Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Advances and Key Focus Areas in Gastric Cancer Immunotherapy: A Comprehensive Scientometric and Clinical Trial Review (1999-2023) " (Manuscript NO.: 87813, Scientometrics). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our research. We have studied comments carefully and have made corrections which we hope meet with approval. The process of change was highlighted with yellow color in the revised manuscript, and I also recorded the paragraph that was changed for this question in each response. The main corrections in the paper and the responses to the reviewer's comments are as follows:

Responds to the Reviewer #1's comments:

This review includes a literature search on immunotherapy for gastric cancer from 1999 to 2023, along with an analysis of research trends using scientometric methods. While the discussion section elaborates on the specifics of immunotherapy, the primary focus of this study lies in tracking research trends. I believe that delving into the intricacies of immunotherapy would have added considerably to the content, potentially making it difficult for readers to grasp the intent of the study. It is my suggestion that the information could have been presented more succinctly for the reader's understanding.

Response: As you suggested, this article focuses on the past, present, and future of gastric cancer immune therapy. In addition to reviewing the literature, we also conducted a systematic analysis of clinical trials and included data from these trials as part of the research trends section. We added an explanation of the therapies in the discussion section for two reasons: (1) to explain the key terms in the literature analysis to facilitate reader understanding; (2) to use

keywords as a foundation to organize and classify the clinical trials section, allowing readers to identify the research areas and their current level of development. We have also made some adjustments to the title based on your suggestions to improve readability. However, due to the importance of retaining key elements, we have maintained the original content in its entirety.

Introduction 1. The abstract states that gastric cancer has the fourth highest cancer mortality rate, while the introduction states that it is the third highest, which is inconsistent.

Response: The incidence and mortality rates of gastric cancer have been updated, and relevant references have been added. The incidence of gastric cancer ranks sixth, and the cancer-related mortality rate ranks third. The relevant literature: Chhikara B.S.; Parang K. Global Cancer Statistics 2022: The Trends Projection Analysis. Chem Biol Lett 2023.

Results 1. In Section 3.1.2, percentages should be reported to the first decimal place.

Response: The percentage data in Section 3.1.2 has been changed to one decimal place.

Reference 1. Reference 19: J. Clin. Oncol. 2023, 41,1471-+ should be corrected to J. Clin. Oncol. 2023, 41,1470-1491.

Response: The reference list has been updated accordingly.

Responds to the Reviewer #2's comments:

1. Can you provide more details about the specific methodologies used in the scientometric analysis? How were the literature and clinical trial data collected and analyzed?

Response: Thanks for your comments, in the revised version we have already added more details for our methodologies illustration in the section of "Materials and methods", and we detailed it here for your reference.

For the details about scientometric analysis: We employed CiteSpace to analyze the emergence of countries, institutions, authors, references, keywords, and timeline in relevant literature, and used VOS Viewer to analyze information such as journals, authors, and keywords. We applied scientometric knowledge to analyze some information in relevant literature in order to reveal future development trends. We conducted a literature search in Web of Science using search terms related to gastric cancer immunotherapy.

For the literature and clinical trial data collected and analyzed:

Collection: The literature search was conducted on Web of Science.

(1) For literature: The retrieval terms in the topic: ("gastric cancer" OR "gastric adenocarcinoma" OR "gastric neoplasm" OR "gastric tumor" OR "stomach cancer" OR "stomach adenocarcinoma" OR "stomach neoplasm" OR "stomach tumor" OR "gastric cancers" OR "gastric adenocarcinoma" OR "gastric neoplasms" OR "gastric tumors" OR "stomach cancers" OR "stomach adenocarcinoma" OR "stomach neoplasms" OR "stomach tumors" OR "tumor of stomach") AND ("immunotherapeutic" OR "immunotherapy" OR "immunotherapies" OR "immunotherapeutics"). The types of documents: Article and Review. Finally, the information for a total of 2013 documents was downloaded as Plain Text Files and Tab Delimited Files, and full records and cited references were contained. After removing duplicates, there were no duplicate records. All of the 2013 documents were included in this analysis.

(2) For clinical trials: The retrieval terms: ("gastric cancer" OR "gastric adenocarcinoma" OR "gastric neoplasm" OR "gastric tumor" OR "stomach cancer" OR "stomach adenocarcinoma" OR "stomach neoplasm" OR "stomach

tumor") AND ("immunotherapy"). There were 228 clinical trials registered, 25 had been completed and 113 were recruiting or not yet recruiting. Then we searched for some main immunotherapies in clinical trials on these two platforms. The research strategy: ("dendritic cells" OR "DNA vaccine" OR "RNA vaccine") AND "gastric cancer" for vaccine clinical trials; (ACT OR TIL OR TCR-T OR CAR-T OR TCR T OR CAR T OR NK OR CIK) AND "gastric cancer" for ACT clinical trials; (ICI OR PD-1 OR PD-L1 OR CTLA-4) AND "gastric cancer" for ICI clinical trials. 274, 137 and 23 clinical trials were incorporated separately.

Analyzation:

The eligible articles retrieved were exported and subjected to bibliometric analysis using CiteSpace and VOS Viewer. Clinical trial data were obtained from ClinicalTrials.gov and the International Clinical Trials Registry Platform (ICTRP), and relevant charts were plotted using Excel. We conducted a preliminary understanding of the content of these clinical trials and analyzed current research hotspots. In the revised manuscript, we have also included the Impact Index Per Article from Reference Citation Analysis (RCA).

2. What were the main findings of the scientometric analysis? Were there any notable trends or patterns identified in the literature and clinical trial data?

Response:

The main findings of the bibliometric analysis are: (1) The spatial-temporal distribution of scholarly publications has been demonstrating a noteworthy ascending trajectory. Between 1999 and 2022, the annual publication output for gastric cancer immunotherapy-related literature increased from 22 to 552, and there has been a significant and steady increase in publications since 2016. (*This information can be located in the revised edition：RESULTS/Bibliometric analysis/Annual distribution of publications and citations*)(2) Keyword analysis: The hot research areas in gastric cancer treatment include TME, MSI, dMMR, DC, ACT, etc. Due to the increasing application of immune checkpoint

inhibitors in gastric cancer immunotherapy and their significant potential, we have also included an analysis of current research achievements and future trends in ICIs. (*This information can be located in the revised edition：RESULTS/Bibliometric analysis/Timeline view of keywords*) (3) Burst word analysis: According to the timeline view and burst analysis of keywords, we can find the evolution of research directions in different eras. ACT and DC have been receiving increasing attention and development over the past two decades, while immunomodulatory mismatch repair and adjuvant chemotherapy have gained more attention in the past five years. Additionally, research on targeted therapy has been increasingly mentioned in the past ten years. (*This information can be located in the revised edition： RESULTS/Bibliometric analysis/Burst analysis of keywords*)

Keywords analysis also detailed in Discussion/Bibliometric analysis/Keywords analyasis

The trends of clinical trials are:

(1) Discovering novel biomarkers to subclassify patients and exploring more specific treatment options. NCT05593419, ChiCTR2100052367, NCT02757391, NCT03158571

(2) Integration of immunotherapy with surgery, radiotherapy, and chemotherapy.

NCT04688801, Chemotherapy ± Immuonotherapy ± Radiotherapy after surgery

(3) Transition from single-agent to multi-agent therapy.

NCT05152147, Trastuzumab(anti-HER2)/Zanidatamab(ZW25, anti-HER2)±Tislelizumab (anti-PD-1) + Chemotherapy

(4) Combination therapy involving various immunotherapies such as ICI, ADC, and ACT.

NCT05269381, Vaccine+ Pembrolizumab(anti-PD-1, ICI)+ Chemotherapy;

NCT05671822, SHR-A1811(HER2, ADC)+SHR-1701(PD-L1 and TGF-β double antibody) +capecitabine+oxaliplatin

NCT05313906, RC48(HER2, ADC)+AK105(anti-PD-1)+cisplatin

(5) Discovery of new immune checkpoint inhibitors.

NCT05187182, CA-4948(IRAK4/FLT3 inhibitor) +FOLFOX+PD-1 Inhibitor ± Trastuzumab(anti-HER2);

NCT05714553, NUC-3373(thymine synthase inhibitors)+ Leucovorin+ Pembrolizumab/ Docetaxel

(*This information can be located in the revised edition: Discussion/The trends of clinical trials:*)

3. Can you explain the significance of the identified clusters and keywords, such as TME, MSI, DC, and ACT, in the context of gastric cancer immunotherapy?

Response: *This information can be located in the "Discussion" section of the revised edition.*

(1) The tumor microenvironment (TME) refers to the non-tumor cells and their metabolites and secretions that are present within the tumor, including immune cells such as myeloid suppressor cells, tumor-infiltrating lymphocytes, macrophages, stromal fibroblasts, endothelial cells, extracellular matrix components, growth factors and cytokines. TME not only provides nutrients and survival signals to cancer cells but also exerts protumorigenic activities. On the other hand, the TME also regulates immune responses in tumors through a range of immunosuppressive mechanisms, including the recruitment of immunosuppressive cells, production of immunosuppressive cytokines, and induction of immune checkpoint inhibitors. For gastric cancer, tumor-associated macrophages provide potential therapeutic targets and regulate immune activity. The tumor microenvironment of gastric cancer patients also has the potential to predict chemotherapy sensitivity, making it a valuable research topic. The content related to the tumor microenvironment in the

revised manuscript is located on page eight. **DISCUSSION**; ***keyword analysis***; TME (#5 tumor microenvironment)

(2) Microsatellite instability (MSI-H) and mismatch repair deficiency (dMMR) are genetic alterations that occur in some cancers, including gastric cancer. MSI-H and dMMR are related to DNA repair mechanisms in cells. MSI-H occurs when DNA microsatellites, which are short repeated sequences in the genome, become unstable due to insertions or deletions within the repeat units. dMMR occurs when the DNA mismatch repair (MMR) system, which normally corrects small errors in DNA during replication or recombination, is dysfunctional. In both cases, this can lead to genetic mutations and altered gene expression, which can contribute to cancer development. In gastric cancer, MSI-H and dMMR have been shown to be markers of good prognosis and may be targets for immunotherapy interventions. MSI-H gastric tumors often have a high number of mutations and are associated with an immune-rich microenvironment. This can make these tumors more sensitive to PD-1/PD-L1 blockade therapy, an immunotherapy treatment that targets the PD-1/PD-L1 pathway to activate antitumor immune responses. The content related to MSI-H and dMMR in the revised manuscript is located on page eight. **DISCUSSION**; ***keyword analysis***; MSI (#0 microsatellite instability) and dMMR (mismatch repair deficiency).

(3) Dendritic cells (DCs) are a type of antigen-presenting cell that is essential for the induction and regulation of adaptive immune responses. DCs are able to phagocytose and process antigens, and present these antigens to naive T cells, then results in the activation, differentiation, and polarization of T cells towards specific effector functions. In gastric cancer immunotherapy, dendritic cells play a key role in the activation and regulation of antitumor immune responses. DCs can be used as adjuvants or vaccine adjuvants to enhance antitumor immunity by presenting tumor-specific antigens to naive T cells. DC-based vaccines can be generated from autologous tumor cells or dendritic cells loaded with tumor-specific peptides or RNA. DCs can also be genetically modified to

express costimulatory molecules or cytokines to enhance antitumor immune responses. Current research has shown that the fusion of gastric cancer cells and dendritic cells can significantly enhance the stimulation of anti-tumor immune responses and have high safety. In addition, the combination of dendritic cells and cytokine-induced killer cells for gastric cancer treatment has shown promising results. Numerous studies are still exploring the promise of dendritic cells in gastric cancer immunotherapy, and progress continues to be made. The content related to DCs in the revised manuscript is located on pages eight and nine. **DISCUSSION**; ***keyword analysis***; DC (#2 dendritic cells).

(4) Adoptive cell therapies (ACTs) refer to the transfer of immune cells, such as lymphocytes or dendritic cells, into a patient to enhance their antitumor immune response. In gastric cancer immunotherapy, ACTs can generate effector T cells that specifically target tumor antigens, and induce long-term antitumor immunity. ACTs can also be used to enhance the function of regulatory T cells, which serve to suppress antitumor immune responses and improve patient outcomes. The main types of ACTs have been studied in the treatment of gastric cancer. such as tumor-infiltrating lymphocyte (TIL) therapy, engineered T cell receptor (TCR) therapy, chimeric antigen receptor (CAR) T-cell therapy, and natural killer (NK) cell therapy. In recent years, the highly concerned CAR-T therapy has also made significant progress in the field of gastric cancer, but further research is still needed due to its inevitable toxicities. In the immunotherapy of gastric cancer, NK cells and CIK cells have also demonstrated effective anti-tumor activity, while TILs have lower off-target toxicity and higher specificity. Additionally, TIL levels can serve as prognostic indicators for gastric cancer patients. The revised manuscript sequentially introduces the application of TIL, TCR, CAR, and NK cells in gastric cancer immunotherapy, summarizes and analyzes the advantages and disadvantages of different ACTs, and predicts future development trends. The content related to ACTs in the revised manuscript is located on pages nine and ten. **DISCUSSION**; ***keyword analysis***; ACT (#4 adoptive immunotherapy).

The above content is either already included in the manuscript or has been added to the manuscript.

4. How do the findings of this analysis contribute to the current understanding of gastric cancer immunotherapy? Are there any novel insights or recommendations for future research?

Response:

Through this article, we have understood that: (1) immunotherapy has become an important treatment modality for gastric cancer, representing the greatest advancement since chemotherapy and anti-HER2 therapy; (2) immunotherapy has evolved from a sole focus on replacing chemotherapy to a concept of combined therapy; (3) immunotherapy has developed from a simple pursuit of efficacy to one that balances efficacy and toxicity; and (4) immunotherapy has progressed from the use of immune checkpoint inhibitors to the exploration of CAR-T therapy.

Future suggestions include: (1) continued exploration of new targets; (2) investigation into new prognostic and predictive biomarkers for immunotherapy, enabling individualized precision treatment; (3) exploration of the optimal treatment modalities for immunotherapy in combination with ADC therapy; (4) investigation into the application scenarios for immune therapy bispecific antibodies; and (5) further development of CAR-T therapy targets and reduction of CAR-T therapy-related toxicities.

We illustrated these views on page fourteen with highlights, **DISCUSSION**, ***Current status and future perspectives.***

5. Can you provide more information about the ongoing clinical trials in the field of gastric cancer immunotherapy? What are the specific interventions and endpoints being studied?

Response: Thank you for your insightful query concerning ongoing clinical trials in the realm of immunotherapy for gastric cancer. We appreciate the

emphasis you place on detailing specific interventions and endpoints in the study. In response to your request, we have reorganized and updated the clinical trial information pertinent to this field, gathered during the compilation of our manuscript. To enhance transparency and provide a comprehensive view, we will include an Excel file as supplementary material that will detail ongoing and recently concluded clinical trials, including: TrialID, Public title, Acronym, Recruitment Status, Condition, Intervention, Phase, Study type, Study design, Target size, Primary outcome, Secondary outcome, Date enrollment.

6. Are there any limitations or challenges in the current research on gastric cancer immunotherapy that need to be addressed? How can these limitations be overcome in future studies?

Response: Currently, there are many limitations and challenges in gastric cancer immunotherapy research that need to be overcome in future studies:

1. Heterogeneity of Gastric Tumors: Gastric cancers are highly heterogeneous, both inter- and intratumorally. This variability affects the response to immunotherapeutic agents and poses challenges for identifying universal targets.

Future Directions: Comprehensive genomic and transcriptomic analyses could identify reliable biomarkers and offer a more individualized treatment approach as breast cancer classification.

2. Lack of Reliable Biomarkers: Current biomarkers like PD-L1 expression, and MSI are not wholly predictive of the treatment response.

Future Directions: The development and validation of new biomarkers or a set of biomarkers are essential for better patient stratification and response prediction.

3. Limited Efficacy in Advanced Stages: Immunotherapies, thus far, have shown limited efficacy in the late stages of gastric cancer.

Future Directions: Combining immunotherapy with other treatment modalities

such as chemotherapy or targeted therapy could potentially synergize to improve outcomes. ADC + immunotherapy.

4. Immune-related Adverse Events: The use of immune checkpoint inhibitors can lead to autoimmunity and other side effects.

Future Directions: Developing methods for early identification and management of adverse events is crucial, or discovering new lower toxic agents.

5. Limited Pre-clinical Models: Lack of clinically relevant animal models (e.g. TIL, ACT, TME/TIME) for gastric cancer hampers the pre-clinical evaluation of immunotherapeutic strategies.

Future Directions: The development of patient-derived xenograft models and organoids could enhance the translational potential of pre-clinical findings.

We illustrated these views on page fourteen with highlights, **DISCUSSION**, ***Current status and future perspectives.***

7. How do the findings of this analysis align with the existing literature and current clinical practice in the field of gastric cancer immunotherapy?

Response: Our findings provide an amalgamated perspective that aligns well with existing literature and ongoing changes in clinical practice, thereby contributing substantively to the body of knowledge in gastric cancer immunotherapy. However, the article has systematically analyzed the ongoing Phase I, II, and III clinical trials, which will require 5-10 years to complete and publish their results. Therefore, the results of this analysis and the future prospects are prospective and challenging to existing clinical practices.

8. Are there any specific recommendations or implications for clinical practice or policy development based on the findings of this analysis?

Response: Our article does not intend to affect existing clinical practices, as it neither performed a meta-analysis on clinical protocols with contentious outcomes nor arrived at decisive conclusions that would modify current protocols.

However, it is imperative to note that the analysis does serve as an important referential guide for future research development in the field of gastric cancer immunotherapy. Through a thorough review of existing Phase I and II clinical trials, our article aims to provide significant heuristic value by laying out the historical, current, and short-term future trends in gastric cancer immunotherapy. This will allow subsequent researchers to systematically grasp the trajectory of this area of study, thus facilitating the quick identification and development of research topics that are both pertinent and timely.

The article serves as a comprehensive repository of key terminology, methodologies, and findings, poised to accelerate both scientific discovery and subsequent therapeutic innovations. Even if the study doesn't directly affect current clinical practices, its capacity to steer future research and inform policy decisions in gastric cancer immunotherapy is notable.

We have elucidated these perspectives in the section titled "DISCUSSION: Current Status and Future Perspectives," where key points are accentuated for emphasis.