Review

Is there a role for maintenance therapy in advanced non-small-cell lung cancer?

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Practice Points

- Maintenance therapy is the continued administration of therapy after a defined number of induction cycles once disease stabilization or maximum tumor response has been achieved, and may be continued until either disease progression or unacceptable toxicity.
- Continuation maintenance is defined when a drug, generally a chemotherapeutic, included in the induction treatment is used as maintenance.
- Switch maintenance is defined when a different drug (chemotherapeutic or targeted agent) not included in the induction therapy is administered.
- Continuation maintenance with pemetrexed has achieved benefit in terms of progression-free survival and overall survival results are pending.
- Switch maintenance treatment has been found to be an effective strategy in prolonging overall survival. The benefit in progression-free survival and overall survival, reported with pemetrexed in patients with nonsquamous histology and erlotinib in unselected patients as switch maintenance, and their favorable toxicity profile allow them to be used as maintenance treatment after induction therapy with platinum-based regimens.
- In our opinion, in the next 5–10 years the main focus of research will be to find other effective agents in addition to pemetrexed and erlotinib for the maintenance treatment of advanced non-small-cell lung cancer.

SUMMARY Although improvements in the treatment of advanced non-small-cell lung cancer have been achieved, the prognosis remains poor for most patients. Thus, the search for new, active and safe drugs or for new strategies is warranted. Maintenance treatment with either a chemotherapeutic agent or a molecularly targeted agent after first-line chemotherapy

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is a very interesting strategy that has been largely investigated in past years. Maintenance treatment can consist of drugs included in the induction regimen (continuation maintenance) or other noncross-resistant agents (switch maintenance). Several Phase III randomized trials have been completed on this topic, and overall they have established the role of switch and continuation maintenance as a possible effective option versus the classic break from cytotoxic chemotherapy after a fixed course in the treatment of advanced non-small-cell lung cancer.

Lung cancer is the most common cancer in the world. From 2003 to 2007 the age-adjusted incidence rate of lung cancer was 62.5 per 100,000 men and women per year with more than 1.35 million cases diagnosed, representing 14–15% of all new cancers in the USA and 12.2% in Europe [1]. Lung cancer is the leading cause of cancer mortality in the USA and worldwide more than 1 million people die from lung cancer every year [2]: the overall 5-year relative survival rate measured by the Surveillance, Epidemiology and End Results (SEER) program in the US was 15.8%. Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers diagnosis.

Unfortunately, most patients have unresectable disease at diagnosis (stage III or IV disease), and those with stage IV disease have a very poor prognosis [3]. Chemotherapeutic agents in the treatment of advanced NSCLC, including squamous carcinoma, adenocarcinoma and large-cell carcinoma, have reached a plateau of effectiveness. First-line therapy with a platinum-based two-drug combination in patients with a performance status (PS) of 0 or 1 is recommended, while nonplatinum cytotoxic doublets are acceptable for patients with contraindications to platinum therapy. A maximum of four cycles of first-line chemotherapy is recommended in patients who are not responding to treatment, while a maximum of six cycles is recommended in patients who are responding to therapy. The development of targeted therapies against the VEGF and its receptors, and against the EGF receptor (EGFR) have improved the outcomes of advanced NSCLC. Bevacizumab, a pure humanized anti-VEGF monoclonal antibody (mAb) is recommended with carboplatin–paclitaxel or cisplatin–gemcitabine, as first-line therapy for nonsquamous NSCLC patients. Also the chemotherapeutic regimen cisplatin plus pemetrexed is to be considered a standard first-line treatment of advanced nonsquamous NSCLC. The first-line use of gefitinib and erlotinib, two small molecule EGFR tyrosine kinase inhibitors (TKIs), may be recommended for patients with known activating EGFR mutations. Docetaxel, pemetrexed or erlotinib are recommended as second-line therapy. Erlotinib is the only drug recommended as third-line therapy for patients who have not received prior EGFR TKIs [4–6].

Maintenance therapy is the continued administration of therapy after a defined number of induction cycles once disease stabilization or maximum tumor response has been achieved, and may be continued until either disease progression or unacceptable toxicity.

A further distinction is that maintenance therapy consists of either a chemotherapeutic or a biologic agent; in addition, it can consist both of drugs included in the induction regimen or other noncross-resistant agents. Continuation maintenance is defined when a drug (generally a chemotherapeutic) included in the induction treatment is used as maintenance, while we can use the term of early second-line or switch maintenance [101] when a different drug (chemotherapeutics or targeted agents) not included in the induction therapy is administered.

In the present paper, we summarize the main data on maintenance therapy trying to define its role in the treatment of advanced NSCLC.

Continuation maintenance

This type of maintenance therapy applies generally to chemotherapeutic agents only, because first-line treatment is mainly based on chemotherapy except for patients with EGFR mutated tumors and because targeted therapies are always administered as maintenance therapies until disease progression.

Continuation maintenance with carboplatin plus paclitaxel

In a Phase III randomized trial, 230 patients with stage IIIB/IV disease were assigned to four cycles of carboplatin plus paclitaxel or to the same treatment given until progression. The results in terms of overall survival (OS)

did not favor the maintenance arm, as median OS resulted as 6.6 months and 8.5 months in the standard arm and in the maintenance arm, respectively (p = 0.63). Also, the safety profiles of the two strategies were similar, with no significant differences in terms of hematologic and nonhematologic toxicities. However, in the prolonged arm a higher rate of neuropathy was reported, with the rate of grade 2–4 neuropathy being 19.9%. In conclusion, in this trial the maintenance strategy did not yield any benefit in terms of efficacy against the standard four-cycle treatment with carboplatin plus paclitaxel. Only progression-free survival (PFS) was prolonged in the maintenance arm [7].

■ Continuation maintenance with gemcitabine

In a Phase III trial, chemotherapy-naive patients with stage IIIB/IV NSCLC received induction therapy with gemcitabine plus cisplatin. Nonprogressed patients were randomized (in a 2:1 ratio) to receive maintenance gemcitabine (1.250 mg/m^2 on days 1 and 8, every 21 days) plus best supportive care, or best supportive care only. After initial therapy had been administered in 352 patients, 206 of these were randomized. The outcomes in terms of time-to-progression (TTP) favored gemcitabine, as it resulted 6.6 and 5 months for the gemcitabine and the best supportive care arms (p < 0.001), respectively. On the contrary, no statistically significant differences were found in terms of median OS (13.0 months for the gemcitabine maintenance arm and 11.0 months for the best supportive care arm; p = 0.195). Maintenance treatment with gemcitabine was well tolerated [8].

In another Phase III randomized trial, patients achieving an objective response or a stable disease after four cycles of carboplatin plus gemcitabine were randomized in a 1:1 ratio to receive maintenance gemcitabine (1000 mg/m² day 1 and 8, every 3 weeks) with best supportive care or best supportive care alone. A total of 255 patients (128 in gemcitabine arm and 127 in control arm) were randomized. The primary end point was the comparison of OS between the two arms and the secondary end point was PFS. The median PFS was 7.4 months for gemcitabine arm and 7.7 months for control group (HR: 1.09; 95% CI: 0.81–1.45; p = 0.575), while median OS was 8.0 versus 9.3 months (HR: 0.97; 95% CI: 0.72–1.30; p = 0.84), respectively [9]. However, in patients with good PS, a statistically significant advantage in OS was reported with maintenance treatment. In conclusion, this trial failed to demonstrate any advantage for gemcitabine maintenance therapy, but it suffers a bias due to its early closure because of the slow accrual and the high rate (64%) of PS two patients included.

■ Continuation maintenance with pemetrexed

A recent trial, named PARAMOUNT, has investigated the role of pemetrexed in this setting in patients with advanced nonsquamous NSCLC who did not progress after four cycles of induction chemotherapy with cisplatin plus pemetrexed [10,11]. The PARAMOUNT trial investigated whether pemetrexed maintenance therapy improves PFS after pemetrexed–cisplatin induction therapy in patients with advanced nonsquamous NSCLC. In this double-blind, placebo-controlled trial, 939 patients participated in the induction phase, specified as four cycles of induction pemetrexed (500 mg/m^2) and cisplatin (75 mg/m^2) on day 1 of a 21-day cycle. Patients who had not progressed during pemetrexed–cisplatin induction and had an Eastern Cooperative Oncology Group PS of 0/1 (n = 539; 57.4%) were randomized (2:1) to maintenance pemetrexed (500 mg/m^2 on day 1 of a 21-day cycle) plus best supportive care (n = 359) or placebo plus best supportive care (n = 180) until disease progression. The primary end point was PFS. Pemetrexed maintenance resulted in a 36% reduction in the risk of progression (HR: 0.64; 95% CI: 0.51–0.81; p = 0.00025). The median independently reviewed PFS (472 patients, 297 events), measured from randomization, was 3.9 months (95% CI: 3.0–4.2) on the pemetrexed arm and 2.6 months (95% CI: 2.2–2.9) on the placebo arm. This benefit was shown in stable and responsive patients both after induction chemotherapy. The disease control rate (percentage of patients with response/stable disease) was 71.8% on the pemetrexed arm, and 59.6% on the placebo arm (p = 0.009) [10]. The drug-related serious adverse event rate was 8.9% on the pemetrexed arm, and 9.2% of patients had grade 3/4 laboratory adverse events. On the placebo arm, the rates were 2.8 and 0.6%, respectively. Discontinuations due to adverse events were 5.3% on the pemetrexed arm, 3.3% on the placebo arm. Maintenance with pemetrexed was well tolerated, with no difference in drug-related

grade 3/4/5 toxicities observed in the continuation maintenance arm. Only neutropenia increased with the long-term administration of pemetrexed (>10 cycles, 8.3% vs ≤10 cycles, 2.2%; p = 0.015). Obviously, as a consequence, the concomitant use of hematopoietic growth factors resulted in an increase in the maintenance arm. However, this increase in the rate of neutropenia did not translate into increased infections. An evaluation in terms of quality of life was also performed in this trial. During maintenance, most Euro quality of life 5-dimensional scale (EQ-5D) assessments were completed: pemetrexed, 84.3% and placebo, 80.9%. At the postdiscontinuation visit, 43.9% of pemetrexed-treated patients and 44.3% of placebo-treated patients completed the EQ-5D. No clinically relevant within-group or treatment differences in index or VAS scores were observed. Thus, authors concluded that long-term use of pemetrexed as a continuation maintenance strategy is safe and well tolerated, without significant decreases in quality of life for the patients [11]. In conclusion PARAMOUNT met its primary end point of prolonging PFS with pemetrexed maintenance and showed that pemetrexed continuation maintenance following pemetrexed–cisplatin induction is also a well-tolerated treatment for patients with advanced nonsquamous NSCLC **(Table 1)**.

AVAPERL1 is another interesting Phase III trial designed to investigate if continuing pemetrexed with bevacizumab offers additional benefit over bevacizumab alone following four cycles of first-line therapy with bevacizumab plus pemetrexed plus cisplatin in the treatment of advanced nonsquamous NSCLC [12]. Approximately 130 patients per arm were randomized. The combination of pemetrexed plus bevacizumab achieved improved outcomes in terms of PFS over bevacizumab-alone treatment (10.2 vs 6.6 months; HR: 0.50; p < 0.001), and this advantage was extended to all the subgroups of patients.

Switch maintenance

In this type of maintenance treatment both chemotherapeutic agents and targeted therapies have been investigated.

Switch maintenance with vinorelbine

In a Phase III randomized trial, patients with stage IIIB–IV NSCLC were assigned, after four cycles of chemotherapy with mitomycin–ifosfamide–cisplatin, either to intravenous vinorelbine at a dose of 25 mg/m^2 weekly for 6 months or no further treatment. After the induction phase 181 were randomized (91 to maintenance vinorelbine and 90 to observation). No differences in terms of OS were found, with a HR for OS for vinorelbine versus observation of 1.08 (95% CI: 0.79–1.47; p = 0.65). PFS results were also similar in the two arms (p = 0.32) [13].

Switch maintenance with docetaxel

Another Phase III randomized study evaluated the role of docetaxel as a switch maintenance agent after induction chemotherapy with carboplatin plus gemcitabine. After four cycles of chemotherapy, patients with stable disease or partial/complete response were randomized to either the immediate docetaxel group (docetaxel 75 mg/m^2 administered on day 1 every 21 days, for a maximum of six cycles) or the delayed docetaxel group (patients given best supportive care after randomization and the same docetaxel regimen after first evidence of progressive disease) treatment arms. Enrollment totaled 566 patients; 398 patients completed the induction therapy and 309 patients were randomly assigned equally to the two docetaxel treatment groups. Overall survival was not statistically different (p = 0.0853) between the two docetaxel arms (12.3 and 9.7 months in the immediate and delayed arms, respectively). PFS analysis (from randomization to first evidence of progressive disease or death) showed a statistically significant (p < 0.0001) improvement in the immediate docetaxel arm (5.7 and 2.7 months, respectively). The safety profile of immediate docetaxel did not differ from the delayed modality. No differences were reported in terms of grade 3/4 neutropenia (28.6 and 26.1% of the patients in the delayed and immediate arms, respectively). Quality of life was not statistically different (p = 0.76) between the two arms. In conclusion, although the benefit achieved in terms of PFS, the switch maintenance with docetaxel did not produce a statistically significant benefit in terms of OS [14]. A possible reason for poorer survival in the delayed arm of this trial might be that many patients (37%) randomly assigned to receive delayed docetaxel at progression never received it. On the contrary 95% of patients in the immediate arm received at least one cycle of docetaxel. If we restrict the analysis only to patients receiving docetaxel in the two

Table 1. Main randomized Phase III trials on continuation maintenance with chemotherapy in advanced non-small-cell lung cancer patients.

Author (year)	Induction therapy	Patients population	Randomization	Patients (n)	Objective response (% patients with response/stable disease)	Progression-free survival (months)	Overall survival (months)	Ref.
Socinski *et al.* (2002)	NA	NA	CBDCA + PAC for four cycles vs	114	22	NR	6.6	[7]
			CBDCA + PAC until PD	116	24	NR	8.5	
Brodowicz *et al.* (2006)	CDDP + GEM for four cycles	Nonprogressed patients	BSC vs	68	45.6[†]	5.0[‡]	11.0	[8]
			GEM until PD	138	50.7[†]	6.6[‡]	13.0	
Belani *et al.* (2010)	CBDCA + GEM for four cycles	Nonprogressed patients	BSC vs	127	6	7.7	9.3	[9]
			GEM + BSC until PD	128	28	7.4	8.0	
Paz-Ares *et al.* (2011)	CDDP + PEM for four cycles	Nonprogressed patients	Placebo + BSC vs	180	71.8[§]	2.6	NR	[10]
			PEM + BSC	359	59.6[§]	3.9	NR	

[†]Objective response related to induction therapy, too.
[‡]Time-to-progression.
[§]Disease control rate.
BSC: Best supportive care; CBDCA: Carboplatin; GEM: Gemcitabine; NA: Not applicable; NR: Not reported; PAC: Paclitaxel; PD: Progression of disease; PEM: Pemetrexed.

arms, the OS result is identical in the two arms (12.5 months). Thus, the trend toward a better survival reported in the immediate arm might only be related to the probability of receiving the drug and not to the timing of administration of the drug (switch maintenance vs classic second-line treatment).

Switch maintenance with pemetrexed

The most important Phase III study on switch maintenance with chemotherapy has evaluated the role of pemetrexed versus placebo. After four cycles of platinum-based induction chemotherapy (not containing pemetrexed), patients were randomized (2:1 ratio) to either pemetrexed (500 mg/m^2, day 1) plus best supportive care, or intravenous placebo plus best supportive care in 21-day cycles until disease progression. As a primary end point, PFS was selected. A total of 663 patients (441 in the pemetrexed arm and 222 in the placebo group) were randomized. Pemetrexed reported better results in terms of PFS, which was 4.3 versus 2.6 months in the pemetrexed and the placebo arms, respectively (HR: 0.50; 95% CI: 0.42–0.61; p < 0.0001), and also for PFS measured from the start of induction treatment, which was 7.7 versus 5.9 months, respectively. The disease control rate was 41.7 and 33.3% in the pemetrexed and the placebo arms (p < 0.0001), respectively. Overall survival was 13.4 months with pemetrexed and 10.6 months with placebo (HR: 0.79; 95% CI: 0.65–0.95; p = 0.012), considering the OS measured from the start of induction treatment was 16.5 versus 13.9 months, respectively. The safety profile of pemetrexed was acceptable, with no drug-related deaths, 5% serious adverse events versus 1% for placebo and 16% grade 3–4 adverse events versus 4.0% for placebo (p < 0.0001) [15]. In the first- and second-line setting, pemetrexed has achieved better results in patients with adenocarcinoma and large cell carcinoma with respect to squamous histology due to a lower thymidylate synthase level, one of the most important targets for the action of pemetrexed, present in these histologic subtypes [16]. Based on the evidence, a prespecified analysis for efficacy by NSCLC histology was also performed in this trial. The outcomes in terms of PFS that had favored pemetrexed versus in the global analysis were not confirmed in the patients with squamous NSCLC, PFS 2.4 versus 2.5 months (HR: 1.03; 95% CI: 0.71–1.49; p = 0.896), in the pemetrexed and the placebo arms, respectively. This type of result for squamous histology tumors was also confirmed in terms of OS, which was similar in both groups: 9.9 and 10.8 months (HR: 1.07; 95% CI: 0.77–1.50; p = 0.678), respectively. On the contrary, the benefit in terms of OS in favor of pemetrexed observed in the analyses of all patients, is larger in patients with nonsquamous NSCLC, 15.5 versus 10.3 months in the pemetrexed and the placebo arms (HR: 0.70; 95% CI: 0.56–0.88; p = 0.002), respectively. PFS was also significantly improved with switch maintenance with pemetrexed in this histologic subgroup (4.4 vs 1.8 months, respectively; HR: 0.47; 95% CI: 0.37–0.60; p < 0.0001) [15]. The data obtained in this trial has led pemetrexed to be the first agent to be licensed for maintenance

treatment of advanced NSCLC in patients with nonprogressing disease after induction platinum-based chemotherapy. However, some biases may have influenced the results of this trial. In fact, among patients who were randomized to the pemetrexed group, 98% received second-line therapy (pemetrexed), and 51% received poststudy therapy. By contrast, among patients randomized to placebo, 67% received poststudy therapy and only 18% received pemetrexed. Thus, the difference in the outcomes of switch maintenance with pemetrexed and placebo may be in part due to the different chance of being administered pemetrexed during the natural history of disease among the two study groups.

Switch maintenance with erlotinib

Switch maintenance with targeted therapies has been recently tested. The most important trial with a targeted agent in this setting is the Phase III trial named Sequential Tarceva in Unresectable Lung Cancer (SATURN). In this study erlotinib was compared with placebo as switch maintenance therapy in approximately 900 patients previously treated with four cycles of chemotherapy and without disease progression. PFS, the primary end point of this trial, significantly favored erlotinib versus placebo in all patients (HR: 0.71; 95% CI: 0.62–0.82; $p < 0.0001$) and in EGFR IHC-positive patients (HR: 0.69; 95% CI: 0.58–0.82; $p < 0.0001$). Interestingly, in all biomarker subgroups erlotinib achieved a benefit in terms of PFS, including patients with wild-type EGFR tumors (HR: 0.78; 95% CI: 0.63–0.96; $p = 0.0285$). However, among the patients with EGFR mutated tumors the benefit in terms of PFS obtained with erlotinib was particularly large (HR: 0.10; 95% CI: 0.04–0.25; $p < 0.0001$). In the global population erlotinib was significantly superior compared with placebo in terms of OS, with a median survival of 12 versus 11 months (HR: 0.81; 95% CI: 0.70–0.95; $p = 0.0088$), respectively . Moreover, it was superior both in EGFR IHC-positive patients (HR: 0.77; 95% CI: 0.61–0.93; $p = 0.0063$) and patients with EGFR wild-type (HR: 0.77; 95% CI: 0.61–0.97; $p = 0.0243$). Although the survival benefit was larger in patients with adenocarcinoma histology, the benefit was extended also to patients with EFGR wild-type tumors [17]. Erlotinib achieved an objective response rate of 11.9 versus 5.4% placebo. Also, the disease control rate favored erlotinib (40.8% with erlotinib vs 27.4% with placebo; $p < 0.0001$). Patients treated with erlotinib reported similar scores of quality of life than those treated with placebo. Erlotinib significantly extended time to pain (HR: 0.61; $p = 0.008$) and time to analgesic use (HR: 0.66; $p = 0.02$). The safety profile of erlotinib was mild, with the majority of adverse events being of grade 1/2. Unfortunately, among the patients randomized in the placebo arm, 72% were able, at the time of disease progression, to receive a second-line therapy and only 21% received an EGFR TKIs. These data could influence the final results of this trial underlining the need of studies whose design should also define the further therapies. Recently, the results coming from this trial led to the registration of erlotinib as monotherapy for maintenance therapy in patients with stable disease, because its efficacy profile is more favorable in this subgroup of patients (median OS was 11.9 months with maintenance erlotinib versus 9.6 months with placebo – HR: 0.72; 95% CI: 0.59–0.89; $p = 0.0019$) [16], after four cycles of standard platinum-based chemotherapy by the EMA [102] and in patients whose disease has not progressed after four cycles of standard platinum-based chemotherapy by the US FDA [103].

The IFCT-GFPC 0502 trial randomized 464 nonprogressing patients after four cycles of cisplatin and gemcitabine induction treatment to receive observation (152 patients) or gemcitabine (1.250 mg/m² day 1 and 8, every 3 weeks [149 patients]) or erlotinib (153 patients). Therefore this trial addressed both the role of continuation and switch maintenance. The primary end points was PFS with OS as secondary end point. The median PFS was 3.8 months for gemcitabine group versus 1.9 months for the control arm (HR: 0.55; 95% CI: 0.43–0.70; $p < 0.0001$) whereas it was 2.9 months for the erlotinib arm versus 1.9 months of the control group (HR: 0.82; 95% CI: 0.73–0.93; $p = 0.002$). Preliminary OS of gemcitabine versus observation reported a HR of 0.86 while for erlotinib versus observation the HR was 0.91. Grade 3–4 adverse events were 2.6% for the observation arm, 27.9% for the gemcitabine arm and 15.5% for the erlotinib group [18]. This is the only trial, performed in this setting, in which postmaintenance treatment was predefined being pemetrexed.

The relationship between the EGFR signaling pathway and the VEGF pathway is well known from preclinical studies [19]. The ATLAS Phase III trial has compared the combination of erlotinib and bevacizumab with bevacizumab alone as a maintenance treatment in patients with advanced NSCLC pretreated with four cycles of platinum-based chemotherapy plus bevacizumab. Approximately 700 patients were enrolled onto this trial. PFS outcomes (the primary end point of the trial) favored the combination of bevacizumab and erlotinib (the median PFS was 3.71 months for bevacizumab alone vs 4.76 months for bevacizumab plus erlotinib [HR: 0.71; p = 0.0006]) [20]. On the contrary, median OS outcomes were similar between the two arms with 15.9 months for the combination arm versus 13.9 months for bevacizumab alone group (HR: 0.90; p = 0.2686). The combination arm was not more toxic than the bevacizumab alone arm. In fact, grade 3 to 4 adverse events were reported in 44.1% of patients enrolled in the bevacizumab plus erlotinib arm and 30.4% of patients in the bevacizumab alone arm. In the subgroup analyses for biomarkers, interestingly median PFS results favored the combination of bevacizumab and erlotinib at a major extent in patients with EGFR FISH-positive (HR: 0.66; 95% CI: 0.39–1.13), EGFR mutated (HR: 0.93; 95% CI: 0.55–1.56) and Kras wild-type (HR: 0.67; 95% CI: 0.49–0.91) tumors [21].

Switch maintenance with gefitinib

A randomized Phase III trial investigated gefitinib, another EGFR TKI, as maintenance therapy. In this trial patients nonprogressing after two to six cycles of any platinum-based induction chemotherapy were randomized to gefitinib 250 mg daily orally (86 patients) or placebo (87 patients). The primary end point was median OS which was 10.9 months for gefitinib and 9.4 months for placebo (HR: 0.81; 95% CI: 0.59–1.12; p = 0.204) while median PFS was 4.1 versus 2.9 months (HR: 0.61; 95% CI: 0.45–0.83; p = 0.002), respectively. Treatment was very well tolerated. Unfortunately this trial, closed early due to a slow accrual, the significant advantage in PFS reported by gefitinib was very promising while the survival end point was biased by low number of enrolled patients [22]. At the last ASCO meeting the INFORM trial was presented. It is a Phase III, randomized, multicenter, parallel group study [104] that investigated the efficacy, safety and tolerability of gefitinib versus placebo as maintenance therapy in patients with locally advanced or metastatic NSCLC following four cycles of standard first-line platinum-based chemotherapy without progression or unacceptable toxicity. PFS was the primary end point. Secondary end points included OS, objective response rate, disease control rate, symptom improvement and tolerability. Approximately 300 patients were randomized. Overall, 54.1% patients were never-smokers, 70.6% had adenocarcinoma and 40.9% were female. PFS results favored gefitinib versus placebo, (median PFS 4.8 versus 2.6 months, respectively; HR: 0.42; p < 0.0001) **(Table 2)**. Most common adverse events (any grade) with gefitinib were rash (49.7%), diarrhea (25.2%) and ALT increase (21.1%), which were generally mild or moderate. The overall incidence of serious adverse events was 6.8% for gefitinib and 3.4% for placebo. The authors concluded that PFS was significantly longer with gefitinib compared with placebo as maintenance therapy in Chinese patients with locally advanced or metastatic NSCLC [23].

A recent meta-analysis on maintenance treatment in advanced NSCLC

As discussed above, several randomized trials have evaluated the role of maintenance treatment in advanced NSCLC. Thus, very recently, Des Guetz *et al.* have performed a meta-analysis of 11 randomized clinical trials, including both studies on continuation and switch maintenance strategies [24]. In five randomized trials evaluating the role of a TKI (gefitinib or erlotinib) the authors found a statistically significant advantage in PFS (HR: 0.76; p = 0.007) favoring the TKI, but not in OS. However, when the analysis was restricted to only the three trials on erlotinib the benefit in terms of PFS was higher (HR: 0.71; p = 0.001) and extended also to OS (HR: 0.85; p = 0.003). Interestingly, switch maintenance with chemotherapy (from the three trials included in this analysis) appeared to be effective in prolonging OS (HR: 0.85; p = 0.02) and PFS (HR: 0.66; p = 0.001). On the contrary, the authors found that continuation maintenance strategy with chemotherapy (four trials included) did not result in effectively prolonging OS.

Table 2. Main randomized Phase III trials on switch maintenance in advanced non-small-cell lung cancer patients.

Author (year)	Induction therapy	Patient population	Randomization	Patients (n)	Objective response (%)	Progression-free survival	Overall survival (months)	Ref.
Fidias *et al.* (2008)	CBDCA + GEM for four cycles	Nonprogressed patients	Delayed TXT for six cycles vs	156	11.2	2.7 months	9.7	[14]
			immediate TXT for six cycles	153	35.9†	5.7 months	12.3	
Ciuleanu *et al.* (2009)	Platinum-based doublets for four cycles	Nonprogressed patients	Placebo vs PEM until PD	222	1.8	5.9 months	13.9	[15]
				441	6.8	7.7 months	16.5	
Cappuzzo *et al.* (2010)	Platinum-based doublets for four cycles	Nonprogressed patients	Placebo until PD vs	451	5.4	11.1 weeks	11.0	[17]
			erlotinib until PD	438	11.9	12.3 weeks	12.0	
Gaafar *et al.* (2011)	Platinum-based doublets for four cycles	Nonprogressed patients	Placebo until PD vs	87	NR	2.9 months	9.4	[22]
			gefitinib until PD	86	NR	4.1 months	10.9	
Zhang *et al.* (2011)	Platinum-based doublets for four cycles	Nonprogressed patients	Placebo until PD vs	148	0.7	4.8 months	16.9	[23]
			gefitinib until PD	148	23.7	2.6 months	18.7	

†*The objective response for single-agent TXT was 11.7%.*
CBDCA: Carboplatin; GEM: Gemcitabine; NR: Not reported; PD: Progression of disease; PEM: Pemetrexed; TXT: Docetaxel.

Conclusion

To date, the most recent international guidelines recommended a maximum of four cycles of first-line platinum-based chemotherapy for PS 0–1 advanced NSCLC patients who reported a stable disease, and a maximum of six cycles in responding ones [2–4]. To date, only the maintenance treatment with a different new generation noncross-resistant agent (i.e., an early second-line or switch maintenance treatment) was shown to be an effective strategy in prolonging OS [25]. The benefit in PFS, but also in OS, reported with pemetrexed in patients with nonsquamous histology and erlotinib in unselected patients as switch maintenance and their favorable toxicity profile allow them to be used as maintenance treatment after induction therapy with platinum-based regimens. However, to date there is a lack of trials comparing this strategy of early second-line to classical second-line administering of the drug not as maintenance but when patients progress after a first-line treatment. Moreover, most trials on maintenance did not specify second-line therapy, and this is a very serious weakness of these trials. Thus, switch maintenance is an option for physicians, as it is acceptable also the classic approach of delayed treatment with a second-line agent after disease progression. Patient preference and physician experience are both important for the choice among these two strategies. The maintenance with an agent already present in the induction phase (continuation maintenance) can be considered a further strategy mainly with pemetrexed because it has obtained advantages in terms of PFS, the primary study end point and OS results are pending. Further studies of maintenance treatment are ongoing to optimize the therapeutic impact of new anticancer drugs in NSCLC, mainly in the treatment of nonsquamous tumors where trials employing both the new agents pemetrexed and bevacizumab are in progress.

Future perspective

After four cycles of first-line chemotherapy, switch maintenance with a different new generation noncross-resistant agent, such as pemetrexed in patients with nonsquamous tumors and erlotinib in unselected patients, is already a standard option. In the near future the role of pemetrexed continuation maintenance after induction with cisplatin plus pemetrexed versus placebo must be further clarified with OS results are eagerly awaited. In our opinion, in the next 5–10 years the main focus will be to find other effective agents in addition to pemetrexed and erlotinib for the maintenance treatment of advanced NSCLC, with particular attention given to squamous NSCLC, a clinical setting with less available options to date.

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