Review Article
Middle East Journal of Cancer; January 2023; 14(1): 1-16

Top 100 Most Cited Publications on CTLA-4 Molecule in Cancer Research: A Bibliometric Analysis

Hossam Hilal El Idrissi*♦, PhD candidate, Ibtissam Balar, PhD candidate**

**Faculty of Medicine and Pharmacy of Casablanca, University of Hassan 2, Casablanca, Morocco*
***Neuropsychology Department, University of Paris 8, Vincennes-Saint-Denis, Paris, France*

Please cite this article as: Hilal El Idrissi H, Balar I. Top 100 most cited publications on CTLA-4 molecule in cancer research: A bibliometric analysis. Middle East J Cancer. 2023;14(1):1-16. doi:10.30476/mejc.2022.90280.1568.

Abstract

The aim of this research is to use bibliometric analysis to investigate the status and patterns of the 100 most frequently cited publications regarding the cytotoxic T-lymphocyte-associated protein (CTLA-4) research for cancer. The articles published on the topic were retrieved from the core collection database of Web of Science and PubMed using the Medical Subject Heading (MeSH) of "CTLA-4" from 1986 to December 6, 2020. The selected articles were examined and the bibliometric data compiled based on the number of citations, the author's name, journal, publication year, institution, country, and co-occurrence keywords. 4,874 eligible papers were returned from the Web of Science Core Collection Database and PubMed. The citation frequency ranged from 2372 to 205, with a median of 460, and the top cited paper had 2372 citations. The journals with the most papers were Cell (n = 8, 3541 citations, Impact Factor (IF) = 41.577) and Journal of Experimental Medicine (n = 7, 2716 citations, IF = 10.790). Most of the published papers were from the United States of America (USA) (41.8%). A total of 485 institutes and 29 countries were involved in these 100 articles. There were 1192 authors and the author with the highest number of papers was the Nobel Prize winner, Professor James P. Allison (17 papers; 8700 citations). CTLA-4 blockade was the most frequent keyword (42.1%), followed by metastatic melanoma (4.26%). This work presents an important bibliographic source and can be saved as a reference for future medical health research on the function of CTLA-4 in cancer immunotherapy.

Keywords: Bibliometric analysis, CTLA-4 protein, Cytotoxic T-lymphocyte antigen 4, Cancer, Immunotherapy

♦Corresponding Author:
Hossam Hilal El Idrissi, PhD candidate
Faculty of Medicine and Pharmacy of Casablanca, University of Hassan 2, Casablanca, Morocco
Email: hossam.hilalelidrissi@gmail.com

Introduction

Cancer is a major public health problem and one of the leading causes of death in most countries. In 2020, about 19.3 million new cancer cases were diagnosed, and almost 10 million cancer deaths were reported.[1] In an unprecedented manner, 2.3 million (11.7 %) of the new diagnoses were related to female breast cancer

Received: February 24, 2021; Accepted: March 07, 2022

replacing lung cancer as the most frequently diagnosed one (11.4 %) followed by colorectal cancers (10.0 %).[1]

Cancer is a multifactorial disease of an unexplained etiology. Cancer immunotherapy is one of the options for treating cancer using the immune system along with surgery and radiation therapy. Efforts to manipulate the immune system to recognize and eradicate tumor cells are very old. In 1808, Louis XVII's physician was already inoculating himself with breast cancer cells in the hope of eradicating soft tissue sarcoma, but to no avail.[2] The concept of immunosurveillance dates back to the early 1950s: effector cells of the immune system are said to actively patrol the body to identify and eradicate emerging tumor cells.[3] Recently, cancer treatment has progressed and has been a point of interest, especially the use of immunological checkpoint inhibitors. This importance has been recognized by the awarding of Nobel Prize for physiology or medicine 2018. James P Allison and Tasuku Honjo were cited for their research on the discovery of cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death 1 (PD-1).[4,5]

CTLA-4, also known as CD152 (cluster of differentiation 152), is an immune checkpoint and a negative regulator of T-cell immune function; the gene that encodes for CTLA-4 in humans is on chromosome 2 (q33).[6] The CTLA-4 is localized in the intracellular compartment of naive T lymphocytes and on the cell surface of activated T lymphocytes.[7] After binding to CD80 or CD 86 on antigen-presenting cells (APCs), an inhibitory signal is transduced into T cells.[8] The inhibitory signal downregulates the action of autoreactive T cells, thereby preventing an autoimmune reaction in naive cells.[9]

Ipilimumab is an anti-CTLA-4 antibody and the first inhibitory checkpoint inhibitor approved by the United States Food and Drug Administration (FDA) for treatment of melanoma.[10] Melanoma patients treated with Ipilimumab have shown favourable survival outcomes up to 3-4 years after starting the therapy.[11]

Different bibliometric analysis studies have been carried out on the immunotherapy of various pathologies, but our results provide a better understanding of the current status and trend of research via investigating their characteristics; this study also summarizes the reasons for high citation and how to improve the understanding and management of the CTLA-4 molecule in cancer immunotherapy and cancer.

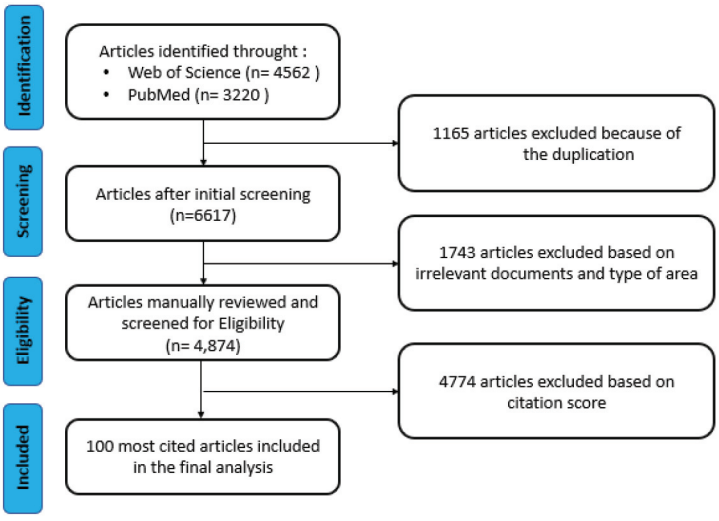

Figure 1. This figure shows the PRISMA diagram describing the collection of the 100 most cited papers on CTLA-4 molecule in cancer research from the Web of Science and PubMed databases.

Methods

Data Sources and index strategies

Bibliometrics study is widely used in clinical research because it provides benchmark data that can be used to understand the technological dynamics, publish research results, make decisions on scientific study topics, and determine the novelty of projects. Extensive research was conducted from the core collection database of Web of Science and from PubMed using the MeSH from 1986 to December 6, 2020 on a single day, so as to avoid any update of the system and exclude any papers irrelevant to CTLA-4 in cancer research.[12] We used the following keywords after multiple iterations to conduct a detailed research: term= (CTLA-4 or CD152 or cytotoxic T-lymphocyte-associated protein or CTLA-4 antigen or CTLA4 protein) and title= (cancer or tumor or tumour or neoplasms or neoplasia or tumors or tumours or cancers). Using such indexing strategies, we analyzed research papers in the areas of CTLA-4 and cancer to select the top 100 most cited papers according to the number of citations with no restrictions on the publication year, language or article type; furthermore, two authors separately read the abstract of each article to avoid any paper that was not related to our topic of study and also to avoid any duplication. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) approach indicates four steps to omitting, identifying and extracting the data for a bibliometric review (Figure 1).[13] If articles shared the same number of citations, they were given the same rank.

Data extraction

The outcomes were discussed in a meeting to record this information: 1) the first author and his/her affiliation, 2) the country and institutes of the first author, 3) the number of citations for each article, 4) the publication year, 5) the category of article's study.

Each journal was evaluated and the following information was collected: 1) the impact factor (IF) of journals was noted from the 2018 Journal Citation Reports (JCR) (Clarivate Analytics, Philadelphia, USA),[14] 2) the number of articles published, 3) the citation number of all articles.

Statistical analysis

The data downloads from PubMed and the core collection database of Web of Science was imported in Histcite version 12.03.17 to export the information comprised of the selected articles: author, journal, publication date, country, institute, the language of papers and keywords.[15]

The bibliographic coupling network (the collaboration map) was designed by use of VOS viewer 1.6.13 (Leiden University's Centre for Science and Technology, Netherlands) to give a view on the connection between authors, countries and institutes using co-authorship relations (the smaller the connection line, the closer the relationship, and vice versa) and also to generate the density and cluster maps of the most common keywords.[16] The VOS viewer is based on three

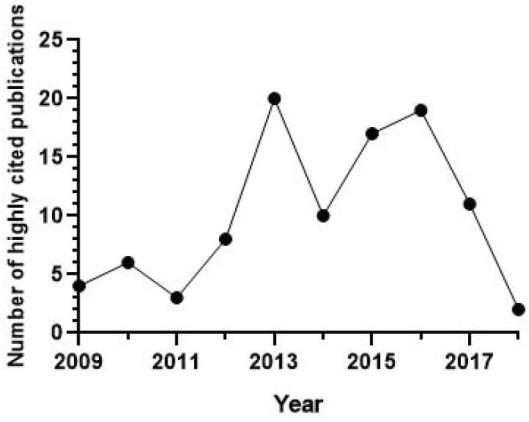

Figure 2. The interest towards CTLA-4 molecule in cancer research was not stable between 2009 and 2018.

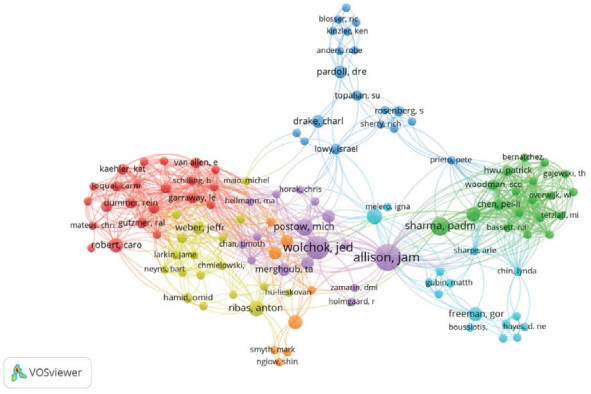

Figure 3. The collaboration between the productive authors on CTLA-4 molecule in cancer research was very high.

characteristics, namely, size, colours, and distance. Each node represents elements such as author and country, and the size of each node indicates the activity of that element.

All the data were presented using descriptive statistics and no statistical significance tests were performed.

Results

Distribution of journals and of the 100 papers

A total of 4,874 publications about the CTLA-4 molecule in cancer research were published in the core collection database of Web of Science and in PubMed from 1992 to 2019, and only the 100 most cited were included in this article (Table 1); as shown in this table, the most cited paper was written by Wolchok JD et al. with 2372 citations.

The 100 most cited papers were published in 40 journals between 2009 and 2018. Among the top journals ranked in descending order, Cell had the most with 8 papers (3541 citations, IF = 31.398), followed by Journal of Experimental Medicine with 7 publications (2716 citations, IF = 10.790).Clinical Cancer Research and Science both had 6 publications (2147 and 4838, citations respectively, IF = 10.199 and 41.058, respectively). The highest IF was attributed to New England Journal of Medicine (IF = 79.258). The USA had the highest number of journals with 24 followed by the United Kingdom (UK) with 11. The Netherlands had 3 journals and Germany and Switzerland both had one journal.

The citation rate index

A possible limitation of this type of study is that historical manuscripts may accrue a larger number of citations despite lacking the impact of newer publications. We controlled for this through creating the citation rate index (dividing citations by the number of years since the paper was published) (Table 2). The citation rate (CR) for the top 10 manuscripts ranged from 338.6 to 186.20; the highest CR belonged to "nivolumab plus ipilimumab in advanced melanoma", and the lowest CR to "Immune Checkpoint Blockade in Cancer Therapy".[17,18] The USA had the most papers in the top 10 citation rate with 9 followed by UK with 1.

Study categories

The categories of the 100 most cited papers of CTLA-4 molecule in cancer research were Oncology (38 publications), followed by Multi-disciplinary Sciences (17 publications), Biochemistry & Molecular Biology and Medicine (both had 8 publications), and Immunology and Research Experimental with 7 papers.

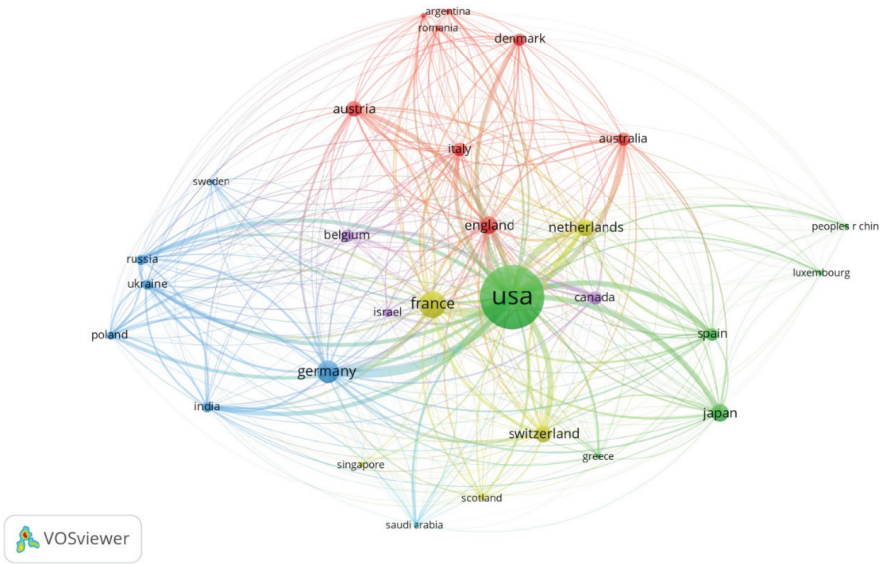

Figure 4. The collaboration between the active countries on CTLA-4 molecule in cancer research was very dynamic.

Table 1. The top 100 cited paper on CTLA-4 molecule in cancer research

R	*Citations*	*First author*	*Location*	*Year*	*Ref*	R	*Citations*	*First author*	*Location*	*Year*	*Ref*
1	2372	Wolchok JD	USA	2013	[17]	51	332	Duraiswamy J	USA	2013	[31]
2	1738	Snyder A	USA	2014	[32]	52	332	Selby MJ	USA	2013	[33]
3	1378	Sharma P	USA	2015	[34]	53	331	O'Day SJ	USA	2010	[35]
4	1248	Topalian SL	USA	2016	[36]	54	328	Peng WY	USA	2016	[37]
5	1208	Weber JS	USA	2015	[38]	55	328	Chen Q	China	2016	[39]
6	1022	Postow MA	USA	2012	[40]	56	321	Sharma P	USA	2011	[41]
7	931	Zang X	USA	2018	[4]	57	310	Slovin SF	USA	2013	[42]
8	880	Curran MA	USA	2010	[43]	58	307	Garbe C	Germany	2011	[44]
9	855	McGranahan N	UK	2016	[45]	59	307	Reck M	Germany	2013	[46]
10	806	Van Allen EM	USA	2016	[47]	60	303	The Cancer Genome Atlas Research Network	USA	2017	[48]
11	802	Gubin MM	USA	2014	[49]	61	296	Geoffrey	USA	2016	[50]
12	743	Ahmadzadeh M	USA	2016	[51]	62	296	Zamarin D	USA	2014	[52]
13	733	Sharma P	USA	2018	[53]	63	296	Nishikawa H	Japan	2014	[54]
14	728	Vetizou M	France	2015	[55]	64	294	Melero I	Spain	2015	[56]
15	723	Webers JS	USA	2014	[57]	65	289	Khalil DN	USA	2016	[58]
16	664	Spranger S	UK	2015	[59]	66	288	Holmgaard RB	USA	2013	[60]
17	658	Topalian SL	USA	2017	[61]	67	288	Haanen J.B.A.G	Netherlands	2017	[62]
18	635	Dewan MZ	USA	2009	[63]	68	282	Gibney GT	USA	2016	[64]
19	633	Chen DS	USA	2017	[65]	69	276	Smyth MJ	Australia	2015	[66]
20	627	Lynch TJ	USA	2012	[67]	70	275	Farkona S	Canada	2016	[68]
21	626	Hugo W	USA	2016	[69]	71	274	Carthon BC	USA	2010	[70]
22	606	Sharma P	USA	2017	[71]	72	274	Boussiotis VA	USA	2016	[72]
23	600	Tirosh I	USA	2016	[73]	73	261	Gao JJ	USA	2017	[74]
24	597	Kwon ED	USA	2014	[75]	74	256	Boutros C	France	2016	[76]
25	587	Simpson TR	USA	2013	[77]	75	254	Dung T Le	USA	2013	[78]
26	579	Chang CH	USA	2015	[79]	76	252	Champiat S	France	2015	[80]
27	568	Woo SR	USA	2013	[81]	77	251	Patsoukis N	USA	2015	[82]
28	553	Michot JM	France	2016	[83]	78	246	Ngiow SF	Australia	2011	[84]
29	550	Akbay EA	USA	2013	[85]	79	245	Page DB	USA	2014	[86]
30	515	Llosa NJ	USA	2015	[87]	80	245	Johnston RJ	USA	2014	[88]
31	499	Peggs KS	USA	2009	[89]	81	239	Bulliard Y	USA	2013	[90]
32	493	Noman MZ	France	2014	[91]	82	238	Victor D	USA	2013	[92]
33	482	Feig C	UK	2013	[93]	83	238	Tanaka A	Japan	2016	[94]
34	471	Antoni R	USA	2018	[95]	84	236	Schachter J	Israel	2017	[96]
35	420	Sahin U	Germany	2017	[97]	85	233	Voskens CJ	Germany	2013	[98]
36	399	Royal RE	USA	2010	[99]	86	232	Bertrand A	France	2015	[100]
37	397	Chalmers ZR	USA	2017	[101]	87	228	Palucka AK	USA	2016	[102]
38	386	Chen LP	USA	2015	[103]	88	228	Chen PL	USA	2017	[104]
39	385	Quezada SA	USA	2010	[105]	89	227	Ravi Ma	USA	2019	[106]
40	378	Buchbinder EI	USA	2016	[107]	90	225	Alfons JM	Netherlands	2019	[108]
41	377	Scott R	USA	2012	[109]	91	225	Voron T	France	2015	[110]
42	372	Okazaki T	Japan	2013	[111]	92	224	Alsaab HO	USA	2017	[112]
43	359	Zeng M	USA	2013	[113]	93	223	Wainwright DA	USA	2015	[114]
44	359	Encouse B	USA	2013	[115]	94	216	Romano E	Swizerland	2015	[116]
45	355	Michael A	USA	2018	[117]	95	213	Jeffrey P	USA	2013	[118]
46	342	Jeffrey S	USA	2009	[119]	96	212	Kathleen M	USA	2016	[120]
47	339	Ott PA	France	2013	[121]	97	211	Kim K	USA	2014	[122]
48	339	Cantwell-Dorris ER	Ireland	2011	[123]	98	208	Charoentong P	Austria	2017	[124]
49	335	Sangro B	Spain	2013	[125]	99	205	Claire M	USA	2016	[126]
50	334	Peter U	USA	2012	[127]	100	205	Wei SC	USA	2017	[128]

R: Rank; Ref: Reference

Annual publications analysis

The publication trend of the papers on the CTLA-4 molecule in cancer research is shown in figure 2. In 2009, only 4 papers were highly cited, while in 2010, there was a significant increase of 2 articles to reach 6 papers. Following this year; however, the papers decreased to only 3 papers. Since 2011, the number of highly cited papers has undergone a remarkable change, going from 3 to 20 papers in 2013. Between 2013 and 2016, there was a small variation with a mean of 16 papers. After 2016, the number of highly cited papers sharply decreased from 19 to 2 papers. These results indicate that the interest towards CTLA-4 molecule in cancer research was not stable between 2009 and 2018.

Distribution of authors and citations

Among all corresponding authors of the above 100 selected papers, Allison JP had the highest number of publications with 17 papers, followed by Wolchok JD with 15 and Robert C and Sharma P both publishing 8 papers (Table 3).

Among these top 10 authors in table 3, Wolchok JD is ranked first with the highest number of citations (10316 citations), followed by Allison JP with 8700 citations and Postow MA with 6868 citations. The network map of 117 authors contained 903 links, meaning the collaboration between productive authors was very high (Figure 3).

Distribution of countries

The 100 most cited papers on CTLA-4 molecule in cancer research were contributed by 29 countries. The greatest number of publications belonged to the USA (n=82) followed by France (n=16) and Germany (n=12) (Table 4). Japan and the UK provided the same number of papers (n= 4), and there is an active collaboration between countries (Figure 4).

Distribution of institutes

Out of 270 institutes contributing to the top 100 publications on the CTLA-4 molecule in cancer research, Memorial Sloan Kettering Cancer Center (USA) had the most contribution with 24 publications, followed by Bristol-Myers Squibb (USA) (15 papers), University of Texas MD Anderson Cancer Center (USA) (13 papers), Dana-Farber Cancer Institute and Harvard University (USA) with 10 papers both, and Weill Cornell Medical College (USA) with 8 papers (Table 5).

As shown in figure 5, the network map of the 153 institutes (from 270 institutes) contained 271 links which signifies that there is an active collaboration between the active institutes (the links between the nodes represent this collaboration).

Co-occurrence of keywords analysis and clusters

A total of 490 keywords were extracted from the top 100 highly cited papers on the CTLA-4 molecule in cancer research, and a density map of these keywords was generated with the co-occurrence (Figure 6). “CTLA-4 blockade” was the highest with 33 (6.73%) co-occurrences, followed by “metastatic melanoma” with 21 (4.26%), “Ipilimumab” and “immunotherapy” with 22 (4.48%), and “expression” with 19 co-occurrences (3.87%).

Clustering analysis was performed by 47 co-occurrence keywords and created 586 links as shown in figure 7. The network map includes 4 clusters: Cluster 1 contains “anti-PD1 antibody” and “clinical activity”; Cluster 2 includes “metastatic melanoma”, “Ipilimumab”,

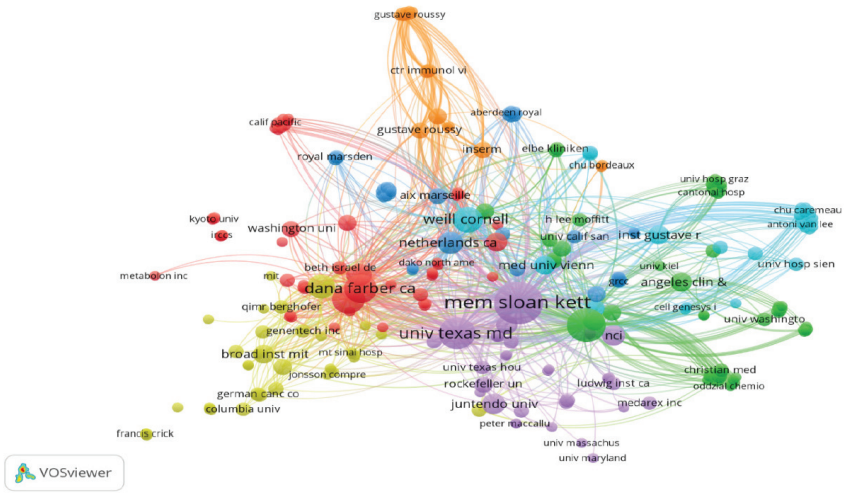

Figure 5. There was an active collaboration between the active institutes on CTLA-4 molecule in cancer research.

Table 2. Top 10 papers with the highest citation rate

Rank	Citation rate	First author	Title	Institution	Country
1	338,86	Wolchok JD	Nivolumab plus ipilimumab in advanced melanoma	Yale University School of Medicine and Yale Cancer Center, New Haven	USA USA
2	289,67	Snyder A	Genetic basis for clinical response to CTLA-4 Blockade in melanoma	Department of Medicine Columbia University Anderson Cancer	
3	275,60	Sharma P	The future of immune checkpoint therapy	Center, Houstons	USA
4	249,60	Topalian SL	Immune checkpoint blockade: a common denominator approach to cancer therapy	University School of Medicine, Baltimore, Maryland Department of Surgery	USA
5	241,60	Weber JS	Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial	Moffitt Cancer Center, Magnolia Campus	USA
6	235,50	Ribas A	Cancer immunotherapy using checkpoint blockade	Parker Institute for Cancer Immunotherapy Center at the University of California Los Angeles	USA
7	213,75	McGranahan N	Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade	The Francis Crick Institute,	UK
8	211,00	Chen DS	Elements of cancer immunity and the cancer–immune set point	Genentech	USA
9	202,00	Sharma P	Primary, adaptive and acquired resistance to cancer immunotherapy	Department of Genitourinary Medical Oncology and Immunology, The University of Texas MD Anderson Cancer Center	USA
10	186,20	Postow MA	Immune checkpoint blockade in cancer therapy	Memorial Sloan Kettering Cancer Center	USA

"lymphocyte-associated antigen 4", "antitumor immunity", "autoimmunity", "anti CTLA-4" and "clinical response"; Cluster 3 consists of "melanoma", "safety", "CTLA-4" and "immunotherapy"; and Cluster 4 comprises "CTLa-4 blockade", "cancer", "expression", "PD-1 blockade" and "regulatory T".

Discussion

The overall purpose of this study was to extract papers through the Web of Science Core Collection Database and PubMed, then review them to collect those related to the CTLA-4 molecule in cancer research and ranked by the number of citations to find out which articles are most cited and which countries and authors are active. Afterwards, we identified 100 papers ranked between 2009 and 2018. During these decades, numerous immunotherapy studies were published regarding different types of cancer, such as brain cancer, sarcomatoid, non-small cell lung cancers and breast cancer.[19-24, 114- 116]

Table 3. The top 10 authors for the top cited publications on CTLA-4 molecule in cancer research

Rank	Authors	Number of publications in top 100	Number of global citations
1	Allison JP	17	8700
2	Wolchok JD	15	10316
3	Robert C	8	2885
4	Sharma P	8	4006
5	Postow MA	7	6868
6	Korman AJ	6	4867
7	Ribas A	6	3953
8	Carbonnel F	5	2077
9	Freeman GJ	5	2147
10	Mateus C	5	2022

The article by Jedd D. Wolchok et al. published in the New England Journal of Medicine in 2013 had the most citations (2372 times). The purpose of this study was to conduct a phase 1 trial of nivolumab associated with ipilimumab in patients with advanced melanoma to understand the effect of this combination on 53 patients.[23]

According to our results, the USA comprised 41.8% of the contribution, while the other 28 countries shared the rest (58.17%). The contribution percentage of USA is similar to those reported by other bibliometric analyses such as anti-CTLA4 in tumor immunotherapy in China (USA: 51.9%, study period :1996 to 2015), PD-1 and PD-L1 in the field of cancer (47.51%, study period: 1991–2018), Holistic Evaluation of PD-1 and PD-L1 (45.7%, study period : 1975 and 2017), and Immunotherapy for Childhood Leukemia (35.21%, Study period : 2000 and 2018).[24-27]

The top eight institutes were all American with 25.20%. The Memorial Sloan Kettering Cancer Center ranked first in this study. This result differs from other bibliometric analyses in which this institute ranked seventh in the 100 most cited cancer immunotherapy studies and tenth in a paper on the holistic evaluation of articles on PD-1 and PD-L1 published between 1975 and 2017.[25,27]

A total of 40 journals were involved in this study. The Cell, Journal of Experimental, Medicine, Clinical Cancer Research, Science Journals together published 27% of the 100 most cited papers. These four journals are issued from the USA. Professor James P. Allison and Jedd Wolchok are the principal authors with 32 papers,

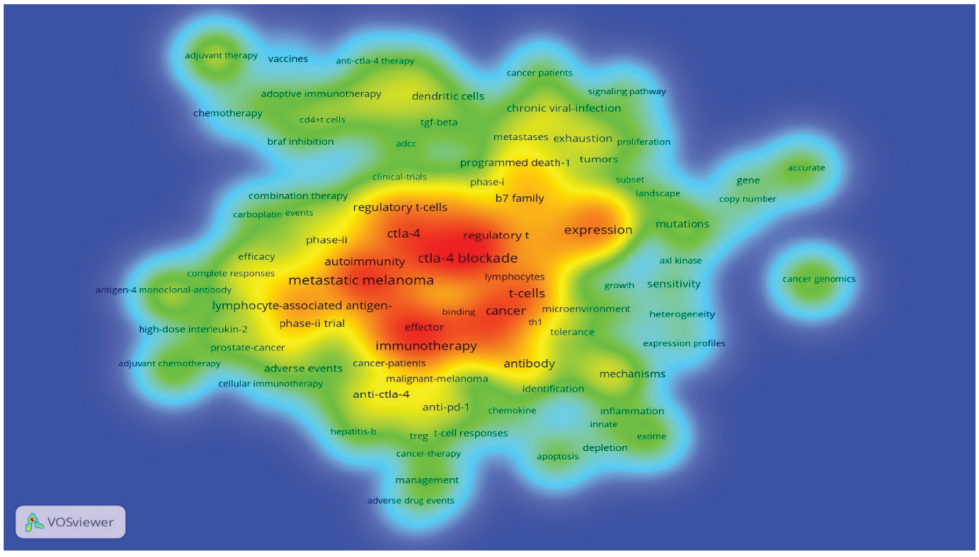

Figure 6. The map of the keywords for the 100 most cited papers on CTLA-4 molecule in cancer research was very dense for the keywords related to immunotherapy.

Table 4. The top 12 countries for the top cited publications on CTLA-4 molecule in cancer research

Rank	Country	Number of publications
1	USA	82
2	France	16
3	Germany	12
4	Japan	8
5	UK	8
6	Netherlands	7
7	Switzerland	7
8	Austria	6
9	Australia	5
10	Canada	5
11	Italy	5
12	Belgium	4

which is normally explained by his discovery of checkpoint molecule.[28]

Based on the results of the co-occurrence keywords, the top 100 most cited articles covered various aspects of immunotherapy in childhood leukemia, such as leukemia type, immunotherapy type and also immunotherapy mechanisms, such as CTLA-4 blockade, Ipilimumab, PD-1 blockade, and regulator T-cells. These keywords play an essential role in tumour immunity.[29] Likewise, the results of keywords were found in the bibliometric analysis of research on PD-1 and PD-L1 in the field of cancer.[24]

This type of study has an impact on other scientific and professional communities, but this manuscript has the potential for several types of bias which may affect the results. Firstly, some articles are not found in the core collection database of Web of Science, but they are in other sources such as Scopus. Second, the number of citations does not prove that the article is very important because of self-citations. Third, this could be explained by the fact that the search based on the title and the content is not specific. Fourth, it is possible that several first authors will have co-authored other papers in the top 100 and are therefore underrepresented in the current study format, a further limitation is the inclusion of

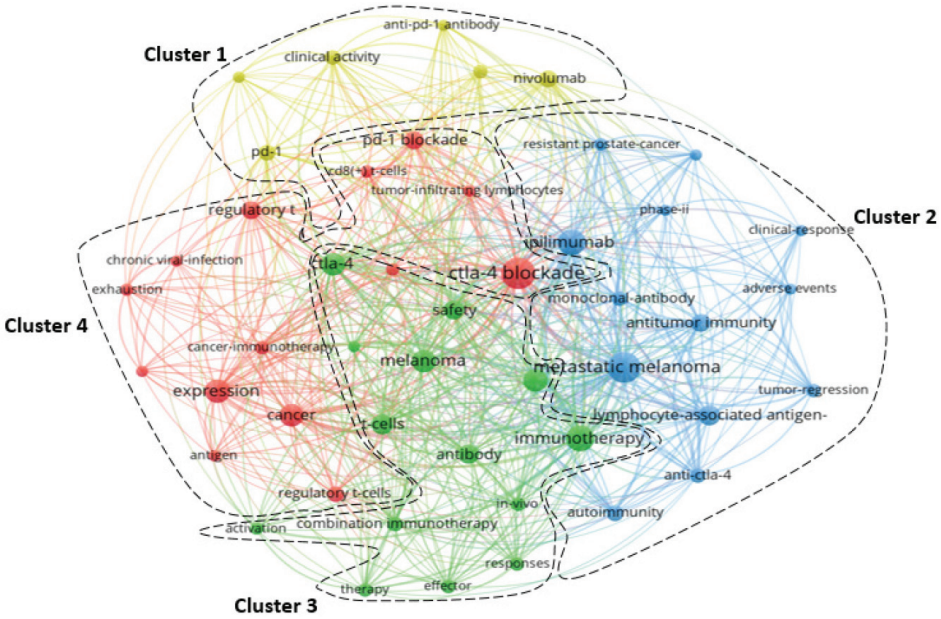

Figure 7. The network map analysis for the 100 most cited papers on CTLA-4 molecule in cancer research was performed by 47 co-occurrence keywords and included 4 separated clusters.

Table 5. The top 10 institutes for the most cited papers on CTLA-4 molecule in cancer research

Rank	Institute	Number of publications
1	Memorial Sloan Kettering Cancer Center	24
2	Bristol-Myers Squibb	15
3	University of Texas MD Anderson Cancer Center	13
4	Dana-Farber Cancer Institute	10
5	Harvard University	10
6	Weill Cornell Medical College	8
7	University California Los Angeles	7
8	Johns Hopkins University	6
9	The Netherlands Cancer Institute	6
10	Juntendo University	5

only first and senior authors and the institution of the first author.

Conclusion

The aim of the present article was to analyse and provide a comprehensive overview of the state of CTLA-4 checkpoint immunotherapy in cancer research. A literature analysis about CTLA-4 molecule in cancer research was performed from the Core Collection Database of Web of Science, followed by a statistical descriptive analysis of the annual publication, suggesting that most of the papers about CTLA-4 molecule decreased sharply after 2016. The countries and authors with the most contributions were all included in the developed classification in the United Nations (UN) rankings.[30] Therefore, this paper could be used as a resource for the research committee and trainees to encourage them to focus more on CTLA-4 immunotherapy research in cancer and to fund more research studies on CTLA-4.

Conflict of Interest

None declared

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN Estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209-49. doi: 10.3322/caac.21660.
2. Ichim CV. Revisiting immunosurveillance and immunostimulation: Implications for cancer immunotherapy. *J Transl Med*. 2005;3(1):8. doi: 10.1186/1479-5876-3-8.
3. Burnet M. Cancer; a biological approach. I. The processes of control. *Br Med J.* 1957;1(5022):779-86. doi: 10.1136/bmj.1.5022.779.
4. Zang X. 2018 Nobel Prize in medicine awarded to cancer immunotherapy: Immune checkpoint blockade - A personal account. *Genes Dis.* 2018;5(4):302-3. doi: 10.1016/j.gendis.2018.10.003.
5. Huang PW, Chang JW. Immune checkpoint inhibitors win the 2018 Nobel Prize. *Biomed J.* 2019;42(5):299-306. doi: 10.1016/j.bj.2019.09.002.
6. Ling V, Wu PW, Finnerty HF, Agostino MJ, Graham JR, Chen S, et al. Assembly and annotation of human chromosome 2q33 sequence containing the CD28, CTLA4, and ICOS gene cluster: analysis by computational, comparative, and microarray approaches. *Genomics.* 2001;78(3):155-68. doi: 10.1006/geno.2001.6655.
7. Linsley PS, Bradshaw J, Greene J, Peach R, Bennett KL, Mittler RS. Intracellular trafficking of CTLA-4 and focal localization towards sites of TCR engagement. *Immunity.* 1996;4(6):535-43. doi: 10.1016/s1074-7613(00)80480-x.
8. Olive D, le Thi S, Xerri L, Hirsch I, Nunès JA. The role of co-inhibitory signals driven by CTLA-4 in immune system. [Article in French] *Med Sci (Paris)*. 2011;27(10):842-9. doi: 10.1051/medsci/20112710012.
9. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. *J Exp Med.* 1995 1;182(2):459-65. doi: 10.1084/jem.182.2.459.
10. Mansh M. Ipilimumab and cancer immunotherapy: a new hope for advanced stage melanoma. *Yale J Biol Med.* 2011;84(4):381-9.
11. Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med.* 2017; 377(14):1345-56. doi: 10.1056/NEJMoa1709684.
12. MeSH Databases. [Internet] NCBI Home MeSH (2020). [cited on: 06 December 2020]. Available from: https://www.ncbi.nlm.nih.gov/mesh
13. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews

and meta-analyses: the PRISMA statement. *PLoS Med.* 2009.21;6(7):e1000097. doi: 10.1371/journal.pmed.1000097.
14. Journal Citation Reports. [Internet] Clarivate Analytics (2018). [cited on: 27 June 2018]. Available from: https://clarivate.com/products/journal-citation-reports/
15. Garfield E, Paris SW, Stock WG. HistCiteTM: A software tool for informetric analysis of citation linkage. *Informatrics.* 2006;57(8):391-400.
16. Van Eck NJ, Waltman L. Software survey: VOSviewer, a computer program for bibliometric mapping. *Scientometrics.* 2010;84(2):523-38. doi: 10.1007/s11192-009-0146-3.
17. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med.* 2013;11;369(2):122-33. doi: 10.1056/NEJMoa1302369.
18. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol.* 2015.10;33(17):1974-82. doi: 10.1200/JCO.2014.59.4358.
19. Petrelli F, De Stefani A, Trevisan F, Parati C, Inno A, Merelli B, et al. Combination of radiotherapy and immunotherapy for brain metastases: A systematic review and meta-analysis. *Crit Rev Oncol Hematol.* 2019;144:102830. doi: 10.1016/j.critrevonc.2019.102830.
20. Kotlowska MP, Rueda AG, Olmedo ME, Benito A, Roldán AS, Fernandez Méndez MA, et al. Efficacy of immunotherapy in sarcomatoid lung cancer, a case report and literature review. *Respir Med Case Rep.* 2019;26:310-4. doi: 10.1016/j.rmcr.2019.02.017.
21. Bates JE, Morris CG, Milano MT, Yeung AR, Hoppe BS. Immunotherapy with hypofractionated radiotherapy in metastatic non-small cell lung cancer: An analysis of the National Cancer Database. *Radiother Oncol.* 2019;138:75-9. doi: 10.1016/j.radonc.2019.06.004.
22. Esteva FJ, Hubbard-Lucey VM, Tang J, Pusztai L. Immunotherapy and targeted therapy combinations in metastatic breast cancer. *Lancet Oncol.* 2019;20(3):e175–86.doi: 10.1016/S1470-2045(19)30026-9.
23. Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. *N Engl J Med.* 2013;369(2):122-33. doi: 10.1056/NEJMoa1302369. Erratum in: *N Engl J Med*. 2018;379(22):2185.
24. Gao Y, Shi S, Ma W, Chen J, Cai Y, Ge L, et al. Bibliometric analysis of global research on PD-1 and PD-L1 in the field of cancer. *Int Immunopharmacol.* 2019;72:374-84. doi: 10.1016/j.intimp.2019.03.045.
25. Zhao X, He L, Mao K, Chen D, Jiang H, Liu Z. The research status of immune checkpoint blockade by anti-CTLA4 and anti-PD1/PD-l1 antibodies in tumor immunotherapy in China: A bibliometrics study. *Medicine (Baltimore)*. 2018;97(15):e0276. doi: 10.1097/MD.0000000000010276.
26. Zhong Q, Li BH, Zhu QQ, Zhang ZM, Zou ZH, Jin YH. The top 100 highly cited original articles on immunotherapy for childhood leukemia. *Front Pharmacol.* 2019;10:1100. doi:10.3389/fphar.2019.01100.
27. Baş Y, Şenel E. A Holistic evaluation of articles on PD-1 and PD-L1 published between 1975 and 2017: A bibliometric analysis. *Cancer Inform.* 2019;18:1–8. doi:10.1177/1176935119852620.
28. Gilman NV. Analysis for science librarians of the 2018 nobel prize in physiology or medicine: The life and work of James P. Allison and Tasuku Honjo. *Sci Technol Libr.* 2019;38(1):1-29. doi: 10.1080/0194262X.2018.1558165.
29. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer.* 2012;12(4):252-64. doi: 10.1038/nrc3239.
30. World economic situation and prospects 2020. [Internet] Department of Economic and Social Affairs of United Nations. [cited on: 06 December 2020].Available from: https://www.un.org/development/desa/dpad/publication/world-economic-situation-and-prospects-2020/
31. Duraiswamy J, Kaluza KM, Freeman GJ, Coukos G. Dual blockade of PD-1 and CTLA-4 combined with tumor vaccine effectively restores T-cell rejection function in tumors. *Cancer Res.* 2013;73(12):3591-603. doi: 10.1158/0008-5472.CAN-12-4100.
32. Snyder A, Makarov V, Merghoub T, Yuan J, Zaretsky JM, Desrichard A, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. *N Engl J Med.* 2014;371(23):2189-99. doi: 10.1056/NEJMoa1406498. Erratum in: *N Engl J Med.* 2018;379(22):2185.
33. Selby MJ, Engelhardt JJ, Quigley M, Henning KA, Chen T, Srinivasan M, et al. Anti-CTLA-4 antibodies of IgG2a isotype enhance antitumor activity through reduction of intratumoral regulatory T cells. *Cancer Immunol Res.* 2013;1(1):32-42. doi: 10.1158/2326-6066.
34. Sharma P, Allison JP. The future of immune checkpoint therapy. *Science.* 2015,3;348(6230):56-61. doi: 10.1126/science.aaa8172.
35. O'Day SJ, Maio M, Chiarion-Sileni V, Gajewski TF, Pehamberger H, Bondarenko IN, et al. Efficacy and safety of ipilimumab monotherapy in patients with pretreated advanced melanoma: a multicenter single-arm phase II study. *Ann Oncol.* 2010;21(8):1712-7. doi: 10.1093/annonc/mdq013.
36. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell.* 2015.13;27(4):450-61. doi: 10.1016/j.ccell.2015.03.001.
37. Peng W, Chen JQ, Liu C, Malu S, Creasy C, Tetzlaff

MT, et al. Loss of PTEN promotes resistance to T cell-mediated immunotherapy. *Cancer Discov.* 2016;6(2):202-16. doi: 10.1158/2159-8290.
38. Weber JS, D'Angelo SP, Minor D, Hodi FS, Gutzmer R, Neyns B, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. *Lancet Oncol.* 2015;16(4):375-84. doi: 10.1016/S1470-2045(15)70076-8.
39. Chen Q, Xu L, Liang C, Wang C, Peng R, Liu Z. Photothermal therapy with immune-adjuvant nanoparticles together with checkpoint blockade for effective cancer immunotherapy. *Nat Commun.* 2016;7:13193. doi: 10.1038/ncomms13193.
40. Postow MA, Callahan MK, Barker CA, Yamada Y, Yuan J, Kitano S, et al. Immunologic correlates of the abscopal effect in a patient with melanoma. *N Engl J Med.* 2012;366(10):925-31. doi: 10.1056/ NEJMoa1 112824.
41. Sharma P, Wagner K, Wolchok JD, Allison JP. Novel cancer immunotherapy agents with survival benefit: recent successes and next steps. *Nat Rev Cancer.* 2011;11(11):805-12. doi: 10.1038/nrc3153.
42. Slovin SF, Higano CS, Hamid O, Tejwani S, Harzstark A, Alumkal JJ, et al. Ipilimumab alone or in combination with radiotherapy in metastatic castration-resistant prostate cancer: results from an open-label, multicenter phase I/II study. *Ann Oncol.* 2013;24(7):1813-21. doi: 10.1093/annonc/mdt107.
43. Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proc Natl Acad Sci USA.* 2010;107(9):4275-80. doi: 10.1073/pnas. 0915174107.
44. Garbe C, Eigentler TK, Keilholz U, Hauschild A, Kirkwood JM. Systematic review of medical treatment in melanoma: current status and future prospects. *Oncologist.* 2011;16(1):5-24. doi: 10.1634/ theoncologist.2010-0190.
45. McGranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, et al. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science.* 2016;351(6280):1463-9. doi: 10.1126/science.aaf1490.
46. Reck M, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in extensive-disease-small-cell lung cancer: results from a randomized, double-blind, multicenter phase 2 trial. *Ann Oncol.* 2013;24(1):75-83. doi: 10.1093/annonc/ mds213.
47. Van Allen EM, Miao D, Schilling B, Shukla SA, Blank C, Zimmer L, et al. Genomic correlates of response to CTLA-4 blockade in metastatic melanoma. *Science.* 2015;350(6257):207-11. doi: 10.1126/science.aad0095.
48. Cancer Genome Atlas Research Network. Electronic address: wheeler@bcm.edu; Cancer Genome Atlas Research Network. Comprehensive and Integrative Genomic Characterization of Hepatocellular Carcinoma. *Cell.* 2017;169(7):1327-41.e23. doi: 10.1016/j.cell.2017.05.046.
49. Gubin MM, Zhang X, Schuster H, Caron E, Ward JP, Noguchi T, et al. Checkpoint blockade cancer immunotherapy targets tumour-specific mutant antigens. *Nature.* 2014;515(7528):577-81. doi: 10.1038/nature13988.
50. Ku GY, Yuan J, Page DB, Schroeder SE, Panageas KS, Carvajal RD, et al. Single-institution experience with ipilimumab in advanced melanoma patients in the compassionate use setting: lymphocyte count after 2 doses correlates with survival. *Cancer.* 2010;116(7):1767-75. doi: 10.1002/cncr.24951.
51. Ahmadzadeh M, Johnson LA, Heemskerk B, Wunderlich JR, Dudley ME, White DE, et al. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. *Blood.* 2009;114(8):1537-44. doi: 10.1182/blood-2008-12-195792.
52. Zamarin D, Holmgaard RB, Subudhi SK, Park JS, Mansour M, Palese P, et al. Localized oncolytic virotherapy overcomes systemic tumor resistance to immune checkpoint blockade immunotherapy. *Sci Transl Med.* 2014;6(226):226ra32. doi: 10.1126/ scitranslmed.3008095.
53. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell.* 2015;161(2):205-14. doi: 10.1016/j.cell.2015.03.030.
54. Tanaka A, Sakaguchi S. Regulatory T cells in cancer immunotherapy. *Cell Res.* 2017;27(1):109-18. doi: 10.1038/cr.2016.151.
55. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, et al. Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. *Science.* 2015;350(6264):1079-84. doi: 10.1126/science. aad1329.
56. Melero I, Berman DM, Aznar MA, Korman AJ, Pérez Gracia JL, Haanen J. Evolving synergistic combinations of targeted immunotherapies to combat cancer. *Nat Rev Cancer.* 2015;15(8):457-72. doi: 10.1038/nrc3973.
57. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. *J Clin Oncol.* 2012;30(21):2691-7. doi: 10.1200/JCO.2012.41.6750.
58. Khalil DN, Smith EL, Brentjens RJ, Wolchok JD. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. *Nat Rev Clin Oncol.* 2016;13(5):273-90. doi: 10.1038/nrclinonc.2016.25.
59. Spranger S, Bao R, Gajewski TF. Melanoma-intrinsic β-catenin signalling prevents anti-tumour immunity.

Nature. 2015;523(7559):231-5. doi: 10.1038/nature14404.
60. Holmgaard RB, Zamarin D, Munn DH, Wolchok JD, Allison JP. Indoleamine 2,3-dioxygenase is a critical resistance mechanism in antitumor T cell immunotherapy targeting CTLA-4. *J Exp Med*. 2013;210(7):1389-402. doi: 10.1084/jem.20130066.
61. Topalian SL, Taube JM, Anders RA, Pardoll DM. Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. *Nat Rev Cancer.* 2016;16(5):275-87. doi: 10.1038/nrc.2016.36.
62. Haanen JBAG, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J,et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017;28(suppl_4):iv119-iv142. doi: 10.1093/annonc/mdx225.
63. Dewan MZ, Galloway AE, Kawashima N, Dewyngaert JK, Babb JS, Formenti SC, et al. Fractionated but not single-dose radiotherapy induces an immune-mediated abscopal effect when combined with anti-CTLA-4 antibody. *Clin Cancer Res.* 2009;15(17):5379-88. doi: 10.1158/1078-0432.CCR-09-0265.
64. Gibney GT, Weiner LM, Atkins MB. Predictive biomarkers for checkpoint inhibitor-based immunotherapy. *Lancet Oncol.* 2016;17(12):e542-e551. doi: 10.1016/S1470-2045(16)30406-5.
65. Chen DS, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature.* 2017;541(7637):321-30. doi: 10.1038/nature21349.
66. Smyth MJ, Ngiow SF, Ribas A, Teng MW. Combination cancer immunotherapies tailored to the tumour microenvironment. *Nat Rev Clin Oncol.* 2016;13(3):143-58. doi: 10.1038/nrclinonc.2015.209.
67. Lynch TJ, Bondarenko I, Luft A, Serwatowski P, Barlesi F, Chacko R, et al. Ipilimumab in combination with paclitaxel and carboplatin as first-line treatment in stage IIIB/IV non-small-cell lung cancer: results from a randomized, double-blind, multicenter phase II study. *J Clin Oncol.* 2012;30(17):2046-54. doi: 10.1200/JCO.2011.38.4032.
68. Farkona S, Diamandis EP, Blasutig IM. Cancer immunotherapy: the beginning of the end of cancer? *BMC Med.* 2016;14:73. doi: 10.1186/s12916-016-0623-5.
69. Hugo W, Zaretsky JM, Sun L, Song C, Moreno BH, Hu-Lieskovan S, et al. Genomic and transcriptomic features of response to anti-PD-1 therapy in metastatic melanoma. *Cell.* 2016;165(1):35-44. doi: 10.1016/j.cell.2016.02.065.
70. BCarthon BC, Wolchok JD, Yuan J, Kamat A, Ng Tang DS, Sun J, et al. Preoperative CTLA-4 blockade: tolerability and immune monitoring in the setting of a presurgical clinical trial. *Clin Cancer Res.* 2010;16(10):2861-71. doi: 10.1158/1078-0432.CCR-10-0569.
71. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. *Cell.* 2017;168(4):707-23. doi: 10.1016/j.cell.2017.01.017.
72. Boussiotis VA. Molecular and biochemical aspects of the PD-1 checkpoint pathway. *N Engl J Med*. 2016;375(18):1767-78. doi: 10.1056/NEJMra1514296.
73. Tirosh I, Izar B, Prakadan SM, Wadsworth MH 2nd, Treacy D, Trombetta JJ, et al. Dissecting the multicellular ecosystem of metastatic melanoma by single-cell RNA-seq. *Science.* 2016;352(6282):189-96. doi: 10.1126/science.aad0501.
74. J Gao J, Shi LZ, Zhao H, Chen J, Xiong L, He Q, et al. Loss of IFN-γ pathway genes in tumor cells as a mechanism of resistance to anti-CTLA-4 therapy. *Cell.* 2016;167(2):397-404.e9. doi: 10.1016/j.cell.2016.08.069.
75. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJ, et al. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2014;15(7):700-12. doi: 10.1016/S1470-2045(14)70189-5.
76. Boutros C, Tarhini A, Routier E, Lambotte O, Ladurie FL, Carbonnel F, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. 2016;13(8):473-86. doi: 10.1038/nrclinonc.2016.58.
77. Simpson TR, Li F, Montalvo-Ortiz W, Sepulveda MA, Bergerhoff K, Arce F, et al. Fc-dependent depletion of tumor-infiltrating regulatory T cells co-defines the efficacy of anti-CTLA-4 therapy against melanoma. *J Exp Med.* 2013;210(9):1695-710. doi: 10.1084/jem.20130579.
78. Le DT, Lutz E, Uram JN, Sugar EA, Onners B, Solt S, et al. Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. *J Immunother.* 2013;36(7):382-9. doi: 10.1097/CJI.0b013e31829fb7a2.
79. Chang CH, Qiu J, O'Sullivan D, Buck MD, Noguchi T, Curtis JD, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. *Cell.* 2015;162(6):1229-41. doi: 10.1016/j.cell.2015.08.016.
80. Champiat S, Lambotte O, Barreau E, Belkhir R, Berdelou A, Carbonnel F, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol*. 2016;27(4):559-74. doi: 10.1093/annonc/mdv623.
81. Woo SR, Turnis ME, Goldberg MV, Bankoti J, Selby M, Nirschl CJ, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. *Cancer*

Res. 2012;72(4):917-27. doi: 10.1158/0008-5472.CAN-11-1620.
82. Patsoukis N, Bardhan K, Chatterjee P, Sari D, Liu B, Bell LN, et al. PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. *Nat Commun.* 2015;6:6692. doi: 10.1038/ncomms7692.
83. Myers G. Immune-related adverse events of immune checkpoint inhibitors: a brief review. *Curr Oncol.* 2018;25(5):342-7. doi:10.3747/co.25.4235.
84. Ngiow SF, von Scheidt B, Akiba H, Yagita H, Teng MW, Smyth MJ. Anti-TIM3 antibody promotes T cell IFN-γ-mediated antitumor immunity and suppresses established tumors. *Cancer Res.* 2011;71(10):3540-51. doi: 10.1158/0008-5472.CAN-11-0096.
85. Akbay EA, Koyama S, Carretero J, Altabef A, Tchaicha JH, Christensen CL, et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. *Cancer Discov.* 2013;3(12): 1355-63. doi: 10.1158/2159-8290.CD-13-0310.
86. Page DB, Postow MA, Callahan MK, Allison JP, Wolchok JD. Immune modulation in cancer with antibodies. *Annu Rev Med.* 2014;65:185-202. doi: 10.1146/annurev-med-092012-112807.
87. Llosa NJ, Cruise M, Tam A, Wicks EC, Hechenbleikner EM, Taube JM, et al. The vigorous immune microenvironment of microsatellite instable colon cancer is balanced by multiple counter-inhibitory checkpoints. *Cancer Discov.* 2015;5(1):43-51. doi: 10.1158/2159-8290.CD-14-0863.
88. Johnston RJ, Comps-Agrar L, Hackney J, Yu X, Huseni M, Yang Y, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. *Cancer Cell.* 2014;26(6):923-37. doi: 10.1016/j.ccell.2014.10.018.
89. Peggs KS, Quezada SA, Chambers CA, Korman AJ, Allison JP. Blockade of CTLA-4 on both effector and regulatory T cell compartments contributes to the antitumor activity of anti-CTLA-4 antibodies. *J Exp Med.* 2009;206(8):1717-25. doi: 10.1084/jem.20082492.
90. Bulliard Y, Jolicoeur R, Windman M, Rue SM, Ettenberg S, Knee DA, et al. Activating Fc γ receptors contribute to the antitumor activities of immunoregulatory receptor-targeting antibodies. *J Exp Med.* 2013;210(9):1685-93. doi: 10.1084/jem.20130573.
91. Noman MZ, Desantis G, Janji B, Hasmim M, Karray S, Dessen P, et al. PD-L1 is a novel direct target of HIF-1α, and its blockade under hypoxia enhanced MDSC-mediated T cell activation. *J Exp Med.* 2014;211(5):781-90. doi: 10.1084/jem.20131916.
92. Fedorov VD, Themeli M, Sadelain M. PD-1- and CTLA-4-based inhibitory chimeric antigen receptors (iCARs) divert off-target immunotherapy responses. *Sci Transl Med.* 2013;5(215):215ra172. doi: 10.1126/scitranslmed.3006597.
93. Feig C, Jones JO, Kraman M, Wells RJ, Deonarine A, Chan DS, et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. *Proc Natl Acad Sci USA*. 2013;110(50):20212-7. doi: 10.1073/pnas.1320318110.
94. Tanaka A, Sakaguchi S. Regulatory T cells in cancer immunotherapy. *Cell Res.* 2017;27(1):109-18. doi: 10.1038/cr.2016.151.
95. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. *Science.* 2018;359(6382):1350-5. doi: 10.1126/science.aar4060
96. Schachter J, Ribas A, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). *Lancet.* 2017;390(10105):1853-62. doi: 10.1016/S0140-6736(17)31601-X.
97. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. *Nature.* 2017;547(7662):222-6. doi: 10.1038/nature23003.
98. Voskens CJ, Goldinger SM, Loquai C, Robert C, Kaehler KC, Berking C, et al. The price of tumor control: an analysis of rare side effects of anti-CTLA-4 therapy in metastatic melanoma from the ipilimumab network. *PLoS One.* 2013;8(1):e53745. doi: 10.1371/journal.pone.0053745.
99. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, Set al. Phase 2 trial of single agent Ipilimumab (anti-CTLA-4) for locally advanced or metastatic pancreatic adenocarcinoma. *J Immunother.* 2010;33(8):828-33. doi: 10.1097/CJI.0b013e3181eec14c.
100. Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. *BMC Med.* 2015;13:211. doi: 10.1186/s12916-015-0455-8.
101. Chalmers ZR, Connelly CF, Fabrizio D, Gay L, Ali SM, Ennis R, et al. Analysis of 100,000 human cancer genomes reveals the landscape of tumor mutational burden. *Genome Med.* 2017;9(1):34. doi: 10.1186/s13073-017-0424-2.
102. Palucka AK, Coussens LM. The basis of oncoimmunology. *Cell.* 2016;164(6):1233-47. doi: 10.1016/j.cell.2016.01.049.
103. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. *J Clin Invest.* 2015;125(9):3384-91. doi: 10.1172/JCI80011.
104 Chen PL, Roh W, Reuben A, Cooper ZA, Spencer CN, Prieto PA, et al. Analysis of immune signatures in longitudinal tumor samples yields insight into biomarkers of response and mechanisms of resistance to immune checkpoint blockade. *Cancer Discov.*

2016;6(8):827-37. doi: 10.1158/2159-8290.
105 Quezada SA, Simpson TR, Peggs KS, Merghoub T, Vider J, Fan X, et al. Tumor-reactive CD4(+) T cells develop cytotoxic activity and eradicate large established melanoma after transfer into lymphopenic hosts. *J Exp Med.* 2010;207(3):637-50. doi: 10.1084/jem.20091918.
106 Madan RA, Mohebtash M, Arlen PM, Vergati M, Rauckhorst M, Steinberg SM, et al. Ipilimumab and a poxviral vaccine targeting prostate-specific antigen in metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol.* 2012;13(5):501-8. doi: 10.1016/S1470-2045(12)70006-2.
107 Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: Similarities, differences, and implications of their inhibition. *Am J Clin Oncol.* 2016;39(1):98-106. doi: 10.1097/COC.0000000000000239.
108 van den Eertwegh AJ, Versluis J, van den Berg HP, Santegoets SJ, van Moorselaar RJ, van der Sluis TM, et al. Combined immunotherapy with granulocyte-macrophage colony-stimulating factor-transduced allogeneic prostate cancer cells and ipilimumab in patients with metastatic castration-resistant prostate cancer: a phase 1 dose-escalation trial. *Lancet Oncol.* 2012;13(5):509-17. doi: 10.1016/S1470-2045(12)70007-4.
109. Ji RR, Chasalow SD, Wang L, Hamid O, Schmidt H, Cogswell J, et al. An immune-active tumor microenvironment favors clinical response to ipilimumab. *Cancer Immunol Immunother.* 2012;61(7):1019-31. doi: 10.1007/s00262-011-1172-6.
110. Voron T, Colussi O, Marcheteau E, Pernot S, Nizard M, Pointet AL, et al. VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. *J Exp Med.* 2015;212(2):139-48. doi: 10.1084/jem.20140559.
111. Okazaki T, Chikuma S, Iwai Y, Fagarasan S, Honjo T. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. *Nat Immunol.* 2013;14(12):1212-8. doi: 10.1038/ni.2762.
112. Alsaab HO, Sau S, Alzhrani R, Tatiparti K, Bhise K, Kashaw SK, et al. PD-1 and PD-L1 checkpoint signaling inhibition for cancer immunotherapy: Mechanism, combinations, and clinical outcome. *Front Pharmacol.* 2017;8:561. doi: 10.3389/fphar.2017.00561.
113. Zeng J, See AP, Phallen J, Jackson CM, Belcaid Z, Ruzevick J, et al. Anti-PD-1 blockade and stereotactic radiation produce long-term survival in mice with intracranial gliomas. *Int J Radiat Oncol Biol Phys.* 2013;86(2):343-9. doi: 10.1016/j.ijrobp.2012.12.025.
114. Wainwright DA, Chang AL, Dey M, Balyasnikova IV, Kim CK, Tobias A, et al. Durable therapeutic efficacy utilizing combinatorial blockade against IDO, CTLA-4, and PD-L1 in mice with brain tumors. *Clin Cancer Res.* 2014;20(20):5290-301. doi: 10.1158/1078-0432.CCR-14-0514.
115. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. *Cancer Immunol Res.* 2013;1(6):365-72. doi: 10.1158/2326-6066.CIR-13-0115.
116. Romano E, Kusio-Kobialka M, Foukas PG, Baumgaertner P, Meyer C, Ballabeni P, et al. Ipilimumab-dependent cell-mediated cytotoxicity of regulatory T cells ex vivo by nonclassical monocytes in melanoma patients. *Proc Natl Acad Sci USA.* 2015;112(19):6140-5. doi: 10.1073/pnas.1417320112.
117. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med.* 2018;378(2):158-68. doi: 10.1056/NEJMra1703481.
118. Weber JS, Dummer R, de Pril V, Lebbé C, Hodi FS; MDX010-20 Investigators. Patterns of onset and resolution of immune-related adverse events of special interest with ipilimumab: detailed safety analysis from a phase 3 trial in patients with advanced melanoma. *Cancer.* 2013;119(9):1675-82. doi: 10.1002/cncr.27969.
119. Weber J, Thompson JA, Hamid O, Minor D, Amin A, Ron I, et al. A randomized, double-blind, placebo-controlled, phase II study comparing the tolerability and efficacy of ipilimumab administered with or without prophylactic budesonide in patients with unresectable stage III or IV melanoma. *Clin Cancer Res.* 2009;15(17):5591-8. doi: 10.1158/1078-0432.CCR-09-1024.
120. Mahoney KM, Freeman GJ, McDermott DF. The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. *Clin Ther.* 2015;37(4):764-82. doi: 10.1016/j.clinthera.2015.02.018.
121. Ott PA, Hodi FS, Robert C. CTLA-4 and PD-1/PD-L1 blockade: new immunotherapeutic modalities with durable clinical benefit in melanoma patients. *Clin Cancer Res.* 2013;19(19):5300-9. doi: 10.1158/1078-0432.
122. Kim K, Skora AD, Li Z, Liu Q, Tam AJ, Blosser RL, et al. Eradication of metastatic mouse cancers resistant to immune checkpoint blockade by suppression of myeloid-derived cells. *Proc Natl Acad Sci U S A.* 2014;111(32):11774-9. doi: 10.1073/pnas.1410626111.
123. Cantwell-Dorris ER, O'Leary JJ, Sheils OM. BRAFV600E: implications for carcinogenesis and molecular therapy. *Mol Cancer Ther.* 2011;10(3):385-94. doi: 10.1158/1535-7163.
124. Charoentong P, Finotello F, Angelova M, Mayer C, Efremova M, Rieder D, et al. Pan-cancer immunogenomic analyses reveal genotype-

immunophenotype relationships and predictors of response to checkpoint blockade. *Cell Rep*. 2017;18(1):248-62. doi: 10.1016/j.celrep.2016.12.01.
125. Sangro B, Gomez-Martin C, de la Mata M, Iñarrairaegui M, Garralda E, Barrera P, et al. A clinical trial of CTLA-4 blockade with tremelimumab in patients with hepatocellular carcinoma and chronic hepatitis C. *J Hepatol*. 2013;59(1):81-8. doi: 10.1016/j.jhep.2013.02.022.
126. Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: A review. *JAMA Oncol*. 2016;2(10):1346-53. doi: 10.1001/jamaoncol.2016.1051.
127. Prieto PA, Yang JC, Sherry RM, Hughes MS, Kammula US, White DE, et al. CTLA-4 blockade with ipilimumab: long-term follow-up of 177 patients with metastatic melanoma. *Clin Cancer Res*. 2012;18(7):2039-47. doi: 10.1158/1078-0432.CCR-11-1823.
128. Wei SC, Levine JH, Cogdill AP, Zhao Y, Anang NAS, Andrews MC, et al. Distinct cellular mechanisms underlie anti-CTLA-4 and anti-PD-1 checkpoint blockade. *Cell*. 2017;170(6):1120-33.e17. doi: 10.1016/j.cell.2017.07.024.