Review Article

Maintenance therapy in non-small-cell lung cancer

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Abstract: With standard doublet chemotherapy for patients with advanced non-small-cell lung cancer (NSCLC), we have reached an outcome plateau of about 10 months median overall survival over the last decades. Several studies have now demonstrated some survival benefits for patients treated beyond induction chemotherapy. In the current discussion about treatment duration, the terms "switch" and "continuation" maintenance therapy are now most commonly used by the scientific community. Switch maintenance is the treatment with an agent with a different mode of action after completion of induction chemotherapy in patients who's tumors have not progressed, whereas continuation maintenance is the continuation of one compound of the induction regimen. Chemotherapeutic compounds successfully investigated in the maintenance setting are Gemcitabine, Docetaxel and Pemetrexed. Targeted agents, recently investigated as maintenance therapy are Bevacizumab, Cetuximab and Erlotinib. New peer-reviewed publications of phase III randomized clinical trials on maintenance chemotherapy have led to a change in current practice guidelines and the use of maintenance therapy represents a new treatment option in advanced NSCLC. The pivotal trials are described and summarized in this review article.

Key Words: Non-small-cell lung cancer; maintenance therapy; Gemcitabine; Docetaxel; Pemetrexed; Bevacizumab; Cetuximab; Erlotinib

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Introduction

According to the American society of clinical oncology (ASCO) guidelines (1) standard first-line treatment for patients with advanced non-small-cell lung cancer (NSCLC) in a good performance status is a platinum containing doublet chemotherapy given for 4 to 6 cycles. Over the last decades this treatment strategy has reached an efficacy plateau of about 10 months of median overall survival in large randomized phase III trials. Many efforts have been undertaken to improve efficacy and prolong overall survival in this group of patients, for example by developing new cytotoxic agents, such as pemetrexed (2). Some new targeted agents, Cetuximab and Bevacizumab, have also demonstrated to significantly improve overall survival when combined with certain combinations of chemotherapy (3,4). However, targeted agents are always maintained until disease progression, bringing up again the question about the role of treatment duration and scheduling in advanced NSCLC. Up to date several studies have demonstrated, that extending the number of cycles did improve progression free survival (PFS) but did not result in a prolongation of overall survival (OS) (5-10).

The ASCO guidelines therefor have just been updated in 2011 particularly with regard to maintenance therapy: "*For patients with stable disease or response after four cycles, immediate treatment with an alternative, single-agent chemotherapy such as pemetrexed in patients with nonsquamous histology, docetaxel in unselected patients, or erlotinib in unselected patients may be considered. Limitations of these data are such that a break from cytotoxic chemotherapy after a fixed course is also acceptable, with initiation of second-line chemotherapy at disease progression.*"

The changes in the guidelines are in response to new peer-reviewed publications of phase III randomized clinical trials on maintenance chemotherapy published recently.

Table 1 Chemotherapeutic agents in maintenance designed trials

Trial	Number randomized	First line agents	Maintenance	Survival in months (Hazard ratio; P-value)
Westeel *et al.* (13)	181	MIC	Vinorelbin	12.3 *vs.* 12,3 (HR=1.08; P=0.48)
Brodowicz *et al.* (14)	206	GC	Gemcitabine	OS 13 *vs.* 11 (HR=n.r.; P=0.195)
Perol *et al.* (15)	464	GC	Gemcitabine	PFS 3.7 *vs.* 2.1 (HR=0.51; P<0.001)
Belani *et al.* (16)	255	GCb	Gemcitabine	OS 8 *vs.* 9.3 (HR=0.97, P=0.84)
Fidias *et al.* (17)	307	GCb	Docetaxel	OS 12.3 *vs.* 9.7 (HR=n.r.; P=0.0853)
Ciuleanu *et al.* (18)	663	Cb/C G/Pac/D	Pemetrexed	OS 13.4 *vs.* 10.6 (HR=0.79; P=0.012)
Paz-Ares *et al.* (19)	539	PemC	Pemetrexed	PFS 3.9 *vs.* 2.6 (HR=0.64; P=0.002)

C=Cisplatin; Cb=Carboplatin; D=Docetaxel; G=Gemcitabine; I=Ifosfamide; M=Mitomycin; Pac=Paclitaxel; Pem=Pemetrexed; V=Vinorelbin; n.r.=not reported

The aim of this article is, to review all newsworthy data from maintenance phase III studies, that have led to a change in clinical practice.

Maintenance therapy: definitions

What does maintenance therapy mean? A lot of different terms are used in the literature, such as switch and continuation maintenance, consolidation, alternating or sequential therapy or early second line therapy. There is no clear definition in the literature about these terms and a general consensus on which terms to use has not yet been reached (11,12).

In principle, maintenance therapy is the administration of treatment after a defined number of chemotherapy cycles, when a patients' tumor has not progressed. The treatment is continued until unacceptable toxicity or disease progression.

If the treatment is continued for a defined number of cycles after the induction chemotherapy, this is usually called consolidation therapy.

There are two different ways to continue treatment: either with a compound from the induction regimen, or with an agent with a different mode of action, not used in the first-line regimen. These two approaches are called "continuation" or "switch" maintenance therapy and these terms have emerged to be most commonly used in the current discussion about maintenance therapy.

Cytotoxic agents as maintenance therapy

A number of phase III trials have investigated the value of cytotoxic agents, both in a "switch" maintenance or a "continuation" maintenance approach. The most important trials are summarized in *Table 1*.

Gemcitabine

Three phase III trials have investigated gemcitabine as a "continuation" maintenance therapy in advanced NSCLC (*Table 1*). One randomized phase III study by Brodowicz *et al*. (14) was performed to show significant difference in median time to progression (TTP) in patients with advanced NSCLC treated with single-agent Gemcitabine maintenance therapy versus best supportive care following Gemcitabine plus Cisplatin initial firstline therapy. 352 patients were enrolled. After initial therapy, 206 patients were randomized and treated with Gemcitabine or best supportive care (BSC). Time to progression (TTP) throughout the study period was 6.6 and 5 months for Gemcitabine and BSC arms, respectively, while values for the maintenance period were 3.6 and 2.0 months (for P<0.001 for both). Median OS throughout study was 13.0 months for Gemcitabine and 11.0 months for BSC arms (P=0.195). The toxicity profile was mild, with neutropenia being most common grade 3/4 toxicities.

Another trial by Belani *et al*. (15) with a similar trial design failed to demonstrate a difference in PFS or OS between the Gemcitabine and the BSC group. However, in this study only 16% of patients in the treatment arm and 16% in the BSC arm received further treatment, which may be explained by the low overall performance status of patients.

In a maintenance trial by Perol *et al*. Gemcitabine and Erlotinib were compared to best supportive care (BSC). 464 patients were randomized to receive either Erlotinib (switch maintenance), Gemcitabine (continuation maintenance) or no further treatment (BSC). Unlike previous maintenance trials, pemetrexed was predefined as second-line therapy in all arms. Primary endpoint was PFS, which was significantly improved for both

maintenance arms, Gemcitabine and Erlotinib compared to the observation arm (3.7 *vs.* 2.8 *vs.* 2.1 months respectively). Overall survival data have not yet been reported.

Docetaxel

A phase III study compared immediate with delayed Docetaxel after front-line therapy with Gemcitabine plus Carboplatin (17). 566 chemotherapy-naïve patients with squamous or nonsquamous NSCLC, stage IIIB with pleural effusion or stage IV, were enrolled. Gemcitabine (1,000 mg/m^2) was administered on days 1 and 8 followed by Carboplatin (AUC 5) on day 1. After four 21-day cycles, patients who did not have progression were randomly assigned either to an immediate Docetaxel group (Docetaxel 75 mg/m^2 on day 1 every 21 days, with maximum of six cycles) or to a delayed Docetaxel group. The primary end point was OS measured from random assignment. Additional analyses included tumor response, toxicity, progression-free survival (PFS), and quality of life (QOL).

398 patients completed Gemcitabine plus Carboplatin and 309 patients were randomly assigned equally to the two Docetaxel treatment groups. Median PFS for immediate Docetaxel (5.7 months) was significantly greater (P<0.0001) than for delayed Docetaxel (2.7 months). Median OS for immediate Docetaxel (12.3 months) was greater than for delayed Docetaxel (9.7 months), but the difference was not statistically significant (P<0.0853). QOL results were not statistically different (P=0.76) between the two groups. It has to be pointed out that the number and percentage of patients who finally assigned and were treated with Docetaxel was different between the two study arms. In the delayed Docetaxel group only 98 of 154 patients have been treated with Docetaxel.

Pemetrexed

In a multicenter randomized double blind placebo controlled phase III trial (JMEN) 663 patients with all NSCLC histological subtypes were included who had not progressed after four cycles of chemotherapy with Cisplatin combined with either Gemcitabine, Paclitaxel or Docetaxel (18). After the induction chemotherapy the efficacy and toxicity of maintenance therapy with Pemetrexed 500 mg/m^2 plus BSC to that of placebo plus BSC were compared. The patients were randomized 2:1 and 441 patients received Pemetrexed plus BSC, 222 placebo plus BSC. In the maintenance treatment, patients received a median number of 5 cycles Pemetrexed and 3.5 cycles placebo. 48.3% of patients received 6 cycles or more of Pemetrexed and 23.4% of patients 10 cycles or more. Pemetrexed significantly improved PFS [4.3 *vs.* 2.6 months; hazard ratio (HR) 0.50, 95% CI, 0.42-0.61, P<0.0001] and OS (13.4 *vs.* 10.6 months; HR 0.79, 0.65-0.95, P=0.012) compared to placebo in the ITT population. Fewer patients on Pemetrexed compared to placebo received systemic post-study therapy [227 (51%) *vs.* 149 (67%); P=0.0001]. In patients with predominantly non-squamous histology median OS was 15.5 *vs.* 10.3 months (P=0.002). In July 2009 Pemetrexed was approved for maintenance treatment in first-line NSCLC stage IIIb/IV.

The question whether patients who receive Pemetrexed in the induction chemotherapy would benefit from "continuation" maintenance treatment with Pemetrexed has currently been investigated in the PARAMOUNT trial (19). The primary endpoint was PFS. After the induction chemotherapy with Pemetrexed plus Cisplatin those 539 patients whose tumors were not progressing were randomized 2:1 to receive either Pemetrexed maintenance therapy or placebo until disease progression. The median number of cycles in the maintenance phase was 4 cycles for both arms. 23% of patients treated with Pemetrexed received more then 6 cycles of maintenance versus 14% in the placebo arm. The study reached its primary endpoint, demonstrating a benefit in PFS for Pemetrexed over placebo (3.9 *vs.* 2.6 months). Overall survival data are not yet mature.

Targeted agents as maintenance therapy

Targeted agents, recently investigated as maintenance therapy are listed in *Table 2*.

Erlotinib

Maintenance Erlotinib was investigated in both, the Saturn and Atlas trial (21,24). In the Saturn trial Erlotinib was compared to placebo after first-line chemotherapy and given until disease progression in patients with advanced NSCLC in both squamous and non-squamous histology, who had not progressed after initial treatment. Patients were stratified prior to randomization, using the adaptive method of Pocock and Simon, to ensure balance between treatment groups for EGFR protein expression by IHC (EGFR Positive versus EGFR Negative versus EGFR undetermined); Stage of disease at start of chemotherapy (IIIb versus IV); ECOG PS (0 versus 1); Chemotherapy regimen (Gemcitabine plus Cisplatin versus Carboplatin plus Docetaxel versus other); Smoking status [current

Table 2 Targeted agents in maintenance designed trials

Trial	Number randomized	First line agents	Maintenance	Survival in months (Hazard ratio; P-value)
Perol *et al*. (15)	464	G,C	Erlotinib	PFS 2.9 *vs.* 1.9 (HR=0.71; P<0.001)
Cappuzzo *et al*. (20)	889	Cb/C, G/Pac/D/Pem	Erlotinib	OS 12 *vs.* 11 (HR=0.81; P=0.0088)
Kabbinavar *et al*. (21)	768	Cb/C, G/Pac/D, Bev	Bevacizumab±Erlotinib	PFS 4.8 *vs*. 3.7 (HR=0.71; P=0.006)
Sandler *et al.* (3)	407	Pac, Cb, Bev15 mg	Bevacizumab 15 mg	OS 12.3 *vs*. 10.3 (HR=0.71; P=0.003)
Reck *et al.* (22)	1,043	G,C,Bev 7.5 mg/15 mg	Bevacizumab 7.5 mg*/15 mg**	*PFS 6.7 *vs.* 6.1 (HR=0.75; P=0.003) **PFS 6.5 *vs*. 6.1 (HR=0.82; P=0.03)
Pirker *et al.* (4)	1,125	C, V, Cet	Cetuximab	OS 11.3 *vs.* 10.1 (HR=0.87; P=0.044)
Lynch *et al*. (23)	676	Cb, Pac, Cet	Cetuximab	OS 9.7 *vs*. 8.4 (HR=0.89; P=0.169)

C=Cisplatin; Cb=Carboplatin; D=Docetaxel; G=Gemcitabine; I=Ifosfamide; M=Mitomycin; Pac=Paclitaxel; Pem=Pemetrexed; V=Vinorelbin; Bev=Bevacizumab; Cet=Cetuximab; n.r.=not reported

smoker (includes patients who had stopped smoking within a year) versus former smoker versus never smoked]; and Region (North America, South America, Western Europe, Eastern Europe, South East Asia and Africa). All patients were required to provide a tumor sample for analysis of EGFR protein expression by IHC. Treatment was continued until progression, death or unacceptable toxicity. There was an improvement in PFS (HR 0.71; P<0.0001) and overall survival was 12 *vs*. 11 month (HR 0.81; P=0.008) in favour of Erlotinib. In a subgroup of patients with tumors positive for EGFR protein expression the PFS hazard ratio was 0.69 (P<0.0001), whereas in the subgroup with negative EGFR protein expression HR is only 0.91. In the subgroup of patients with tumors positive for EGFR mutation the PFS hazard ratio was best with 0.1 (P<0.0001), whereas in the subgroup with EGFR wildtype HR is 0.78 (P=0.0185) . In the non-squamous subgroup the benefit of OS was 13.7 *vs*. 10.5 month (P=0.0194), in the squamous histology the difference was modest. OS for Erlotinib was 11.3 month and for Placebo 11.1 month, HR 0.86 (0.68,1.10), P=0.2369. The ATLAS (21) trial confirmed the significant survival benefit shown in the SATURN trial.

Monoclonal antibodies

A series of randomized studies have exlpored Cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR) in the treatment of advanced NSCLC. In the first-line setting, the phase III FLEX study (First- Line Erbitux in Lung Cancer) randomized 1,125 patients with EGFRexpressing tumors in stage, wet IIIB/IV, including all NSCLC histologies. The study showed that the addition of Cetuximab to cisplatin and vinorelbine followed by Cetuximab maintenance therapy significantly improved survival when compared with Cisplatin plus vinorelbine alone (11.3 *vs*. 10.1 months, HR 0.87, P=0.044) (4). Another study with a similar study design, BMS099 (Bristol-Myers Squibb 099), exploring Paclitaxel plus Carboplatin with or without Cetuximab, showed a comparable numeric overall survival benefit for the patients treated with Cetuximab. However, this difference was not statistically significant, assumably due to the significantly lower number of patients (median OS 9.7 versus 8.4 months, HR 0.89, P=0.169) (23).

The vascular endothelial growth factor has also been proven to be an effective therapeutic target in this setting. The Eastern Cooperative Oncology Group (ECOG) 4,599 study demonstrated, that the addition of Bevacizumab to Paclitaxel plus carboplatin followed by Bevacizumab maintenance therapy significantly improved overall survival compared to Paclitaxel plus Carboplatin alone. (12.3 *vs*. 10.3 months, HR 0.79, P=0.003) (3). Another study, AVAiL (Avastin in Lung Study), investigated Cisplatin plus Gemcitabine with either Bevacizumab, at 7.5 or 15 mg/kg, or placebo (each administered concurrently with chemotherapy and as a maintenance treatment until disease progression). Patients treated with Bevacizumab had a significant improvement in PFS compared with chemotherapy plus placebo, for either the 7.5 or 15 mg/kg Bevacizumab regimens (13.6 and 13.4 versus 13.1 months, HR 0.93 and HR 1.03, P=0.420 and P=0.761, respectively). However, overall survival was not different between the treatment arms.

From the design of these four randomized studies no conclusions can be drawn as to whether the clinical benefit associated with the addition of the targeted agent to standard

first-line chemotherapy was conferred to the induction chemotherapy, maintenance, or indeed both phases of treatment. To demonstrate if those agents are effective as maintenance therapy, alternative study designs are needed.

Summary

Two randomized phase III studies have recently investigated Pemetrexed and Erlotinib as "switch" maintenance therapy. Both trials have met their primary endpoints and overall survival was significantly improved in the maintenance arms. Based on this convincing data these two compounds have now been registered for "maintenance therapy". A recently presented study has now demonstrated also survival benefit for Pemetrexed in a "continuation" maintenance approach, when Pemetrexed was used already in the induction regimen. Thus, Pemetrexed could be a new option for both strategies, switch and continuation maintenance therapy.

According to the European Medicines Agency (EMA) "Alimta now is indicated as monotherapy for the maintenance treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology in patients whose disease has not progressed immediately following platinumbased chemotherapy. First line treatment should be a platinum doublet with Gemcitabine, Paclitaxel or Docetaxel".

Regarding Erlotinib the Committee for Medicinal Products for Human Use (CHMP) adopted a new indication as follows: "Tarceva is indicated as monotherapy for maintenance treatment in patients with locally advanced or metastatic non-small cell lung cancer with stable disease after four cycles of standard platinum-based first-line chemotherapy. When prescribing Tarceva, factors associated with prolonged survival should be taken into account".

Bevacizumab, a monoclonal antibody against VEGF, and Cetuximab, a monoclonal antibody against EGFR, have demonstrated clinical benefit for patients, when added to firstline chemotherapy and continued until disease progression. However, to clarify whether the effect of the targeted agents is attributed to the maintenance of the agents after induction therapy, alternative study designs are required.

Bevacizumab is registered in the following indication: "Bevacizumab in addition to platinum-based chemotherapy, is indicated for first-line treatment of patients with unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology".

Although Cetuximab has reached its primary endpoint in the phase III trial, it has not yet been approved for the treatment of lung cancer in Europe.

A recent meta-analysis by Zhang *et al.* (25) has statistically analyzed most of the above randomized controlled trials altogether. The results of this meta-analysis suggest, that OS and PFS are clearly in favor of maintenance therapy for both, switch and continuation strategy. However, to give a clear recommendation for the future, many other aspects like costeffectiveness and toxicity must be taken into account.

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