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## Single agent maintenance therapy for advanced stage non-small cell lung cancer: A meta-analysis

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### Abstract

**Background**—Maintenance therapy is a new treatment paradigm for advanced non-small cell lung cancer (NSCLC). We conducted a meta-analysis of randomized studies with single agent maintenance therapy.

**Methods**—An electronic literature search of public databases (MEDLINE, EMBASE, Cochrane library) and manual search of relevant conference proceedings was performed. A formal meta-analysis was conducted using Comprehensive Meta Analysis software (Version 2.0). Outcome data were pooled and reported as hazard ratio (HR). The primary outcome of interest was overall survival (OS) and secondary outcome was progression free survival (PFS).

**Results**—Twelve studies were included (5 meeting abstracts, 7 full manuscripts) with a total of 4286 patients (maintenance arm/control arm- 2449/1837, median age 61 years, males -69 %). The OS (HR 0.86, 95% confidence intervals [CI] 0.80-0.92; P=0.0003) and PFS (HR 0.80, 95% CI 0.77-0.84; P<0.0001) were superior with maintenance therapy. ‘Switch’ maintenance was associated with significant OS and PFS improvement (OS HR 0.84, 95% CI 0.77-0.91; P=0.00026; PFS HR 0.62, 95% CI 0.57-0.67; P<0.0001). Despite a modest improvement in PFS (HR 0.90, 95% CI 0.85-0.95; P=0.007), “continuation” maintenance was not associated with survival benefit (HR 0.927, 95% CI 0.78-1.09; P=0.33). Improvements in OS and PFS were observed with both EGFR-targeted agents (HR 0.83, 95% CI 0.74-0.92; P=0.004; HR 0.64, 95% CI 0.58-0.71 P<0.0001) and cytotoxic agents (HR 0.89, 95% CI 0.80-0.98; P=0.018; HR 0.85, 95% CI 0.80-0.89; P < 0.0001).

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### CONFLICT OF INTEREST STATEMENT

Suresh Ramalingam has served on adhoc advisory board meetings for Lilly, Genentech, Astellas and Pfizer.

Chandra P Belani has served as a consultant for Lilly and Genentech.

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**Conclusions**—Single agent maintenance therapy improves overall survival, though statistical significance was only noted with ‘switch’ maintenance.

### Keywords

Maintenance therapy; non-small cell lung cancer; NSCLC; EGFR; pemetrexed; erlotinib; gefitinib

## INTRODUCTION

Lung cancer is the leading cause of cancer-related deaths globally<sup>1</sup>. The majority of the patients have advanced stage disease at the time of diagnosis, for which there are no curative treatment options. Non-small cell lung cancer (NSCLC) accounts for nearly 85% of all cases of lung cancer in the United States. For patients with advanced stage NSCLC, systemic therapy is the recommended treatment. Platinum-based combination chemotherapy regimens have demonstrated modest improvements in overall survival and in quality of life for advanced NSCLC patients who have a good performance status<sup>2</sup>. Four to six cycles of combination chemotherapy are considered the standard of care for advanced NSCLC. The median progression-free survival with standard combination chemotherapy regimens is approximately 4 months with a median overall survival of approximately 8 to 11 months for patients with a good performance status<sup>3</sup>.

Maintenance therapy, also referred to as consolidation therapy, refers to the use of systemic therapy in patients who benefit from combination chemotherapy in order to extend the duration of disease control<sup>4</sup>. The initial studies employed prolongation or continuation of combination chemotherapy until progression of disease<sup>5, 6</sup>. When compared to chemotherapy for a defined duration, there was no improvement in overall survival with the use of prolonged combination chemotherapy. In addition, the increased incidence of cumulative toxicities was a major impediment. Therefore, combination chemotherapy is usually not recommended beyond 4 to 6 cycles for advanced NSCLC. In recent years, administration of a single agent as maintenance therapy following 4 cycles of combination chemotherapy has been studied in randomized clinical trials. Pemetrexed, an anti-folate compound and erlotinib, an inhibitor of the epidermal growth factor receptor (EGFR) have both demonstrated modest improvements in overall survival compared to placebo in the maintenance setting<sup>7, 8</sup>. Both of these agents have now been approved by the United States Food and Drug Administration for maintenance therapy of advanced NSCLC. Other agents that have been evaluated in the maintenance setting such as gemcitabine, docetaxel, vinorelbine, paclitaxel and gefitinib have not demonstrated improvement in overall survival<sup>9-13</sup>. Therefore, a number of questions remain open regarding the use of maintenance therapy in advanced NSCLC.

Soon and colleagues reported on a meta-analysis of randomized clinical trials that reported on the role of maintenance therapy for advanced NSCLC<sup>14</sup>. The analysis included some clinical trials that utilized combination chemotherapy as maintenance and others that employed single agent therapy. There was a statistically significant improvement in progression-free survival and overall survival for maintenance therapy. However, the analysis did not specifically address the role of single agent maintenance therapy that is now the commonly utilized approach in routine practice. Furthermore, the data from recent randomized studies not included in the meta-analysis by Soon et al has shed further light on the benefits of maintenance therapy for advanced NSCLC<sup>8</sup>. With the availability of both targeted agents and chemotherapy for maintenance therapy, it has now become important to determine personalized treatment based on individual patient characteristics. Another relevant issue regarding optimizing maintenance therapy is whether the agent used has or has not been given as part of the first-line combination regimen. Continuing one of the

agents used as front-line therapy (continuation maintenance) vs. incorporating an agent that the patient has not previously received (switch maintenance) are the two utilized strategies<sup>7, 15</sup>. In order to understand the impact of each of these strategies on the outcomes for patients with advanced NSCLC, we conducted a meta-analysis of randomized studies that evaluated only single agent maintenance therapy.

## METHODS

### Search Methodology

We conducted an electronic literature search of public databases (MEDLINE, EMBASE, Cochrane library) and a manual search of conference proceedings. Relevant search terms, such as “non-small cell lung cancer, maintenance therapy, anti-neoplastic agents” were included in the search strategy. The list of retrieved studies was then manually searched and reviewed for eligible trials. The annual meeting proceedings of ASCO and the World Conference on Lung Cancer from 1994-2011 were hand searched for eligible trials. Prospective trials registers were explored for relevant ongoing trials.

### Inclusion Criteria, Selection of Trials and Data Collection

Randomized controlled trials that reported the effect of single agent maintenance therapy on survival or progression-free survival in histologically or cytologically proven stage IIIB or IV NSCLC patients were included. Studies were considered for this review if they measured clinical outcomes such as, overall survival (OS), progression-free survival (PFS), objective response (OR), treatment-related morbidity, treatment-related mortality, or quality of life (QOL) measures. The list of references was reviewed and studies were identified by three co-authors. Abstracts that seemed eligible were screened for further review. The full-text of any abstract that appeared to be eligible was carefully examined for inclusion. Any disagreements were resolved by consensus.

Two reviewers independently extracted the data from the selected articles using standardized data compilation forms. Original data from meeting presentations for qualifying abstracts were accessed through virtual meeting. The name of the first author and the publication year has been used to identify the article in the review. We extracted data related to the clinical outcomes, and also on the methodological quality of the trials.

### Outcome Measures

A formal meta-analysis was conducted using Comprehensive Meta Analysis software (Version 2.0). The outcome data were pooled and reported as hazard ratio (HR). The primary outcome of interest was overall survival (OS) and secondary outcomes included progression free survival (PFS), objective response rate and toxicities. All the included studies, except one reported OS data.

### Statistical Analysis

The appropriate outcome data was extracted from individual published reports of the included trials using methods described in the literature<sup>16, 17</sup>. The data was then pooled for meta-analysis and the final summary statistics is reported as hazard ratios (HR), where the HR of less than 1 signifies an advantage for maintenance therapy. The meta-analysis results are displayed as forest plots. The statistical heterogeneity of trial results was determined from the forest plot statistics. A p-value of greater than 0.1 for  $\chi^2$  test and  $I^2$  value of less than 0.25 reflects the low level of heterogeneity<sup>18</sup>. A fixed-effect model was used to perform the primary analyses.

## Subgroup Analyses

The trials were stratified into four different categories for subgroup analyses to evaluate the effect of- 'continuation' maintenance (5 trials); 'switch' maintenance (8 trials); cytotoxic agents (9 trials); EGFR targeted agents (4 trials). The OS and PFS are reported as summary results from each subgroup analysis.

## Objective Response Rate, Quality of Life and Adverse Events

The data for these outcome measures have been reported diversely across the trials, which made it complicated for statistical pooling. A qualitative assessment of these outcomes is provided in this report.

## RESULTS

### Search Strategy/Study selection Results

The search strategy and selection steps for the eligible studies are summarized in the consort diagram shown in Figure 1. We included 12 trials for final analysis with a total of 4286 patients. Of the included studies, 5 are meeting abstracts and 7 are peer-reviewed full journal articles.

### Characteristics of Included Studies

A summary of characteristics of the 12 included studies is provided in Table 1. The median sample size was 275.5 patients ranging from 130 to 663. The median age of all included patients was 61 years. Continuation maintenance was evaluated in 5 trials and 'switch' maintenance was evaluated in 8 trials. Nine of the trials evaluated cytotoxic agents for maintenance and 4 of the trials used EGFR targeted agents. Males (69%), Caucasians (75%), adenocarcinoma/squamous cell carcinoma (51%/28%), Stage III/IV (21%/78%), smokers (69%), performance status 0/1/2 (34%/69%/8%) are some of the characteristics of the patients included in this analysis.

### Overall Survival

Single agent maintenance therapy was superior in improving OS (HR 0.86, 95%CI 0.80-0.92; P= 0.0003; Figure 2). There was no significant heterogeneity in the HRs of individual trials (P= 0.92,  $I^2 < 0.05$ ). Switch maintenance was found to be significantly better (HR 0.84, 95% CI 0.77-0.91; P =0.00026; Figure 3) whereas 'continuation' maintenance was not associated with a statistically significant survival benefit (HR 0.92, 95% CI 0.78-1.09; P= 0.33; Figure 3). Pooled data from trials that evaluated cytotoxic agents as maintenance therapy showed significant improvement in OS (HR 0.89, 95% CI 0.80-0.98; P=0.018; Figure 4). EGFR-targeted therapy, evaluated in 4 trials, was associated with significant improvement in OS (HR 0.83, 95% CI 0.74-0.92; P= 0.004; Figure 4).

### Progression-free survival

A statistically significant improvement was seen in PFS in patients with maintenance therapy (HR 0.80, 95% CI 0.77-0.84; P < 0.0001; Figure 5). Switch maintenance was associated with significant improvement in PFS (HR 0.62, 95%CI 0.57- 0.67; P <0.0001) whereas continuation maintenance showed a relatively modest improvement in PFS (HR 0.90, 95% CI 0.85-0.95; P=0.007). Cytotoxic agents were associated with significant improvement in PFS (HR 0.85, 95% CI 0.80-0.89; P < 0.0001) and similar benefit was seen with EGFR-targeted maintenance therapy (HR 0.64, 95% CI 0.58-0.71, P< 0.0001).

## Response Rate, QOL and Adverse events

The ORR in the maintenance arm was 21.25 % (7 trials; n= 1520) as compared to 7% in control arm (6 trials, n= 1110). In assessing AEs of grade 3 and above, 18% of the patients had toxicities in the maintenance arm (8 trials; n=2006) and 5% of patients in the control arm (7 trials; n=1400). Quality of life as assessed from 2 trials (Johnson 2008, Fidias 2009) was not significantly better in the maintenance arm.

## DISCUSSION

This meta-analysis was conducted to define the optimal maintenance therapy for patients with advanced stage NSCLC. Single agents, rather than prolonged platinum-based combination therapy, are better suited for maintenance strategy to avoid cumulative toxicity and preserve quality of life. The results from single agent maintenance therapy trials have been varied, raising a number of questions regarding optimal strategy in this setting. This provided the rationale to conduct the meta-analysis. Salient limitations of the study include the fact that the present meta-analysis was not based on individual patient data. Furthermore, five of the twelve included studies have only been presented in abstract format at conferences but not yet published as full manuscripts in peer-reviewed journals. Though another recent publication evaluated this topic, it did not include five of the twelve trials included in our report<sup>19</sup>. Two of the studies in this analysis reported the time to progression (TTP), but not the PFS. Therefore, TTP was included in lieu of PFS for the analysis.

We observed a statistically significant benefit with single agent maintenance therapy, and this was observed with both cytotoxic agents and EGFR inhibitors. The hazard ratio for targeted agents was slightly better than with chemotherapy. Our analysis of EGFR inhibitors did not account for the mutation status. In clinical trials, both erlotinib and gefitinib have demonstrated very robust PFS results for patients with an activating EGFR mutation<sup>8, 13</sup>. It is notable that the results with pemetrexed, the only approved cytotoxic agent in the maintenance setting demonstrated the best hazard ratio of 0.79 for overall survival<sup>7</sup>. It appears that the inclusion in this analysis of other cytotoxic agents with more modest benefit diluted the overall risk reduction associated with cytotoxic agents. Among the studies included in our analysis, Johnson et al evaluated the role of carboxyaminoimidazole as maintenance therapy. Since this is not an agent with established anti-cancer effects in NSCLC, we conducted an analysis excluding this trial and found that no significant difference in the hazard ratio for PFS or OS.

Another aspect of the pemetrexed switch maintenance study that merits consideration is that it included patients with all sub-histologies of NSCLC rather than the non-squamous subset where the magnitude of benefit is higher. It is important to emphasize that pemetrexed is only approved for use in the non-squamous subset based on its efficacy. In the past few years, subset analyses from several randomized studies have documented the lack of efficacy with pemetrexed in squamous histology<sup>20, 21</sup>. Therefore, we conducted an additional analysis excluding the squamous patients enrolled to the pemetrexed study. There was a minor favorable change in the hazard ratio with the use of single agent cytotoxic chemotherapy in the maintenance setting, as would be expected. The PARAMOUNT study included only patients with non-squamous histology and therefore a separate analysis was not required<sup>15</sup>.

Switch maintenance therapy was associated with survival benefit, but continuation therapy was not in this analysis. A potential caveat to this observation is the fact that the survival data from the PARAMOUNT study have not been reported<sup>15</sup>. The PARAMOUNT study demonstrated significant improvement in progression-free survival with pemetrexed as continuation maintenance therapy following initial therapy in combination with cisplatin.

Continuation maintenance strategy is currently being used in routine clinical practice with bevacizumab, a monoclonal antibody against the vascular endothelial growth factor. It is usually continued as maintenance therapy following initial administration in combination with platinum-based chemotherapy<sup>22</sup>. Similarly, cetuximab, an antibody to the epidermal growth factor receptor, is also given as continuation maintenance therapy following combination administration with chemotherapy<sup>23</sup>. This paradigm emerged from the design of the pivotal studies that utilized these agents as maintenance therapy in the investigational arm in patients with responding or stable disease. To date, the role of these agents in the maintenance therapy setting has not been definitively studied. Therefore, our meta-analysis was not able to evaluate the role of continuation maintenance therapy with these targeted agents.

Another important consideration with the use of maintenance therapy is the potential impact on the patient's quality of life. Given the modest degree of benefit with certain agents, the decision to use maintenance therapy in routine practice depends on a variety of patient-specific factors. Prime among these are quality of life and symptomatic benefits. Only two studies included in our meta-analysis provided detailed reports on quality of life. In the recently reported PARAMOUNT study, there was no difference in quality of life parameters between pemetrexed and placebo, but the actual results were not reported. Taken together, we believe that current evidence is insufficient to make conclusions regarding the effect of maintenance therapy on quality of life.

In patients that receive maintenance therapy, the survival outcomes are influenced by the use of post-study therapy. In many of the studies included in the analysis, detailed information regarding the effect of post-study therapy on survival has not been reported<sup>9, 11, 12</sup>. Therefore, this analysis could not determine whether the survival benefit with maintenance therapy was altered to a significant extent with post-study therapy compared to those who did not receive any treatment after progression. In the phase III study by Fidas et al, though maintenance docetaxel was associated with a favorable outcome, the median survival was similar for patients that received docetaxel either as maintenance therapy or second line therapy<sup>12</sup>. In this instance, the observed improvement in overall survival (not statistically significant) was attributed to a higher proportion of patients in the maintenance arm receiving an active agent after first line therapy. This observation was also supported by the Perol study that had similar post-study therapy use for patients in the maintenance setting and control arms<sup>24</sup>. Though the progression-free survival was improved, there was no improvement in overall survival with maintenance therapy. In routine practice, approximately two-thirds of the patients receive second line therapy after first-line combination therapy<sup>25</sup>. Since it is not possible to identify *a priori* the patients that will not be able to receive second line therapy, the use of maintenance therapy provides the opportunity to administer an active anti-cancer therapy in the aftermath of favorable response with front-line combination chemotherapy. However, this has to be weighed in parallel to the wishes of many patients to have a 'treatment-holiday' after completion of combination chemotherapy.

Our knowledge of maintenance therapy is bound to expand when the results of several ongoing clinical trials mature over the next few years. The present meta-analysis provides clear evidence in support of the use of maintenance therapy as a 'standard of care' for patients with advanced NSCLC. The decision to use maintenance therapy should be based on an individualized approach that includes patient-specific factors and tumor-specific biomarkers.



## Supplementary Material

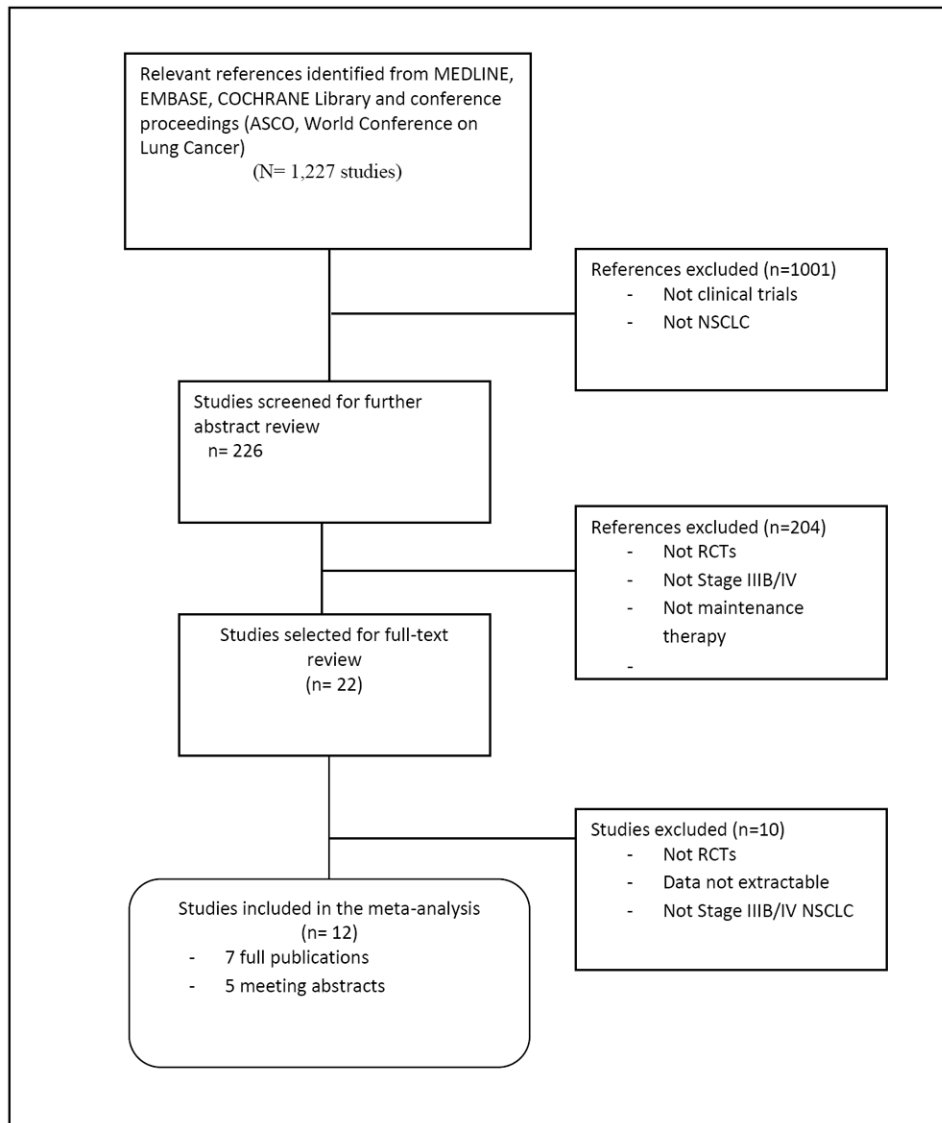
Refer to Web version on PubMed Central for supplementary material.

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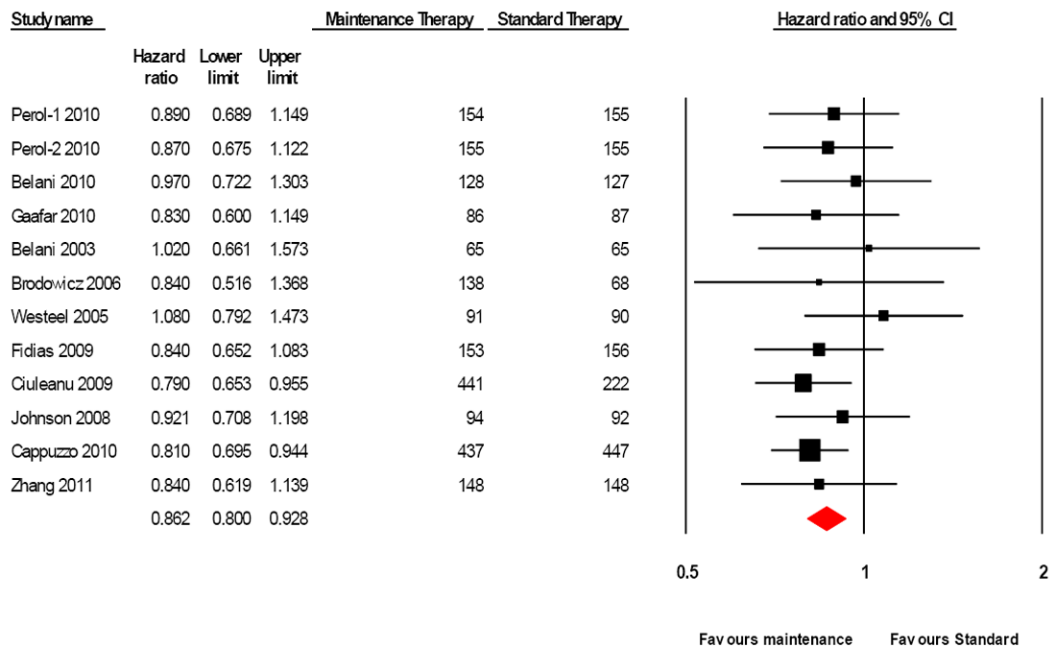
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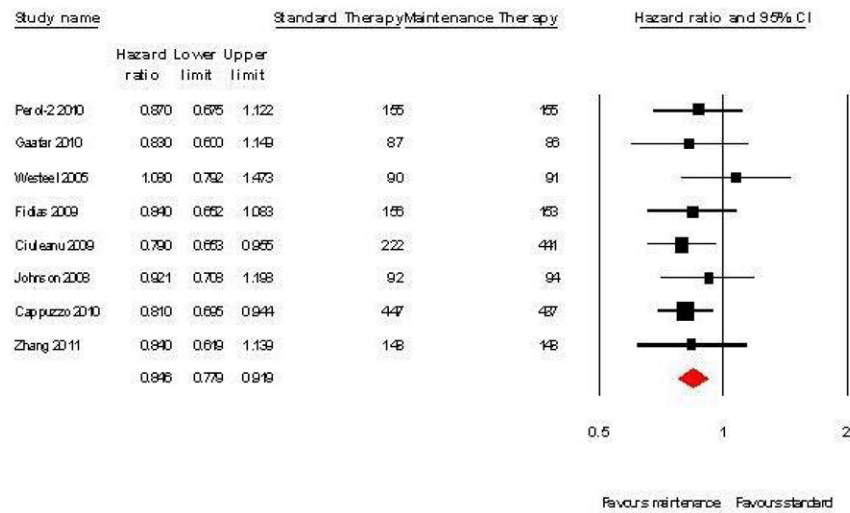


**Figure 1.** CONSORT diagram- Search Strategy and Study Selection

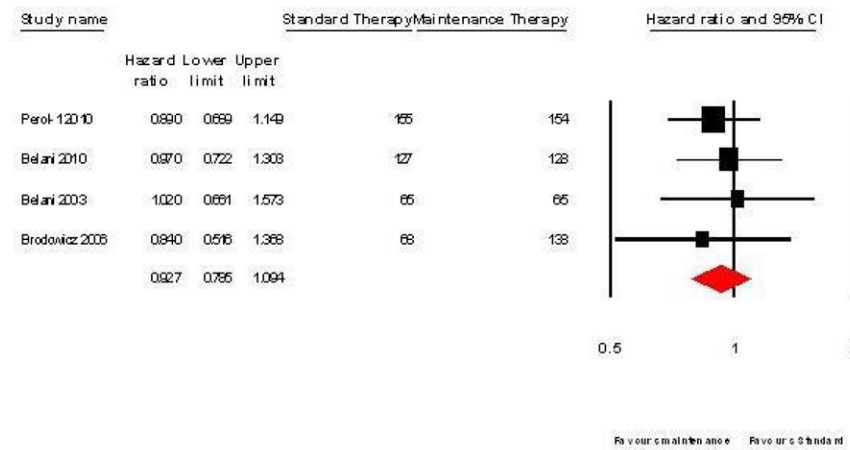


Overall survival: HR 0.86 ( CI 0.80 0.92) ; P Value 0.0003

**Figure 2.**  
 Forest plot for overall survival with maintenance therapy  
 Test of heterogeneity: P-value= 0.92, I<sup>2</sup> < 0.05



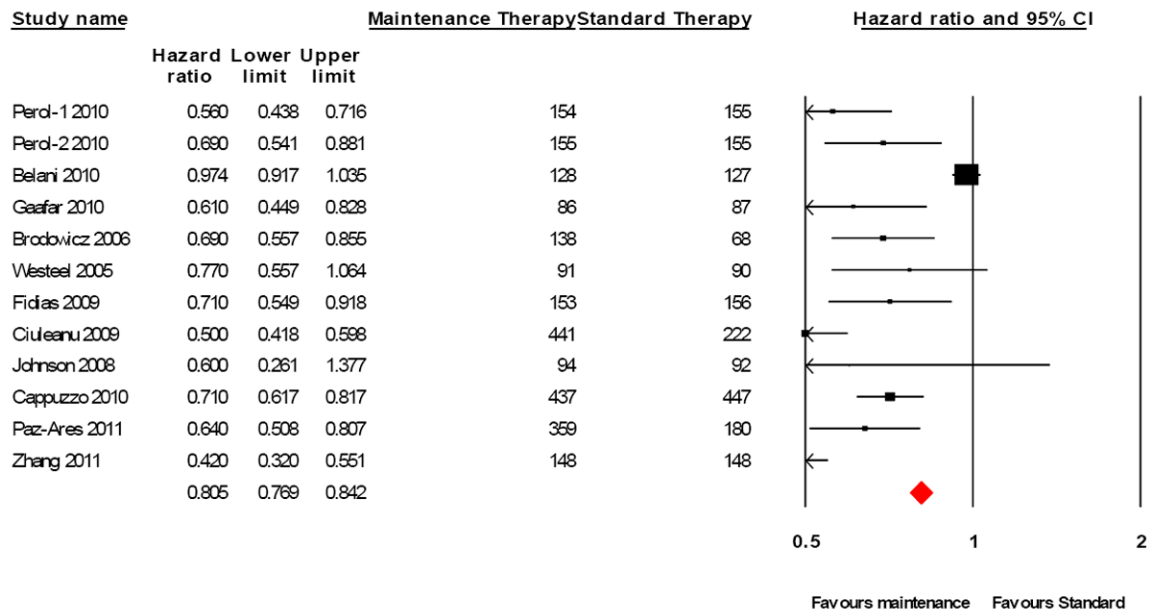
Overall survival- Switch Maintenance HR 0.84 (CI 0.77-0.91); P< 0.00026



Overall survival- Continuation Maintenance HR 0.92 (CI 0.78-1.09); P= 0.33

**Figure 3.** Forest plots for overall survival with Switch and continuation maintenance therapy





PFS: HR 0.80 ( CI 0.77 0.84) ; P Value < 0.0001

**Figure 5.**  
Forest plot for progression-free survival for maintenance therapy

**Table 1**

Trial Characteristics

Study	Type of article	Total enrolled	Median age of participants	Maintenance arm	Control	Type of maintenance	Primary end point	Significant in primary end point	Methodologic quality of trial
Perol 2010 <sup>26</sup>	Abstract	464	Not reported	Gemcitabine; Erlotinib	Observation	Cytotoxic agent/continuation maintenance; EGFR targeted agent/switch maintenance	PFS	Yes	Study was statistically powered; Data about double blinding, allocation concealment, ITT principle not available
Belani 2010 <sup>27</sup>	Abstract	255	67	Gemcitabine	BSC	Cytotoxic agent/continuation maintenance	OS	No	Study was powered; Data about blinding allocation concealment, ITT principle not reported.
Gaafar 2010 <sup>28</sup>	Full Manuscript	173	61	Gefitinib	Placebo	EGFR targeted therapy/Switch maintenance	OS	No	Study was powered; double-blind design
Belani 2003 <sup>11</sup>	Full Manuscript	130	65.5	Paclitaxel	Observation	Cytotoxic agent/continuation maintenance	TTP	No	Phase II design
Brodowicz <sup>10</sup> 2006	Full Manuscript	206	57	Gemcitabine	BSC	Cytotoxic agent/continuation maintenance	TTP	Yes	Study was powered
Westeel 2005 <sup>9</sup>	Full Manuscript	181	62.5	Vinorelbine	Observation	Cytotoxic agent/Switch maintenance	OS	No	Study was powered; Central randomization
Fidias 2009 <sup>12</sup>	Full Manuscript	309	65	Immediate Docetaxel	Delayed Docetaxel	Cytotoxic agent/Switch maintenance	OS	No	Study was powered; central randomization; ITT analysis; QOL assessed
Ciuleanu 2009 <sup>12</sup>	Full Manuscript	663	60.5	Pemetrexed	Placebo	Cytotoxic agent/Switch maintenance	PFS	yes	Study was powered; central randomization; double blinded; ITT analysis.
Johnson 2008 <sup>29</sup>	Full Manuscript	186	66	CAI	Placebo	Cytotoxic agent/Switch maintenance	OS	No	Study was powered; central randomization; double blinded; QOL assessed
Cappuzzo 2010 <sup>8</sup>	Full Manuscript	884	60	Erlotinib	Placebo	EGFR targeted therapy/Switch maintenance	PFS	Yes	Study was powered; adaptive randomization via third party IVRS; ITT analysis.
Paz-Ares 2011 <sup>15</sup>	Abstract	539	61	Pemetrexed	Placebo	Cytotoxic agent/continuation maintenance	PFS	Yes	Study was powered; double blinded
Zhang 2011 <sup>13</sup>	Abstract	296	54	Gefitinib	Placebo	EGFR targeted therapy/Switch maintenance	PFS	Yes	Study was powered; 1:1 randomization; parallel design; ITT analysis