Peer Review File

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Reviewer A

Comment 1: First, the abstract is not adequate. The background needs to describe the current knowledge gap and potential clinical significance of this research focus. In the methods more information for obtaining the cost and effectiveness data is needed. The results need to present detailed data for the sensitivity analysis.

Reply 1: . We have carefully reviewed your comments and made the necessary adjustments to our abstract in response to your suggestions (**please see Page 2, lines 20-46**). The revised text now includes a more comprehensive background section that highlights the current knowledge gap and emphasizes the potential clinical significance of our research focus. Additionally, we have expanded the methods section to provide further details on how the cost and effectiveness data were obtained.

Changes in the text: The revised abstract now reads:

*"**ABSTRACT***

Background: While the tremelimumab plus durvalumab combined with chemotherapy (T+D+CT) has shown promise in treating epidermal growth factor receptor/anaplastic lymphoma kinase (EGFR/ALK) wild-type metastatic non-small-cell lung cancer (mNSCLC), particularly in patients with low or no PD-L1 expression, the economic implications of its high cost remain poorly understood. This study fills a critical gap in knowledge by evaluating the cost-effectiveness of T+D+CT from a US health care perspective, offering valuable insights for clinical and policy decision-making.

Methods: A 10-year Markov model was crafted to track the disease progression, survival, and treatment-related toxicities of a patient cohort with EGFR/ALK wild-type mNSCLC. Transition probabilities were derived from the POSEIDON trial, while health state utilities were obtained from the literature. Cost data, including drug acquisition and administration, subsequent anticancer therapies, and adverse event management were estimated using the Centers for Medicare and Medicaid Services and the Healthcare Cost and Utilization Project databases, with additional costs sourced from current literature. All cost and effectiveness measures were discounted at an annual rate of 3%. The model's robustness was assessed through deterministic sensitivity analysis (DSA), probabilistic sensitivity analysis (PSA), and

scenario analysis.

Results: T+D+CT compared to chemotherapy alone yielded incremental cost-effectiveness ratios (ICERs) of $370,208 to $691,960 per quality-adjusted life-year (QALY) gained, exceeding the standard willingness-to-pay (WTP) threshold of $100,000 to $150,000 per QALY. Against durvalumab plus chemotherapy, T+D+CT was only cost-effective in subgroup with PD-L1 expression ≥50%. DSA results for patients with PD-L1 expression <1% showed that the ICER for first-line T+D+CT remained above the WTP threshold range, even with substantial changes to model inputs. PSA revealed a higher likelihood of T+D+CT being cost-effective as WTP thresholds increased. Scenario analysis confirmed the study's primary findings, with the exception of a scenario where durvalumab was offered at no cost.

Conclusions: The findings suggests that T+D+CT may not be a cost-effectiveness first-line treatment for EGFR/ALK wild-type mNSCLC in the US, given its high ICERs and limited cost-effectiveness in the majority of PD-L1 expression subgroups.

Comment 2: Second, in the introduction, it is necessary to review the payment and medical care insurance systems in the United States, analyze the importance of the cost-effectiveness data for the healthcare insurance system, and clearly indicate the clinical and public policy needs for this research focus.

Reply 2: Thank you for your feedback. We have integrated the suggested modifications into the third paragraph of our introduction (**refer to Page 4-5, lines 88-103**). The updated text now includes a comprehensive review of the payment and medical care insurance systems in the United States, along with an analysis of the significance of cost-effectiveness data for the healthcare insurance system, and a clear indication of the clinical and public policy needs for this research focus .

Changes in the text: The revised third paragraph of our introduction now reads:

"The dual immunotherapy and chemotherapy combination offer a promising and well-tolerated treatment option for patients with this disease. However, concerns about the treatment's high cost may hinder its widespread adoption. In 2023, an estimated 202,589 new cases of mNSCLC were projected in the US (3,21), with around 65-75% of these cases exhibiting low or negative PD-L1 expression, rendering about 142,000 patients eligible for this treatment. The US healthcare insurance system is complex, with varying levels of physician and pharmaceutical access. By 2021, over half of Americans are privately insured, 8.6% are uninsured, and the rest are covered by public sources like Medicaid, Medicare, or the US military (22). Health insurance plays a pivotal role in determining access to care and

health outcomes for cancer patients in the US (23). Given the imperative need for high-quality and affordable medications to improve cancer survival, effective healthcare resource allocation is crucial. Therefore, conducting cost-effectiveness analyses is imperative to ascertain if a novel, albeit costly, treatment regimen provides a clinical benefit at a justifiable cost to inform resource allocation decisions. This study aimed to evaluate the cost-effectiveness of tremelimumab with durvalumab, combined with chemotherapy (T+D+CT) , as the first-line therapy for patients with EGFR/ALK wild-type mNSCLC from a US healthcare perspective. We present this article in accordance with the CHEERS reporting checklist (24)."

Comment 3: Third, in the methodology, I suggest the authors to describe the data sources for cost and effectiveness in detail and explain why these parameters are suitable. I also suggest the authors to briefly describe the commonly used theoretical model for cost-effectiveness analysis.

Reply 3: Thank you for your valuable input. We have incorporated your suggestions into our manuscript. Please refer to **Page 5, lines 109-114** in the first paragraph of the **Overviews** subsection of the **Methods** section for a brief description of the commonly used theoretical model for cost-effectiveness analysis. Additionally, detailed information on the sources for effectiveness data can be found on **Pages 6-7, lines 145-176** in the **QALYs** subsection of the **Methods** section, while the data sources for cost have been elaborated on **Pages 7-8, lines 177-206** in the **Costs** subsection of the **Methods** section.

Changes in the text: The revised text now states:

Page 5, lines 109-114 : *"The Markov model divides mNSCLC disease progression into distinct health states, with patients transitioning between states at discrete time intervals called cycles. Each state is linked to costs and health outcomes, with transition probabilities guiding movement between states (25). Markov models allow for the simulation of disease progression and treatment effects over time, enabling the evaluation of costs and outcomes associated with different cancer treatment strategies"*

Pages 6-7, lines 145-176: ***"QALYs***

QALY, a common metric in cost-effectiveness analysis, considers both quality of life and life years gained. It is calculated by multiplying health state utilities (ranging from 0 for death to 1 for perfect health), by the time spent in each health state determined by transition probabilities (29).

Transition probabilities between health states were estimated based on the data from the POSEIDON trial, the only study investigating the clinical efficacy and safety of T+D+CT, D+CT and CT in the first-line setting. Survival data for first-line CT were extracted by digitizing Kaplan-Meier (KM) curves from the trial using the GetData Graph Digitizer software (version 2.26; http://www.getdata-graphdigitizer.com/index.php). Goodness-of-fit tests were then conducted to select the optimal survival distribution for these recreated survival data, considering criteria such as the Akaike information criteria (AIC) and Bayesian information criteria (BIC), as well as graphical evaluation of fits versus observed data. Lower AIC and BIC values, along with greater overlap between the fitted and observed curves, indicated a better fit. Based on the results of the goodness-of-fit tests, the Weibull and log-logistic distributions were chosen to model and extrapolate OS and PFS for first-line CT (see Supplement Table S3 and Figure S1-S2). Transition probabilities for first-line T+D+CT and D+CT were estimated using the hazard ratios (HRs) of these two strategies relative to first-line CT, derived from the POSEIDON trial. A specific formula (30) was utilized to estimate the survival rate for these two strategies: (30). In the base-case analysis, HRs stratified by PD-L1 expression were used to provide a comprehensive understanding of the first-line use of T+D+CT for EGFR/ALK wild-type mNSCLC..

Transition probabilities for the temporary health state were estimated using safety data from the POSEIDON trial (Supplement Table S4), with the model focusing solely on immunotherapy discontinuation caused by AEs. This decision was made due to the lack of explicit data on the discontinuation of first-line chemotherapy drugs, which are generally cheaper than immunotherapy drugs.

In the absence of health-related quality of life (HRQoL) data from the POSEIDON trial during the analysis, we utilized health utility values sourced from published literature. A health utility score of 0.754 was assigned to the PFD health state, while a score of 0.569 was assigned to the PD health state (31-32). The impact of AEs on HRQoL was assessed by incorporating utility decrements based on a report by the Institute for Clinical and Economic Review (33), as well as estimated episode durations for AEs from Yang et al.'s study (34). Further details on AE-related utility decrements can be found in Supplement Table S5."

Pages 7-8, lines 177-206: "***Costs***

We analyzed our model from a US healthcare perspective, considering costs such as first-line drug acquisition and administration, subsequent anticancer therapy, adverse events (AEs) and disease management, best supportive care (BSC), and palliative care. Biomarker testing costs were not included in the model, as all patients were assumed to have known PD-L1

expression status. All costs were converted to 2023 US dollars based on the Personal Consumption Expenditures-Health index (35).

Acquisition costs for first-line drugs were estimated using the dosage and schedule provided in Supplement Table S1, with average sales prices (ASP) sourced from the Centers for Medicare & Medicaid Services (CMS) (36). Drug administration costs were calculated based on infusion duration and corresponding infusion prices from the CMS Physician Fee Schedule Look-up Tool (37). Drug dosage calculations were based on a mean body surface area of 1.79 m2 from Criss SD et al.'s economic evaluation, which analyzed data from over 3500 lung cancer patients treated at Partners Healthcare hospital (38).Additionally, a mean creatinine clearance rate of 70 ml/min for model patients was ascertained from Wan X et al.'s study (39). In the POSEIDON trial, subsequent anticancer therapies included radiotherapy, immunotherapy, cytotoxic chemotherapy, and targeted therapy (19). As the specific drugs used in subsequent anticancer therapies were not disclosed in the trial, the subsequent regimens were modeled based on the preferred regimens recommended by the latest NCCN Guidelines (27). The costs for subsequent anticancer therapies were calculated and presented in Supplement Table S2..

In this CEM, grade 3/4 AE costs were considered. To calculate AE management costs for each arm, unit AE costs were initially obtained from the Healthcare Cost and Utilization Project (HCUP) using Clinical Classification Software Refined (CCSR) diagnosis codes (40). Subsequently, these costs were multiplied by the reported incidence of each AE for each arm and then aggregated to determine the total AE management costs for each arm (refer to Supplement Table S6). The medical resources necessary for managing mNSCLC varied depending on the health state, encompassing services such as routine outpatient visits, computed tomography scans, magnetic resonance imaging, ultrasounds, and X-rays. Health state-specific disease management costs were sourced from literature (34), as well as costs for best supportive care (BSC) and palliative care (38). Further details can be found in supplementary Table S7"

Comment 4: Finally, some potentially related papers are helpful for this study and need to be cited:

1. Zhang Z, Liang G, Zhang P, Zhao Z, He Z, Luo F, Chen Z, Yang Z, Zhang Z, Xia T, Liu X, Zhang Y, Ye W. China county-based prostate specific antigen screening for prostate cancer and a cost-effective analysis. Transl Androl Urol 2021;10(10):3787-3799. doi: 10.21037/tau-21-779.

2. Mitzman B, Varghese TK Jr, Akerley WL, Nelson RE. Surgical-decision making in the setting of unsuspected N2 disease: a cost-effectiveness analysis. J Thorac Dis 2024;16(2):1063-1073. doi: 10.21037/jtd-23-1538.
3. Dempke WCM, Fenchel K, Reuther S, Murphy MF. Durvalumab plus novel agents in non-small cell lung cancer—a new COAST on the horizon? Transl Lung Cancer Res 2022;11(4):697-701. doi: 10.21037/tlcr-21-1002.
4. Akkad N, Thomas TS, Luo S, Knoche E, Sanfilippo KM, Keller JW. A real-world study of pneumonitis in non-small cell lung cancer patients receiving durvalumab following concurrent chemoradiation. J Thorac Dis 2023;15(12):6427-6435. doi: 10.21037/jtd-22-1604.

Reply 4: Thank you for your valuable comment. We have referenced paper 3-4 in the second paragraph of the **Introduction** section (**Pages 4, lines 73-75**), paper 1 to describe the commonly used theoretical model for cost-effectiveness analysis in the first paragraph of the **Overviews** subsection of the **Methods** section (**Pages 5, lines 109-114**), and paper 2 to explain QALY calculation in the first paragraph of the QALYs subsecton of the **Methods** section (**Pages 6, lines 146-148**) .

Changes in the text: The revised text now states:

Pages 4, lines 73-75: “Durvalumab, a highly selective human IgG1 monoclonal antibody, disrupts PD-L1 interactions with PD-1 and CD80, empowering T cells to target and eliminate tumor cells, showing potential in non-small cell lung cancer when combined with novel agents (17-18).”

Pages 5, lines 109-114:“The Markov model divides mNSCLC disease progression into distinct health states, with patients transitioning between states at discrete time intervals called cycles. Each state is linked to costs and health outcomes, with transition probabilities guiding movement between states (24).”

Pages 6, lines 146-148:“QALY, a common metric in cost-effectiveness analysis, considers both quality of life and life years gained. It is calculated by multiplying health state utilities (ranging from 0 for death to 1 for perfect health), by the time spent in each health state determined by transition probabilities (29).”

Reviewer B

1. Ref.40 was not cited in the main text, please check and cite it in order.

Reply 1: We apologize for the oversight. Ref.40 has been cited in the main text as requested

(**Page 8, Line 199**). Thank you for bringing this to our attention.

2. Ref.33 is not Yang et al.'s study, please check.

472 report by the Institute for Clinical and Economic Review, as well as estimated episode durations for

473 AEs from Yang et al.'s study (33-34). Further details on AE-related utility decrements can be found in

Reply 2: Thank you for pointing out the error. Ref.33 is not Yang et al.'s study but the report of the Institute for Clinical and Economic Review, while Ref.34 is Yang et al.'s study. To clarify, we have revised the sentence in the fourth paragraph of the QALYs subsection of the Methods section to: *"The impact of AEs on HRQoL was assessed by incorporating utility decrements based on a report by the Institute for Clinical and Economic Review (33), as well as estimated episode durations for AEs from Yang et al.'s study (34)."* Thank you for your attention to detail (**Page 7, Line 173-175**).

3. Is it possible for you to resubmit an editable Figure 1?

Reply 3: Thank you for your request. We have resubmitted an editable Figure 1 in PowerPoint presentation format and attached it to this email.

4. And please supplement a summarized legend for Figure 1.

872 **Figure 1.** XXX

873 (A) Markov model structure used to compare 3 strategies for treating EGFR/ALK wild-type mNSCLC.

874 (B) Health states network showing the possible transitions between 4 health states. *NSCLC* non-small

Reply 4: Thank you for your request. We have supplemented a summarized legend for Figure 1 as " **Markov model diagram"**.

5. Table 1: Two table headers are not suggested, please further revise the table.

Palliative care	3,089	3,081	3,171	3,140	3,162	3,171	3,126	3,133	3,171	3,128	3,169	3,171
Total costs	307,168	262,377	133,171	257,724	195,531	133,171	274,578	224,783	133,171	266,399	184,473	133,171
Incremental Results												
		vs D+CT	vs CT		vs D+CT	vs CT		vs D+CT	vs CT		vs D+CT	vs CT
Incremental LYs			0.65		0.19	0.27		0.06	0.38		0.35	0.36
Incremental QALYs			0.47		0.11	0.18		0.03	0.27		0.23	0.24

Reply 5: Thank you for your suggestion. We have revised the table. Please refer to the

updated Table in the email attachment.