APPENDIX A. SEARCH STRATEGY FOR SYSTEMATIC REVIEWS AND COST-EFFECTIVENESS ANALYSES (SEARCH #1)

TREATMENT OF METASTATIC NON-SMALL-CELL LUNG CANCER
SEARCH METHODOLOGY

SEARCH STRATEGY #1 (SYSTEMATIC REVIEWS):
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1966-3/16/2012
Cochrane Database of Systematic Reviews – All years

SEARCH STRATEGY (PUBMED):
lung neoplasms OR lung cancer
AND
non-small-cell OR non-small cell OR "non small cell"
AND
metastatic* OR metastasi* OR advanced
AND
Systematic[sb]

NUMBER OF RESULTS: 436

SEARCH STRATEGY (COCHRANE):
(Lung neoplasm* OR lung cancer):ti,ab,kw
AND
(Non-small cell OR "non small cell" OR non-small-cell):ti,ab,kw

NUMBER OF RESULTS:13

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SEARCH STRATEGY #2 (COST-EFFECTIVENESS):
DATABASE SEARCHED & TIME PERIOD COVERED:
PubMed – 1966-3/16/2012
Cochrane Economic Evaluations – All years

PUBMED:
lung neoplasms OR lung cancer
AND
non-small-cell OR non-small cell OR "non small cell"
AND
metastatic* OR metastasi* OR advanced
AND

cost OR costs OR cost-effective* OR cost-benefit OR cost utility OR cost-utilities OR cost analysis OR cost analyses OR economic OR economics
NOT
Results of Search #1

NUMBER OF RESULTS: 347

COCHRANE
(Lung neoplasm* OR lung cancer):ti,ab,kw
AND
(Non-small cell OR "non small cell" OR non-small-cell):ti,ab,kw

NUMBER OF RESULTS: 30

APPENDIX B. SEARCH STRATEGY FOR TRIALS (SEARCH #2)

NON-SMALL CELL LUNG CANCER – RCTS
SEARCH METHODOLOGY

DATABASE SEARCHED & TIME PERIOD COVERED:
Medline on OVID – 2007-5/8/2012

LANGUAGE:
English

SEARCH STRATEGY:
(systematic review? or systematic overview?).tw. OR meta-analysis/ OR meta analysis.pt. OR metaanalys$.tw. OR meta analys$.tw. OR meta-analys$.tw. OR randomized controlled trials/ or randomized controlled trial.pt. OR random allocation/OR (random$ and (trial* or stud$)).ti,ab
AND
carcinoma, non-small-cell lung/ or nscls.ti,ab.OR (lung and (cancer$ or neoplasm$ or carcinom$ or malignan$ or tumo?r$)).ti,ab.
AND
(paclitaxel or taxol or docetaxel or taxotere or gemcitabine or gemzar or vinorelbine or navelbine or irinotecan or campto or camptosar or CPT-11 or pemetrexed or alimta or erlotinib or tarceva or gefitinib or iressa or bevacizumab or avastin or cetuximab or crizotinib).ti,ab.

NUMBER OF RESULTS: 772

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DATABASE SEARCHED & TIME PERIOD COVERED:
Embase – 2007-5/8/2012

LANGUAGE:
English

SEARCH STRATEGY:
paclitaxel:ti OR taxol:ti OR docetaxel:ti OR taxotere:ti OR gemcitabine:ti OR gemzar:ti OR vinorelbine:ti OR navelbine:ti OR irinotecan:ti OR campto:ti OR camptosar:ti OR 'cpt 11':ti OR pemetrexed:ti OR alimta:ti OR erlotinib:ti OR tarceva:ti OR gefitinib:ti OR iressa:ti OR bevacizumab:ti OR avastin:ti OR cetuximab:ti OR crizotinib:ti OR paclitaxel:ab OR taxol:ab OR docetaxel:ab OR taxotere:ab OR gemcitabine:ab OR gemzar:ab OR vinorelbine:ab OR navelbine:ab OR irinotecan:ab OR campto:ab OR camptosar:ab OR 'cpt 11':ab OR pemetrexed:ab OR alimta:ab OR erlotinib:ab OR tarceva:ab OR gefitinib:ab OR iressa:ab OR bevacizumab:ab OR avastin:ab OR cetuximab:ab OR crizotinib:ab OR 'paclitaxel'/exp OR paclitaxel
AND

((‘lung’/exp AND (cancer* OR neoplasm* OR carcinoma* OR malignan* OR tumor* OR tumour*) AND non:ti OR non:ab)) OR ‘lung non small cell cancer’/exp OR nsclc:ti OR nsclc:ab
AND
(randomized AND controlled AND trial*) OR (random AND allocation) OR (random* AND (trial* OR stud*))
AND
HUMAN
AND
‘article’/it OR ‘article in press’/it

NUMBER OF RESULTS: 659

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DATABASE SEARCHED & TIME PERIOD COVERED:
Cochrane Register of Controlled Trials: 2007-5/8/2012

SEARCH STRATEGY:
“paclitaxel or taxol or docetaxel or taxotere or gemcitabine or gemzar or vinorelbine or navelbine or irinotecan or campto or camptosar or CPT-11 or pemetrexed or alimta or erlotinib or tarceva or gefitinib or iressa or bevacizumab or avastin or cetuximab or crizotinib in Title, Abstract or Keywords
AND
non-small cell lung OR nonsmall cell lung OR nsclc in Title, Abstract or Keywords

NUMBER OF RESULTS: 516

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TOTAL NUMBER OF RESULTS AFTER REMOVAL OF DUPLICATES & NON-RELEVANT MATERIAL (INCLUDING PHASE II TRIALS); 820

APPENDIX C. SCREENER FORMS USED FOR SYSTEMATIC REVIEWS AND COST-EFFECTIVENESS ANALYSES

ID:
Author:

1. Is it a cost-effectiveness analysis?
   - Yes ..... ☐
   - No ..... ☐STOP

2. Does it present data on metastatic non-small cell lung cancer?
   - Yes ..... ☐
   - No ..... ☐STOP
   - Stage I ..... ☐STOP
   - Stage II ..... ☐STOP
   - Stage III ..... ☐
   - Stage IV ..... ☐
   - "Advanced" ..... ☐

3. Which kind of therapy is assessed? (Check all that apply)
   - First line ..... ☐
   - Second line ..... ☐
   - Maintenance ..... ☐
   - Not Stated ..... ☐

4. Which treatments is assessed?
   _____

5. Where are the data from?
   - Multiple studies ..... ☐
   - Single study ..... ☐
     Name: _____

6. What perspective is the analysis?
   - US payer ..... ☐
   - Non-US payer ..... ☐
   - Societal ..... ☐
   - _____ ..... ☐

7. What outcome is used?
   - QALYs ..... ☐
   - Life expectancy ..... ☐
   - _____ ..... ☐

KEEP FOR BACKGROUND ☐

NOTES

8. Conclusions per abstract:

ID:
Author:

1. Is it a systematic review?
   Yes ☐
   No ☐STOP

2. Does it present data on metastatic non-small cell lung cancer?
   Yes ☐
   No ☐STOP
   Stage I ☐STOP
   Stage II ☐STOP
   Stage III ☐
   Stage IV ☐
   "Advanced" ☐

3. Which kind of therapy is assessed? (Check all that apply)
   First line ☐
   Second line ☐
   Maintenance ☐
   Not Stated ☐

KEEP FOR BACKGROUND ☐

6. Which databases were searched?
   Pubmed/Medline ☐ Embase ☐
   Cochrane ☐ Other ☐

7. How many studies were included?
   _____

8. What outcomes were reported?
   Overall survival ☐
   Progression free survival ☐
   Overall response rate ☐
   Adverse events ☐
   _____
   _____
   _____

9. Conclusions per abstract:
   _____
   _____
   _____
   _____
   _____
   _____

4. Which treatments are captured? None below: ☐STOP

	Bevacizumab	Cetuximab	Platinum agent/therapy	Gemcitabine+taxol	Gemcitabine+platinum	Pemetrexed	Erlotinib	Crizotinib	Endostar	Docetaxel	Ciefitinib	Vandetanib	Placebo	Immunotherapy	Paclitaxel	Gifitinib	Various
Bevacizumab																	
Cetuximab																	
Platinum agent/therapy																	
Gemcitabine+taxol																	
Gemcitabine+platinum																	
Pemetrexed																	
Erlotinib																	
Crizotinib																	
Endostar																	
Docetaxel																	
Ciefitinib																	
Vandetanib																	
Placebo																	
Immunotherapy																	
Paclitaxel																	
Gifitinib																	

NOTES:

5. What was the end date of the search?

January ☐	June ☐	November ☐	2008 ☐
February ☐	July ☐	December ☐	2009 ☐
March ☐	August ☐	NS ☐	2010 ☐
April ☐	September ☐		2011 ☐
May ☐	October ☐		NS ☐

APPENDIX D. PEER REVIEWER COMMENTS AND RESPONSES

Comment	Response
Pre-Results	
I note that the attribution to the 1st line guideline is Goffin et al. Similar to this VA project, I led what was a group effort. At some (or all) points, it would be appropriate to indicate that the guideline was the work of the Cancer Care Ontario Program in Evidence-Based Care (CCO PEBC or CCO)	We have updated the report to include the CCO
In the search methods, there is no indication of searching conference abstracts? Was this done.	We did not search conference abstracts
P.10 "(the exception being the same of the never…orally)": This wording in the parentheses makes no sense. What does "the exception being the same of" mean? I think you mean 'newer" targeted therapies, not 'never'	This typo has been corrected.
Key Question #1	
There is very little mention of the importance of molecular markers in the management of advanced NSCLC	Molecular markers are mentioned in the targeted therapy section. We did not identify studies using molecular markers to guide therapy outside of this area. We did identify studies that used molecular markers as a means for assessing overall prognosis, but that was not one of our key questions.
p.16 "The five additional trials…docetaxel plus cisplatin." : This is incorrect according to your table and the reference. Docetaxel plus cisplatin had superior survival over vindesine plus cisplatin.	This typo has been corrected.
Page 17. Summary 1.1. Given that survival is arguably the most important endpoint, QoL perhaps second, and others of lesser importance, I recommend specifying the "outcome" being considered as much as possible. Here it is survival.	We have specified that this is survival.
Page 18. Summary 1.2 As per 1.1, does one trial indicating a trend toward improvement with doublet negate the meta-analysis indicating survival improvement. Thus, the recommendations might continue to support a 'survival' improvement rather than just a response improvement.	We have added survival to this conclusion.
Page 18- first paragraph- New study presented at ASCO2012 by Lilenbaum, et al showed that 2 agents were better than 1 in PS 2 patients. This study has not been included in the discussion.	This study has now been included
P. 19 "There was no difference… grade 3/4 toxicities": Should be 8.6 months, not 86	This typo has been corrected.
Last paragraph of page 22- It is important to point out that in the meta-analyses by Ardizonni, et al the benefit with cisplatin compared to carboplatin was more pronounced in non-squamous patients and when combined with newer agents.	We added the data about non squamous histology.

Comment	Response
Page 24. Summary 1.5. Is it worth mentioning the differences in toxicity profiles between cisplatin and carboplatin in this palliative setting?	We have added this.
P27. Additional relevant papers for 1.7.1: Mitsudomi et al Lancet Oncol. 2010 Feb;11(2):121-8.	This study has now been included
P27. Additional relevant papers for 1.7.1: Han, JCO, 2012, 30(10):2233-28	This study has now been included
P27. Additional relevant papers for 1.7.1: Rosell et al, EURTAC, Lancet Onc 13:239-46, 2012 ß this last trial is relevant in extending the several Asian studies to a Caucasian population.	This study has now been included
Table F5 needs to be updated. There are now more studies.	This has been updated
Page 27, Summary 1.7. is confusing, as it seems to suggest an OS advantage to EGFR TKI, where this has not technically been shown. I would be clear the 'outcome' is PFS. Also, bevacizumab may or may not improvement survival in the general population. Is it specific to carboplatin and paclitaxel, and is it better in the Asian population?	We have clarified the outcome as progression-free survival and the qualifier about the Asian subgroup.
P. 27: Add ";" to "other outcomes progression-free survival of 10.1.."	This typo has been corrected.
It may also be worth specifying that in the absence of a mutation, first line tki is associated with a worse survival and should be avoided, as seen in the TORCH study. See URL: http://jco.ascopubs.org/content/early/2012/07/09/JCO.2011.41.2056.full.pdf#page=1&view=FitH	This study has now been included
Page 29, New Lit. I would rewrite this for clarity as it jumps around a bit. Opening para could indicate "2 studies found assessing cytotoxics specifically in the elderly, and 2 studies examining first line egfr tki's assessed subsets of elderly." Second para could discuss the cytotoxic studies, third the TKI's.	We have re-arranged this section.
Unsure why reference 113 Georgoulias is included in this elderly section. Median age 63 is a 'young' lung cancer population, and no subset is specified. Would remove.	We left this article in at the request of another technical expert, but added the additional qualifier about the age.
Page 30. Summary 1.12. I dispute the "Grade=low" for survival benefit. The benefit may be very modest (which is common to most NSCLC trials) but data quality is not. Looking at the 70-80 population, I highly doubt we will see a new trial indicating that a doublet is bad. Caveats about the 80+ population might be reasonable.	We agree our initial GRADE was too conservative and have reclassified to moderate based on RCT data that are sparse (only 6 trials and all of different regimens, 4 of which found a benefit for doublet therapy and 2 of which did not).
P.30 1.12 summary: You should mention here that the data for monotherapy is from subgroup analyses	This caveat has been added.
On page 30 summary of key sub-question 1.12- Please mention that the only study evaluating a platinum based combination showed a survival advantage in elderly patients compared to single agent therapy.	This addition has been made.

Comment	Response
Key Question #2	
Page 32. First sentence of the page repeats itself between its first and second clause.	This typo has been corrected.
Page 32. Existing Systemic Reviews. Re Qi review 2012: The approval or non-approval of a drug seems irrelevant to the notion efficacy. More important might be the heterogeneity of the drugs in question and the phase II nature of some of the references.	To be relevant to VA, a drug has to be FDA approved for use in the US, although not necessarily approved for the particular use in question. We revised and increased the discussion of bortezomib and vandetanib.
P.32: Only bortezomib and vandetanib are FDA approved, but not for NSCLC; the other two agents are not approved	This has been corrected.
P.32, Table on p. 34: This is misspelled here and in the Table on Page 34=bortezomib not bortezonib;	This typo has been corrected.
P. 32, p. 37, p. 38: Vandetanib is FDA approved, but not for NSCLC (also see the same statement on pages 37 and 38)	This has been corrected.
On page 32 the authors have missed the study by von Pawel, et al presented at ASCO 2011. Also please include the meta-analyses by Di Maio M, J Clin Oncol 2007.	This study has now been included
Page 32, 33 please include the TAILOR study presented at ASCO 2012 by Garassino, et al, comparing docetaxel and erlotinib	This study has now been included
Page 33. Para "The fifth system review…" appears to be a combination of first and second line studies. Also, the 'overall' survival was for which comparison? It would be useful to specify.	This has been clarified; the overall survival result comes from the BR.21 study.
Para "The conclusions…" Third bullet. Might be pointed out this was a phase II study only.	This has been added.
Page 37. Does it add value to singly review the studies which were already included in the systemic reviews already mentioned (assuming those reviews were of sufficient quality). Or does this just add document length?	We agree and have deleted the text about trials contained in existing systematic reviews that we discuss in detail in the prior section. However, we retained the description of trials that were otherwise only included in the reviews by Qi and colleagues as we did not discuss these reviews in detail.
Page 38. Para "The last of the trials…" The paragraph suggests "no significant difference" between vandetanib and erlotinib. It should then specify whether a test for non-inferiority was achieved. Otherwise they sound truly equivalent.	This was a superiority trial, which failed. Then a test for non-inferiority was done with non-inferiority defined as "at least 50% of the efficacy" of erlotinib. We have added this to the description.
Page 39. "New Agents" . For these studies, it is likely useful to specify whether these were 'all comers' or 'mutation only' patients as the distinction has become relevant. Readers should know there is utility for the mutation negative population, as not all will be aware.	This has been added.

Comment	Response
Page 40 Para "Sekine and colleagues…." I would addend this to the preceding paragraph as the QoL component as it seems like a completely different study until the last sentence and adds undue length.	This change has been made.
Page 40. "Kim and colleagues…." Specifying non-inferiority vs. failed superiority will aid the audience in understanding how to use these drugs. If it is a failed superiority study only, it should not become part of the armamentarium. Similarly for other studies in this section.	We have now indicated that the primary analysis in this study was a superiority analysis, which was not statistically significant.
Page 40. Last sentence just before "Pemetrexed" section. Much higher? 13 vs. 6%.	This has been revised.
THOUGHT: for Table S2, alter the columns such that there is only one column indicating the Systemic Review Y/N: this can either be "Di Maio" "Qi 2012" etc, or "No". The other columns are freed for other items, possibly: "n" "non-inferiority comparison Y/N or p= ", "HR for OS", etc. More data, less wasted space.	This table has been revised to include only the studies in existing systematic reviews. Some of the other suggested columns are already included in Table S3, to which we have added histology and EGFR mutation status.
Page 45. Having a summary of the "trials not in reviews" in isolation is not helpful. The whole section appears to read as an unordered catalogue. A net synthesis seems is required. In fact, at the end of the second line section, a reader new to the topic will have little idea has to how they should practice. One might consider ordering it as the data built up historically: 1) it was found that docetaxel was better than best supportive care; 2) Pemetrexed was compared to docetaxel and found to be essentially equivalent but more friendly and thus caught on; 3) The EGFR TKI's were new and are even more friendly, and were thus studied. Importantly, they were studied as 2nd/3rd line vs. BSC, and thus may be kept in reserve after another second-line therapy. In any case, there is data they are equivalent to docetaxel in second line, and thus serve as an option; and 4) LUMP: other studies have been done, which have not added much to the second line notion: more ain't better; other sexy drugs haven't yet added much. Then one could give corresponding recommendations. This section could also be arranged by approved agents, citing the trials supporting the use of each, comparisons, etc, then going on to the 'other' agents.	We have reorganized this section following this suggestion.
NOTE that treatment by histology has had no mention here (it only seems to come up under cost-effectiveness). Histology now plays an important role in chemotherapy choice, particularly in 2nd/maintenance lines. The survival differences between docetaxel and pemetrexed by histology are at least as large/important as comparisons such as doublets vs. single agents. Although a portion of this data is from subsets, a document aiming to encompass 1st line, 2nd line, and maintenance is obligated to cover histology.	We have added a conclusion about pemetrexed and histology.

Comment	Response
Similar reference to histology for first line seems appropriate.	The issue of histology and pemetrexed use in first-line therapy is presented in the discussion of the prior reviews by Goffin and colleagues.
P. 47 "The erlotinib group had an overall survival… 1.09)": This should be HR=0.9, not 0.90 months; also you should include a p value of 0.2686	This has been corrected.
Key Question #3	
Table M1. 1st box under 'what was compared' gefitinib is spelled incorrectly with all i's.	This typo has been corrected.
Page 48. Just before reference 158. Cisplati is missing an 'n'.	This typo has been corrected.
P.50: I question how you rated maintenance therapy improving OS as High based on the data. For the continuous therapy there was only a trend towards benefit in OS. For the switch trials, the upper bound of the HR in all but one of the trials crossed 1	The GRADE of strong is based on the meta-analytic pooling of the trials in the Zhang meta-analysis. While each individual trial may have not yielded a statistically significant favorable result, combining them statistically did yield a statistically significant benefit for the switch strategy (HR=0.85, 95% CI: 0.79-0.92) and for continuous therapy the pooled result was a similar hazard ratio of 0.88, with a 95% CI that just crossed the null value (0.74-1.04). With the interaction being completely nonsignificant (p=0.78), the most likely explanation for the difference in the upper bound crossing the null value is fewer studies contributing to the continuous pooled analysis (n=3) than the switch pooled analysis (n=6).
P. 50 Switch therapy finding: However, there is only a trend of benefit in continuous therapy but there are two drugs approved for use for switch therapy. I think this needs to be better addressed in this entire section.	We have made this point.
Key Question #4	
Page 56. Would change "unclear whether or not EGFR receptor status" to "…not EGFR mutation status" at end of first paragraph.	This change was made.
Page 56. 2nd paragraph. The notations "(ref 498, 449)" are probably leftovers.	This typo has been corrected.
Page 59. Key sub-question 1.12. missing an 'r' in elotinib.	This typo has been corrected.
Page 61. Table comparison with NCCN. Although commonly referenced, I don't believe the NCCN 'guidelines' meet criteria for guideline quality and are more akin to consensus documents. Would a comparison with the ASCO guidelines be better?	Perhaps this would be better, but our key questions specifically mentioned the "NCCN guidelines" and that is why these are included here and referred to as "guidelines."

Comment	Response
General	
I find the answers or summaries of the Key Questions to be rather broad and lacking specific direction, making implementation difficult or impossible, therefore they are no better than the NCCN guidelines. While I appreciate the need for numerous subquestions for Key Question 1, it would be helpful for implementation to summarize the overall subquestion findings for Key Question 1 : doublets better than single, cisplatin over carbo if tolerated, pemetrexed for non-squamous histology, erlotinib for EGFR mutation, etc. I feel the summary of the maintenance therapy question needs major overhauling to make sense of the data and provide direction based on the available data.	With the exception of the "pemetrexed for nonsquamous histology," these conclusions are all currently in the report. In second-line therapy we have a conclusion that pemetrexed is more effective in nonsquamous histology. With respect to the maintenance therapy conclusions, these were formulated from the data. The peer reviewer seems to be asking for recommendations similar to those one might find in a guideline, which is not within the scope of this review.
There is very little mention of the importance of molecular markers in the management of advanced NSCLC	This has been added.
The results of the PARAMOUNT study were updated at ASCO2012. These updated results are relevant in many portions of this report.	This has been added.