What's The Next Era Of Immune Checkpoint Inhibitors Of Renal Cell Carcinoma In Clinical Practice: An Evidence From Extended Bibliometric Analysis

Zhenjie Yin
Affiliated Sanming First Hospital, Fujian Medical University
Lifeng Zhu
Affiliated Sanming First Hospital, Fujian Medical University
Bingyong You
Affiliated Sanming First Hospital, Fujian Medical University
Yingming Sun
Affiliated Sanming First Hospital, Fujian Medical University
Yu Zhao
Affiliated Sanming First Hospital, Fujian Medical University
Yuanyuan Bai
Affiliated Sanming First Hospital, Fujian Medical University
Daoxun Chen
Affiliated Sanming First Hospital, Fujian Medical University
Yongmei Chen
Affiliated Sanming First Hospital, Fujian Medical University
Shangfan Liao
Affiliated Sanming First Hospital, Fujian Medical University
Dongming Lu
Affiliated Sanming First Hospital, Fujian Medical University
Fabiao Zhang
Affiliated Sanming First Hospital, Fujian Medical University
Yongyang Wu (wuyyfj@fjmu.edu.cn)
Affiliated Sanming First Hospital, Fujian Medical University

Research Article

Keywords: Bibliometric analysis, Immune checkpoint inhibitor, Renal cell carcinoma, Clinical practice, Grey data

Posted Date: March 10th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1422181/v1

Abstract

Objectives: To use bibliometric analysis to articles regarding RCC treating by ICIs, extended analysis effect, and safety of enrolled paper to interpret the current situation and future trend of clinical trials.

Methods: We searched in the WoSCC Database on May 30, 2021. Articles were ranked in descending order based on their total citations. Also, we investigated the uncovered trials registered in ClinicalTrials.gov to analyze the trend of the future of ICI treatment.

Results: The top 30 most cited articles were identified and analyzed. The most productive year was 2020, with 12 articles published. The USA and Memorial Sloan Kettering Cancer Center were the most effective country and institutions. The 15 journals contributed to these articles, and the top five keywords were survival, therapy, nivolumab, everolimus, and immunotherapy. The 13 original articles registered on ClinicalTrials.gov: monotherapy was 38.5% and combined therapy was 61.5%. The ORR of monotherapy and combined therapy was 24.05% vs 49.03% (P< 0.001). The mPFS of monotherapy was shorter than combined therapy (4.01 mo vs 14.51 mo, P< 0.001). The incidence of grade 3/4 adverse events in single-agent was significantly lower than combined therapy (19.76% vs 59.38%, P< 0.001). 91 grey data were extracted from ClinicalTrials.gov, which included single-agent (11%) and combination therapy (89%).

Conclusions: Although the side effect is unfavorable, the combined therapy will replace the single-agent ICI treatment in the future clinical trial design. The effect of treatment based on PD-1, PD-L1, and CTLA-4 has almost reached the bottleneck, the scientist should focus on new targets of checkpoints in clinical research.

1 Introduction

Renal cell carcinoma (RCC) is a common malignancy of the urinary system, accounting for 2–3% of adult malignancies [1]. RCC is mainly divided into clear cell RCC, papillary RCC, and chromophobe RCC, which account for around 75%, 20%, and 5%, respectively [2]. In recent years, the incidence and mortality of RCC have been on the rise [3, 4]. Despite the urology technology is well developed, the prognosis of advanced RCC remains unfavorable [5].

Although immune checkpoint inhibitors (ICIs) alter the outcome of advanced RCC, most patients do not get durable clinical benefits from these drugs and eventually progress to remoted metastasis [6]. The enhanced immune response enabled by ICIs would lead to some side effects called immune-related adverse events (irAEs) [7–10]. irAE occurs as a consequence of impaired self-tolerance from loss of T-cell inhibition and it is also an indicator to evaluate whether the patient needs to stop medication [11]. Nowadays, new immune checkpoints represent by lymphocyte activation gene-3, T cell immunoglobulin, and mucin-domain-containing-3 have been gradually discovered and studied [12–14]. A variety of innovative immunotherapies are currently under clinical development for the treatment of patients with RCC. ICIs targeting programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic t lymphocyte antigen 4 (CTLA-4) have been used in the clinic, still, traditional targeted drugs are the main clinical treatment options for RCC [15]. The Food and Drug Administration has approved several treatments that use ICIs alone or in combination [16]. The reason for this is inseparable from the design and progress of clinical trials.

As we know, the citations are not the only evaluation standard to measure the academic quality of the research article, however, it is a reliable index to evaluate the impact of a paper on medical development [17]. Bibliometric analysis, a statistical evaluation of published articles, study the clinical and scientific significance of manuscripts

by developing and applying mathematical models and techniques to communications [18, 19]. Bibliometric analysis has been used in research papers in oncology and urology [20, 21], including surgical therapy [22], immunotherapy [23, 24], signaling pathway studies [25, 26], etc. To date, no study has been undertaken to identify the most influential clinical research papers on the use of ICIs in the field of the RCC.

The purpose of this study was to investigate the 30 most cited clinical trials in the field of the contributions of authors, institutions, journals, and countries immunotherapy by utilizing VOSviewer, CiteSpace, and other tools. Through the comparative analysis and correlation analysis of the publication time of the article, prognostic indicators (such as median overall survival (mOS), median progression-free survival (mPFS) and objective response rate (ORR)), and grade 3/4 adverse events, we seek a breakthrough for the selection of clinical treatment plans and the design of clinical trials in the future. Moreover, we collected and analyzed the results of unpublished clinical studies (grey data) to investigate the trend of ICI therapy.

2 Methods

2.1 Data source and search strategy

Relevant articles were extracted from the Web of Science Core Collection (WoSCC) Database (Clarivate Analysis, Boston, USA) [27]. We searched publications by exploiting keywords "((Immune checkpoint inhibitor) or (Nivolumab) or (Pembrolizumab) or (Avelumab) or (Atezolizumab) or (Durvalumab) or (Ipilimumab) or (Tremelimumab) or (Cemiplimab) or (Immune checkpoint) or (Programmed death 1) or (Programmed death ligand 1) or (PD-1) or (PD-L1) or (CD279) or (CD274) or (B7-H1) or (PDCD1) or (cytotoxic t lymphocyte antigen 4) or (CTLA-4) or (CD152) or (Siglec-15) or (sialic acid binding Ig like lectin 15) or (CD33L3) or (CD33 antigen-like 3) or (LAG3) or (lymphocyte-activation gene 3) or (CD223) or (T cell immunoglobulin and ITIM domain) or (TIGIT) or (WUCAM) or (VSTM3) or (VSIG9) or (TIM-3) or (HAVCR2) or (Recombinant human t cell immunoglobulin and mucin domain-3) or (Hepatitis a virus cellular receptor 2)) and ((renal cell carcinoma) or (kidney cancer) or (renal cancer))" from WoSCC Database on May 30, 2021. No language restrictions were imposed. The time span we selected is all years. By this query, 3276 records were generated. Two researchers (ZJ. Yin and BY. You) screened the abstract independently for qualified papers. The list of top 30 most cited clinical trial articles was extracted to Microsoft Excel 2010. We extracted data including the title, author, institution, journal, year of publication, total citations, and the type of study. Moreover, "Full record and cited references" were downloaded and raw data were transformed into TXT format which allowed for the analysis of bibliometric tools.

On the website of *ClinicalTrials.gov*, we applied "renal cell carcinoma" for "Condition or disease". The keywords used for the search were "PD-1" or "PD-L1" or "CTLA-4" or "Nivolumab" or "Pembrolizumab" or "Avelumab" or "Atezolizumab" or "Durvalumab" or "Ipilimumab" or "Cemiplimab" or "Toripalimab" or "Sintilimab" or "Tremelimumab" for " other terms". As 13 articles already posted the result, we counted 91 pieces of grey data from 104 records.

2.2 Criteria for enrolled researches for these studies

Inclusion criteria: 1. The object of study is RCC patients; 2. The research content involves immune checkpoints and immune checkpoint inhibitors; 3. Document category: the original registered and completed phase II/III/IV clinical trials.

Exclusion criteria: 1. The main body of the research and none of the content does not meet the requirements; 2. Secondary research, cluster analysis research, and non-academic paper type data (such as meeting abstract, editorial material, news item, proceedings paper, book chapter, correction, and other types of data.); 3. Original studies such as case reports, case series, case-control studies, cohort studies, etc.

2.3 Data display

The distribution and contribution of authors, institutes, countries, and research areas of literature were analyzed, which was retrieved from WoSCC Database. The data were analyzed using CiteSpace (Chaomei Chen, Drexel University, USA) and VOSviewer (Ludo Waltman, Leiden University of Centre for Science and Technology Studies, Netherlands) for comprehensive science mapping analysis of extensive bibliographic metadata.

CiteSpace (Version 5.7.R5W 64-bit), a Java-based computer program designed by professor Chen from Drexel University, served as an indicator of the most active area of scientific community research. Several types of bibliometric studies such as co-word analysis, author co-citation analysis, document co-citation analysis, and text and geospatial visualizations are supported by this software. VOSviewer (Version 1.6.16) was utilized for recognizing association among journals, and constructing collaboration networks, which referred to term clustering, countries /institutions/authors, and quotation systems of cited journals [27, 28].

2.4 Statistical analysis

We used Statistical Product and Service Solutions (SPSS) for statistical analysis. Qualitative data were presented as a frequency in percentage. The quantitative data were presented as average or medium and *t*-test or *Mann–Whitney U* test were used to calculate the statistical difference. The *p*-value < 0.05 considered statistical significant.

2.5 Ethical Requirements

Due to the fact that this research did not involve intervention or data collection in animal experiments or clinical trials, approval from an ethical committee was not required.

3 Results

3.1 Citation range

A total of 3267 articles were extracted from WoSCC Database. The top 30 most cited clinical trial articles were listed in Supplementary Table 1. The citation count of articles ranged from five to 3192 (total number of citations, 9005). The article with the largest citation number, 3192 times, was about a treatment of advanced RCC by nivolumab and everolimus published in 2015 [29]. The article with the least citation number, three times, was patient-reported outcomes in a phase 2 study comparing atezolizumab alone or with bevacizumab vs sunitinib in previously untreated metastatic RCC in 2020 [30].

3.2 Year of publication

The top 30 most cited clinical trial articles were published between 2015 and 2021. Data is input in the flow diagram (Figure 1). The number of articles published per year had not exceeded five until 2019, but since then it has increased dramatically. The largest number of clinical trial articles was published in 2020, with a total of 12 articles.

3.3 Distribution and contribution of global countries/regions and institutions

Thirty countries/ regions in total have published researches on clinical trials of immune checkpoints for RCC. It happened that one piece of literature was published by authors from diverse countries. The top ten most productive countries were listed in Supplementary Table 2. It happened that one paper was published by authors from diverse countries/regions. According to the overlay visualization map made by Citespace and VOSviewer, the USA, France, Japan, UK, and Germany had the most intense publication density (Supplementary Figure 1).

A total of 2,75 institutions have published papers. Supplementary Table 3 revealed the top ten institutions with the most publications. Due to the difficulty, every clinical trial is completed by many different institutions from all over the world. The institution with the largest number of papers was led by the Memorial Sloan Kettering Cancer Center of the USA (n=20). It is worth noting that the most represented institutions were associated with the highest countries.

3.4 Analysis of journals of publication

The 30 articles are published in 15 different journals. New England Journal of Medicine contributed the most articles to our list (both n=5), followed by Journal of Clinical Oncology and Lancet Oncology (both n=4). Journals of 30 articles are listed in Supplementary Table 4 with their impact factors.

3.5 Analysis of authors

294 authors participated in the 30 highly cited articles. Motzer RJ, from the USA, had 21 authorships mainly in this field, followed by Rini BI (n=16) and Escudier B (n=15). We have compiled the top ten authors' information, which is attached in Supplementary Table 5. Due to the same research finished by the multiple authors, we used CiteSpace and VOSviewer to analyze co-authorship and citation networks among authors and to reveal the most highly cited researchers and collaboration among researchers (Supplementary Figure 2).

3.6 Analysis of keywords

We have compiled the top ten keywords attached in Table 6. The content of the network analysis of the keywords is listed in Figure 2A. The results show that "survival, therapy, nivolumab, everolimus, immunotherapy " is highly central. The time zone view of the cluster nodes illustrated that the research progress was centered around the above keywords over time (Figure 2B). In Table 8, therapy is the keyword with the highest amount of publications (n =14), followed by survival (n=11) and nivolumab (n=10).

3.7 Comparative analysis of enrolled researches

Among the 30 top most cited clinical trial articles, 13 were original articles registered on ClinicalTrials.gov, ten were follow-up analyses, four were subgroup analyses of clinical trials and three were patient-reported outcomes of previous studies. A detailed list of the 13 registered clinical trial articles can be found in Supplementary Table 7. According to the selection of clinical treatment, the 13 registered clinical trial articles were divided into different research focuses: single-agent (5/13, 38.5%), and combined therapy (8/13, 61.5%). In these 13 articles, nine involved in anti-PD-1 immunotherapy (nivolumab: n=7, pembrolizumab: n=2), four involved in anti-PD-L1 immunotherapy (atezolizumab: n=3, avelumab: n=1), and one involved in the anti-CTLA-4 immunotherapy (ipilimumab: n=1) (Table 1).

Table 1 Clinical information of 13 registered studies.

	Register Number	Drugs	Phase	Drug administration		Evaluation indicator			
				Single-agent	Combined therapy	mOS (mo)	ORR (%)	mPFS (mo)	Grade 3/4 adverse events (%)
1	NCT01668784	Nivolumab	III	√		25.00	25.00	4.60	19.00
2	NCT02231749	Nivolumab + Ipilimumab	III		√	NA	42.00	11.60	46.00
3	NCT02853331	Pembrolizumab + Axitinib	III		√	NA	59.30	15.10	75.80
4	NCT01354431	Nivolumab	II	√		25.50	22.00	4.00	11.00
5	NCT02684006	Avelumab + Axitinib	III		√	13.80	55.20	13.80	71.20
6a	NCT01984242	Atezolizumab + Bevacizumab	II		√	NA	32.00	11.70	63.00
6b	NCT01984242	Atezolizumab	II	√		NA	25.00	6.10	40.00
7	NCT02420821	Atezolizumab + Bevacizumab	III		√	NA	43.00	11.20	40.00
8	NCT03013335	Nivolumab	II	√		NA	NA	2.45	12.50
9	NCT02724878	Atezolizumab + Bevacizumab	II		√	NA	33.00	8.30	33.00
10	NCT03126331	Nivolumab	II	√		NA	29.00	7.97	NA
11	NCT03141177	Nivolumab + Cabozantinib	III		√	NA	55.70	16.60	75.30
12	NCT02348008	Pembrolizumab + Bevacizumab	II		√	NA	60.90	20.70	NA
13	NCT02596035	Nivolumab	IV	√		16.30	13.60	2.20	13.60

Due to the incomplete data of mOS, we did not perform statistical analysis on all the studies. The average ORR of monotherapy and combined therapy was 24.05% vs 49.03% (P< 0.001). The mPFS of monotherapy was shorter than combined therapy (4.01 mo vs 14.51 mo, P< 0.001). The average of grade 3/4 adverse events of single-agent was 19.76%. But the average of grade 3/4 adverse events of combined therapy was 59.38%. The incidence of grade 3/4 adverse events of single-agent was significantly lower than that of combined therapy (P< 0.001).

3.8 Analysis of the grey data

A total of 91 records were extracted from ClinicalTrials.gov (Supplementary Table 8). The phase II trials had the largest number of experiments (n=68), followed by phase III trials (n=21) and phase IV trials (n=2) (Figure 3A). The 91 grey data were divided into different types: single-agent (10/ 91, 10.99%) and combined therapy (81/ 91, 89.01%), including single ICI + target (35/ 91, 38.46%), double ICIs (17/ 91, 18.68%), double ICIs + target (8/ 91, 8.79%), and others (21/ 91, 23.08%) (Figure 3B).

4 Discussion

This is the first bibliometric analysis of clinical trials which are associated with the treatment of RCC by ICIs. In this article, we enrolled only top cited 30 clinical trial articles instead of top 50–100 ones [22, 31], because we restricted a rigorous range of search terms and design scientific and specific inclusion and exclusion criteria. Due to the minority of clinical trials in the treatment of RCC by ICIs, we believed that 30 is the most appropriate and scientific number.

In our analysis, a five citations paper was enrolled, which was published in December 2020. The reason for the low citations may be limited by factors such as publication time and clinical guidelines. For the analysis of authors, institutions, and countries, we discover that experts from many medical research institutions in the USA are the initiators of this type of scientific research, and they are also the main authors of the article. In addition, medical institution collaborators from Europe are also the main force in such clinical research. Also, we found large-scale clinical RCT research articles tend to be published in high-scoring journals, but their follow-up analyses or subgroup analyses published in journals are slightly inferior to the original studies. The main reason may be influenced by the research significance, sample size, and workload, but there is no lack of other external or man-made interference factors. This article also examined the keyword distribution of the most cited articles. Among the top ten keywords listed with the highest frequency, specific drug names account for 50%. Terms related to ICIs are less than those related to traditional non-specific cytokine therapy and targeted therapy, which also reflects targeted drugs still occupy half of the sky in the treatment of advanced RCC. Therefore, we cannot ignore its powerful curative effect.

At present, the FDA has approved many ICIs, including pembrolizumab, nivolumab, avelumab, atezolizumab, durvalumab, cemiplimab, ipilimumab, tremelimumab, etc [32–34]. However, there are only three drugs approved for the treatment of RCC. According to the analysis of the results of Table 3, anti-PD-1 displayed a great effect on the treatment of RCC, and anti-CTLA-4 may be close to a curtain call of clinical research. Keiichiro et al. revealed that patients with metastatic RCC who received anti-PD-1 combination therapy in first-line may obtain more benefits than anti-PD-L1 combination therapy [35]. This still requires researchers to further explore. In recent years, other types of ICIs have gradually entered phase III clinical trials, we also analysis the grey data of clinical trials, and found the anti-PD-L1 treatment was the hotspot of researchers.

In addition, we found combined therapy may replace the single agent in the future. As a result, the median publication time of single immunotherapy is longer than combined therapy. The FDA approved combined therapy for RCC from 2018 to 2019, and the use of nivolumab and pembrolizumab alone is even longer. We believed a single-agent therapy in renal cancer did not show a satisfactory effect in clinical practices. Still, we did not the fine best combination for treating RCC, many grey data will release in 3–5 years and we believe the traditional ICIs do not have a big room to improve. New targets of checkpoints, such as TIM-3, LAG-3, should be more explored.

The augmented immune response enabled by ICIs has led to some irAEs. irAEs occur as a consequence of impaired self-tolerance from loss of T-cell inhibition and it is also an indicator to evaluate whether the patient needs to stop the medication. The incidence of severe toxicities differs depending on the agent administered, the dose, interval, and duration of therapy. The main irAEs include diarrhea, colitis, hepatitis, skin toxicities, and endocrinopathies such as hypophysitis and thyroid dysfunction [36]. It has been reported that grade 3/4 irAEs were more common with CTLA-4 mAbs compared with PD-1 (31% versus 10%) [37]. Ipilimumab, as the first anti-CTLA-4 monoclonal antibody (mAb) entering the clinic, was approved for the treatment of malignant melanoma in 2011 [38] but was not approved for the treatment of RCC in combination with nivolumab until 2018 [39]. Therefore, the drug coming into the market has an inseparable relationship with the occurrence of adverse events. According to our results, seven

were involved in nivolumab, and one focused on ipilimumab in these 13 articles. This result is consistent with the above analysis.

The use of an OS end point is significant in the studies investigating the combination of two or more anti-cancer drugs [40]. Among the indicators for evaluating prognosis, ORR and mPFS are easier to obtain than mOS, because of the difference in follow-up time and the failure of the mOS in some experiments. During the follow-up period, the objective response rate of patients receiving single-agent was 22.09%, and the mPFS was 4.07 months. However, the objective response rate of patients receiving the combination was about 47.64%, and the mPFS was approximately 13.63 months. The combined treatment of ORR and PFS is two and three times more than that of a single-agent. Although the grade 3/4 adverse events of the combined therapy are greater than that of the single-agent, ORR and PFS values have the opposite results. In view of the better prognosis of dual-drug therapy, combined therapy accounted for a larger portion both in clinical treatments or clinical trials. This result is the same as the analysis of the time of publication.

Although the side effect is unfavorable, the combined therapy will replace the single-agent ICI treatment in the future clinical trial design. The effect of treatment based on PD-1, PD-L1, and CTLA-4 has almost reached the bottleneck, the scientist should focus on new targets of checkpoints in clinical research.

Declarations

Author Contributions

YW, YS and ZY designed the study. LZ and BY conducted the literature search and analyzed the data. ZY drafted the manuscript. YB and YZ drew the pictures. SL, DL, and FZ prepared the tables. DC and YC reviewed and revised the manuscript. All authors contributed to the article and approved the submitted version.

Data Availability

Our data are from the analysis of articles and can be provided when necessary.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgement

This work was supported by the "Natural Science Foundation of Fujian Province, China" (No.2019J01590) to Yongyang Wu; "Natural Science Foundation of Fujian Province, China" (No.2019J01588) to Dongming Lu; "Natural Science Foundation of Fujian Province, China" (No.2020J011272) to Fabiao Zhang; "Natural Science Foundation of Fujian Province,China" (No.2020J01126), Health Commission of Fujian Province Young & Middle-Aged Medical Backbone Talents Project (2020GGA077), and the Scientific Fund of Sanming Science and Technology Bureau (N0.2018-5-1(7)) to Yingming Sun which provided funds for our research.

References

1. *Global cancer observatory: cancer today*. International Agency for Research on Cancer. Retrieved March 31 from https://gco.iarc.fr/today

2. Deleuze A, Saout J, Dugay F, et al. Immunotherapy in Renal Cell Carcinoma: The Future Is Now. *Int J Mol Sci*, *21*(7). https://doi.org/10.3390/ijms21072532

3. Wu C, Li M, Meng H, et al. Analysis of status and countermeasures of cancer incidence and mortality in China. *Sci China Life Sci*, *62*(5), 640-647. https://doi.org/10.1007/s11427-018-9461-5

4. Attalla K, Weng S, Voss MH,Hakimi AA. Epidemiology, Risk Assessment, and Biomarkers for Patients with Advanced Renal Cell Carcinoma. *Urol Clin North Am*, *47*(3), 293-303. https://doi.org/10.1016/j.ucl.2020.04.002

5. Barata PC,Rini BI. Treatment of renal cell carcinoma: Current status and future directions. *CA Cancer J Clin*, *67*(6), 507-524. https://doi.org/10.3322/caac.21411

6. Makhov P, Joshi S, Ghatalia P, Kutikov A, Uzzo RG,Kolenko VM. Resistance to Systemic Therapies in Clear Cell Renal Cell Carcinoma: Mechanisms and Management Strategies. *Molecular cancer therapeutics*, *17*(7), 1355-1364. https://doi.org/10.1158/1535-7163.MCT-17-1299

7. Teufel A, Zhan T, Härtel N, Bornschein J, Ebert MP,Schulte N. Management of immune related adverse events induced by immune checkpoint inhibition. *Cancer Lett*, *456*, 80-87. https://doi.org/10.1016/j.canlet.2019.04.018

8. Hamashima R, Uchino J, Morimoto Y, et al. Association of immune checkpoint inhibitors with respiratory infections: A review. *Cancer Treat Rev*, *90*, 102109. https://doi.org/10.1016/j.ctrv.2020.102109

9. Boland P, Heath J,Sandigursky S. Immune checkpoint inhibitors and vasculitis. *Current opinion in rheumatology*, *32*(1), 53-56. https://doi.org/10.1097/BOR.0000000000000672

10. Huang Y-T, Chen Y-P, Lin W-C, Su W-C,Sun Y-T. Immune Checkpoint Inhibitor-Induced Myasthenia Gravis. *Frontiers in neurology*, *11*, 634. https://doi.org/10.3389/fneur.2020.00634

11. Das S,Johnson DB. Immune-related adverse events and anti-tumor efficacy of immune checkpoint inhibitors. *J Immunother Cancer*, *7*(1), 306. https://doi.org/10.1186/s40425-019-0805-8

12. Qin S, Xu L, Yi M, Yu S, Wu K,Luo S. Novel immune checkpoint targets: moving beyond PD-1 and CTLA-4. *Molecular cancer*, *18*(1), 155. https://doi.org/10.1186/s12943-019-1091-2

13. Das M, Zhu C,Kuchroo VK. Tim-3 and its role in regulating anti-tumor immunity. *Immunological reviews*, *276*(1). https://doi.org/10.1111/imr.12520

14. Kumar D,Xu ML. Microenvironment Cell Contribution to Lymphoma Immunity. *Frontiers in Oncology*, *8*, 288. https://doi.org/10.3389/fonc.2018.00288

15. Motzer RJ, Jonasch E, Boyle S, et al. NCCN Guidelines Insights: Kidney Cancer, Version 1.2021. *Journal of the National Comprehensive Cancer Network : JNCCN*, *18*(9), 1160-1170. https://doi.org/10.6004/jnccn.2020.0043

16. Nunes-Xavier CE, Angulo JC, Pulido R,López JI. A Critical Insight into the Clinical Translation of PD-1/PD-L1 Blockade Therapy in Clear Cell Renal Cell Carcinoma. *Current urology reports*, *20*(1), 1. https://doi.org/10.1007/s11934-019-0866-8

17. Molléri JS, Petersen K,Mendes E. Towards understanding the relation between citations and research quality in software engineering studies. *Scientometrics*, *117*(3), 1453-1478. https://doi.org/10.1007/s11192-018-2907-3

18. Choudhri AF, Siddiqui A, Khan NR,Cohen HL. Understanding bibliometric parameters and analysis. *Radiographics : a review publication of the Radiological Society of North America, Inc*, *35*(3), 736-746. https://doi.org/10.1148/rg.2015140036

19. Mingers J,Leydesdorff L. A review of theory and practice in scientometrics [Review]. *European Journal of Operational Research*, *246*(1), 1-19. https://doi.org/10.1016/j.ejor.2015.04.002

20. He L, Fang H, Wang X, et al. The 100 most-cited articles in urological surgery: A bibliometric analysis. *International journal of surgery (London, England)*, *75*, 74-79. https://doi.org/10.1016/j.ijsu.2019.12.030

21. Ma C, Su H,Li H. Global Research Trends on Prostate Diseases and Erectile Dysfunction: A Bibliometric and Visualized Study. *Frontiers in Oncology*, *10*, 627891. https://doi.org/10.3389/fonc.2020.627891

22. Jackson SR,Patel MI. Robotic Surgery Research in Urology: A Bibliometric Analysis of Field and Top 100 Articles. *Journal of endourology*, *33*(5), 389-395. https://doi.org/10.1089/end.2018.0866

23. Gao Y, Shi S, Ma W, et al. Bibliometric analysis of global research on PD-1 and PD-L1 in the field of cancer. *International immunopharmacology*, *72*, 374-384. https://doi.org/10.1016/j.intimp.2019.03.045

24. Lu K, Yu S, Yu M, et al. Bibliometric Analysis of Tumor Immunotherapy Studies. *Medical science monitor : international medical journal of experimental and clinical research*, *24*, 3405-3414. https://doi.org/10.12659/MSM.910724

25. Wu L-Z, Weng Y-Q, Ling Y-X, et al. A Web of Science-based scientometric analysis about mammalian target of rapamycin signaling pathway in kidney disease from 1986 to 2020. *Translational andrology and urology*, *10*(3), 1006-1017. https://doi.org/10.21037/tau-20-1469

26. Fang J, Pan L, Gu Q-X, et al. Scientometric analysis of mTOR signaling pathway in liver disease. *Annals of translational medicine*, *8*(4), 93. https://doi.org/10.21037/atm.2019.12.110

27. Yu Y, Li Y, Zhang Z, et al. A bibliometric analysis using VOSviewer of publications on COVID-19. *Annals of translational medicine*, *8*(13), 816. https://doi.org/10.21037/atm-20-4235

28. van Eck NJ,Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics*, *84*(2), 523-538. https://pubmed.ncbi.nlm.nih.gov/20585380

29. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. *N Engl J Med*, *373*(19), 1803-1813. https://doi.org/10.1056/NEJMoa1510665

30. Pal SK, McDermott DF, Atkins MB, et al. Patient-reported outcomes in a phase 2 study comparing atezolizumab alone or with bevacizumab vs sunitinib in previously untreated metastatic renal cell carcinoma. *BJU Int*, *126*(1), 73-82. https://doi.org/10.1111/bju.15058

31. Ahmad P, Vincent Abbott P, Khursheed Alam M,Ahmed Asif J. A bibliometric analysis of the top 50 most cited articles published in the Dental Traumatology. *Dental traumatology : official publication of International Association for Dental Traumatology*, *36*(2), 89-99. https://doi.org/10.1111/edt.12534

32. Ahmed SR, Petersen E, Patel R,Migden MR. Cemiplimab-rwlc as first and only treatment for advanced cutaneous squamous cell carcinoma. *Expert review of clinical pharmacology*, *12*(10), 947-

951. https://doi.org/10.1080/17512433.2019.1665026

33. Vaddepally RK, Kharel P, Pandey R, Garje R,Chandra AB. Review of Indications of FDA-Approved Immune Checkpoint Inhibitors per NCCN Guidelines with the Level of Evidence. *Cancers (Basel)*, *12*(3). https://doi.org/10.3390/cancers12030738

34. Kaplon H,Reichert JM. Antibodies to watch in 2019. *mAbs*, *11*(2), 219-238. https://doi.org/10.1080/19420862.2018.1556465

35. Mori K, Pradere B, Quhal F, et al. Differences in oncological and toxicity outcomes between programmed cell death-1 and programmed cell death ligand-1 inhibitors in metastatic renal cell carcinoma: A systematic review and meta-analysis. *Cancer Treat Rev*, *99*, 102242. https://doi.org/10.1016/j.ctrv.2021.102242

36. Spain L, Diem S,Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev*, *44*, 51-60. https://doi.org/10.1016/j.ctrv.2016.02.001

37. Khoja L, Day D, Wei-Wu Chen T, Siu LL,Hansen AR. Tumour- and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. *Annals of oncology : official journal of the European Society for Medical Oncology*, *28*(10), 2377-2385. https://doi.org/10.1093/annonc/mdx286

38. Cameron F, Whiteside G,Perry C. Ipilimumab: first global approval. *Drugs*, *71*(8), 1093-1104. https://doi.org/10.2165/11594010-000000000-00000

39. Gao X,McDermott DF. Ipilimumab in combination with nivolumab for the treatment of renal cell carcinoma. *Expert opinion on biological therapy*, *18*(9), 947-957. https://doi.org/10.1080/14712598.2018.1513485

40. Gyawali B,Prasad V. Combining drugs and extending treatment - a PFS end point is not sufficient. *Nature reviews. Clinical oncology*, *14*(9), 521-522. https://doi.org/10.1038/nrclinonc.2017.72

Figures

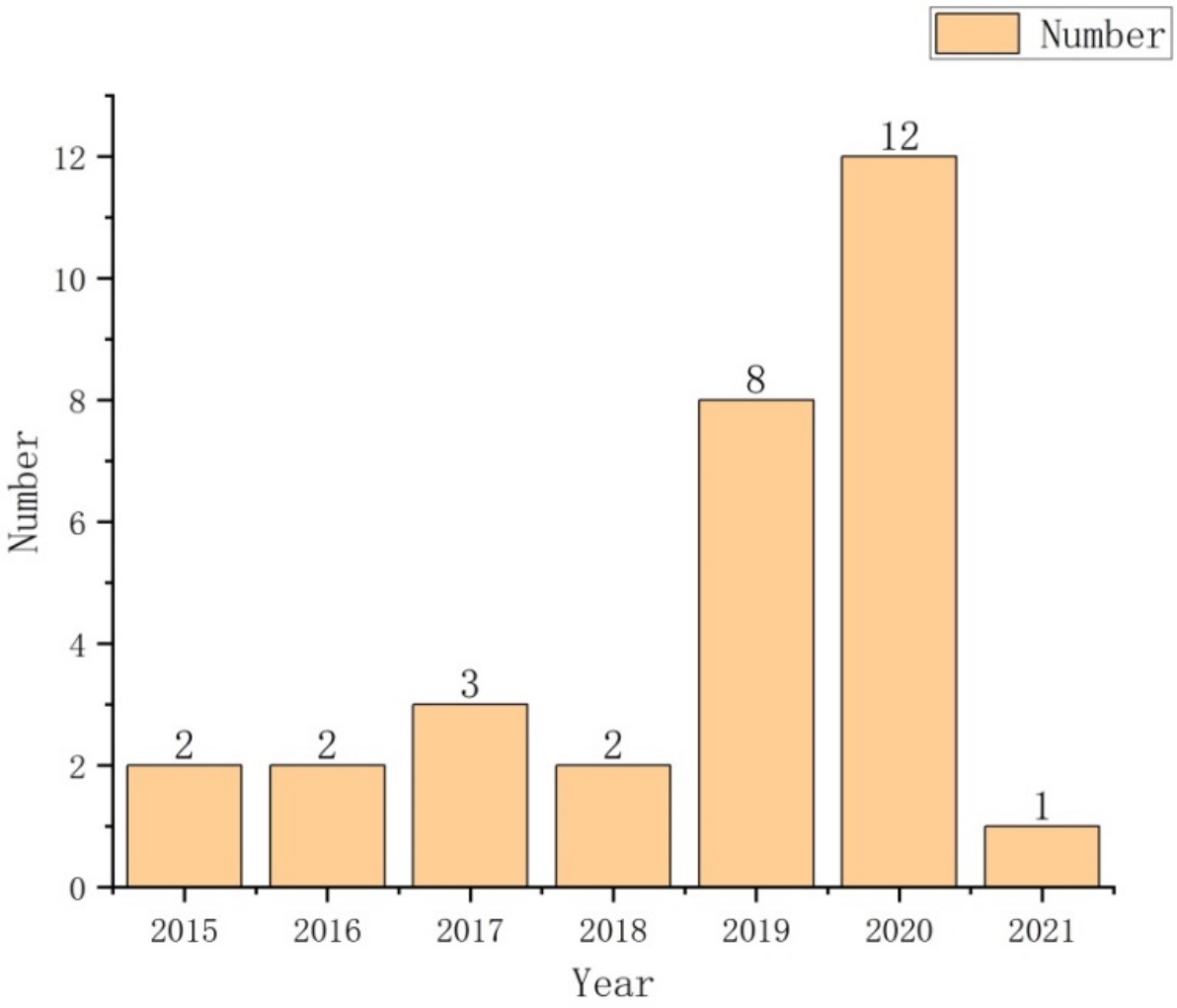

Figure 1

Distribution of top-cited clinical trial articles per year.

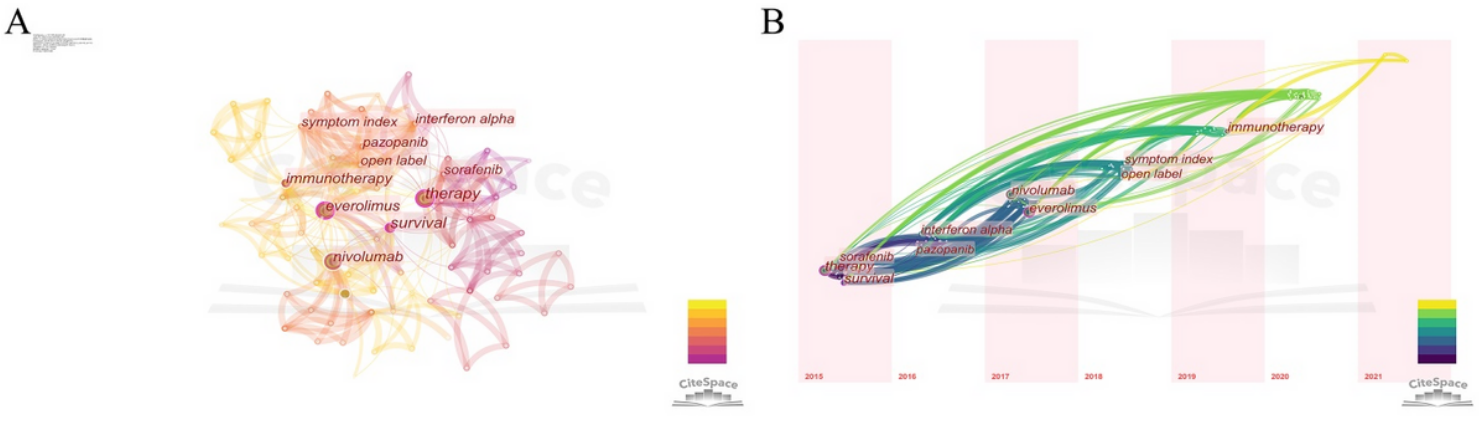

Figure 2

(A) The network visualization of keywords. (B) The visualization of the time zone view of cluster nodes.

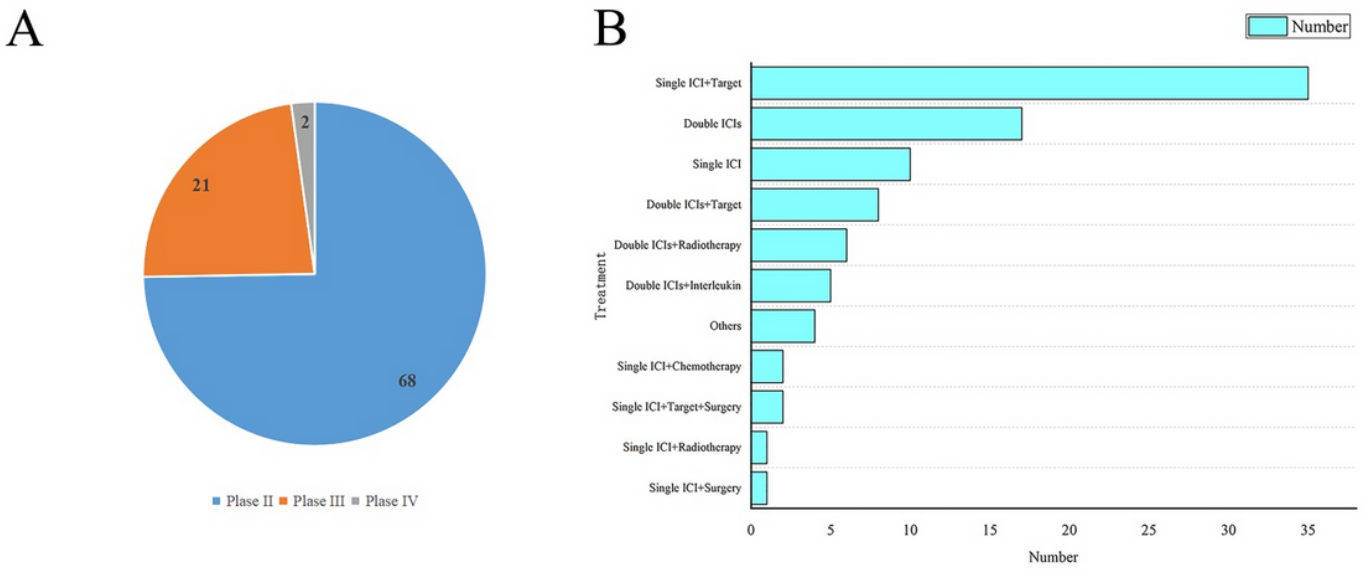

Figure 3

(A) Distribution of Phase II/III/IV trials. (B) Different therapeutic schedules in 91 grey data.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryMaterial.docx