

# Treatment of Metastatic Non-Small Cell Lung Cancer: A Systematic Review of Comparative Effectiveness and Cost Effectiveness

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# Introduction

- **Lung cancer is the leading cause of cancer death in both men and women in the United States.**
- **About 7500 veterans are diagnosed with lung cancer each year.**
- **Most patients with lung cancer are diagnosed when the cancer is already advanced (stage III or IV), and they are no longer candidates for surgical resection.**
- **Small cell lung cancer and non-small cell lung cancer (NSCLC) are treated as different diseases in terms of therapy.**
- **There is a vast amount of new clinical trial data every year on the treatment of lung cancer.**
- **This review was requested to evaluate the current evidence on the effectiveness and cost-effectiveness of treatments for advanced NSCLC.**

# The key questions were:

- **Key Question #1.** For patients with metastatic non-small cell lung cancer (NSCLC) what is the comparative effectiveness of the different recommended (e.g. NCCN guidelines) first line chemotherapy regimens?
- **Key Question #2.** For patients with metastatic NSCLC what is the comparative effectiveness of the different recommended (e.g. NCCN guidelines) second line chemotherapy regimens?
- **Key Question #3.** For patients with metastatic NSCLC what is the benefit of maintenance therapy following first line chemotherapy regimens compared with no maintenance therapy?
- **Key Question #4.** What is the relative cost and cost-effectiveness of the different approaches in Key Questions 1-3?

# Methods

- **We searched for both existing systematic reviews and clinical trials.**
- **If we identified a high quality systematic review, we used it as a starting point.**
- **We updated high quality systematic reviews with new trial data.**
- **For areas without a high quality systematic review, we narratively summarized new clinical trials.**

# Methods

- **We limited searches to peer-reviewed, English language literature. We also obtained a list of key publications from the technical expert panel. Additionally, systematic reviews identified were reference mined for relevant trials.**
- **Exclusion criteria included duplicate publications, not presenting data on NSCLC, presenting data only for Stage I or II NSCLC.**
- **To be included trials and systematic reviews had to address first line, second line, or maintenance therapy for advanced non-small cell lung cancer.**

## A summary of GRADE's approach to rating quality of evidence

Study design	Initial quality of a body of evidence			Quality of a body of evidence
		Lower if	Higher if	
Randomized trials	High	Risk of Bias	Large Effect	High
	Low	-1 Serious	+1 Large	Moderate
Observational studies	Low	-2 Very serious	+2 Very large	Low
		Inconsistency	Dose response	Very low
		-1 Serious	+1 Evidence of a gradient	
		-2 Very serious	All plausible residual confounding	
		Indirectness	+1 Would reduce a demonstrated effect	
		-1 Serious	+1 Would suggest a spurious effect if no effect was observed	
		-2 Very serious		
		Imprecision		
Publication Bias				
		-1 Likely		
		-2 Very likely		

# RESULTS

- **We screened 736 titles for systematic reviews and cost effectiveness analyses and 820 titles for trials. We screened 88 potential systematic reviews and cost effectiveness analyses in more detail.**
- **We identified 55 systematic reviews for inclusion:**
  - 24 were relevant to Key Question #1
  - 6 were relevant to Key Question #2
  - 3 were relevant to Key Question #3
  - 22 were cost effectiveness analyses relevant to Key Question #4.
- **From the trial citations:**
  - 120 were potential includes after the title screen
  - **60 met final inclusion criteria:**
    - 43 articles relevant to Key Question #1
    - 14 relevant to Key Question #2
    - 3 relevant to Key Question #3.
- **Peer review identified a few additional studies for inclusion, most of which were more recent than the end date of the search.**

## **Key Sub-question 1.1. Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with Doublets Using Older Agents?**

- **A 2007 high quality systematic review included an earlier meta-analysis which itself consisted of six RCTs; and five additional RCTs.**
- **Since 2007, we identified seven new RCTs relevant to this key sub-question.**
- **The cumulative evidence indicates that any differences in survival between platinum-based doublets are modest (GRADE=High).**

## **Key Sub-question 1.2. Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with a New Single Agent Alone or to a Platinum Agent Alone?**

- **A 2007 high quality review included a meta-analysis, which itself included eight trials of 2,374 patients.**
- **Since 2007, we identified one new published trial relevant to this Key Sub-question.**
- **During peer review, we were directed to a recently presented abstract of a second relevant study.**
- **The cumulative evidence indicates that doublet chemotherapy including a platinum agent has a higher survival rate and a higher response rate than a single agent (GRADE=High).**

## **Key Sub-question 1.3. Which Doublet Chemotherapy Regimen Consisting of a Platinum Agent Plus a New Agent is most Effective in Improving Clinical Outcomes?**

- **A 2007 high quality review identified two meta-analyses and nine studies, three of which were included in one of the two meta-analyses.**
- **Since 2007, nine additional studies were identified and two subsequent meta-analyses relevant to this Key Sub-question.**
- **We also identified one clinical trial comparing doublet chemotherapy regimens, but neither included a platinum agent.**
- **The cumulative evidence indicates that any differences in outcomes between platinum-based regimens are modest (GRADE=High).**

## **Key Sub-question 1.4. Does Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with Nonplatinum Combination Chemotherapy Including a New Agent?**

- **A 2007 high quality review identified two meta-analyses and four additional relevant RCTs.**
- **Since 2007 we identified three trials that did not find a significant difference between agents.**
- **The cumulative evidence indicates that doublet chemotherapy including a platinum agent probably has a slight advantage over non-platinum doublets in one year survival (GRADE=moderate), but platinum agents in general have greater toxicity.**

## **Key Sub-question 1.5. Are New Doublets Containing Cisplatin more Effective than Doublets Containing Carboplatin?**

- **A 2007 high quality review identified three relevant meta-analyses.**
- **Since 2007 we found one additional trial, but the nonplatinum agents in the two areas differed, precluding conclusions about the differences in platinum agents.**
- **The cumulative evidence indicates that cisplatin combinations may have a slight advantage over carboplatin combinations in terms of survival and response rate. However, carboplatin generally has a milder toxicity than cisplatin (GRADE=moderate).**

## **Key Sub-question 1.6. Does Triplet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Clinical Outcomes Compared with Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent?**

- **A 2007 high quality review identified updated guidelines published by the ACCP in 2007 which contained a meta-analysis of 28 trials and 12 additional RCTs where the addition of a third chemotherapeutic agent failed to show superiority over conventional doublets.**
- **We identified a systematic review by Azim not in the 2007 review that was relevant to this question.**
- **Since 2007 we identified four new trials, one of which was included in the review by Azim.**
- **We also found one trial that compared a platinum-based triplet versus a non-platinum doublet.**
- **The cumulative evidence indicates that triplet cytotoxic therapy might have some slight advantages in terms of response rate but at an increased risk of toxicity (GRADE=High).**

## **Key Sub-question 1.7. Does the Addition of Targeted Therapy to Doublet Chemotherapy Consisting of a Platinum Agent Plus a New Agent Improve Outcomes Compared with Doublet Chemotherapy Consisting of a Platinum Agent and a New Agent?**

- **A 2007 high quality review identified eight trials of adding targeted therapy to conventional chemotherapy.**
- **Since 2007 our update search identified an additional 10 trials relevant to this sub-question.**
- **New trials of a number of novel targeted agents have so far failed to find results equivalent to the increases in progression-free survival seen with erlotinib (in patients with EGFR mutations) and 1 study of bevacizumab (in an Asian population subgroup analysis) (GRADE=moderate).**

## **Key Sub-question 1.7.1 Does targeted monotherapy improve outcomes in selected patient populations?**

- We identified seven publications (from six trials) that assessed the use of targeted monotherapy compared to conventional chemotherapy, primarily in the population of patients with the EGFR gene mutation.**
- We identified two recently published meta-analyses of tyrosine kinase inhibitors as part of an update search.**
- Erlotinib or gefitinib monotherapy is in general superior in terms of response rate, progression free survival and toxicity than cytotoxic chemotherapy in patients with EGFR mutations (GRADE=high).**
- Overall survival favors treatment with erlotinib or gefitinib, but this has not reached statistical significance.**

## **Key Sub-question 1.8. Is a Doublet Regimen Better than a Single Agent for the Elderly Population?**

- **A 2007 high quality review identified six trials were identified as being relevant to the treatment of elderly patients with NSCLC.**
- **Since 2007 we identified four new trials that compared single agents to doublet regimens in the elderly population.**
- **The cumulative evidence indicates that with the exception of studies of gefitinib and erlotinib monotherapy (in patients with EGFR mutations), doublet chemotherapy probably has a slight benefit in terms of survival compared to singlet therapy, but causes more toxicity (GRADE=moderate).**

# Summary of Key Question 2: Second Line Therapy

- **The conclusions from existing relevant systematic reviews can be summarized as:**
  - **Doublet second line cytotoxic therapy might offer slight benefits in progression-free survival and response rate, not overall survival, but at a cost of increased toxicity.**
  - **Erlotinib produces modest increases in overall survival. New trials indicate that this effect is restricted to patients who never smoked and/or have EGFR mutations.**

## Summary of Key Question 2: Second Line Therapy

The summary of trials not included in existing systematic reviews is:

- **Considering data from first line and maintenance therapy studies in addition to second line studies, there are sufficient data to support the conclusion that histology type influences the effectiveness of potential treatments. Pemetrexed is more effective in nonsquamous NSCLC (GRADE=moderate).**
- **Tyrosine kinase inhibitors, when used as second line therapy in patients unselected for EGFR mutation status, produce overall survival similar to docetaxel (GRADE=strong). This is probably due to a mix of EGFR wild type and mutation positive patients in the population, with TKI effective only for the latter.**
- **There is insufficient data to support effectiveness of other drugs, or drugs in combinations, in second line therapy (GRADE=moderate).**
- **The above second line studies are typically undertaken after evidence of disease progression, and should be distinguished from maintenance therapy, which is undertaken when a patient has at least stable disease during treatment (typically four cycles).**

## Summary of Key Question 3: Maintenance Therapy

- We identified a 2010 high quality systematic review and 4 additional trials. The cumulative evidence indicates that:
  - Study design issues limit the ability to make strong conclusions about maintenance therapy and survival.
  - There is insufficient evidence to reach conclusions regarding whether a continuous or a switch strategy is superior (GRADE=very low). However, two drugs have been approved for switch therapy.
  - Patients with EGFR mutations should be treated with tyrosine kinase inhibitors (erlotinib, gefitinib).

## Summary of Key Question 4: Cost-Effectiveness Analyses

- **There are a large number of published cost-effectiveness analyses, but approximately two thirds of such studies are supported by the makers of the drugs being assessed.**
- **Invariably, studies supported by the makers concluded that their drug was cost-effective. Of the cost-effectiveness analyses not supported by industry, the addition of bevacizumab to first line therapy was found in one study to be not cost-effective, erlotinib was found in one study to be marginally cost-effective, and the differences between erlotinib and docetaxel maintenance therapy were slight in another study (GRADE=low).**

# Cost effectiveness analysis of adding bevacizumab to carboplatin + paclitaxel

- Comparison is B + Carb + P v. Carb + P
- Data for outcomes come from ECOG 4599 trial
- Discount rate 3% per year
- ICER for adding bevacizumab was:
  - \$560,000 per QALY
  - \$390,000 per life year gained

# Cost effectiveness analysis of erlotinib compared to placebo

- Data come from the BR.21 study
- No discounting
- ICER for overall study: \$94,000/life year
- Some subgroups were much better:
  - Never smoked = \$39,000
  - EGFR positive = \$64,000
  - EGFR gene copy high = \$33,000

# LIMITATIONS

- **Some comparisons of interest have not been studied in direct head-to-head studies, leaving comparisons to be made using indirect methods. Such indirect methods are highly susceptible to bias and are less reliable when differences between agents are small, as in this review.**
- **There is a paucity of cost effectiveness analyses by someone other than the maker of the drug.**

# RECOMMENDATIONS FOR FUTURE RESEARCH

- **Since VA policy makers are greatly interested about cost effectiveness in the VA setting a proper cost effectiveness analysis, using VA data and adjusting the population characteristics for VA patient characteristics, is needed to reach strong conclusions about cost effectiveness of these drugs in VA setting.**
- **Such a study should be possible by combining data from this review on effectiveness with data from VA databases on the number of patients being treated, how they are being treated, the resources used, and their outcomes.**
- **Sensitivity analysis can be used to estimate the degree to which baseline assumptions would need to change in order to reach different conclusions about cost-effectiveness.**

# THANK YOU

- **VA Greater Los Angeles**
  - Evidence Synthesis Program & Southern California/RAND Evidence-based Practice Center
  - Center for Surgical Outcomes and Quality
- **VA Health Services Research & Development Service**