

## Response Letter

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**What should be the future direction of development in the field of  
prostate cancer with lung metastasis?**

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Dear editors:

On the behalf of my co-authors, I would like to sincerely thank you and  
the reviewers for reviewing our manuscript. These comments are all valuable  
and very helpful for revising and improving our paper, as well as the important

guiding significance to our researches. We have studied comments carefully and have made corrections which we hope meet with approval. Enclosed is our revised manuscript and the responses. Below are specific responses to each comment. Our responses are italicized and in blue. And in the manuscript are highlighted in yellow where they were primarily modified.

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Accept (General priority)

**Specific Comments to Authors:** In General: it's a good paper and the subject of the manuscript is applicable and useful. Title: the title properly explains the purpose and objective of the article Abstract: abstract contains an appropriate summary for the article, the language used in the abstract is easy to read and understand, and there are no suggestions for improvement. Introduction: authors do provide adequate background on the topic and reason for this article and describe what the authors hoped to achieve. MATERIALS AND METHODS: - The variables selected for the study are described clearly and are appropriate, given the nature of the question asked. - The research design is described in detail. - The research design is appropriate and does not contain particular weaknesses. - The measurement instrument, including its psychometric qualities, is described clearly. - The population of interest and the sampling procedure are defined clearly. - The data collection procedure is clearly described. - The setting in which the study took place is described. - The data analysis procedures are stated in precise terms. - The data analysis procedures are appropriate. Results: the results are presented clearly, the authors provide accurate research results, and there is sufficient evidence for

each result, Specific data accompany the result statement, and Tables and figures are used efficiently. Conclusion: in general: Good and the research provides sample data for the authors to make their conclusion. Grammar: There are a lot of grammatical errors. This must be taken care of and addressed. . (Check The Paper Comments).

*Answer: We are very grateful for your appreciation of our research. Regarding the issue of grammar errors in this article, We have invited native language experts from the renowned polishing agency SCRIBENDI to provide in-depth polishing for this article. For example, We changed the "pose" on page 4 to "impose". We changed the "From Figure 3, we can identify" on page 7 to " Figure 3 illustrates that ". Please refer to the revised manuscript for other modification details. The following is the proof of polishing for this article:*



Reviewer #2:

**Scientific Quality: Grade C (Good)**



**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** The paper aims to provide a systematic knowledge framework for PCLM by conducting a bibliometric analysis of the research output in this field and exploring the molecular mechanisms of PCLM. The authors collected data from 280 high-quality papers and performed enrichment analysis and protein-protein interaction analysis to summarize and explore the mechanisms of PCLM. They also discussed the current treatment strategies and highlighted the need for further research to improve the prognosis and find a thorough cure for PCLM. Overall, the paper provides valuable insights into the current state of research in the field of PCLM and identifies potential directions for future development. The use of bibliometric analysis and molecular mechanism exploration adds depth and credibility to the study.

*Answer: We are very grateful for your appreciation of our research. Regarding the issue of grammar errors in this article, We have invited native language experts from the renowned polishing agency SCRIBENDI to provide in-depth polishing for this article. For example, We changed the "pose" on page 4 to "impose". We changed the "From Figure 3, we can identify" on page 7 to " Figure 3 illustrates that ". Please refer to the revised manuscript for other modification details. The following is the proof of polishing for this article:*





However, there are a few areas that could be further improved. Questions And Suggestions:

1) Can the authors provide more details about the criteria used for the selection of the 280 papers included in this study? Specifically, how were the high-quality papers identified and what were the inclusion and exclusion criteria?

*1)Answer: These high-quality papers were initially screened by publication date, writing language, and paper type. Then, two authors independently conducted an in-depth reading and analysis of these initially screened papers.*

*First, we required that the main research content of these papers should be related to prostate cancer lung metastasis.*

*Second, we required these papers to have reliable methods and evidence. High-quality papers should provide clear and detailed descriptions of the study design and methods, as well as adequate data support and experimental evidence. The research methodology should be scientifically reliable and follow academic research ethics and standards. For example, the study "68 Ga-PSMA-PET/CT for the evaluation of pulmonary metastases and opacities in patients with prostate cancer" by Jonathan Damjanovic et al., examined 739 prostate cancer patients, providing a clear and detailed description of the data, imaging protocol, imaging analysis, etc., and demonstrating its reliable methodology and empirical evidence. Moreover, their studies were approved by the relevant institutional ethical review boards, which complied with academic research ethics and standards.*

*Furthermore, we required that the results and analyses of these papers should be accurate and credible, and the conclusions of the studies be of academic and practical significance. For example, the results of the study "Autophagy deficiency promotes lung metastasis of prostate cancer via stabilization of TWIST1" by Y X Shi et al., were jointly confirmed by a variety of highly credible experimental methods and concluded that ATG5-mediated autophagy controls prostate cancer metastasis via regulation of p62 abundance and stabilization of TWIST1. This conclusion provides a potential target for the treatment of prostate cancer lung metastasis, which is of great significance for related basic research and clinical practice.*

*Finally, two authors performed a summary analysis. Disagreements that arose between these two authors were discussed, resolved by all authors of this paper, and finally agreed upon.*

**2) The paper mentions the uneven spatial distribution of PCLM research. Can the authors provide more information about the reasons behind this uneven distribution and the potential implications for future research?**

2) *Answer:* Thank you very much for your suggestions. We further discuss in depth the reasons behind this uneven distribution and the potential implications for future research **at 4.1 on page 11** of the revised manuscript. The additions and modifications are as follows:

However, the uneven distribution of scientific output in the field of PCLM across regions in the spatial dimension may be related to the social and scientific development capabilities of those regions[24]. This implies that the uneven country/region distribution of scientific output about PCLM in the spatial dimension may be related to two factors. First, developed countries and regions have invested more in healthcare resources and scientific research infrastructure. Second, they have a higher number of research institutes, laboratories, and researchers. In contrast, some developing countries or poor regions may face the challenges of limited funding and inadequate research conditions, resulting in a relative lag in scientific research. In this way, a contradiction has arisen between developing countries with limited medical technology but high PC morbidity and mortality and developed countries with advanced medical technology but reduced PC morbidity and mortality[25,26]. Therefore, developed countries should proactively conduct international exchanges and cooperation in the field of PCLM to promote the sharing of data, funds and equipment, technology and methods, and the establishment of international cooperation networks. Developing countries should increase their investment in PCLM-related research and actively seek transnational cooperation in the future. This will not only benefit the lives and health of the world's people but will also benefit the development of the field of PCLM by making full use of clinical resources and research due to the international cooperation network and the improvement of the technological level of developing countries.

3) The paper discusses the current treatment strategies for PCLM, including chemotherapy and immunotherapy. Can the authors provide more details



about the limitations and challenges associated with these treatment approaches? Are there any emerging therapies or approaches that show promise for PCLM treatment?

**3)Answer:** Thank you very much for your suggestions. We have further added and revised the information on the limitations and challenges of chemotherapy and immunotherapy. Based on this, we have revised the statement on **pages 14 and 15-16** of the manuscript regarding the limitations and challenges of chemotherapy and immunotherapy as follows:

**Page 14:** In the field of immunotherapy for PC, treatment plans have limitations. One example is sipuleucel-T, the only United States Food and Drug Administration-approved immunotherapeutic agent for metastatic desmoplasia-resistant PC, but it is indicated for asymptomatic or minimally symptomatic patients only[38]. Immune resistance poses another challenge in PC treatment. Factors like low tumor mutation loads and the presence of immunosuppressive cells can disrupt the immune system and create an immunosuppressive tumor microenvironment, leading to reduced therapeutic efficacy[39]. Additionally, there can be adverse effects associated with immunosuppressant therapy. For instance, patients may experience immune-related adverse events, such as ulceration of the lower lip[40]. Furthermore, the clinical utility of certain treatments has yet to be validated. For example, a study by Komaru et al. that is currently in the animal experimentation stage has a long way to go before its potential in clinical practice can be determined[41]. In addition, there have been fewer studies on relatively well-established immunotherapies in the field of PCLM relative to other treatments.

**Page 15-16:** Chemotherapy is utilized in PCLM treatment, but it has limitations and challenges. One issue is resistance, such as the enhancement of doxorubicin resistance in PC by the TrkB protein[56]. Additionally, PC cells display inherent and





acquired resistance to cisplatin, making it ineffective as a first-line chemotherapeutic agent for PC[57]. Most PC patients who undergo ADT eventually develop castration-resistant disease[58]. Chemotherapy also has adverse effects. For instance, potentially life-threatening events like neutropenia and febrile neutropenia can occur in patients with metastatic PC who receive doxorubicin-related chemotherapy[59]. Furthermore, ADT for PC increases the risk of cardiovascular and metabolic syndrome, which can lead to fatal outcomes[60]. Despite these treatment efforts, chemotherapy alone cannot fully cure PCLM. However, in the context of the limitations of other non-traditional treatments, chemotherapy has been widely adopted in clinical practice, and its efficacy has been clearly demonstrated, whether applied alone or in combination with other therapeutic means.

As to whether chemotherapy is expected to be used in the treatment of PCLM? As mentioned above, in the context of facing the limitations of other non-traditional therapies, chemotherapy has been widely adopted in clinical practice, whether or not it is applied alone or in combination with other therapies, and its efficacy has been clearly verified. Therefore, chemotherapy, although not a complete cure for PCLM, is still widely used in the treatment of PCLM against the background of the limited role of emerging therapies.

As for whether immunotherapy is expected to be used for PCLM treatment? To our knowledge, although there are many reports of immunotherapy completely curing metastatic melanoma and lung cancer. However, there are no mature reports on the use of immunotherapy in PCLM. Therefore, immunotherapy, although very promising for curing PCLM, still has a long way to go.

4) The paper highlights the importance of exploring and enhancing mechanisms such as cytokine-cytokine receptor interaction and ribosome in PCLM research. Can the authors provide more details about the specific roles



of these mechanisms in PCLM and the potential implications for future research and treatment development?

*4)Answer: Thank you very much, however our viewpoint on the importance of mechanisms such as cytokine-cytokine receptor interactions and ribosomes in PCLM research is mainly based on our calculation results, such as pathway enrichment analysis. Moreover, there is currently no more mature research on the mechanisms of cytokine-cytokine receptor interactions and ribosomes in PCLM. However, this result provides us with insights into the molecular mechanism of PCLM. In the future, our group will conduct relevant in vitro and in vivo studies to further validate these mechanisms. Thank you again for your suggestions and questions.*

5) The paper briefly mentions the association between COVID-19 and pathways related to PCLM. Can the authors provide more information about this association and its potential impact on PCLM research and treatment?

*5)Answer: We are very sorry about this. Our result of a possible association between COVID-19 and PCLM-related pathways is currently based mainly on the inference of computational results such as our pathway enrichment analysis. And to our knowledge, there is currently no more mature research on the relationship between COVID-19 and PCLM-related pathways. However, this result suggests that there may be a certain correlation between COVID-19 and PCLM-related pathways. In the post-pandemic era today, we believe that studying the association between PCLM and COVID-19 is of great significance for the prevention and treatment of PCLM. Therefore, in the future, our group will conduct relevant research to further verify this correlation. Thank you again for your suggestions and questions.*

6) Can the authors discuss the potential role of targeted therapy in PCLM treatment? Are there any specific targets or pathways that show promise for targeted therapy in PCLM?

*6)Answer: Thank you for your question. It is true that there are targets or pathways such as androgen receptor, miR-33b-3p, DOCK4, prostate-specific membrane antigen (PSMA), CCR4, etc. that show promise for PCLM targeted therapy. Based on this, we modify and add to the discussion on targeted therapy on **page 16** as follows:*

*In addition, in the field of targeted therapy, enzalutamide, a next-generation AR inhibitor, has been proven to significantly prolong the survival of patients with metastatic PC, despite the inevitable resistance mediated by SPP1 through the PI3K/AKT and ERK1/2 pathways or the reactivation and splice variants of the AR[61-63]. MiR-33b-3p inhibits metastasis by targeting DOCK4 in PC[64]. We could enhance miR-33b-3p expression to overcome the poor efficacy of proteasome inhibitors in metastatic PC in the future. It has also been reported that treatment with Lu-177-PSMA radioligand showed significant efficacy in PC patients and responded favorably to the treatment and regression of lung metastases after prostate-specific membrane antigen radioligand therapy (Lu-PRLT)[31]. High expression of CCL2 induced the production of CCR4 in PC cells, which promotes migration and invasion of PC cells through enhanced Akt phosphorylation[65]. This study reveals CCR4 as a potential target for the treatment of PCLM. Putz et al. found that the cytokine signaling checkpoint CIS plays an important role in the occurrence of PC with LM and has a promising future in the treatment of PCLM[66]. Furthermore, in recent years, the emergence of abiraterone acetate has been confirmed by numerous studies to alleviate lung metastases and significantly prolong the survival of PCLM patients, and it has*



been regarded as a safe and effective treatment for many advanced PCLM patients[8,54,67,68].

7) The paper mentions the importance of translating basic research findings into clinical applications. Can the authors provide more details about the challenges and potential strategies for translating basic research findings in the field of PCLM?

**7)Answer:** Thank you for your question. We modify and add to the discussion on [page 19-20](#) about the challenges and potential strategies for translating basic research results in the PCLM field as follows:

Finally, the presence of phrases such as “rats” suggests that many research results are still in the cellular, animal, and in vitro stages of experimentation and are still some distance from clinical translation. For example, the studies by Komaru et al., Pan et al., and Azhati et al. are still in the cellular, animal, and in vitro experimental stages and a long way from clinical practice[41,90,93]. As mentioned above, PCLM scientific outputs represent countries/regions with a high level of PCLM research but with fewer clinical case data due to the small number of PCLM patients, while countries/regions with high PCLM morbidity and mortality have a relatively weak level of research on PCLM. This may also be a major obstacle to the translation of basic research results into clinical practice. For this reason, international collaboration and knowledge sharing are particularly important. In addition, basic research often involves complex cellular, molecular, and biological processes, which may lead to problems of instability and reproducibility of results. One strategy to address this challenge is to increase the reliability and reproducibility of results through multicenter studies, validation experiments, and mutual evaluation. Clinical translation requires significant financial and resource support. However, research funding is often limited, and industry needs to consider commercial viability. Strategies to address this challenge include seeking





support from public and private funding, building partnerships, and exploring new sustainable financing models. Thus, the translation of basic research findings into clinical applications is urgent in the context of the limited effectiveness of contemporary treatment options. In conclusion, basic research on PCLM is important but underdeveloped at the present time.

8) Can the authors discuss the potential role of precision medicine in the treatment of PCLM? Are there any specific biomarkers or genetic alterations that could be targeted for personalized treatment approaches?

8)Answer: Thank you very much for your advice. Precision medicine is now playing an important role in a wide range of diseases. Therefore, the future of precision medicine in PCLM is immeasurable. For this reason, we have added a narrative on [page 16-17](#) about precision medicine and biomarkers or genes that can be used as personalized therapy. The details are as follows:

In recent years, precision medicine has played an important role in a variety of diseases. In particular, tumors involve alterations in the biological behavior of multiple genes. The biological behaviors of various tumors are complex and diverse. Therefore, precision medicine with personalized treatment characteristics is a solution to the difficult problem of PCLM, which is hard to cure completely. One study reported that AR plays dual and opposite roles in vasculature encapsulating tumor clusters, emphasizing the complex function of AR and its importance in individualized cancer therapy[69]. This study provides new insights into the complex regulatory network of AR in metastatic tumors and lays the foundation for relevant precision medicine. It has also been reported that AuNSs@PDA-Ce6 nanoprobe significantly reduced tumor growth and inhibited LM, which has considerable potential for precise therapeutic diagnosis and metastasis inhibition[70]. In addition, Hlavac et al. revealed the characterization of prognostically distinct subgroups with precision medicine value by

*targeted sequencing of blood and archival samples from LM patients[71]. However, regrettably, no mature precision medicine or personalized treatment for PCLM has been reported. In the future, precision medicine will also be an important endeavor in the field of PCLM.*

We sincerely thank you once again for your valuable suggestions on our manuscript. Your suggestion has greatly improved our research. Thank you very much for your time and consideration.

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