## ORIGINAL ARTICLE \_\_

# The most cited articles on cancer immunotherapy: An update study

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## Summary

**Purpose:** The purpose of this bibliometric study was to point out the emergence and development of immunotherapy in cancer treatment and shifting tendencies on this field in the last years. We aimed to create an ease of access for the researchers of this dynamic field.

Methods: Cancer immunotherapy as a search term was queried into Thomson Reuter's Web of Science database of 2019 to list all the articles about this term. The top 100 cited articles were analyzed by topic, journal, author, year, institution, level of evidence, adjusted citation index and also the correlations between citation, adjusted citation index, impact factor and length of time since publication.

Results: 46,606 eligible articles were found and we had chosen the top 100 cited in the cancer immunotherapy field by bibliometric criteria. The mean citation number for the highly cited articles was 1027±794 (range:446-5746). The most cited article on cancer immunotherapy was a phase 1 clinical trial

about immune check-point inhibitor (5,271 citations) conducted by Topalian et al. The Science, AAAS journal made the biggest contribution to the top 100 list with 14 articles, whereas the most cited article originated from the New England Journal of Medicine. The country and year with most publications were the USA (n=93) and 2012 (n=10) respectively. National Institutes of Health (n=30) and National *Cancer Institute (n=30) were the most prolific institutions.* 

**Conclusion:** Cancer immunotherapy is a rapidly developing and changing subspecialty in the realm of oncology. Despite some flaws, this trend topic study has identified the most significant contributions to cancer immunotherapy research over the years and it has revealed many important scientific breakthroughs and landmarks that had took place during this time.

Key words: cancer, immunotherapy, bibliometric analysis

## Introduction

Cancer is the uncontrolled growth of some cells in a specific part of the body. The Word "Cancer" is derived from the ancient Greek physician Hippocrates who first coined the word "Karkinos" (meaning "crab") in the 5 century BC. The prevalence of the newly diagnosed cancers is increasing continuously year by year and there are more than 100 types of cancer which affect the human body [1,2]. According to the statistics of World Health Organization (WHO), cancer is the most fatal dis-

is estimated that approximately 9.6 million people died of cancer during 2018 [3]. Radiotherapy, chemotherapy, surgery, immunotherapy, hormone therapy, targeted therapies and biological therapies like gene therapy can be used alone or with a combination during the cancer treatment. Cancer immunotherapy is a treatment type which aims to use the immune system for the recognition and annihilation of the cancer cells unlike chemotherapy. This type of treatment aims not to destroy the ease following the cardiovascular diseases and it cancer cells directly, but it uses activated immune

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system cells to kill the tumor cells [4,5]. Various immunotherapy types which use different mechanisms like cytokines [6], vaccines [7], monoclonal antibodies [8], oncolytic viral therapies [9], adoptive cell transfer (ACT) [10], immune check-point inhibitors (ICPI) [11) are used in the current therapy. Bibliometric studies are important types of studies that show the trend topics in a field. This journey, which had started with the first bibliometric analysis of Garfield in 1987 in JAMA [12] also continued with the bibliometric studies that had been conducted in different fields of the medical science [13-16]. Classical citation analysis or the most cited articles regarding cancer immunotherapy could significantly contribute to this field in terms of exhibiting up-to-date academic information, progress and tendencies. In the present study, we systematically analyzed the Top 100 cited articles (T100) "key papers or classic papers" according to the data obtained from Web of Science (WoS) and PubMed in the field of cancer immunotherapy. Nowadays the quality of an article is defined by the citations it got, and the impact factor (IF) of the journal it was published. IF is a measure of the frequency with which the average article in a journal has been cited in a particular year. The calculation is based on two-year period and involves dividing the number of times articles were cited by the number of articles that are citable. It is used to measure the importance or rank of a journal by calculating the times its articles are cited [17].

In this classical papers study, we determined the number of citations with ranking, adjusted citation index (ACI), citations and publications by years, publishing journals, institutions and countries of origin, the most common subject of frequently cited articles, authorship status of classical papers and correlations analysis between citation, ACI, IF and length of time as years since publication.

## Methods

#### Study design

Study type: Retrospective clinical research. Level of evidence: 3 or Group B (Scottish Intercollegiate Guidelines Network-SIGN 50) [18,19].

#### Data collection and inclusion rules

Data used in this bibliometric citation analysis was obtained from Thomson Reuters' WoS Core Collection database (Philadelphia, Pennsylvania, USA) and PubMed (US National Library of Medicine-National Institutes of Health). We accessed the WoS database (accessed date: February 21, 2019) using the keyword "cancer immunotherapy" between the years 1975 and 2019. Consequently, we obtained 46,606 articles and conducted analysis of the T100 among these results. Articles that were not relevant to "cancer immunotherapy" were excluded from our study and we included original research articles, editorials, correspondences, reviews articles and news. Besides, we benefit from PubMed to reach additional data related to the study. Two of the authors (E.C. and M.D.) independently identified T100 with a consensus. We limited quantitative values as "2 or more and 3 or more" in order to shorten most of the tables. SIGN 50 was used for source information relating to level of evidence [19]. Since an article published earlier is more prone to have more citations, ACI showed in Appendix 1, was used on our bibliometric study to eliminate time bias. Formula of, number of citations/(2019-Year of publication) is used for the ACI calculations [20] and also ACI may be considered as the average number of citations an article gets each year following the publication.

#### Statistics

Mostly descriptive statistical methods were used in this study. All data obtained are defined as a percentage, number, bar chart, or mean±standard deviation (SD) in the tables. Besides, we analyzed the correlations between citation, ACI, IF and length of time since publication. All statistical analyses were performed using SPSS package software for Windows<sup>®</sup> (version: 21.0) and p<0.05 was considered statistically significant.

## Results

We found that the average citation for the T100 on the cancer immunotherapy was 1027±794 (range 546-5271). All of the evaluated articles were published in English language. T100 and ACI were listed in Appendix 1 and ranked by the number of citations in a decreasing manner. We found that the most cited article (times cited: 5271) on cancer immunotherapy is the phase 1 clinical trial conducted by Topalian et al about ICPI with following title: "Safety, activity, and immune correlates of anti-PD-1 antibody in cancer" published in N Engl J Med 2012;366:2443-54. Additionally, we had determined that, there are 29 articles that got more than 1000 citations and the article with the highest ACI is the article located on the top spot of T100 list. Also, according to the Appendix 1, 6 of the articles were included in both the highest ACI and the top 10 cited article list.

T100 were published between 1986 and 2017. When the publication dates of the T100 were seen in 2012 there were 10 publications and the highest number of citations was seen in 2017 with 13560 citations (Appendix 2 and Appendix 3). The oldest study among the T100 list was conducted by the Rosenberg et al and it was published on the "Science, AAAS". The newest study among the T100 list was conducted by Le et al, and, likewise, it was published on the "Science, AAAS". Eighty-two of the T100 list were published after 2000 and 45 after 2010.

In the T100 list, 83 were clinical and 17 were experimental animal studies. The clinical articles included 27 review articles, 1 news. Sixty-eight of 83 clinical articles were reviews and clinical studies, aiming to treat the patients. These 68 articles are shown on Table 1 along with their level of evidence and types of cancer immunotherapy. Thirtyeight of these 68 clinical articles were published in the last 10 years and 21 of 38 clinical articles were related to ICPI. Moreover 13 of 68 clinical articles were published in the last 5 years and 10 of 13 clinical articles were related to ICPI. Clinical studies conducted for the treatment of patients and reviews are shown in Appendix 4 with their respective modalities in cancer immunotherapy and publication dates. Studies on antibodies (n=3)and oncolytic viruses (n=1) are not shown in Appendix 4 due to the small size. It was observed that in these years especially ICPI and ACT therapies were rising over the cytokine and cancer vaccines in the field of cancer immunotherapy.

The first ICPI study in the T100 list had been published by Phan et al in 2003 in the Proceedings of the Journal of National Academy of Sciences of the United States of America. In this study cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) blockade and ICPI activity and side effect profile were studied on 14 patients with diagnosis of metastatic melanoma [21].

In the present study, 91 of T100 were published in 17 journals that had an IF of  $\geq$ 4.53 (Table 2). We determined that the average IF of these 17 journals were 28.45±19.58 (range 4.53-79.20) (according to Clarivate Analytics, 2017). Most of the articles were published in the "Science, AAAS", and the journal with the highest IF, New England Journal of Medicine, published 11 of T100 list. "Quartile Score" category of all the journals were Q1 (according to Scimago Journal and Country Rank, 2019). When the correlation analysis for the citation numbers, ACI, IF, length of time since publication parameters had been conducted for articles in the T100

Туре	Level 1	Level 3	Level 4	Total (n=68)
Immune checkpoint inhibitor	2	14	7	23
Adoptive cell transfer	1	15	5	21
Vaccine	4	4	4	12
Cytokine	2	3	1	6
Antibody	-	2	1	3
Adoptive cell transfer/Cytokine	-	2	-	2
Oncolytic viruses	1	-	-	1

**Table 1.** Types of cancer immunotherapy and level of evidence of the clinical articles (n=68) in the Top 100

Table 2. List of journals in which two or more articles were published

Rank	Journal	Number of articles	Impact factor*	Quartile score**
1	Science	14	41,05	Q1
2	Nature Medicine	11	32,62	Q1
3	New England Journal of Medicine	11	79,20	Q1
4	Journal of Clinical Oncology	9	26,36	Q1
5	Nature Reviews Cancer	6	42,78	Q1
6	Nature Reviews Immunology	6	41,98	Q1
7	Journal of Experimental Medicine	5	10,79	Q1
8	Nature	5	41,57	Q1
9	Annual Review of Immunology	4	22,71	Q1
10	Blood	3	15,13	Q1
11	Journal of Immunology	3	4,53	Q1
12	Proceedings of the National Academy of Sciences of the USA	3	9,5	Q1
13	Science Translational Medicine	3	16,71	Q1
14	Clinical Cancer Research	2	10,19	Q1
15	Journal of Clinical Investigation	2	13,25	Q1
16	Lancet	2	53,25	Q1
17	Lancet Oncology	2	36,42	Q1

\*2017 Journal Citation Reports<sup>®</sup> (Clarivate Analytics); \*\*2019 Scimago Journal and Country Rank



Figure 1. The correlations between citation, adjusted CI, IF and length of time since publication.

	Number*
United States of America	93
The Netherlands	10
France	9
Germany	7
Canada	4
Australia	3
Switzerland	3
Belgium	2
England	2
Italy	2
Japan	2
Spain	2
Brazil	1
Chile	1
Israel	1
South Korea	1

Table 3. Geographic origin of the top 100 articles

\*More than 100 countries were listed in total due to international collaboration during certain publications

list; citation and ACI (r=0.751, p<0.01), citation and IF (r=0.347, p<0.01), ACI and IF (r=0.458, p<0.01) had a positive correlation, whereas ACI and length of time since publication (r= -0,499, p <0.01) had a negative correlation (Figure 1). It was also observed that citation and length of time since publication (r= -0,05, p=0.965), IF and length of time since publication (r= -0,178, p=0,076) did not have any correlation.

According to the geographic origin of the T100 list, 16 countries had made contributions to T100 list, and U.S.A (n=93) was the most contributing country which was followed by the Netherlands and France respectively (Table 3).

Two institutes which contributed to T100 list were National Institutes of Health (NIH) (n=30) and National Cancer Institute (NCI) (n=30) of the United States. In addition one can see that 23 of the 25 institutions originated from United States of America (Table 4). We had also determined that 68 of the T100 list in cancer immunotherapy received grant support and 24 funding agencies had provided funding support for more than one study.

Rank	Institution	Number*
1	National Institutes of Health (USA)	30
2	National Cancer Institute (USA)	30
3	Dana Farber Cancer Institute (USA)	12
4	Harvard University (USA)	12
5	University of California (USA)	12
6	VA Boston Healtcare System (USA)	12
7	Johns Hopkins University (USA)	11
8	Johns Hopkins Medicine (USA)	10
9	Memorial Sloan Kettering Cancer Center (USA)	10
10	University of Texas System (USA)	9
11	Bristol Myers Squibb (USA)	8
12	Johns Hopkins Oncology Center (USA)	8
13	UT MD Anderson Cancer Center (USA)	8
14	Netherlands Cancer Institute (Netherlands)	7
15	Washington University WUSTL (USA)	7
16	H Lee Moffitt Cancer Research Institute (USA)	6
17	Mayo Clinic (USA)	6
18	State University System of Florida (USA)	6
19	Unicancer (France)	6
20	University of Pennsylvania (USA)	6
21	University of South Florida (USA)	6
22	University of Washington (USA)	6
23	University of Washington Seattle (USA)	6
24	Howard Hughes Medical Institute (USA)	5
25	University of California Los Angeles (USA)	5

Table 4. Institutions of origin with 5 or more of the top 100 cited articles

\*Number of times listed of total 25 institutions in the top 100 cited articles

"INTRAMURAL NIH HHS" (14 studies), "NCI NIH HHS" (14 studies), "MELANOMA RESEARCH AL-LIANCE" (10 studies) were the top three funding agencies (according to WoS database, 2019).

It was seen that 11 authors were the first author in more than one article located in T100 list (Appendix 1). Rosenberg had contributed to 27 articles and was first author in 9 of them and he became the author who had contributed to the highest number of articles in the T100 list (Table 5). Restifo and Yang contributed to 16 articles each, and they follow Rosenberg in this category. "Web of Science" category of the T100 was analyzed in the field of cancer immunotherapy and the following articles ranked under medicine research experimental (n=22), multidisciplinary sciences (n=22), immunology (n=21) and oncology (n=21) were the most featured ones respectively (Appendix 5).

## Discussion

The first application of cancer immunotherapy on a patient with osteosarcoma was conducted by the bone surgeon William Bradley Coley. He tested the bacterial toxin he had developed on his patient

Table 5. The most con	nmon authors	with 5 of	r more in the
top 100 cited articles			

Author	Number of Top 100 articles			
_	Author	First author	Co-author	
Rosenberg SA	27	9	18	
Restifo NP	16	2	14	
Yang JC	16	-	16	
Topalian SL	13	3	10	
Dudley ME	12	2	10	
Pardoll DM	9	1	8	
Wunderlich JR	9	-	9	
Chen LP	7	-	7	
Sherry RM	7	-	7	
White DE	7	-	7	
Morgan RA	6	2	4	
Robbins PF	6	1	5	
Allison JP	5	-	5	
Hughes MS	5	-	5	
Hwu P	5	-	5	
Kammula US	5	-	5	
Mavroukakis SA	5	-	5	
Schwartzentruber DJ	5	-	5	
Seipp CA	5	-	5	
Weber JS	5	1	4	

who had inoperable sarcoma and he had published an article on Annals of Surgery journal in 1891 which shows the remission of the tumor [22]. The options for immunotherapy in cancer treatment had increased throughout the years and immunotherapy started to get used more frequently. When we evaluate the current literature, there are only few of bibliometric analysis studies on cancer immunotherapy field. Kaining et al [23] had analyzed 2945 articles, which were published between 2014-2017 related with the tumor immunotherapy, bibliometrically based on the immunotherapy modality and cancer type. Another bibliometric study was conducted by Zhao et al [24] which determined that 14.3% of the studies related to ICPI were conducted in China. To the best of our knowledge, our study is the first cancer immunotherapy bibliometric analysis study, which includes classical articles related with all of the modalities in cancer immunotherapy without having a time limitation.

Interleukin-2 (IL-2), the first cytokine found to have therapeutic benefit, was discovered in 1976 by Robert Gallo, and Francis Ruscetti [25]. About 10 years later Steven Rosenberg successfully cured several patients with advanced metastatic renal cell cancer and melanoma by using IL-2 [26]. The first U.S. Food and Drug Administration (FDA) approved cancer immunotherapy agent of the history, IL-2, is still being used to treat metastatic melanoma and renal cell cancer. The knowledge related with the cancer immunotherapy, like cancer vaccines, ACT, antibodies, ICPI, oncolytic viral therapy is added into the cancer immunotherapy options as an addition to cytokines.

Updating studies that were conducted with the classical papers about different fields of medical sciences can show the historical development in this field [13-15]. Citation is an important metric, which shows the quality and attractiveness of an article. A certain amount of time should pass after the publication of an article to reach higher numbers of citations. For that reason, the number of citations is inadequate to determine the quality of an article when used solely. In this study, ACI were used for eliminating the time bias while evaluating older articles against the newer articles [20]. Even though it was not utilized in our study, altmetric score or analysis is also an important indicator which shows the social media interest shown to an article [27]. In our study, we had found a strong correlation between citation and ACI. In addition, as a result of our correlation analysis it was determined that the publications that were published in journals with higher impact factors are getting more citations. The negative correlation between ACI and length of time since publication is

an indicator that shows the ACI value of an article is decreasing as it gets older. Even though it can be expected that the relatively older studies have higher numbers of citations, a meaningful correlation between citation and length of time since publication is not found at all.

Year of publication and the number of citations for an article are closely related and the number of citations grows as the time passes [28]. For this reason, the articles with higher number of citations are expected to be old. On the contrary, articles with higher citations and newer publication dates are showing that the up to date studies on this area are attractive and reflecting the changing tendencies in that field. When the T100 list was evaluated, 82% of the cancer immunotherapy studies were conducted after 2000 and, moreover, 45% of all the articles published in the field of cancer immunotherapy were published in the last 10 years. When the publication year of the 5 most cited studies was examined, one can see that 3 of them were published in 2012, one was published in 2000 and one was published in 2010. According to the "Melanoma citation classics" published by the Joyce et al [13] in 2014, 78% of the T100 list were older than 10 years and the most cited 5 articles were published in 1992, 1969, 1970, 2001 and 1988. Contrary to Joyce et al, our study had current studies with higher citation numbers because the discovery of ICPI and successful usage of them in cancer treatment had drawn an immense interest towards the cancer immunotherapy in the last decade. In our study, when we made our sorting based on the ACI, 7 of the first 10 articles were related with the ICPI and this fact is supporting the existence of this immense interest. In fact, James P. Allison and Tasuku Honjo were awarded with the Nobel Prize in Medicine with their research related with the immune checkpoint blockade. As a result, ICPI can be regarded as an immunotherapy modality that had started a new era in cancer treatment and it is a new trend topic. That shows the changing tendencies in cancer immunotherapy during the last decade [29-31].

Seventeen of T100 were animal studies, 68 of them were reviews and researches related with the treatment efficacy of immunotherapy in cancer patients and the remaining 15 were articles related with the prognosis or etiopathogenesis. According to Table 1, the majority of the 68 articles trying to determine the treatment efficacy are either related with ICPI or ACT. In melanoma citation classics study, 23.8% of the 67 studies had a level 1 evidence, and in our study 14.7% of the 68 clinical studies has a level 1 evidence [13]. Even though the articles of the cancer immunotherapy T100 list are the most cited publications on this field, 85.3% of the clinical studies (n=68) was level 3 and 4 evidence (according to SIGN 50) and it is remarkable that the number of the clinical studies with higher a quick and direct reach to determine topic trends level of evidence is lower than expected.

When the article types were evaluated, 27 of T100 were reviews and one of them was a news. It is observed that 72% of the Top 100 list are original research articles, but this rate is lower when it is compared with the "top 100 cited" studies conducted in different fields of the literature [13,32]. All of the 27 reviews in the T100 originated from USA and the Netherlands. USA had contributed to 26 of the reviews, and the Netherlands had contributed 2 of the reviews (one review was written with the cooperation of USA and the Netherlands). Three most frequent contributing countries were USA, the Netherlands and France, respectively. USA had contributed 93 of the 100 articles. USA is the biggest contributor of the T100 list by far. Existence of multiple large well-funded cancer centers and extensive amount of patient population in USA is causing a concentration of cancer immunotherapy publications in this country thus the high quality researches were conducted in this country.

The journals with highest contribution to Top 100 list are the 3 journals with high levels of IF and these are "Science, AAAS" (n=14), "Nature Medicine" (n=11) and "the New England Journal of Medicine (the NEJM)" (n=11). All of these 3 journals are high quality general medicine journals that are not oncology-specific. Authors of the popular cancer immunotherapy studies could have considered the IF on their choice of journal, and articles related with the cancer immunotherapy could have been deemed as interesting by the general medicine journals.

American surgeon Steven A. Rosenberg contributed to 27 of the Top 100 articles and in 9 of these articles Rosenberg was the first-author. The oldest study on the T100 list was also published by Steven A. Rosenberg et al in 1986 on "Science, AAAS". In this study, a combination of tumor-infiltrating lymphocytes, IL-2 and cyclophosphamide had been given to rats with metastatic colon cancer and a regression in tumor had been observed. According to the T100 list, studies up until 2000 were focused on cytokines and vaccines but after the 2000, ICPI and ACT modalities definitely became more popular. The fact that 77% of the 57 treatment-related clinical studies and reviews that had been conducted after 2000 which are located on the T100 list are related with ICPI (n=23) and ACT (n=21) is an important landmark of this fact. Likewise, when looking at Appendix 4 the shifting tendencies in cancer immunotherapy field can be seen.

#### Strengths

The strength of this study is the provision of and up-to-date information regarding cancer immunotherapy with no requirements of any advanced analysis or statistical methods. Addition of ACI and correlation analysis to this trend topic study make it possible to evaluate the classical articles with a versatile perspective.

## Limitations

Only the total number of citations (excluding self-citations) and the total number of self-citations are presented in this study, and no articlebased self-citation analyses were performed, and this fact stands as a limitation for this study. In addition, conducting bibliometric analyses based on citations is a subjective constraint to prove the quality of a research, to determine the number of publications by year as well as to evaluate authors' scientific efficiency or h-index.

## **Future directions**

In contrast with advanced research methods, occasional bibliometric analyses for different medical disciplines and sub-specialties demonstrate the improvements in that field from a nominative perspective. The data of current studies may provide cost-effectivity in planning and funding future research projects. Bibliometric studies are relatively subjective, initial and basic researches in terms of scientific value. In the last decade, altmetric studies, including multiple evaluations of classical articles, were preferred as they are scientifically more objective.

## Conclusion

Even though the number of citations is not the sole indicator of quality for the articles, articles with higher number of citations are more notable and draw more attention in the world of science. Despite some flaws and criticism surrounding it, bibliometric citation analyses on cancer immunotherapy, as in many scientific fields, enable the systematic identification of true landmark publications and the distribution of citations of these publications by years, main topics, institutions of influential papers, published scientific journals, level of evidence, and correlation analysis, thus resulting in great academic contribution to oncological researches.

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# Authors' contributions

The two authors have made substantial contributions to the conception and design, acquisition, analysis and interpretation of the data in this study. All have also been involved in drafting the manuscript or revising it critically for important intellectual content and all have given final approval of the version to be published.

## **Compliance with ethical standards**

Ethical statement: All authors declare that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects." This study did not need to be approved by an ethics commit- received no financial support.

tee because it performed a bibliometric analysis or citation analysis of existing published classical studies.

## Informed consent

Informed consent is not necessary as our work is a retrospective international data study.

## **Conflict of interest**

No conflict of interest was declared by the authors.

## **Financial disclosure**

The authors declared that this study has

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Appendix 1. The top 100	cited articles in	cancer immunotherapy
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Artic	Article		ACI*
1.	Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366:2443-54.	5271	753
2.	Banchereau J, Briere F, Caux C, Davoust J, Lebecque S, Liu YJ, et al. Immunobiology of dendritic cells. Annu Rev Immunol. 2000;18:767-811.	4724	248,63
3.	Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12:252-64.	3840	548,57
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\*ACI: Adjusted Citation Index.

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Appendix 3. Citations in each year (source: Web of Science database)







Appendix 5. Web of Science categories associated with cancer immunotherapy

