Reviewer's report

Title: Cost-effectiveness analysis of pemetrexed versus docetaxel in the second-line treatment of non-small cell lung cancer in Spain: results for the non-squamous histology population

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Reviewer: Bernardo Goulart

Reviewer's report:

To the editor of BMC Cancer


SUGGESTION FOR EDITORS: Accept with minor review. See comments below.

General comments: The authors conducted a cost-utility and cost-effectiveness study of second-line pemetrexed compared with second-line docetaxel in patients with advanced NSCLC who had tumor progression after first-line chemotherapy. They used clinical inputs from a published retrospective analysis of two phase III trials involving pemetrexed, one being a trial of second-line pemetrexed against docetaxel. The authors obtained chemotherapy cost inputs from a national Spanish database, and used survey data to obtain costs on adverse events and best supportive care. They concluded that second-line pemetrexed is a cost-effective intervention compared with docetaxel, based on an ICER of $23,967 euros per QALY gained.

Overall, the authors addressed a scientifically relevant question of how cost-effective second-line therapies in advanced NSCLC are when compared to the best available alternative. The methodology was sound for both the cost-utility (for QALYs) and cost-effectiveness (for Life Years gained) analyzes, and the authors described them with transparency and moderate clarity. They approached the uncertainty inherent to their models with appropriate sensitivity analyzes. I believe the results do support their conclusions, and that this manuscript should be considered for publication, provided that the authors address several comments and concerns.

Minor Essential Revisions:

- The authors based their survival outcome measures on a post-hoc retrospective subgroup analysis of the pivotal phase III randomized trial of pemetrexed against docetaxel, conducted by Hanna et al. Retrospective subgroup analysis are not considered optimal evidence of efficacy or effectiveness of an intervention, and we usually regard findings of such analyzes as hypothesis-generating only. However, there is currently sufficient evidence from other randomized trials in
advanced NSCLC that show a differential survival benefit for patients with non-squamous histologies treated with pemetrexed, both in the setting of first-line chemotherapy, as well as in the setting of maintenance chemotherapy. The authors need to acknowledge that their data source for survival outcomes was a post-hoc retrospective analysis, and this is a potential limitation of the study. The authors may want to temper this comment by saying that there are additional randomized trials that reinforce their survival findings, including the trials they mentioned in the fourth paragraph of their discussion.

- The authors argue that the lower toxicity profile of pemetrexed relative to docetaxel accounted for a cost offset in adverse events that favored pemetrexed. Their data suggest that, at least in part, the cost-effectiveness of pemetrexed relative to docetaxel is due to the lower toxicity of the former. In order to make this conclusion, authors need to clearly explain how they estimated the costs of adverse events, especially neutropenia and febrile neutropenia, which constituted the two most expensive toxicities. The authors used a Spanish retrospective study to determine the unit costs of neutropenia and febrile neutropenia, which seemed a reasonable approach, since cost outcomes were not measured in the clinical trial by Hanna et al. What is not entirely clear is why the costs of neutropenia are nearly two thirds of the costs of febrile neutropenia. Neutropenia per se does not lead to hospital admissions, although febrile neutropenia more often than not does. Patients usually recover spontaneously from neutropenia, which would require one additional blood count test to confirm that the patients can receive the next cycle of chemotherapy. If this is the case, it is hard to imagine that neutropenia costs approach the costs of febrile neutropenia, a more severe complication of chemotherapy that requires at a minimum an admission to hospitals and intravenous antibiotics. The only possible explanation for the elevated costs of neutropenia is the use of granulocyte colony growth factors (G-CSF) to prevent further episodes of neutropenia. In the paper by Hanna et al, investigators had the option of reducing the doses of chemotherapy by two levels or to prescribe G-CSF. Nineteen percent of patients treated with docetaxel received G-CSF or GM-CSF, compared with 2.6% of patients treated with pemetrexed. The authors need to clarify the proportions of patients treated with growth factors in each arm of their study, and need to state what proportion of the neutropenia costs were due to use of growth factors. If authors have no access to this data, they need to state this is a limitation in their study.

- In the original study conducted by Hanna et al, 47% of patients randomized to pemetrexed and 37% of patients randomized to docetaxel received posterior anticancer therapies off study, respectively. Do the authors know these proportions in the non-squamous carcinoma subgroup? If not, the authors need to acknowledge in the discussion that differences in the number of patients treated with third-line chemotherapy or beyond could have confounded the survival advantage attributed to pemetrexed. If the authors do know these proportions, they need to clearly state them in the results section.

- Authors need to clarify if they included the costs of hospitalizations in the costs
of AEs.

- Page 22, 2nd paragraph. Explain why you reduced by 50% the costs of BSC during chemotherapy. Do not patients need BSC during chemotherapy, maybe even more intensively than in the post-treatment state? Please, clarify that.

- Page 25, 2nd paragraph. Authors should clearly state that the reasons for the median of 4 cycles for both drugs could include not only AEs, but also consent withdraw, or tumor progression.

- The authors do not put in perspective the cost-effectiveness of second-line chemotherapy in advanced NSCLC compared to best supportive care (BSC) alone. The discussion should definitely include one short paragraph stating whether their comparator, docetaxel, is or is not a cost-effective intervention when compared to BSC. There are at least two published cost-effectiveness analyzes exploring exactly that question (Holmes et al, Pharmacoeconomics 2004; Leighl et al, Journal of Clinical Oncology, 2002). These studies concluded that, in fact, second-line docetaxel is cost-effective when compared to BSC. The authors should include these articles in the reference list.

- Introduction, paragraph 3. This paragraph is unnecessary, and authors should remove it from the text, in order to make their manuscript more concise.

- Introduction, paragraph 8. Do authors really believe that cost-effectiveness studies help clinicians make decisions for individual patients? I would not agree with this statement. Most physicians do not take cost-effectiveness evidence when they are considering interventions for individual patients. Cost-effectiveness analysis help decision makers allocate resources in a particular health institution in the setting of a fixed budget. Authors should remove this statement from the paragraph.

- It seems that the model does not include the possibility of progressive disease during chemotherapy, but only after patients complete their assigned chemotherapy regimen. Was it the case? Please, clarify that in the methods section.

- Page 8, paragraph 2. Please, define EMEA and SmPC.

- Page 9, paragraph 1. The authors state that “The exponential distribution is often used for the modeling of failure times and is applicable for use in time-to-event data”. Please, include a reference that supports this statement.

- The model assumes that patients spend most of their time admitted to a hospital or nursing homes during terminal care. Could a proportion of patients receive terminal care at their own home as well? If so, how would that affect the cost estimates for terminal care?

- Page 11, paragraph 1. Please, define VAT.

- If possible, please include the 2 reports from the IMS Health HEOR Spain
survey in the reference list.

- Page 12, paragraph 4. Please, correct the word anaemia by changing it to anemia.

- Page 15, paragraph 2. Please, explain in the text why you assumed that patients had grade 3/4 fatigue after completing chemotherapy and assigned a respective utility value to this degree of fatigue. Patients do report fatigue during chemotherapy, especially with docetaxel. However, chemotherapy related-fatigue subsides within 2 weeks after completion of chemotherapy. Are you assuming that patients remained fatigued from cancer symptoms? Does not chemotherapy improve cancer-related fatigue to at least a state better than grade 3 or 4? Please, clarify that.

- Page 20, paragraph 1. The word “tumour” is misspelled.

- Page 20, paragraph 2. The authors state $23,967 per QALY gained. On the same coin, the authors should state that “…is well within the $30,000 threshold for QALY gained” and not “…is well within the $30,000 threshold for LYG” as written in the text.

- Explain why BSC costs in active treatment, post-treatment, and at tumor progression are $503 higher on average for pemetrexed compared with docetaxel. Is it because patients on pemetrexed arm had longer progression free survival?

- The 4th paragraph of the discussion is too long and contains statements that are not relevant for the manuscript. The authors should remove all sentences starting from “These efficacy differences…” to the end of the paragraph.

- Page 23, paragraph 1. The sentence should say “… ICER to $26,741, still below the accepted threshold” and not “…within the accepted threshold”.

- Page 24, paragraph 2. The first sentence sounds awkward. I suggest removing the statement “Another output” of the PSA and keeping the remaining sentence.

- Page 25, paragraph 1. Please, make a reference for this cost-utility analysis.

- Page 25, paragraph 3. I do not agree. Societal perspective would include an opportunity cost for funding interventions that are more cost-effective than second-line chemotherapy in NSCLC, as well as indirect costs of both interventions, like loss of productivity. It is not clear if pemetrexed would result in less productivity loss than docetaxel. The survival gains from pemetrexed would also be diluted amongst the entire society, as opposed to only in patients with advanced lung cancer. One could argue that, from a societal perspective, pemetrexed might not be cost-effective at all. I suggest authors to either say that they do not know if pemetrexed is cost-effective from a societal perspective or to abandon this topic altogether.

- Page 36 (table 3): please, erase the word “respectively” from above the table.
Discretionary Revisions:

A less important concern is that the writing style was often times lengthy and unclear, with too much emphasis on passive voice, which compromises clarity. I suggest authors to give preference to the active voice when writing a scientific manuscript.

- Introduction, paragraph 8. I suggest that authors do not start a sentence with “But...”.

- Page 20, paragraph 1. I suggest changing the expression “prolonged survival” to “prolonging survival”.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.