancer group Phase II study: erlotinib as maintenance therapy alter concurrent chemoradiotherapy in patients (p) with stage III non-small cell lung cancer (NSCLC). *J. Clin. Oncol.* 28(Suppl. 15), Abstract 7091 (2010).
- 21 Klein R, Wielage R, Muehlenbein C *et al.*: Cost-effectiveness of pemetrexed as first-line maintenance therapy for advanced nonsquamous non-small cell lung cancer. *J. Thorac. Oncol.* 5(8), 1263–1272 (2010).
- 22 Fidias PM, Dakhil SR, Lyss AP *et al.*: Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. *J. Clin. Oncol.* 27(4), 591–598 (2009).

- Immediate administration of docetaxel following four cycles of carboplatin and gemcitabine in advanced NSCLC is not superior to delayed docetaxel.
- 23 Hensing TA, Schell MJ, Lee JH, Socinski MA: Factors associated with the likelihood of receiving second line therapy for advanced non-small cell lung cancer. *Lung Cancer* 47(2), 253–259 (2005).
- 24 Patel JD, Bonomi P, Socinski MA et al.: Treatment rationale and study design for the pointbreak study: a randomized, open-label Phase III study of pemetrexed/carboplatin/ bevacizumab followed by maintenance pemetrexed/bevacizumab versus paclitaxel/ carboplatin/bevacizumab followed by maintenance bevacizumab in patients with

stage IIIb or IV nonsquamous non-small-cell lung cancer. *Clin. Lung Cancer* 10(4), 252–256 (2009).

Websites

- 101 National comprehensive cancer network www.nccn.org/professionals/physician_gls/ PDF/nscl.pdf
- 102 Clinical trials www.clinicaltrials.gov
- 103 AVAPERL1 Study: A Study of Avastin (Bevacizumab) With or Without Pemetrexed as Maintenance Therapy After Avastin in First Line in Patients With Non-Squamous Non-Small Cell Lung Cancer http://clinicaltrials.gov/ct2/show/ NCT00961415