Erlotinib as maintenance therapy in patients with advanced non-small cell lung cancer: a pooled analysis of three randomized trials

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Three randomized trials (SATURN, ATLAS and IFCT-GFPC 0502) have demonstrated that the oral antiepidermal growth factor receptor tyrosine kinase inhibitor erlotinib can improve progression-free survival (PFS) and overall survival (OS), as maintenance therapy after first-line chemotherapy in advanced non-small cell lung cancer. We pooled the results of these three trials by performing a meta-analysis of hazard ratios (HRs) and the 95% confidence intervals (CIs) for the PFS and the OS for maintenance erlotinib versus observation, standard therapy or placebo. The benefits in the predefined subgroups of patients [according to histology, sex, performance status (PS), and smoking status] were assessed. The OS was superior in the 963 patients treated with erlotinib than in the 979 nontreated patients [HR = 0.87 (P = 0.003), corresponding to a 13% reduction in the risk of death. The pooled HR for the PFS is 0.76 (P < 0.00001), corresponding to a 24% lower risk of being progression free]. All the patients in the subgroup analysis experienced a benefit from erlotinib and, in particular, never-smoking women with nonsquamous histology with a PS of 0. Both responders and those with stable disease obtain PFS benefit. The addition of maintenance erlotinib significantly improves PFS and OS in patients with advanced non-small cell lung cancer who had not progressed after four cycles of first-line chemotherapy. The benefit does not seem to be limited to a particular subgroup, although it is more pronounced in never-smoking women patients with nonsquamous carriers with a PS of 0. *Anti-Cancer Drugs* 22:1010–1019 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Platinum-based doublet regimens are the mainstay of chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) and good performance status (PS) [1]. Although in previous studies of cytotoxic chemotherapy, it had been demonstrated that no survival advantage can be achieved by prolonging its duration beyond 4–6 cycles; recent results in the maintenance setting suggest that prolonged therapy or the early administration of an approved second-line drug (pemetrexed, erlotinib or docetaxel) should be performed [2–4]. In particular, these trials implement pemetrexed, an antifolate cytotoxic drug, and erlotinib, an antiepidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. In the pemetrexed trial [2], 663 patients with stage IIIB or IV disease who had not progressed after four cycles of platinum-based chemotherapy were randomly assigned (2 : 1 ratio) to receive pemetrexed [500 mg/m^2, day 1] plus best supportive care (n = 441) or placebo plus best supportive care (n = 222) in 21-day cycles until disease progression. Pemetrexed significantly improved the progression-free survival (PFS) [4.3 months (95% CI: 4.1–4.7) vs. 2.6 months (1.7–2.8); HR 0.50, 95% CI: 0.42–0.61, P < 0.0001] and the overall survival (OS) [13.4 months (11.9–15.9) vs. 10.6 months (8.7–12.0); HR 0.79, 0.65–0.95, P = 0.012] compared with placebo, in particular in patients with adenocarcinoma. Two studies of erlotinib administered as maintenance therapy have shown some benefits in patients whose disease was controlled after four cycles of chemotherapy [3,5,6]. The SATURN trial [3] was a double-blind, phase III study that enrolled 1949 patients with previously untreated advanced NSCLC. The patients received four cycles of a platinum-based doublet chemotherapy regimen and were then assessed for tumor response. The patients who showed no evidence of disease progression (n = 889) were randomly assigned to receive maintenance therapy with administration of 150 mg of erlotinib per day or placebo until disease progression. The second trial, which implemented bevacizumab/erlotinib as maintenance therapy, is the ATLAS trial [5,6]. It was a large study that accrued 1160 patients with previously untreated stage IIIB or IV NSCLC. All patients received four cycles of a platinum-based chemotherapy plus bevacizumab as first-line therapy. The patients who showed no evidence of disease progression (n = 743) were randomly assigned to receive continuous administration of 15 mg/kg of bevacizumab every 3 weeks plus either erlotinib (150 mg/day) or placebo. The maintenance therapy was continued until disease progression. The PFS was

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significantly prolonged among the patients in the erlotinib group compared with those treated with placebo. At a meeting of the American Society of Clinical Oncology (ASCO) in 2010, an updated analysis of OS was presented. According to the SATURN data, the Food and Drug Administration has approved erlotinib as maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease had not progressed after four cycles of platinum-based first-line chemotherapy, whereas the European Medicine Agency only licensed the drug for patients with stable disease after induction therapy. A third French trial [7] (IFCT-GFPC 0502) presented in abstract form at an ASCO meeting in 2010 had randomized patients with stage IIIB/IV NSCLC to receive either erlotinib or gemcitabine or observation after four cycles of cisplatin plus gemcitabine with predefined second-line chemotherapy that included the administration of pemetrexed.

We performed a meta-analysis of these three trials with the aim of discovering whether erlotinib prolongs the PFS and OS in patients with advanced NSCLC who had not progressed after four cycles of platinum-based chemotherapy.

This study attempts to answer the question as to whether there is a population of patients with NSCLC that could benefit from this treatment option.

Materials and methods

Study selection and data source

We calculated the pooled HRs of the three erlotinib trials in terms of PFS and in terms of OS by collecting data from various publications (published full articles or abstracts). The first trial, conducted by Cappuzzo *et al.* [3], has recently been published as a full paper. The HRs of PFS and OS are taken from this publication. The second trial (by Miller *et al.*) was presented in abstract form during the ASCO Meeting in 2009 and updated with OS data at the ASCO Meeting in 2010 [5,6]. The French trial was presented for the first time in abstract form by Perol *et al.* [7] at the ASCO Meeting in 2010.

Hypothesis and clinical endpoints

Erlotinib is superior to standard of care and placebo in terms of PFS and in terms of OS in patients whose disease had not progressed after four cycles of platinum-based doublets and advanced NSCLC.

In the SATURN trial, the coprimary endpoints were PFS in all analyzable patients, regardless of the EGFR status, and PFS in patients with EGFR immunohistochemistry-positive tumors. The assessment of the PFS included both objective progression and clinical progression, and a two-sided log-rank test was performed for a basic comparison of the two treatment groups (erlotinib vs. placebo). The median PFS was estimated according to the Kaplan–Meier method. HRs and the 95% confidence intervals (CIs) were calculated with the Cox regression analysis. The secondary endpoints were OS in the intention-to-treat population and in patients with EGFR immunohistochemistry-positive tumors and PFS in patients with EGFR-negative tumors, time to progression, tumor response, time to deterioration of symptoms, and quality of life. All time-to-event endpoints were measured from randomization. To compare the treatment groups in terms of overall survival, time to progression, time to symptom deterioration, quality of life, and PFS in the EGFR-negative subgroup, two-sided log-rank tests were performed. Assessments of the effects of the treatment have been expressed as HR including the 95% CI: calculated according to the Kaplan–Meier method.

The primary endpoint in the ATLAS trial was PFS, whereas the secondary endpoints were OS, safety, and biomarker analysis. The OS was defined as the time from randomization to death. The study was not powered to detect OS differences. The first OS analysis was prespecified to occur at the time of the primary PFS analysis (18 July 2008 cutoff point). At the time of the primary OS analysis, some deaths had occurred (31% of patients had died). Two post-hoc analyses of the OS were performed after more deaths had occurred (data cutoffs, 28 January and 19 June 19 2009).

The primary endpoint of the IFCT–GFPC 0502 trial was PFS from randomization and was evaluated by an independent panel review (98% of patients' status reviewed). The secondary endpoints were OS, safety, symptom control, and prognostic/predictive value of the EGFR status. The trial was designated to independently address two questions: (1) Is maintenance gemcitabine better than observation?; and (2) Is maintenance erlotinib better than observation?

Patients and methods

The characteristics of the randomized patients are reported in Table 1. In the SATURN trial, 1949 patients were included in the run-in phase (four cycles of platinum-based chemotherapy) between December 2005 and May 2008. At the end of the run-in phase, 889 patients who did not have progressive disease and who met the criteria of completion of four-cycle standard platinum-doublet chemotherapy without disease progression (e.g. complete or, partial response or stable disease), an Eastern Cooperative Oncology Group (ECOG) PS of 0 or 1, an adequate renal, hepatic, and hematological function or a negative pregnancy test for women of child-bearing age were selected for the main study; they were randomly assigned to receive erlotinib (150 mg/day; $n = 438$) or placebo ($n = 451$) until progression or unacceptable toxicity levels according to a 1 : 1 adaptive randomization method through a third-party interactive voice response system. The patients were stratified

Table 1 Characteristics of patients randomized in the SATURN and ATLAS trials

Reference	Number of patients	Induction CT	Maintenance	Sex/median age	Smoking status	PS	Histology	Race	Stage
Cappuzzo *et al.* [3]	889	Platinum-based (except bev/pem)	Erlotinib vs. plac	M/F 73/27%/ 60 years	Never 18%/ current + former 72%	0 (31%) 1 (69%)	Adeno + BAC 47% Squamous 38% Other 15%	Caucasian 84% Asian 14%	IIIB 26% IV 74%
Miller *et al.* [5] and Kabbinavar *et al.* [6]	743	Platinum-based + bev	Bev + erlotinib vs. bev + plac	M/F 52/48%/ 64 years	Never 16%/ current + former 84%	0 (48%) 1 (52%)	Adeno + 81.3% Other 18.7%	White 79% Asian 11.6%	IIIB 8.7% IV 91.3%
Perol *et al.* [7]	464	CDDP/GEM	Erlotinib vs. GEM vs. observation	M/F 73/27%/ 56 years	Never 38%/ ever smokers 62%	0 (38%) 1 (56%)	Adeno + 63% Squamous 17% Other 20%	Not reported	IIIB 7% IV 93%

Adeno, adenocarcinoma; BAC, bronchioloalveolar; bev, bevacizumab; CDDP, cisplatin; F, female; GEM, gemcitabine; M, male; Plac, placebo.

according to EGFR immunohistochemistry status, stage, ECOG PS, chemotherapy regimen, smoking history, and region.

A total of 743 patients were randomized in the ATLAS trial [5,6], 370 of whom were in the bevacizumab/erlotinib arm and the other 373 were in the bevacizumab/placebo arm. The study was originally designed to include only nonsquamous NSCLC cases, but after the initiation of the study, the trial was amended to also include other types of tumor. The patients enrolled in the ATLAS trial were bevacizumab eligible (including patients with treated brain metastases and patients receiving low-molecular weight heparins); peripheral and/or extrathoracic squamous tumors were included. The patients received four cycles of bevacizumab (15 mg/kg q3 weeks) plus platinum-containing doublet chemotherapy. The patients whose disease was not progressive after four cycles of bevacizumab plus chemotherapy and had no significant toxicity were randomized to receive bevacizumab plus erlotinib (150 mg/day) or bevacizumab plus placebo as maintenance therapy. The patients were stratified according to sex, ECOG performance status, smoking history, and chemotherapy regimen.

The results were calculated from the intent-to-treat population, which consisted of 743 patients (370 in the bevacizumab plus placebo arm and 373 in the bevacizumab plus erlotinib arm).

In the IFCT–GFPC 0502 trial, 454 patients (with stable or responding disease after four cycles of induction chemotherapy with cisplatin and gemcitabine) were randomized to observation ($n = 155$), gemcitabine ($n = 154$) or erlotinib administered at doses of 150 mg/day ($n = 155$). Pemetrexed was the preplanned second-line therapy. The patients were predominantly ever-smoking men with adenocarcinoma histology (73/62/63% in the three arms respectively carrying adenocarcinoma). The patients were stratified according to sex, histology, smoking status, center, and response versus stabilization to induction chemotherapy.

The characteristics of the randomized patients were well balanced between the erlotinib and the nonerlotinib arms in all three trials, with the exception of a greater presence of adenocarcinoma cases in the ATLAS trial (> 80% vs. 44 and 63% in SATURN and IFCT–GFPC 0502 trials, respectively) and of never-smoking patients in the French study (38% vs. 18 and 16.5% in SATURN and ATLAS trials, respectively).

Statistical analysis

RevMan 5.0.24 (Cochrane IMS) was used for statistical analysis. For the meta-analysis, we used either a fixed-effect model (weighted with inverse variance) or a random-effect model [8]. For each meta-analysis, Cochran's Q statistic and I^2 statistics were calculated first, to assess the heterogeneity among the proportions of the included trials.

In the case that the *P* value was found to be less than 0.1, the assumption of homogeneity was then deemed invalid and the random-effect model was reported after exploring the causes of heterogeneity [9]. Otherwise, the fixed-effect model was reported. A two-tailed *P* value of less than 0.05 was considered statistically significant.

Results

A total of 963 patients were randomized in the erlotinib maintenance arms and 979 in the standard therapy (including bevacizumab in one trial), observation or placebo arms.

In the first trial, the SATURN study [3], after a median follow-up of 11.4 months for the erlotinib group and 11.5 months for the placebo group, the median PFS was found to be significantly longer with erlotinib than with placebo: 12.3 weeks for the patients in the erlotinib group versus 11.1 weeks for those in the placebo group (HR 0.71, 95% CI: 0.62–0.82; $P < 0.0001$). The OS has also significantly improved (HR, 0.81; median, 12.0 vs. 11.0 months).

In the second trial, the ATLAS trial [5,6] after a median follow-up of 8.3 months (first analysis), the median PFS was 4.76 and 3.75 months in the investigational arm and in the control arm, respectively (HR: 0.722; 95% CI: 0.592–0.881; $P = 0.0012$). This result represented an improvement of 1 month in the median PFS compared with the SATURN trial, which reported only a 1.2-week improvement in the median PFS with erlotinib maintenance therapy. This improved PFS persisted over time, and the 6-month PFS was 40.3% versus 28.4% in the erlotinib and the placebo groups, respectively. Two post-hoc analyses for the OS were performed after the first analysis, because deaths had occurred. The last analysis (June 2009) showed that the median OS was respectively 15.9 versus 13.9 in the investigational and in the standard arms (HR: 0.90; 95% CI: 0.74–1.09; $P = 0.2686$). Differences in median survival, however, are not meaningful. Overall, HRs for PFS are very similar in ATLAS and SATURN trials, which means that there is the same level of benefit.

The PFS in the French trial evaluated by an independent review (98% patients assessed in the May 2010 update presented orally during the ASCO meeting) was significantly prolonged by gemcitabine (HR: 0.55; 95% CI: 0.43–0.70) and erlotinib [HR: 0.82; (0.73–0.93); $P = 0.002$] versus observation. After a median follow-up of 21.6 months, the preliminary OS data for erlotinb were HR: 0.91; and 95% CI: 0.8–1.04.

The pooled HR for the PFS is 0.76 (95% CI: 0.70–0.83), according to a fixed-effect model (*P* for heterogeneity 0.26, $P < 0.00001$). This result is of significant value because it means that the risk of being progression free was lowered by 24% (Fig. 1).

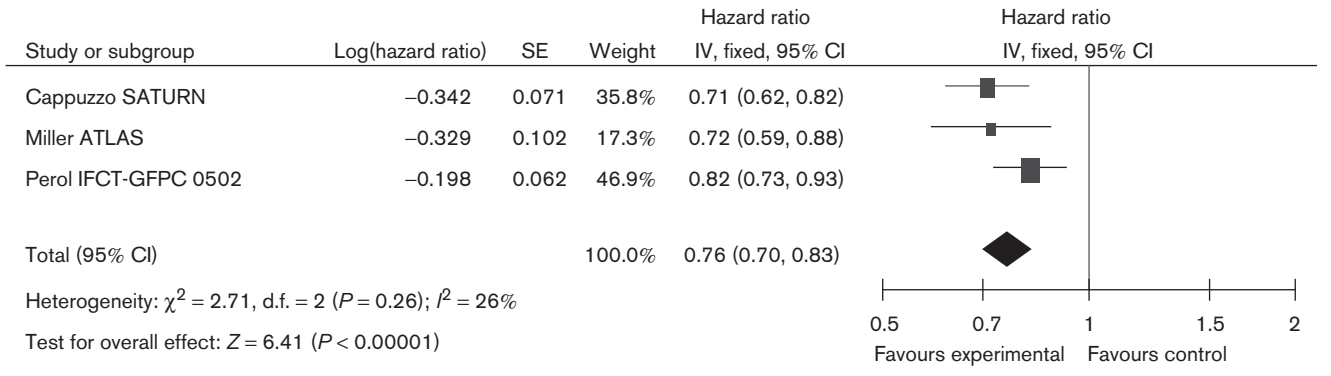
The corresponding value for the OS is 0.87 (95% CI: 0.80–0.95), according to a fixed-effect model (*P* for heterogeneity 0.49, $P = 0.003$), which corresponds to a 13% reduction in the risk of death (Fig. 2).

The pooled HRs for the PFS in the subgroups of patients analyzed in all trials (histology, sex, PS, and smoking status) are reported in Figs 3–6. Similar data are not available for OS.

Cappuzzo and Perol trials investigated whether erlotinib maintenance offered a different benefit in patients with responsive or stable disease to induction chemotherapy. The results of meta-analysis of PFS according to response to first-line therapy show that the gain in progression is significant both after a stabilization than after a shrinkage of the disease (Fig. 7a and b). In SATURN trial, however, OS results are significant only for nonresponding patients.

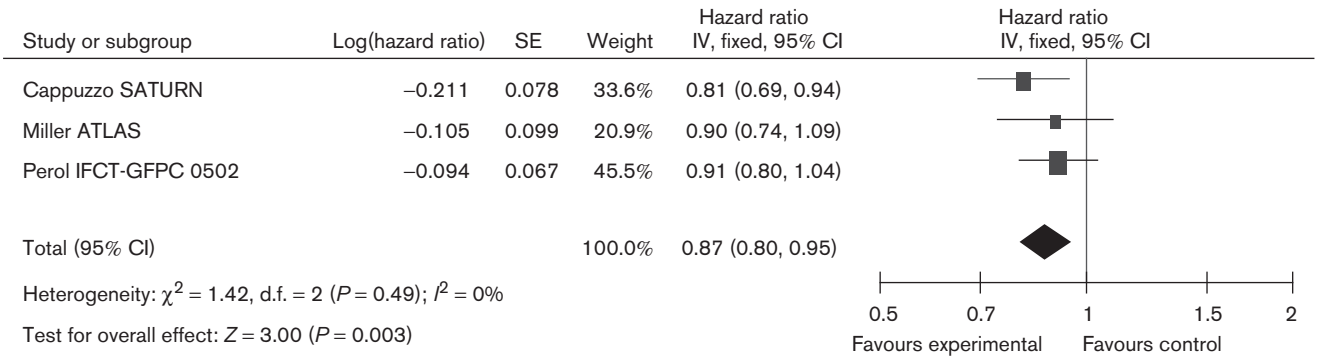
Finally, the proportions of patients free of disease progression at 3 and 6 months show that the risk of progression is 27 and 52% higher without maintenance erlotinib. The results are impressive and highlight the

Fig. 1



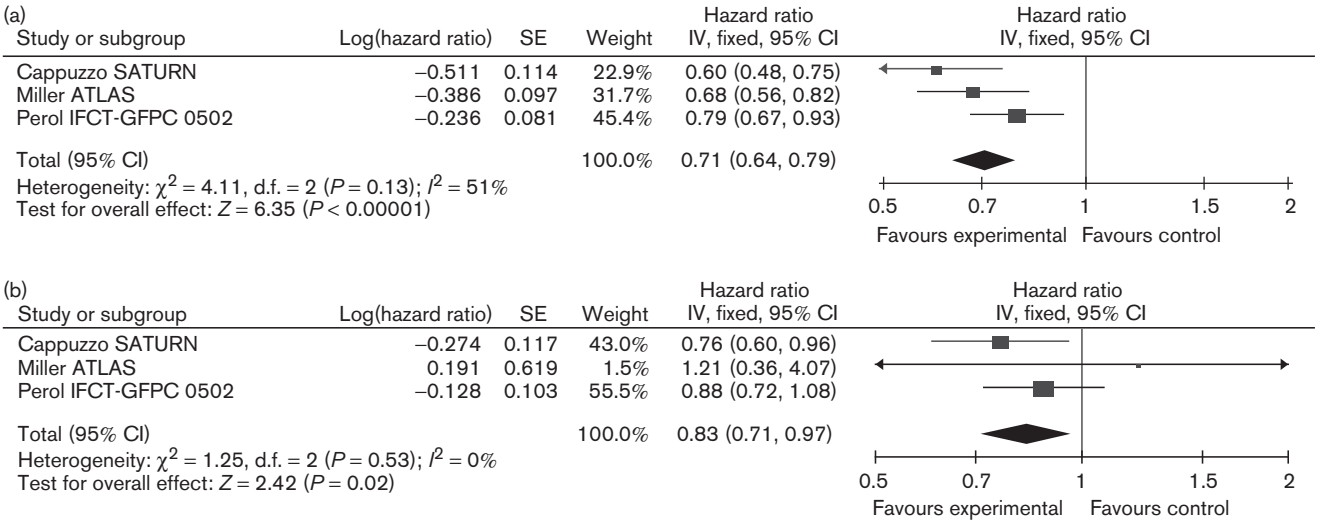
Meta-analysis of (hazard ratio) HR for (progression-free survival) PFS; fixed-effect model.

Fig. 2



Meta-analysis of hazard ratio (HR) for overall survival (OS); fixed-effect model.

Fig. 3



(a) Meta-analysis of hazard ratio (HR) for progression-free survival (PFS) (nonsquamous histology; fixed-effect model). (b) Meta-analysis of HR for PFS (squamous histology; fixed-effect model).

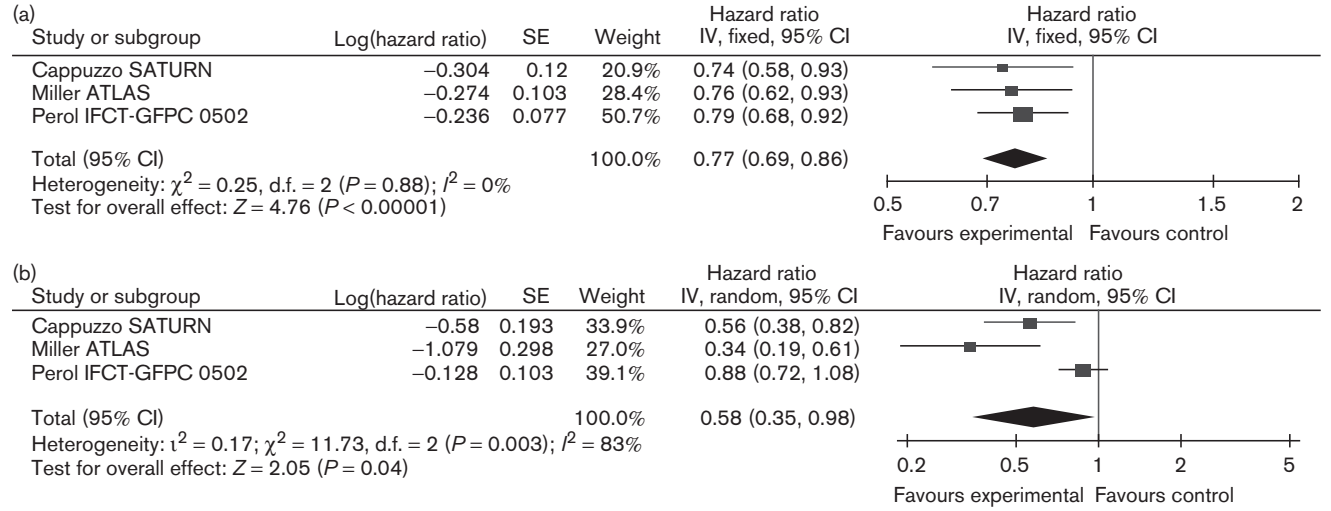
durable progression-delaying effect of erlotinib (Fig. 8a and b).

Discussion

The results of this meta-analysis confirm the benefit of maintenance erlotinib in patients with advanced NSCLC who had not progressed after four cycles of induction (platinum-based) chemotherapy. Erlotinib leads to a significant 24 and 13% reduction in the risk of progression and death. The results of these trials, SATURN in particular, led the Food and Drug Administration and the EMEA to approve erlotinib (in patients whose disease had not progressed or had stabilized after four cycles of platinum-based first-line chemotherapy) as maintenance therapy in this setting. This meta-analysis overall shows consistent and robust results with regard to the benefit in PFS (the primary endpoint of all meta-analyzed studies) and OS in the overall population and, only for PFS, in all subgroups analyzed. The PFS data, in particular, are also corroborated by the independent review analysis of this endpoint in both Cappuzzo and Perol trials, which account for more than 80% of the weight of the PFS meta-analysis.

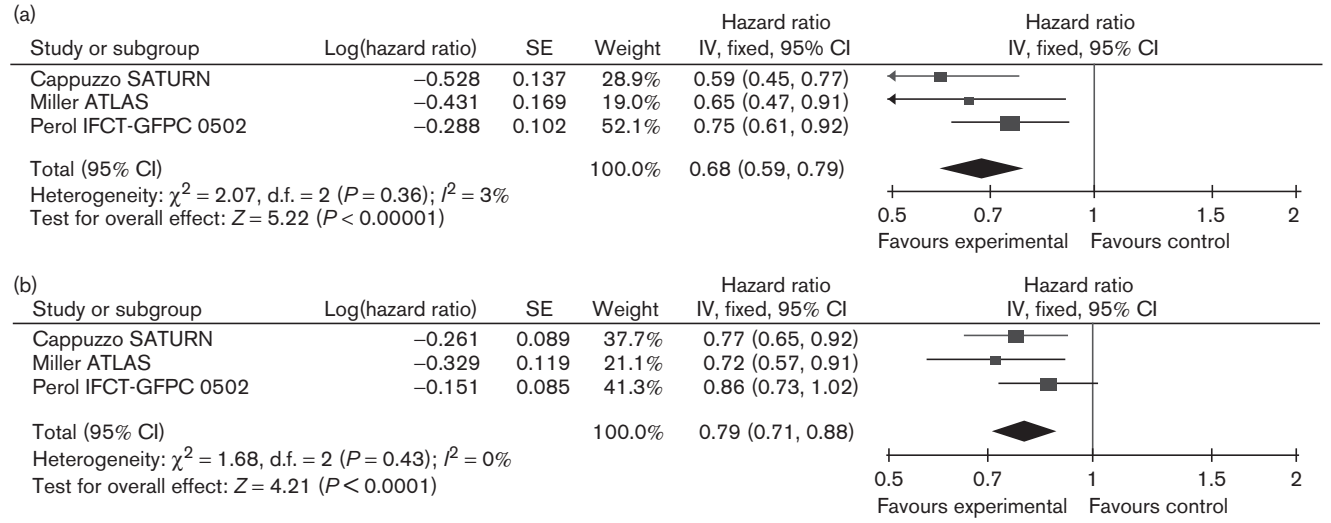
This demonstrates that for the first time an anticancer (nonantiblastic) targeted drug prolongs disease control after first-line (platinum-based) treatment in patients with advanced NSCLC with adenocarcinoma as well as with other (squamocellular) histologies. Obviously, it must be

Fig. 4



(a) Meta-analysis of hazard ratio (HR) for progression-free survival (PFS) (current/ever smokers; fixed-effect model). (b) Meta-analysis of HR for PFS (never smokers; random-effect model).

Fig. 5

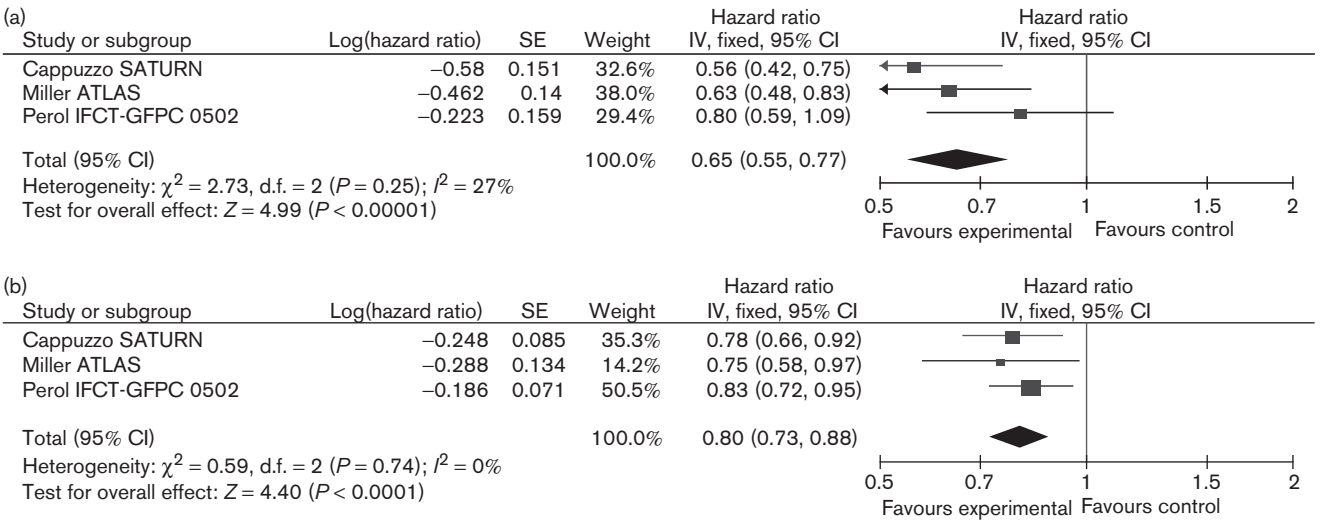


(a) Meta-analysis of hazard ratio (HR) for progression-free survival (PFS) (PS 0; fixed-effect model). (b) Meta-analysis of HR for PFS (PS 1; fixed-effect model).

said that the target population selected for maintenance therapy is the best from a prognostic point of view. In fact, it is well known that obtaining the control of the disease with first-line chemotherapy is generally associated with better PFS and OS. Maintenance therapy could thus simply select an 'emergent' good prognosis-population with a better outcome *per se* in the presence of some form of treatment (either chemotherapy or targeted agents).

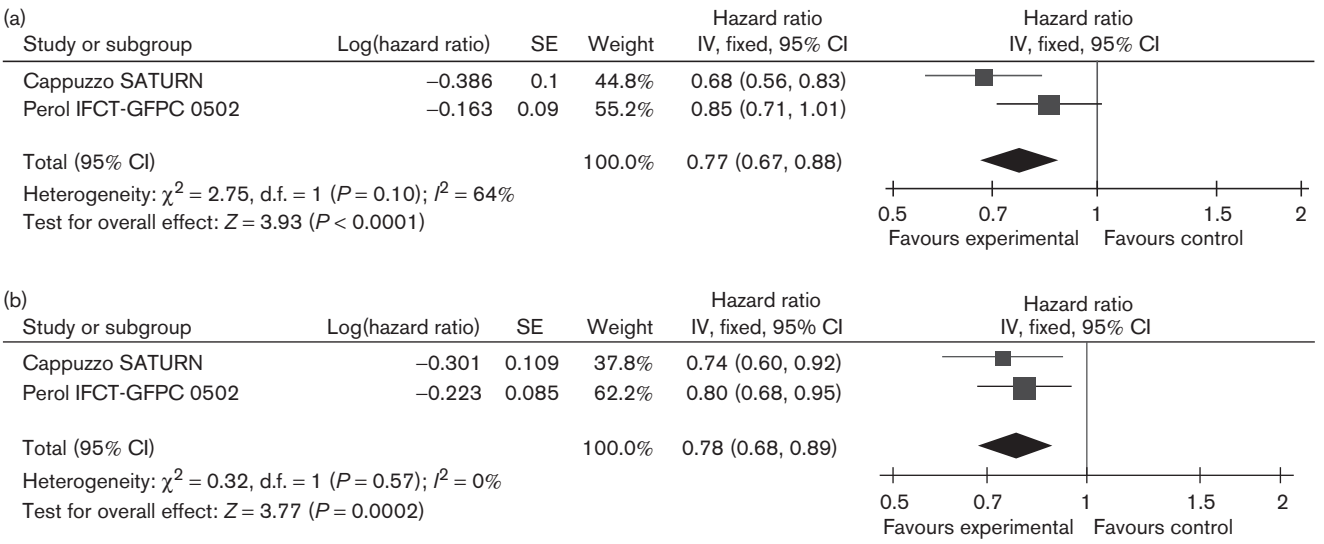
Therefore, the question is which are the main endpoints of a maintenance treatment? Not only survival but also PFS could be reasonable targets during the maintenance phase. It is known that survival represents the primary endpoint of a first-line (chemotherapy-based) treatment. PFS has not yet replaced OS as the surrogate endpoint for a first-line trial in advanced disease and in colorectal cancer; but is this true even in a targeted therapy setting? In a 2009 publication, 24 phase II trials and four phase III trials,

Fig. 6



(a) Meta-analysis of hazard ratio (HR) for progression-free survival (PFS) (female sex; fixed-effect model). (b) Meta-analysis of HR for PFS (male sex; fixed-effect model).

Fig. 7

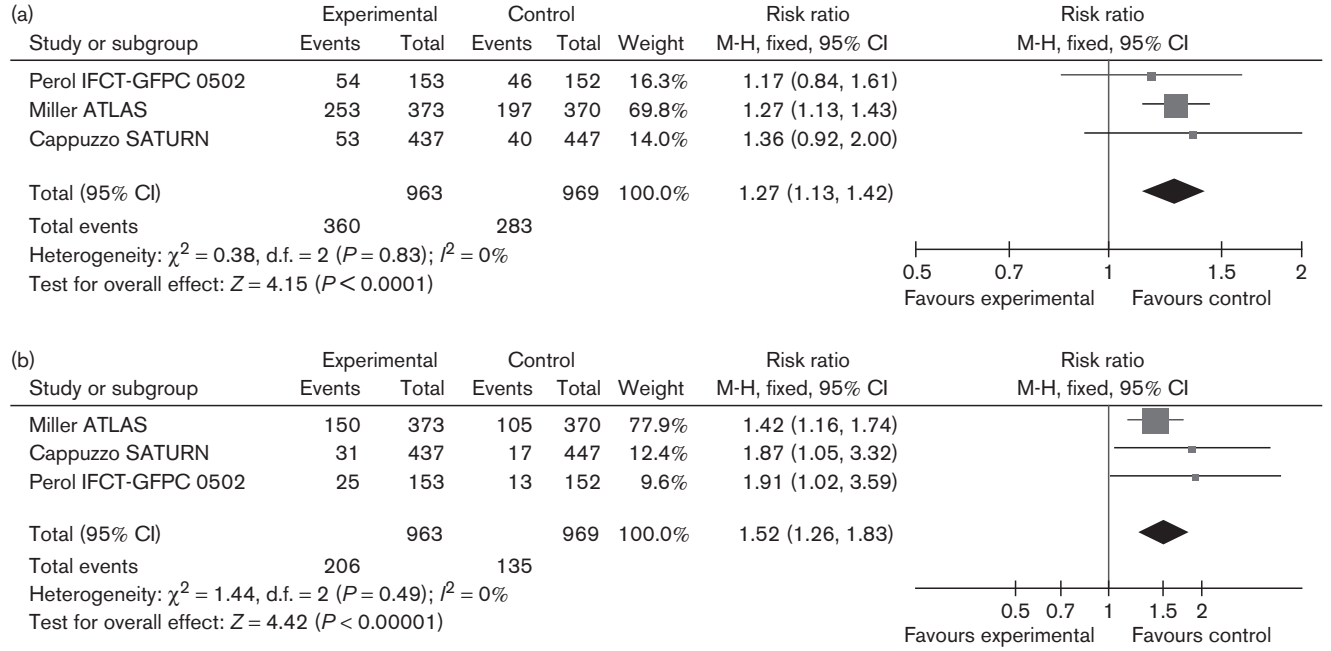


(a) Meta-analysis of hazard ratio (HR) for progression-free survival (PFS) (stable disease after induction; fixed-effect model). (b) Meta-analysis of HR for PFS (objective response after induction; fixed-effect model).

including 22 arms for the gefitinib group and eight arms for the erlotinib group, were analyzed for correlation between response and survival. Both relative risk and disease control rate strongly correlated with median survival time ($P < 0.0001$ and $P = 0.003$, respectively) [10]. Therefore, what is the real objective of a maintenance treatment? In reality, to make the disease a chronic condition, to delay the clinical deterioration, to maintain the control of symptoms, and finally to prolong time to disease objective/clinical progression are considerable targets of a maintenance drug. The future update of all studies will give us information about specific subgroup benefits in terms of OS (as EGFR mutations carriers, data available only for Cappuzzo trial).

Overall, it seems that the early introduction of (maintenance) erlotinib represents a valid option for a selected group of patients (never smokers, good PS, responding or

Fig. 8



(a) Meta-analysis of hazard ratio (HR) for progression-free survival (PFS) (risk of progression at 3 months timepoint; fixed-effect model). (b) Meta-analysis of HR for PFS (risk of progression at 6 months timepoint; fixed-effect model).

with stable disease after induction chemotherapy, and also in case of EGFR mutation) whatever the histology of their disease, who may receive approved second-line agents (pemetrexed or docetaxel) as a subsequent line of treatment. A new finding derived from this analysis states that, in particular, the benefit in both PFS and OS (but only in Cappuzzo trial) is confined to stable patients after induction therapy. We calculate a significant benefit, but only in PFS, even in responder patients (meta-analysis of Perol and Cappuzzo trials). These data are difficult to explain but could be driven by the major effect of erlotinib (linked to a different intrinsic biology) in the subgroup of patients (possibly with EGFR mutated disease) that conversely obtained a high rate (40%) of stable disease to standard combination chemotherapy (see IPASS trial). Moreover, the effect of delaying the progression of erlotinb is maintained after randomization and is continuous and durable (the risk of disease progression is reduced by a half at 6 versus 3 months of therapy) at predefined time points.

The recent results achieved by an Asiatic IPASS [11] trial compared gefitinib with chemotherapy as an initial approach in advanced NSCLC. The patients were selected according to clinical predictors (carriers of EGFR mutations), drawing attention to the use of antiEGFR inhibitors even earlier in the natural history of the disease. The EGFR mutation status was found to be highly predictive of response to gefitinib. The biomarker analysis for the *EGFR* mutation status of the SATURN study showed that erlotinib was active (both in terms of PFS and in terms of OS) in patients with *EGFR*-activating mutations (HR: 0.10, 95% CI 0.04–0.25; $P < 0.0001$) and in those with wild-type *EGFR* (HR: 0.78; 95% CI: 0.63–0.96; $P = 0.0185$). Although the number of patients carrying such mutations is limited and not available, at the moment of this meta-analysis for ATLAS and perol trials, this result is impressive and suggests several hypotheses. Similarly, the subgroup analyses of the PFS by clinical characteristics in these trials showed a PFS improvement with erlotinib rather than with placebo among all the analyzed subgroups, it has to be noted that this benefit was observed regardless of histology (nonsquamous and squamous). This is not the case of the ATLAS trial, where squamous cell NSCLCs did not experience any benefit from erlotinib. These findings confirm those of BR.21, where never-smokers and patients with EGFR-positive tumors experienced an enhanced benefit from erlotinib, and even ever-smoking men and squamous cell histology achieved some survival advantage [12]. In the pooled analysis, all types of histology, sex, and smoking status as well as PS 0 and 1 experienced a benefit in PFS, with the highest values recorded among nonsquamous histology (HR 0.71), never-smokers (HR 0.58), PS 0 (HR 0.68), and those of the female sex (HR 0.65). These are probably the categories that most frequently harbor EGFR mutations.

A prolongation of the treatment beyond the standard four cycles of platinum-based doublets has to be balanced with the several side effects patients are exposed to. Hence, it can be said that the tolerability of a maintenance treatment is a key point to its acceptance. An overall withdrawal due to adverse events occurred in 20 patients (5%) in the erlotinib group from the SATURN trial. The corresponding result obtained in the erlotinib BR.21 trial by Shepherd *et al.* [13] was 5%. Serious adverse events have been reported as 11 and 22% in the SATURN and the ATLAS trials, where the latter value increase may be due to concomitant bevacizumab administration. Severe cutaneous rash and diarrhea turned out to be the most frequent side effects (9/2 and 10/9% in SATURN and ATLAS trial), in comparison with the BR.21 second-line trial where the corresponding values were 9 and 6%. In the French trial, the major severe toxicities were rash and asthenia (9 and 2.6%). It seems that erlotinib as maintenance therapy, administered immediately after a platinum-based chemotherapy, has the same good toxicity profile as the second-line setting. Severe anorexia is infrequent (1–2%). In ATLAS trial hypertension, hemorrhage, arterial and venous embolic events, proteinuria, and cardiac events (severe: approximately 1–5% of cases) are likely related to bevacizumab and are similar in the bevacizumab/placebo arm. Where reported, grade 3–4 neutropenia is episodic (< 1%). In the Socinski *et al.* [14] paclitaxel/carboplatin maintenance study (defined versus a continuous number of cycles), the rate of grade 2 to 3 neuropathy increased from 19.9% at cycle four to 43% at cycle eight. It is to be noted that erlotinib has virtually no cumulative toxicity and is easy to administer orally. Data for PFS are also significant for symptomatic patients, who are less likely to tolerate aggressive treatments. Cost-effective analysis of erlotinib maintenance has not yet been presented, but a similar maintenance pemetrexed analysis shows that it is cost-effective [15], particularly in patients with nonsquamous cell histology. This emphasizes the importance of predictive factors in identifying the appropriate patient for maintenance therapy.

This meta-analysis, however, has some clear weaknesses. It is not a meta-analysis of data obtained from individual patients, is based on studies with limited follow-up, and is based on HRs obtained from a single published study and two studies presented only in the abstract form and without presenting survival data in the various subgroups. The strongest points of criticism aimed at these maintenance studies are, in particular, the relatively short follow-up time (ranging between 11 and 21 months) and poststudy treatments (second lines and beyond). In Cappuzzo's trial, only 21% of the patients in the placebo arm received erlotinib in subsequent lines of therapy. In the ATLAS trial, an equal number of patients (39%) in two arms received it. In Perol's trial, approximately 4 and 49.6% of patients in the observation arm received erlotinib as second-line and third-line treatment because pemetrexed was essential as the second-line (76 vs. 63% of observation and erlotinib arms received pemetrexed but conversely 10% vs. 40% of the same arms received docetaxel as second/third lines). Pemetrexed and docetaxel rate of administration imbalance (more pemetrexed but less docetaxel rate of administration in observation versus erlotinib arm) in two arms could have 'balanced' the effect with regard to the overall OS benefit of the study. The proponents of the concept of maintenance therapy argue that approximately 60–70% of patients who are about to receive second-line treatment are exposed to these agents. They report the data collected by Fidias *et al.* [4] that compared immediate versus delayed docetaxel after first-line induction. Of the 153 patients who started the docetaxel therapy immediately after random assignment, 145 (94.8%) received at least one treatment cycle. However, only 98 (62.8%) out of the 156 patients randomly assigned to the delayed docetaxel arm received the first cycle of the docetaxel therapy, principally due to the progression of the disease, which prevented the programmed second-line therapy. Overall, the fact that the three studies do not define erlotinib as essential for the patients who do not receive it during the maintenance phase may have confounded and ameliorated at least the survival data for the maintenance arm.

Whether or not this amount of benefit (approximately one month) is actually clinically meaningful remains to be debated. By selecting patients for known molecular predictive factors of response (as EGFR mutation), the benefit of maintenance erlotinib would probably turn out to be better than what has been reported in this meta-analysis, even if, in this case, it would be administered as first-line treatment and continued until progression. This 'selection strategy' can further prolong the benefit now reachable with modern agents (e.g. bevacizumab) that led for the first time to a median survival of more than twelve months.

Conclusion

In conclusion, this meta-analysis of three erlotinib maintenance trials shows that this strategy may significantly prolong PFS in the overall population (HR 0.71), other than in the subgroups analyzed, and median survival (HR 0.84 for the global population) in an unselected population of advanced NSCLC patients who have not progressed after first-line (platinum-based) chemotherapy. For survival only, Cappuzzo's trial reports subgroup analysis where younger, women patients with PS 1 adenocarcinoma (with stable disease) seem to benefit more. In conclusion, the immediate introduction of erlotinib as maintenance or early second-line therapy represents a viable option leading to an improvement in the outcome of advanced (unselected) NSCLC populations. In the meantime, better predictive criteria for the selection of patients are being evaluated.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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