

The Top 100 Most Frequently Cited Publications Concerning Anti-PD-1/PD-L1 Therapy for Lung Cancer: A Bibliometric Analysis

This article was published in the following Dove Press journal:
Cancer Management and Research

Yang Li¹
Moyang Lv²
Jingting Liu³
Jun Ma⁴
Man Liang^{5,*}
Na Zheng^{6,*}

¹Department of Thoracic Surgery, The First Hospital of Jilin University, Changchun, People's Republic of China; ²Grade 2018 Clinical Medicine, Army Medical University, Chongqing, People's Republic of China; ³Grade 2017 Nursing, Shenzhen University Health Science Center, Shenzhen, People's Republic of China; ⁴Department of Radiology, Affiliated Hospital of Beihua University, Jilin, People's Republic of China; ⁵Department of Forensic Science, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, People's Republic of China; ⁶Department of Pathology, Shenzhen University Health Science Center, Shenzhen, People's Republic of China

*These authors contributed equally to this work

Background: Globally lung cancer is one of the most common cancers, and is responsible for almost 20% of all cancer care costs. As a potential treatment for lung cancer, anti-PD-1/PD-L1 therapy has become a novel scientific hotspot in recent decades. The present study aims at exploring the status and trends of the top frequently cited publications about the anti-PD-1/PD-L1 therapy for lung cancer via bibliometric analysis.

Methods: The publications concerning anti-PD-1/PD-L1 therapy for lung cancer were searched on the core collection database of Web of Science, setting the time period for retrieval from 1950 to 2019. The top 100 most frequently cited publications were retrieved, and the bibliometric data were mainly accessed through an open online analysis platform and VOSviewer software.

Results: The cited frequencies about the top 100 cited publications ranged from 218 to 6248. These articles were published in 39 publications, which were mainly ranked in Q1. The top journal in terms of the number of the articles was the *New England Journal of Medicine* (16 articles). The most frequently nominated author was Brahmer, JR from Sidney Kimmel Comprehensive Cancer Center, while the most contributing institution was Memorial Sloan Kettering Cancer. The United States acted as the pioneer in this new field of research and led plentiful of national and international co-operations. Immunotherapy, nivolumab, cell lung-cancer, safety, and docetaxel appeared more frequently as keywords.

Discussions: To sum up, high quality journals, influential authors and institutions and research with high quality evidence were apt to attract more attention and possess more public credibility. Moreover, the bibliometric analysis is yielding up its advantage of identifying and analyzing the characteristics and changes in the intellectual structures of a special topic.

Keywords: anti-PD-1/PD-L1 therapy, bibliometrics, lung cancer, VOSviewer

Introduction

Cancer ranks as the second or even the first cause of premature death in most countries,¹ for instance, lung cancer is persistently the leading cause of cancer death both in males and females. Therefore, as a disease, it contributes substantially to the global burden and health care costs, and is responsible for almost 20% of all cancer care costs.² Many endeavors focus on the prevention, screening, treatment, and palliation to curb the economic burden related to lung cancer.^{1,3} Fortunately, the improvements in treatment and early detection, as well as declines in smoking, have resulted in a continuous decline in the lung cancer death rate in recent decades.⁴

Correspondence: Man Liang
Department of Forensic Science, Tongji Medical College, Huazhong University of Science & Technology, Wuhan, People's Republic of China
Email liangman@hust.edu.cn

Na Zheng
Department of Pathology, Shenzhen University Health Science Center, Shenzhen, People's Republic of China
Email 19629194@qq.com

Important advancements in the treatment of lung cancer have been achieved over the past two decades, increasing the understanding of the mechanisms of tumor progression, or tumor escape.

Immunotherapies of lung cancer, which are developed mainly based on the mechanisms of tumor escape, manipulate the immune system to reactivate the antitumor immune response and to overcome the pathways leading to escape. Multiple mechanisms have been described to account for the evolution of this escape, the most attractive one is up-regulating the expression of immune checkpoint proteins.⁵ Programmed cell death protein 1 (PD-1, or B7-H1) is a co-stimulation receptor expressed by activated T cells, and binds to its ligand programmed death ligand 1 (PD-L1) leading to a transient or permanent inhibition of CD8+ T cells cytotoxic properties. PD-L1 protein expressions and tumor mutational burden have emerged as the most well-validated biomarkers in amount of lung cancer patients. Therefore, as a significant part of immune checkpoint inhibitors therapy, anti-PD-1/PD-L1 therapy, can help the immune system fight cancer. Over the past few decades, anti-PD-1/PD-L1 therapy has developed targeting cancer at a striking rate. Continued research into novel first-line and second-line drugs and combination therapies have expanded the clinical benefit to a broader population and improved outcomes in non small cell lung cancer (NSCLC).⁶ Even though, significant overall survival benefits with the addition of PD-L1 antibody to standard chemotherapy have been shown in the treatment of extensive stage small cell lung cancer (SCLC), the overall benefit of immunotherapy in SCLC remains somewhat disappointing in comparison with the results seen in NSCLC.⁷ Currently, there are several PD-1/PD-L1 blocking agents available in clinics, and immunotherapy-based regimen alone or in combination with chemotherapy is now the preferred option, including nivolumab, pembrolizumab, and atezolizumab.⁸ Evidence shows that the use of immunotherapy has led to unprecedented survival benefits especially compared to treatment with chemotherapy alone in selected patients. The breakthroughs in immunotherapy have greatly benefited a subset of lung cancer patients, not only the NSCLC, but also the extensive-stage SCLC,⁹ and the most important is that they are bringing forth a paradigm shift in the drugs approved for cancer treatment¹⁰ Antibody-drug conjugate therapy, another anti-PD-1/PD-L1 therapy, has been widely concerned. Antitumor activity of lung cancer has been accomplished by conjugating antibodies with different effector molecules that accomplish cell death after antibody binding and internalisation. As an effective anti-PD-1/PD-L1 therapy, growing clinical application highlights

the importance of the recognition and management of its unique toxicity profile in lung cancer patients. Involving the dermatologic toxicity, gastrointestinal toxicity, endocrine toxicity, pneumonitis, and rheumatologic toxicity, the adverse effects of anti-PD-1/PD-L1 therapy of lung cancer have been recognized recently.⁵

Anti-PD-1/PD-L1 therapy is important in treating lung cancer, but there is no bibliometric analysis on researches in this field. The purpose of our study is to use bibliometric methods to analyze the top 100 most cited articles on anti-PD-1/PD-L1 therapy for lung cancer, hoping to have a better understanding of current status and trend of those researches via analyzing their characteristics, and to summarize the reasons of high citation.

Materials and Methods

Data Sources

Publications concerning anti-PD-1/PD-L1 therapy for lung cancer were retrieved from the Core Collection Database of the Science Citation Index in Web of Science of from 1950 to 2019 (updated to March 3, 2020). The search strategy was that combined the terms related to “lung cancer” and “anti-PD-1/PD-L1,” shown in the [Supplementary Table S1](#). The inclusion criteria were as follows: (a) publications were written in English; (b) the types of publications were original articles and reviews. Retrieved publications were arranged in descending order according to the cited frequencies, and the top 100 most cited publications were finally pooled. Two independent reviewers separately evaluated the retrieved scientific works to identify those that were concerned with anti-PD-1/PD-L1 therapy for lung cancer. If there were different opinions, a third reviewer would be consulted, and consensus was finally achieved through discussion.

Data Extraction

The top 100 most frequently cited articles were retrieved, and the following information was extracted: the authors, the affiliations of the first authors and the corresponding authors, countries, the years of publication, the cited frequencies, article title, article types, journals, key words, and impact factor of the journals (2018 edition of Journal Citation Reports).

Statistical Analysis

The data were imported in Microsoft Excel 2007 software to descriptive statistical analyse, including those on publication year, authors, the affiliations, countries, journals, cited frequencies, etc. Apart from the Excel software, the

bibliometric analysis were performed based on the online platform (<https://bibliometric.com>) and VOSviewer 1.6.14, which were applied to construct the bibliographic coupling network based on key words and co-authorship relations, so as to implement network visualization analysis.

Results

Characteristics of Included Studies

A total of 4,976 publications were retrieved from the Core Collection Database of Web of Science concerning to anti-PD-1/PD-L1 therapy for lung cancer, and the flow diagram for screening was shown in Figure 1. All of the 100 most frequently cited publications were published between 2002 and 2018, from 0 to 27 articles each year, and 86% were published between 2014 and 2018. Of the publications, 81 were articles and 19 were reviews. These scientific works were published by researchers from 10 countries, and most were from the United States, France, Germany, Spain,

and Italy (Figure 2). They were published in 39 journals, and the impact factors ranged from 2.776 to 70.67 based on the 2018 edition of Journal Citation Reports, and the basic information of the journals is shown in Table 1. The average and median cited frequencies, range of citation number, and interquartile range of the 100 articles were 736, 368.5, 218 to 6248, and 268.5, respectively. The information of these scientific works was listed in Supplementary Table S2.

The Top 10 Authors

Among the 100 publications, the researcher who published most articles was Brahmer JR from Sidney Kimmel Comprehensive Cancer Center, USA, reaching a total of 11 publications, while the second author Pardoll DM came from the same institution (Table 2). Among the top 10 authors, all of them were from United States. Moreover, only three authors, Hellmann MD, Wolchok JD, and Rizvi NA, contributed to the research “Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer,”¹¹ while another seven authors all contributed to the most frequently cited research “Safety, activity, and immune correlates of Anti-PD-a antibody in cancer.”¹² All the authors had the H-index of at least 45, which meant that at most 45 of all one’s papers were cited at least 45 times. It is a certain that an higher h-index means the greater effect of publications.

The Top 10 Institutions

Memorial Sloan Kettering Cancer Center (Mem Sloan Kettering Canc Ctr) contributed to 45% of the top 100 cited articles, followed by The University of Texas MD Anderson Cancer Center (Univ Texas MD Anderson Can Ctr, 29%), and Johns Hopkins University (Johns

Study flow diagram

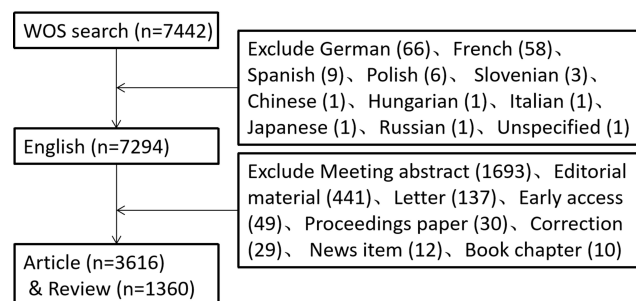


Figure 1 The study flow diagram for screening.

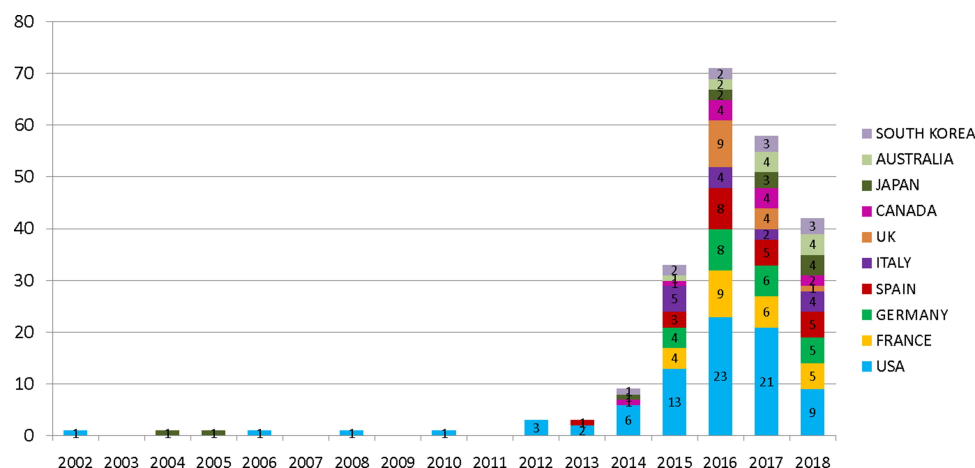


Figure 2 The no. of publications of different countries.

Table 1 Journals Publishing the Top 100 Most Frequently Cited Articles

Journal	No. of Articles	Quartile in Category	Impact Factor	H Index	Citation Count	Country
<i>New England Journal of Medicine</i>	16	Q1	70.67	933	11,466	United States
<i>Lancet Oncology</i>	9	Q1	35.386	274	6032	United States
<i>Journal of Clinical Oncology</i>	8	Q1	28.245	494	2564	United States
<i>Clinical Cancer Research</i>	8	Q1	8.911	292	3643	United States
<i>Annals of Oncology</i>	6	Q1	14.196	210	1790	England
<i>Lancet</i>	5	Q1	59.102	700	2890	England
<i>Science</i>	5	Q1	41.037	1058	2261	United States
<i>Nature</i>	3	Q1	43.07	1096	2921	England
<i>Journal of Thoracic Oncology</i>	3	Q1	12.46	113	955	United States
<i>Cell</i>	2	Q1	36.216	705	673	United States
<i>Nature Reviews Clinical Oncology</i>	2	Q1	34.106	127	445	England
<i>Cancer Discovery</i>	2	Q1	26.37	119	1627	United States
<i>JAMA Oncology</i>	2	Q1	22.416	61	540	United States
<i>Nature Communications</i>	2	Q1	11.878	248	1044	England
<i>European Journal of Cancer</i>	2	Q1	6.68	193	831	England
<i>Molecular Cancer Therapeutics</i>	2	Q1	4.856	157	983	United States
<i>Nature Reviews Cancer</i>	1	Q1	51.848	396	713	England
<i>Nature Reviews Immunology</i>	1	Q1	44.019	351	875	England
<i>Nature Medicine</i>	1	Q1	30.641	497	2541	England
<i>Cancer Cell</i>	1	Q1	23.916	295	433	United States
<i>Immunity</i>	1	Q1	21.522	355	263	United States
<i>Science Translational Medicine</i>	1	Q1	17.161	168	628	United States
<i>Blood</i>	1	Q1	16.562	462	303	United States
<i>Journal of Clinical Investigation</i>	1	Q1	12.282	447	404	United States
<i>Trends in Molecular Medicine</i>	1	Q1	11.028	160	220	England
<i>Journal for Immunotherapy of Cancer</i>	1	Q1	8.676	36	282	United States
<i>Cancer Treatment Reviews</i>	1	Q1	8.332	116	305	England
<i>Journal of the National Comprehensive Cancer Network</i>	1	Q1	7.57	88	398	United States
<i>British Journal of Cancer</i>	1	Q1	5.416	212	303	England
<i>Cancer Epidemiology Biomarkers & Prevention</i>	1	Q1	5.057	177	218	United States
<i>Lung Cancer</i>	1	Q1	4.599	114	220	Netherlands
<i>International Immunology</i>	1	Q1	4.168	124	237	England
<i>Frontiers in Pharmacology</i>	1	Q1	3.845	62	277	Switzerland
<i>Neoplasia</i>	1	Q2	3.836	115	371	United States
<i>Laboratory Investigation</i>	1	Q1	3.684	140	477	United States
<i>Medical Oncology</i>	1	Q1	3.252	64	352	United States
<i>American Journal of Clinical Oncology-cancer Clinical Trials</i>	1	Q2	3.015	72	436	United States
<i>Clinical Therapeutics</i>	1	Q2	2.935	123	228	United States
<i>PLOS One</i>	1	Q1	2.776	268	252	United States

Hopkins Univ, 26%) (Table 3). As shown in Figure 3, the cooperation among 28 institutions presented visually. In consociation with Mem Sloan Kettering Canc Ctr, the network about institutions showed that there were 27 institutions, which were Weill Cornell Med Coll, Columbia Univ, Univ Sydney, INSERM, Genetech Inc, Univ Calif Los Angeles, Mayo Clin, Harvard Univ,

Johns Hopkins Univ, Yale Univ, Massachusetts Gen Hosp, Beth Israel Deaconess Med, Sidney Kimmel Comprehens Canc, Univ Michigan, Dana Farber Canc Inst, Bristol Myers Squibb Co, Vanderbilt Univ, Yale Canc Ctr, Univ Chicago, Merck&Co Inc, Univ Washington, Bristol Myers Squibb, Univ Texas MD Anderson Canc Ct, Fox Chase Canc Ctr, Duke Univ,

Table 2 Top 10 Authors Who Most Frequently Contributed to the Articles

Rank	Author	No. of Articles	As First Author	As Corresponding Author	H Index	Affiliation
1	Brahmer, JR	11	2	2	69	Sidney Kimmel Comprehensive Cancer Center
2	Pardoll, DM	10	0	1	126	Sidney Kimmel Comprehensive Cancer Center
3	Hellmann, MD	10	2	4	56	Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine College
4	Chen, LP	9	0	1	52	Yale Cancer Center & Yale University
5	Wolchok, JD	9	0	1	114	Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine College
6	Horn, L	8	0	0	45	Vanderbilt University
7	Topalian, SL	8	3	4	83	Sidney Kimmel Comprehensive Cancer Center and Johns Hopkins University
8	Antonia, SJ	8	3	2	57	University of Florida
9	Rizvi, NA	7	2	2	55	Memorial Sloan Kettering Cancer Center and Weill Cornell Medicine College
10	Taube, JM	7	1	1	46	Sidney Kimmel Comprehensive Cancer Center

Ohio State Univ, Emory Univ. Moreover, three items were organized by cooperation, represented as different colors, red, green, and blue. Just as shown in the blue item, Mem Sloan Kettering Canc Ctr and Weill Cornell Med Coll were in the same item. Meanwhile, in the red item, Yale Can Ctr and Yale Univ were within their own

item. This suggested that different functional departments referred to the same institution.

Researcher Coauthored Network Visualization

To analyze the coauthorship network based on the information of the authors, setting the minimum number of coauthors at 2, and then, 85 authors meet the thresholds of the total 843 authors. In network visualization shown in [Figure 4](#), each circle and label represented an author, and the size of circles represented the frequency of occurrence. The larger the circle was, the more frequently the circle-represented body appeared. As shown, the circles representing brahmer, jr., pardoll, dm., hellmann, md., chen, l., wolchok, jd., etc., mainly the same as [Table 2](#) shown were larger than others, which indicated that they contributed to more collaborating articles. And then, the more relevant the authors were, the closer the circles were located,¹³ such as chen, l and sznol, mario. Lines linking two circles indicated that the two authors had appeared in the same publication. Therefore, connection lines derived from the former five authors were denser and thicker, indicating their closer relationship. Seven items were developed, which were mainly due to their contributions to the same publication.

Table 3 The Top 10 Institutions Contributing to the 100 Most Frequently Cited Articles

Institutions	Countries	No. of Publications
Mem Sloan Kettering Canc Ctr	United States	37
Univ Texas MD Anderson Can Ctr	United States	26
Johns Hopkins Univ	United States	20
Dana Farber Canc Inst	United States	19
Yale Univ	United States	15
Univ Paris Saclay	France	15
Massachusetts Gen Hosp	United States	14
Bristol Myers Squibb Co	United States	13
INSERM	France	13
Mayo Clin	United States	10

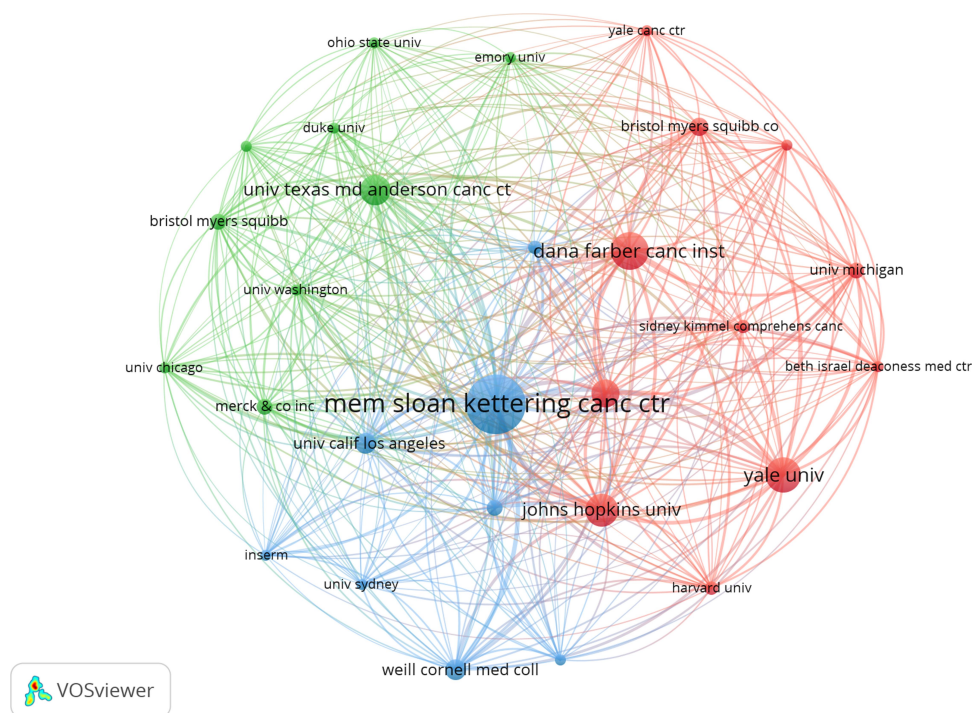


Figure 3 Institutions co-operation network visualization of the 100 most cited publications.

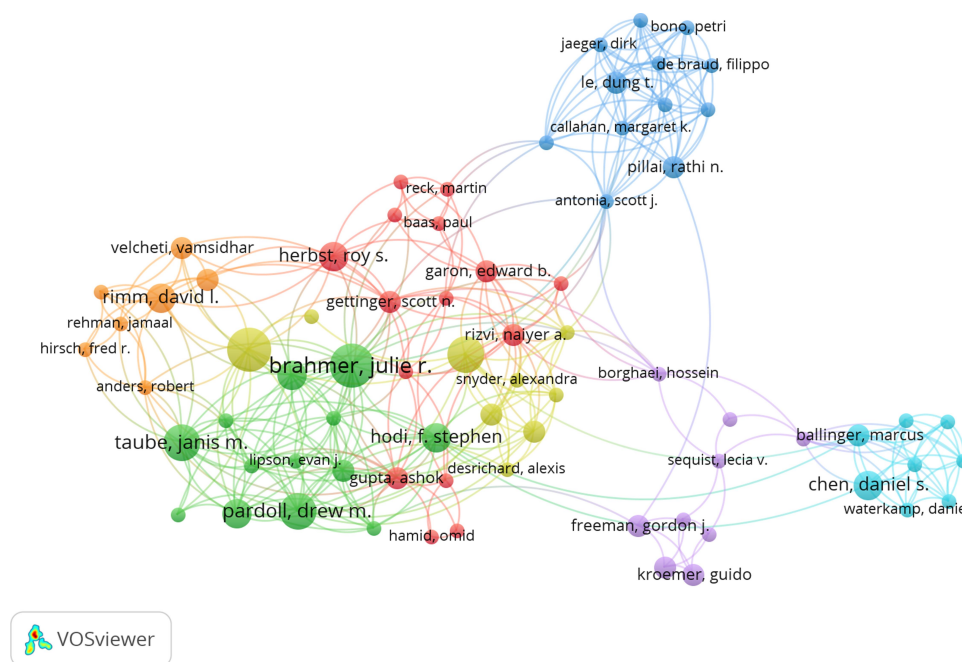


Figure 4 Authors coauthorship network visualization of the 100 most frequently cited publications.

Keyword Co-Occurrence Network Visualization

VOSviewer software was also used to draw the network of keywords co-occurrence, setting the minimum number of occurrences at 10. As shown in [Figure 5](#), for the circles, larger

circles representing keywords such as immunotherapy, nivolumab, cell lung-cancer, safety, and docetaxel, indicated that these keywords appeared more frequently. Immunotherapy, the origin of the anti-PD-1/PD-L1 therapy, has been extensively studied, and linked to 42 (87.5%) keywords.

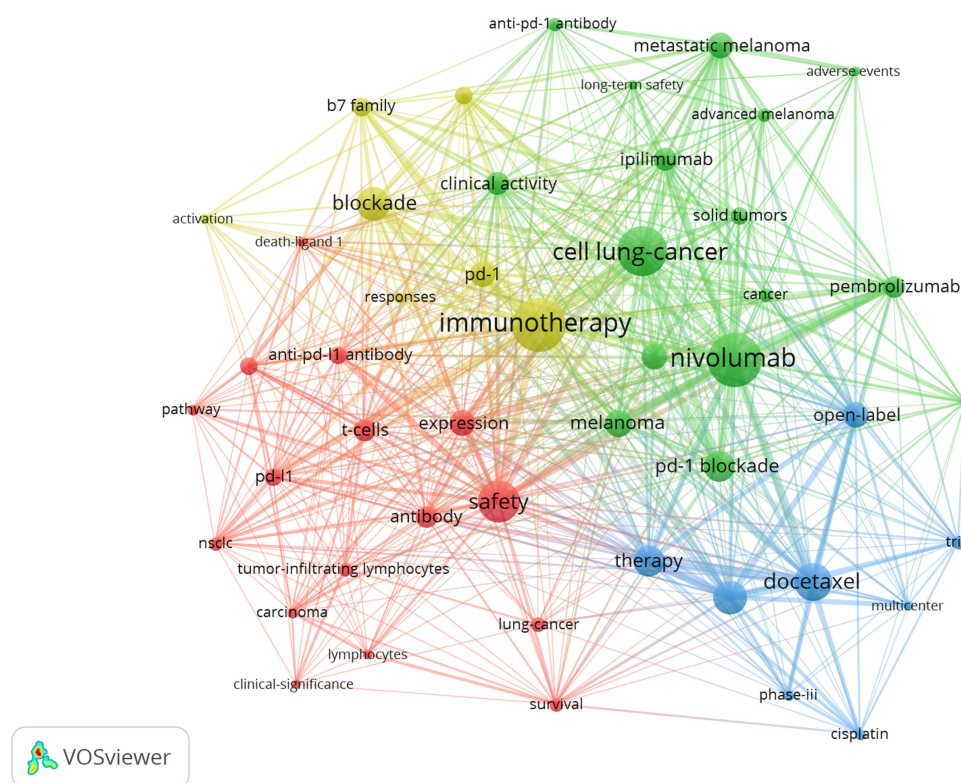


Figure 5 Keywords co-occurrence network visualization of the 100 most frequently cited publications.

In network visualization, circles adopting various colors in graph represented different clusters. Four clusters were separated based on their association. In cluster 1, which was colored red, most of them were associated with the expression of PD-1, PD-L1 in lymphocytes, tumor-infiltrating lymphocytes, or T-cells of the patients with lung cancer, and the survival and safety of the treatment. In cluster 2, which was colored green, a portion of them were associated with the specific PD-1 blockade, such as pembrolizumab, and another drug nivolumab in combination with ipilimumab, while others were mainly associated with the specific patient, such as patients with solid tumors, cell lung cancer, melanoma, advanced melanoma, metastatic melanoma, and untreated melanoma. In cluster 3, which was colored blue, a portion of them were associated with the levels of the trials, such as multicenter, and phase-iii, while others were mainly associated with the specific second-line chemotherapy drugs, such as docetaxel, and cisplatin. In cluster 4, which was colored yellow, most of them were associated with the biological effect of immunotherapy, such as activation, antitumor immunity, and responses.

Discussion

Bibliometric analysis or bibliometric methods, which originating from the field of library and information and motivating by the fast development of computers and the Internet, are now firmly established as scientific specialties and act as an integral part of research evaluation methodology especially within the scientific and applied fields.^{14,15} The methods are used increasingly in analyzing various aspects of science. In the present study, the top 100 most frequently cited publications in the field of anti-PD-1/PD-L1 therapy for lung cancer were retrieved to perform a bibliometric analysis.

Since the first article published in 2002, it had been cited for 2541 times, which provided implications for the design of T cell-based cancer immunotherapy mediated by one or more receptors other than PD-1.¹⁶ The study concerning the anti-PD-1/PD-L1 therapy for lung cancer was still an emerging approach, which manifested as a large amount of scientific works and had attracted more attention in recent years. Among the top 100 cited articles, albeit the totally cited times ranged from 218 to 6,248, it was different sorting by the cited frequencies per year. In total, 33% of the publications were cited less than 100

times per year, while 8% were cited less than 50 times per year. In 2019, a clinical research was cited for 138 times, which was more than 100 times per year,¹² followed by a review and two articles cited 89, 80, and 50 times, which were cited no less than 50 times per year.^{17–19} The comparison suggested that the index cited times per year might be more precise to assess the academic influence of the publications. No matter what, the frequently cited publications, including the articles in 2019, which had higher levels of evidence, were more apt to be cited. Most of the articles about clinical research included randomized, large scale samples, and especially registered at clinical trials.gov.^{17,19,20}

Among the 39 journals, except for three journals rating at Q2, *Neoplasia*, *American Journal of Clinical Oncology-Cancer Clinical Trials*, and *ClinicalTherapeutics*, other journals were all rating at Q1. More than half of the articles were published in seven journals, including *New England Journal of Medicine*, *Lancet Oncology*, *Journal of Clinical Oncology*, *Clinical Cancer Research*, *Annals of Oncology*, *Lancet*, and *Science*. Three of them were comprehensive journals, while other four focused on the research of oncology. The *New England Journal of Medicine*, which published most articles (16%) and possessed the highest impact factor in the present study, had published the top three cited articles,^{12,21,22} with the total citation reaching 13,835 times. For the three articles, they were associated with the safety, activity of anti-PD1 antibody in the patients with NSCLC, which suggested that the clinical outcome might be more attractive than the preclinical research about the mechanism of the PD-1 and PD-L1 checkpoint signaling inhibition. For the journals, all of them are peer-reviewed journals, and the publications are only possible because the articles are high quality, including novel or at least prospective design, use of standardised definitions.²³ Apart from the above predefined criteria, the sample size and type of patient population also matter. Setting an example, research about the treatment of glioblastoma published in *New England Journal of Medicine*, which was cited more than 10,000 times, included a total of 573 patients from 85 centers.²⁴

According to the data of GLOBOCAN 2018, the highest incidence rates among men are observed in Micronesia/Polynesia, in Eastern Asia (rates are more than 40 per 100,000 in China, Japan, and the Republic of Korea), and in much of Europe, especially in Eastern Europe.¹ The incidence rate of lung cancer in Europe were much

more than that in America. Nonetheless, most of the articles were from United States of America, European countries, and some developing Asian countries. The most significant reason is that the United States and Europe are pioneers in cancer immunotherapy. The first related article was published by an institution in the USA about the development a novel treatment paradigm. Moreover, the best-known pharmaceutical factory, Bristol-Myers Squibb, as the producer of the anti-PD-1/PD-L1 agent Nivolumab (OPDIVO®) is located in the USA. Another reason is that Nivolumab (OPDIVO®) was approved by the FDA earlier than in other countries.

The statistics about the authors and the institutions suggested that the United States was the major country contributing to the studies in the field of immunotherapy for lung cancer. The top 10 authors carried influence in the academic world, presented as their higher H-index. They were all did their research at institutions in the USA, while four of them work in Sidney Kimmel Comprehensive Cancer Center, and three in Memorial Sloan Kettering Cancer Center & Weill Cornell Medicine College. In addition, the top 10 institutions showed that 80% of them were located in USA, while the rest of them were in France. In network visualization of the institutions, the most important institution was Memorial Sloan Kettering Cancer Center, which co-operated with more than 25 native institutions, and two foreign institutions, INSERM, and Univ Paris Saclay. The cooperation among different institutions or different departments might be beneficial to data collection and to decrease the racial differences in the studies.^{24,25} More than that, the studies with big scale samples cooperated with multiple centers, another reason was that some authors were employed by different institutions.

In the coauthored network, outstanding researchers in this field were relatively concentrated, moreover, less of them had published more articles. Researchers such as Brahmer JR, Pardoll DM, and Taube JM from Sidney Kimmel Comprehensive Cancer Center had published more articles and they were in close contact with each other in the field. The reason may be that the chance of working together among them is much more than that of others due to they work in the same situation, which is beneficial to discuss the research designing, samples collecting, etc. The reason of close contact for other authors is probably due to multi-center research, even some international cooperations.²²

In the visualization of co-occurrence based on all keywords, the top 100 highly cited articles covered various aspects of anti-PD-1/PD-L1 therapy for lung cancer, such as the drugs used as immunotherapy, chemotherapy, and cell lung-cancer, for example, nivolumab, docetaxel,^{22,26} another crucial topic in the clinical research, therapy, blockade, safety, and clinical activity,¹² and expression, blockage, b7 family, and CTLA-4 blockade, which concerned in the type of anti-PD1/PD-L1 and other immune checkpoint blockade inhibitors.²⁷ In recent years, a variety of immunotherapies have been approved for clinical lung cancer, especially in NSCLC treatment.

In network visualization, the links between different keywords were also analyzed. The origin of the present study was to explore the acknowledge of immunotherapy for lung cancer, 42 keywords (87.5%) linked to immunotherapy. Based on the total link strength, the linking between immunotherapy and nivolumab, cell lung-cancer, safety, chemotherapy, docetaxol, blockage, b7 family, pd-1, pd-L1, expression, were ranked in sequence. Just as shown, the most important drugs as anti-PD1/PD-L1 treatment for cell lung-cancer were nivolumab and docetaxol. Nivolumab (OPDIVO[®], Bristol-Myers Squibb), as PD-1 inhibitors, has been approved by the FDA and EMA as second-line therapy in metastatic NSCLC irrespectively of PD-L1 expression. The biological efficacy of Nivolumab on treatment for NSCLC was evident, however, development of immune-related adverse events was associated with survival outcomes of nivolumab treatment in patients with advanced or recurrent NSCLC, and then early recognition and proper management of immune-related adverse events are important to maximize the therapeutic benefit of immune-checkpoint inhibitors in patients with NSCLC.²⁸ Another strategy to improve the efficacy of Nivolumab monotherapy in lung cancer is to combine it with ipilimumab, both in SCLC and NSCLC.^{29,30} Among patients with advanced NSCLC, the response rate was better with nivolumab plus ipilimumab than with nivolumab monotherapy, more than that, the first-line treatment with nivolumab plus ipilimumab resulted in a longer duration of overall survival than did chemotherapy in patients with late stage or recurrent NSCLC. The microtubule inhibitor, docetaxol (Taxotere[®], Sanofi) was evaluated as second-line treatment for NSCLC. Considering that the checkpoint inhibitors in combination with chemotherapy are going to become the standard-of-care for first-line therapy, the combination of antiangiogenic drugs, such as nintedanib or ramucirumab, plus docetaxel, may become

the new options for second-line therapy of nonsquamous NSCLC patients.³¹ Docetaxel plus ramucirumab was associated with a significant improvement in overall survival and progression-free survival, relative to docetaxel, regardless of patient type. In other words, the efficacy of combined therapy of Docetaxel plus Ramucirumab showed irrespective of PD-L1 expression in NSCLC patients.³² While Docetaxel plus nintedanib showed similar efficacy to docetaxel plus ramucirumab in the nonsquamous populations.³³

The management of lung cancer, especially NSCLC, has shifted dramatically in recent decades with an increase in the understanding of the biological characteristics and with the development of precision medicine. Different immune checkpoint inhibitors: anti PD-1 (nivolumab and pembrolizumab) and PD-L1 (atezolizumab, durvalumab, and avelumab) medications were used in the patients with advanced lung cancer. Amount of data on the combinations of PD-1/PD-L1 inhibitors with other therapies, such as immunotherapy, targeted therapy and chemotherapy, have been addressed, involving in the toxicity profile, and the efficacy of these agents. Immunotherapy has definitely altered the paradigm on the treatment of lung cancer, and the future is promising for the benefit of patients.

In general, the top 100 most frequently cited articles on anti-PD-1/PD-L1 therapy for lung cancer were analyzed via bibliometrics combined with network visualization analysis, which yielding up the advantage of identifying and analyzing the characteristics and changes in the intellectual structures of a special topic. Most of the scientific works were published after the year 2000 on top journals, such as the *New England Journal of Medicine*. The United States acted as the pioneer and kept its leadership in this new field of research. The most important key words, such as immunotherapy, nivolumab, cell lung-cancer, safety, and docetaxel, were stressed. To sum up, the most important reason for the frequent citation of the publications might include the high quality journals, research with high quality evidence, and influential authors and institutions. Most importantly, this topic has attracted much more attention globally in recent years, suggesting that numerous studies on anti-PD-1/PD-L1 therapy for lung cancer may arise in the future.

Disclosure

The authors report no conflicts of interest for this work.

References

- Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018;68(6):394–424. doi:10.3322/caac.21492
- Goodwin PJ, Shepherd FA. Economic issues in lung cancer: a review. *J Clin Oncol*. 1998;16(12):3900–3912. doi:10.1200/JCO.1998.16.12.3900
- Urman A, Hosgood HD. Curbing the burden of lung cancer. *Front Med*. 2016;10(2):228–232. doi:10.1007/s11684-016-0447-x
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin*. 2020;70(1):7–30. doi:10.3322/caac.21590
- Kennedy LB, Salama AKS A. A review of cancer immunotherapy toxicity. *CA Cancer J Clin*. 2020;70(2):86–104. doi:10.3322/caac.21596
- Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. *Nature*. 2018;553(7689):446–454. doi:10.1038/nature25183
- Ragavan M, Das M. Systemic Therapy of Extensive Stage Small Cell Lung Cancer in the Era of Immunotherapy. *Curr Treat Options Oncol*. 2020;21(8):64–77. doi:10.1007/s11864-020-00762-8
- Lim SM, Hong MH, Kim HR. Immunotherapy for Non-small Cell Lung Cancer: current Landscape and Future Perspectives. *Immune Neww*. 2020;20(1):e10. doi:10.4110/in.2020.20.e10
- Horn L, Mansfield AS, Szczesna A, et al. First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer. *N Engl J Med*. 2018;379(23):2220–2229. doi:10.1056/NEJMoa1809064
- Saab S, Zalzal H, Rahal Z, et al. Insights Into Lung Cancer Immune-Based Biology, Prevention, and Treatment. *Front Immunol*. 2020;11:159. doi:10.3389/fimmu.2020.00159
- Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science*. 2015;348(6230):124–128. doi:10.1126/science.aal1348
- Topalian SL, Hodi FS, Brahmer JR, et al. Safety, Activity, and Immune Correlates of Anti-PD-1 Antibody in Cancer. *N Engl J Med*. 2012;366(26):2443–2454. doi:10.1056/NEJMoa1200690
- van Eck NJ, Waltman L. Software survey: vOSviewer, a computer program for bibliometric mapping. *Scientometrics*. 2010;84(2):523–538. doi:10.1007/s11192-009-0146-3
- Bar-Ilan J. Informetrics at the beginning of the 21st century—a review. *J Informetr*. 2008;2(1):1–52. doi:10.1016/j.joi.2007.11.001
- Ellegaard O, Wallin JA. The bibliometric analysis of scholarly production: how great is the impact? *Scientometrics*. 2015;105(3):1809–1831. doi:10.1007/s11192-015-1645-z
- Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: A potential mechanism of immune evasion. *Nat Med*. 2002;8(8):793–800. doi:10.1038/nm730
- Mok TSK, Wu Y-L, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non-small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, Phase 3 trial. *Lancet*. 2019;393(10183):1819–1830. doi:10.1016/S0140-6736(18)32409-7
- Chan TA, Yarchoan M, Jaffee E, et al. Development of tumor mutation burden as an immunotherapy biomarker: utility for the oncology clinic. *Ann Oncol*. 2019;30(1):44–56. doi:10.1093/annonc/mdy495
- Reck M, Rodríguez-Abreu D, Robinson AG, et al. Updated Analysis of KEYNOTE-024: pembrolizumab versus platinum-based chemotherapy for advanced non-small-cell lung cancer with pd-l1 tumor proportion score of 50% or greater. *J Clin Oncol*. 2019;37(7):537–546. doi:10.1200/JCO.18.00149
- Ott PA, Bang Y-J, Piha-Paul SA, et al. T-cell-inflamed gene-expression profile, programmed death ligand 1 expression, and tumor mutational burden predict efficacy in patients treated with pembrolizumab across 20 cancers: KEYNOTE-028. *J Clin Oncol*. 2019;37(4):318–327. doi:10.1200/JCO.2018.78.2276
- Brahmer JR, Tykodi SS, Chow LQM, et al. Safety and Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer. *N Engl J Med*. 2012;366(26):2455–2465. doi:10.1056/NEJMoa1200694
- Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. *N Engl J Med*. 2015;373(17):1627–1639. doi:10.1056/NEJMoa1507643
- Allegranzi B, Bagheri Nejad S, Combescure C, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet*. 2011;377(9761):228–241. doi:10.1016/S0140-6736(10)61458-4
- Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996. doi:10.1056/NEJMoa043330
- Vanbutsele G, Pardon K, Van Belle S, et al. Effect of early and systematic integration of palliative care in patients with advanced cancer: a randomised controlled trial. *Lancet Oncol*. 2018;19(3):394–404. doi:10.1016/S1470-2045(18)30060-3
- Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med*. 2015;373(2):123–135. doi:10.1056/NEJMoa1504627
- Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252–264. doi:10.1038/nrc3239
- Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. *JAMA Oncol*. 2018;4(3):374–378. doi:10.1001/jamaoncol.2017.2925
- Hellmann MD, Callahan MK, Awad MM, et al. Tumor mutational burden and efficacy of nivolumab monotherapy and in combination with ipilimumab in small-cell lung cancer. *Cancer Cell*. 2018;33(5):853–861.e4. doi:10.1016/j.ccell.2018.04.001
- Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus Ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med*. 2019;381(21):2020–2031. doi:10.1056/NEJMoa1910231
- Rossi A. New options for combination therapy for advanced non-squamous NSCLC. *Expert Rev Respir Med*. 2019;13(11):1095–1107. doi:10.1080/17476348.2019.1667233
- Yoshimura A, Yamada T, Okuma Y, et al. Retrospective analysis of docetaxel in combination with ramucirumab for previously treated non-small cell lung cancer patients. *Transl Lung Cancer Res*. 2019;8(4):450–460. doi:10.21037/tlcr.2019.08.07
- Vickers AD, Winfree KB, Cuyun Carter G, et al. Relative efficacy of interventions in the treatment of second-line non-small cell lung cancer: a systematic review and network meta-analysis. *BMC Cancer*. 2019;19(1):353. doi:10.1186/s12885-019-5569-5

Cancer Management and Research**Dovepress****Publish your work in this journal**

Cancer Management and Research is an international, peer-reviewed open access journal focusing on cancer research and the optimal use of preventative and integrated treatment interventions to achieve improved outcomes, enhanced survival and quality of life for the cancer patient.

The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/cancer-management-and-research-journal>