Heliyon 10 (2024) e34068

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Combination therapy of targeting CD20 antibody and immune checkpoint inhibitor may be a breakthrough in the treatment of B-cell lymphoma

Xin Wu [a,1], Xiaoying Sun [b,c,1], Woding Deng [d], Rong Xu [e,**], Qiangqiang Zhao [f,g,*]

[a] Department of Spine Surgery, Third Xiangya Hospital, Central South University, Changsha, 410013, China
[b] School of Nursing, Sun Yat-sen University, Guangzhou, 528406, China
[c] The First Hospital of Sun Yat-sen University, Guangzhou, Guangdong, 510080, China
[d] Xiangya School of Medicine, Central South University, Changsha, China
[e] Department of Pathology, Changde Hospital, Xiangya School of Medicine, Central South University (The First People's Hospital of Changde City), Changde, 415003, Hunan, China
[f] Department of Hematology, Liuzhou People's Hospital Affiliated to Guangxi Medical University, Liuzhou, 545026, China
[g] Department of Hematology, The Qinghai Provincial People's Hospital, Xining, 810007, China

ARTICLE INFO

Keywords:
Lymphoma
CD20
Combination therapy
Immunotherapy
Rituximab

ABSTRACT

Background: CD20 is a membrane protein extensively expressed on the surface of B cells at various stages of development and differentiation. Herein, we conducted a bibliometrics analysis of the literature on CD20-targeting antibody therapy in lymphoma.

Methods: A total of 6663 articles were downloaded from the web of science core collection (WOSCC) from 1999 to July 23, 2022. Bibliometric.com was used for citation and annual publications analysis. VOSviewer was used to map countries/institutions/authors/journals nodes and links, extract hotspot keywords, and analyze the time trend of keywords. Citespace was employed to recognize the turning points based on the centrality value of countries, define the topic distribution of academics according to the map of dual-map overlay of journals, and characterize the emerging topics or landmark articles in a field based on references citation bursts.

Results: All articles were cited 225,032 times, averaging 33.77. The number of articles increased from 1999 to 2002, while the growth rate entered the platform after 2002. The USA was the most publication country, and China was the largest emerging country. Hotspots in this field still focus on the efficacy of rituximab in treating non-Hodgkin's lymphoma and the pathogenesis of lymphoma Application of generation CD-20 antibodies or molecule inhibitors in clinical research and cellular therapy/immunotherapy, such as CAR-T and PDL1/PD1 were the emerging research topics.

Conclusion: This study provides essential information and the tendency of the CD20-targeting antibody therapy in lymphoma by using bibliometric and visual methods, which would provide helpful references for clinical experiments and basic scientific research.

* Corresponding author. Department of Hematology, Liuzhou People's Hospital affiliated to Guangxi Medical University, Liuzhou, 545026, China.
** Corresponding author.
E-mail addresses: 278548453@qq.com (R. Xu), zgxyws@163.com (Q. Zhao).
[1] These authors have contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e34068
Received 28 June 2023; Received in revised form 20 January 2024; Accepted 3 July 2024
Available online 8 July 2024

1. Introduction

Blood system-related diseases have always been a problem that plagues human beings, and lymphoma is one of the most difficult parts [1–6]. Lymphomas can be divided into non-Hodgkin (90 %) and Hodgkin (10 %) types according to the tumor cells clinically [7]. The estimated new cases in 2022 of non-Hodgkin represent 4.2 % of all new cancer cases and 3.3 % of all cancer deaths in the US. At the same time, the estimated new cases of Hodgkin's represent 0.4 % of all new cancer cases and 0.2 % of all cancer deaths in the US. The number of new cases and deaths was far lower than in non-Hodgkin [8]. Regarding cell origin, most lymphomas (90 %) originate from B cells but can also be T cells or natural killer cells [9]. Generally, targeted therapies for b-cell lymphomas: 1. CD20-targeting antibodies, such as rituximab, ofatumumab, and Obinutuzumab; 2. Chimeric antigen receptor-modified T-cell (CAR-T); 3. Inhibitors that target the B-cell receptor signaling pathway. Of note, abnormal epigenetic signaling pathways exist in B- and T-cell lymphomas, epigenetic inhibitors such as belinostat, vorinostat, and romidepsin are approved by the Food and Drug Administration for T-cell lymphomas. Besides, some therapies targeting the tumor microenvironment could provide supportive care to reduce adverse reactions [10].

CD20-targeting antibody was applied to improve outcomes for patients with B-cell malignancies [11]. Although CD20-targeting antibody was designed for treating B-cell Lymphomas, monoclonal anti-CD20 antibodies' applicability in CD20-positive extranodal NK/T cell lymphoma or Hodgkin lymphoma was not well delimitated [12–14]. The information about clinical outcomes with anti-CD20 monotherapy or combined drug therapy using a classic regimen will improve the applicability of anti-CD20 antibodies.

Rituximab, a specific monoclonal anti-CD20-antibody, is the first drug approved for clinical use and can be shown to improve response rates and response duration [15]. Despite extensive use of rituximab in treating B cell-derived tumors, some patients fail to respond to initial therapy or relapse earlier than expected [16]. Therefore, next-generation anti-CD20 monoclonal antibodies have been developed, such as ofatumumab, Obinutuzumab, ublituximab, and the research status of anti-CD20 monoclonal antibodies in lymphoma was not clear.

Bibliometric is an established scientific methodology that can use software such as VOSviewer, and Citespace to analyze and visualize the further identifying essential issues in the research field and links between authors, institutions, and counties, which other methods including review, meta-analysis, or experiment article cannot perform. Bibliometrics, despite its limitations including dependency on specific databases and an emphasis on data quantification over quality or depth, plays a crucial role in uncovering historical shifts and projecting future trends in academic research through the analysis of keyword and topic frequencies. This analysis significantly contributes to the advancement of interdisciplinary research. Furthermore, by supplying objective data, bibliometrics assist academic institutions and funding bodies in optimizing resource distribution and pinpointing nascent research domains. Additionally, bibliometrics bolster research efficacy, fortify scientific discourse, and offer vital insights to the global scientific community. In this study, we studied this science citation index (SCI) articles from WOSCC, analyzed the global publication landscape, and identified influential countries and journals. This study aims to analyze the literature concerning CD20-targeting antibodies in treating lymphoma to identify its course of development and structural relationships in this research field.

2. Materials and methods

2.1. Data collection

Current documents were retrieved from the web of science core collection on May 31, 2022. The keywords "CD20" and "lymphoma or Malignant lymphoma or lymphocytic lymphoma" were used to extract publications. Exclude the literature published in 2022. The language was limited to English. Full records and cited references in the form of UTF-8 and ciw for use in further analysis.

2.2. Cell experiment

Cell Preparation and Culture: Human lymphoma cell lines OCI-LY8 and Raji were acquired from the Cell Bank of the Chinese Academy of Sciences. These cells were cultured in RPMI 1640 medium supplemented with 10 % fetal bovine serum (FBS), maintained at 37 °C in a 5 % CO2 atmosphere. Medium renewal occurred bi-daily. Upon reaching 70–80 % confluence, cells were either passaged for continued culture or utilized in experiments.

Drug Preparation and Treatment: Obinutuzumab was sourced from F. Hoffmann-La Roche Ltd, while the PD1 inhibitor Nivolumab was supplied by Bristol Myers Squibb. Treatment groups were as follows: Group 1 with Obinutuzumab (200 μg/ml), Group 2 with Nivolumab (72 μg/ml), and Group 3 with a combination of Obinutuzumab (200 μg/ml) and Nivolumab (72 μg/ml), each treated for a duration of 24 h.

Apoptosis Detection: Post-treatment, OCI-LY8 and Raji cells were gathered in 15 mL centrifuge tubes at a density of approximately 5 × 10^5 cells. Cells underwent triple washing with phosphate-buffered saline (PBS) at 179×*g* for 300 s each cycle. Post-resuspension in 100 μL binding buffer and supernatant removal, a mixture of Annexin V-fluorescein isothiocyanate (FITC)/PI was added and incubated for 15 min in a dark, room temperature environment. Following staining, 400 μL of 1 × binding buffer was incorporated, and the cells were gently agitated. After 60 min, single-cell suspensions were analyzed.

2.3. Statistical analysis

A total of 6663 articles were retrieved from the WOSCC. Citespace (Version 5.8.2R), VOSviewer (Version 1.6.16.0), and

bibliometric.com were used to analyze the country, institutions, authors, references, and keywords.

Citespace performed the most powerful citation bursts of reference and visualization of reference. Every node indicates a reference. The node's size represents its citation frequency, while the links between nodes indicate a coworker or co-citation. Analysis of reference with citation bursts or reference with the most significant citation provides the most influential reference over a while.

Co-citation countries, institutions, journals, authors, and co-occurrence of keywords were analyzed by VOSviewer. The network visualization showed the distribution of hotspots and the relationship between each node. Time-dependent overlay visualization emphasizes the annual change, which might provide emerging trends in a field. Density visualization focuses on the density of occurrence.

Bibliometric.com is an online software for bibliometric analysis. In this study, it is used for annual publication analysis. Microsoft Excel 2016 was used to import data and calculate linear and exponential fit.

3. Results

3.1. Annual publications

Articles increased steadily over 2002 (Fig. 1A), and the publications increased gently after 2002. Besides, the growth of publications in 1999–2002 was likely to be in accord with Price's law, the equation y = 117.91e0.22× (with a correlation coefficient of 0.9492) was obtained from its exponential curve, and another equation y = 47.6x+93.5 (with a correlation coefficient of 0.9186) followed by a linear fit (Fig. 1B). As shown in Fig. 1C, the USA published the most significant articles, and the number of articles published by Japan has changed little. Interesting, the growth of publications in China was increasing year by year. Besides, the distribution of citations on CD20-targeting antibody therapy in lymphoma by year, present in Fig. 2, shows an increasing trend. We calculate linear and exponential formulas to verify whether the citation growth conformed to Price's Law. The equation y = 721.26x+887.26, R2 = 0.9226 was obtained from its linear fit, and y = 1042.1 e 0.1511×, R2 = 0.6517 followed by an exponential curve. In sum, the continuous increase in citations indicates that CD20-targeting antibody therapy in lymphoma obtains wide attention.

3.2. Research field and type of articles

To investigate the main research field of CD20-targeting antibody therapy in lymphoma, we retrieved data about research areas from the WOSCC database. The result shown in Fig. 3A, the current research mainly focuses on oncology research areas, followed by hematology, pathology, and immunology. While among the 6663 articles, a large number of articles were original, accounting for 72.58 %, followed by reviews (14.813 %. and other types of articles, such as meeting abstracts, letters, and editorial materials.) (Fig. 3B).

3.3. Contribution of countries and institutions

This research involved several 5990 institutions in 104 countries. The topmost countries were listed in Table 1, which includes essential evaluation indices, such as the number of articles and centrality. As shown in Table 1 and Fig. 4A, the USA obtained the most significant number of articles (1883), and the second number of publications originated from Japan (599), followed by China (410). Although the number of articles published in Italy and England was not listed in the top three, the centrality of these countries was more than 0.1, which means there are more important in this research field. Moreover, the USA has the most prominent publications and centrality values, which indicated its most remarkable contributions in this research field, and high-quality articles were derived from it. The time-dependent overlay map showed that China, Russia, Iran, the Czech Republic, and India began this research later than other countries (Fig. 4B).

All 5990 institutions were interrelated in this research field. The top 10 productive institutions are listed in Table 2. University of Texas MD Anderson Cancer Center (n = 151) ranked first, followed by the University of Washington (n = 140) and Mayo Clinic (138).

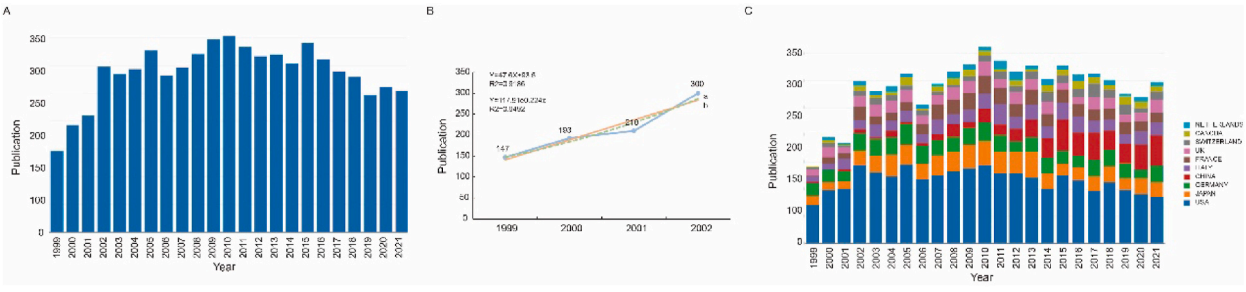

Fig. 1. Number of publications of CD20-targeting antibody therapy in lymphoma A. Number of publications per year. B. The growth trend of publications in 1999–2002. C. The top 10 relative countries in the number of publications.

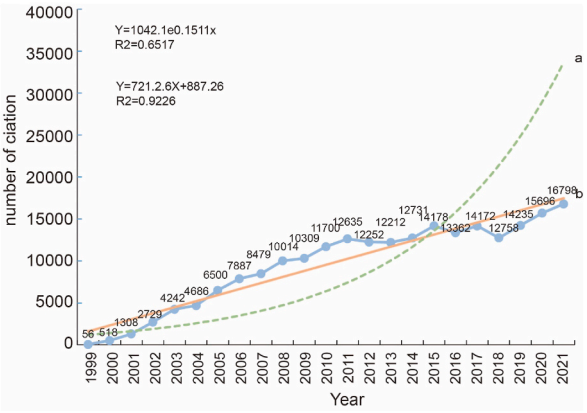

Fig. 2. The number of citations of CD20-targeting antibody therapy in lymphoma. Exponential adjustment (a): y = 1042.1 e $^{0.1511x}$, R^2 = 0.6517; Linear adjustment (b): y = 721.26x+887.26, R^2 = 0.9226.

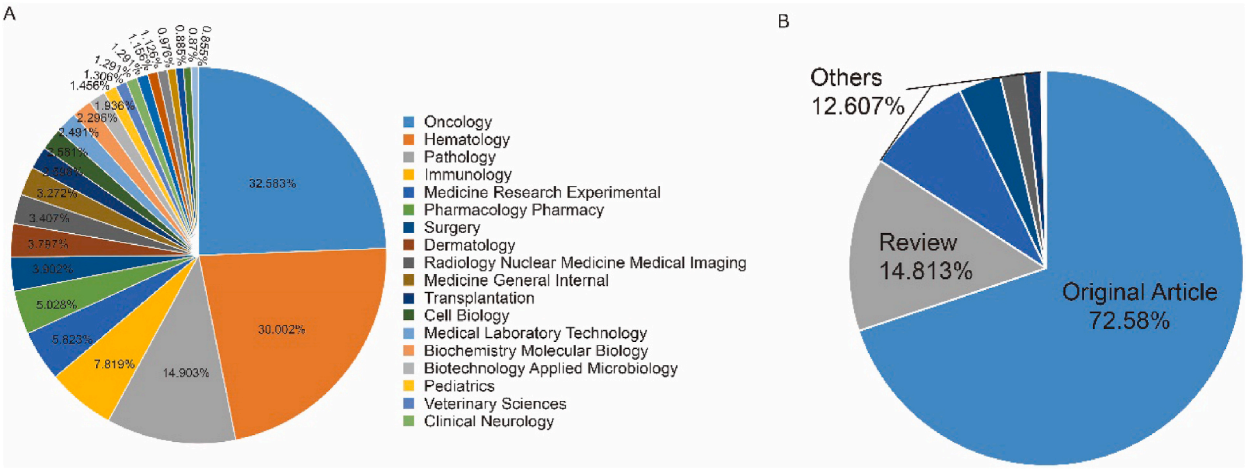

Fig. 3. Countries and institutions contributed to CD20-targeting antibody therapy in lymphoma. A. The distribution of research area on CD20-targeting antibody therapy in lymphoma. B. The distribution of articles type of CD20-targeting antibody therapy in lymphoma.

Table 1
Top 10 most productive countries.

Rank	Country	Articles	Centrality
1	USA	1883	0.56
2	JAPAN	599	0.08
3	CHINA	410	0.02
4	GERMANY	408	0.07
5	FRANCE	333	0.06
6	ITALY	333	0.14
7	ENGLAND	255	0.27
8	SWITZERLAND	166	0.05
9	CANADA	129	0.04
10	SPAIN	124	0.07

Among them, Fred Hutchinson Cancer Research Center, an institution engaged in research on cancer and fatal infectious diseases, has the highest average citations (83.96078). The articles of more than 5 in 717 institutions were visualized in Fig. 4C. Cluster analysis of institutions revealed the connection between institutions. According to the link strength of institutions' co-occurrence, the network was divided into three clusters. The first cluster was dominated by Stanford University and Mayo Clinic. University of Texas MD Anderson Cancer Center mediates the second cluster, and Memorial Sloan Kettering Cancer Center dominates the third cluster.

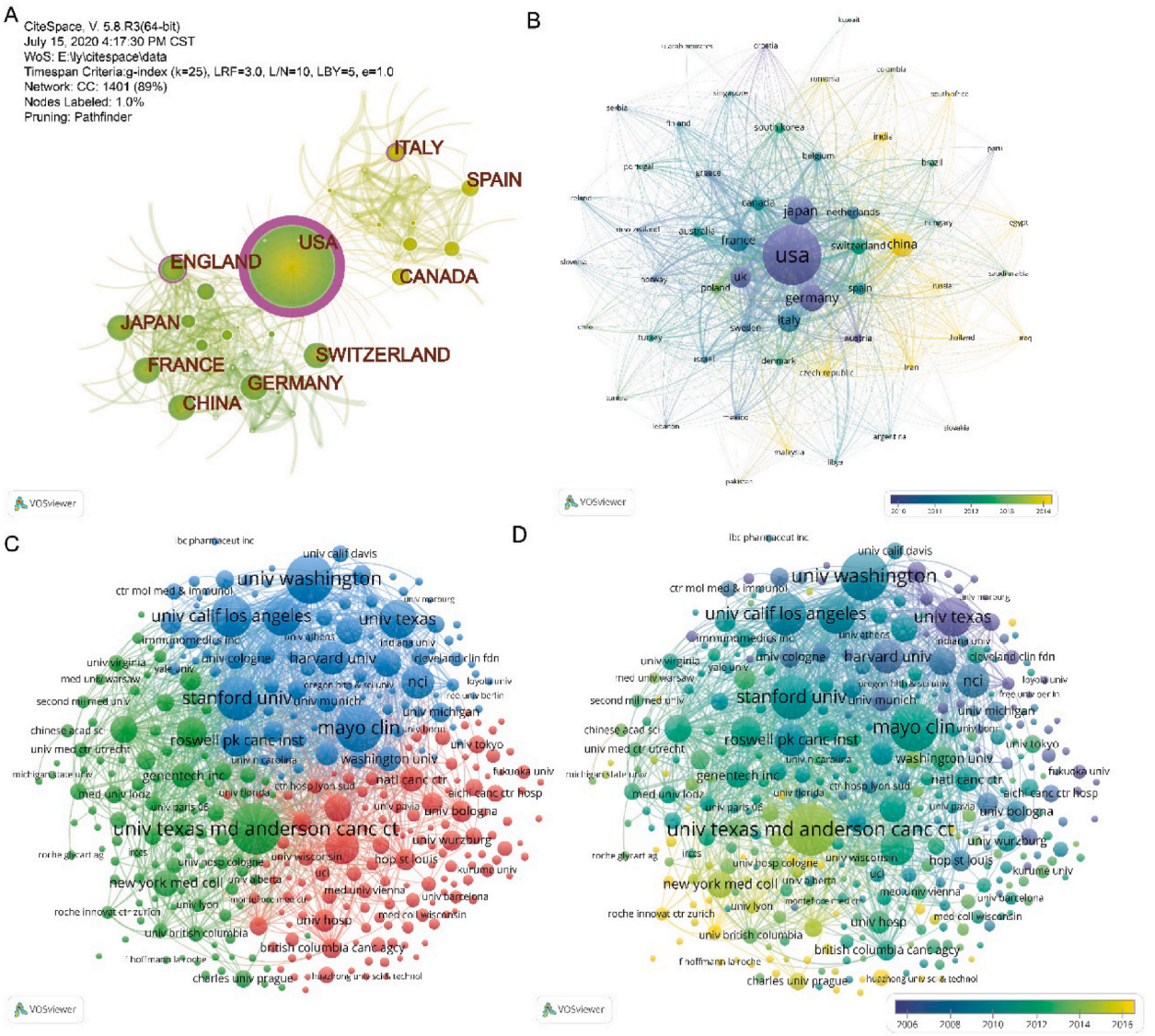

Fig. 4. Cooperation and citation relationship among countries and institutions. A: visualization of the top 10 countries with the highest number of articles. B: time-dependent overlay map of countries. C: overlay visualization of institutions. D: time-dependent overlay map of institutions.

Table 2
Top 10 most productive institutions.

Rank	institutions	countries	Documents	Citations	Average citation
1	Univ Texas MD Anderson Canc Ctr	USA	151	5826	38.58278
2	Univ Washington	USA	140	7393	52.80714
3	Mayo Clin	USA	138	6596	47.7971
4	Stanford Univ	USA	122	10201	83.61475
5	Univ Calif Los Angeles	USA	115	9635	83.78261
6	Univ Texas	USA	104	7128	68.53846
7	Fred Hutchinson Canc Res Ctr	USA	102	8564	83.96078
8	Mem Sloan Kettering Canc Ctr	USA	89	4666	52.42697
9	NCI	USA	87	5602	64.3908
10	Harvard Univ	USA	85	6029	70.92941

3.4. Landmark authors and publications

Altogether, 30991 authors were involved in producing 6663 related articles; on average, 4.7 researchers worked as a group to publish an article. One thousand three authors with more than five articles were visualized. The higher number of citations, the larger size of the node, and the lines between nodes indicate the active degree of cooperation (Fig. 5A). Besides, according to the color of nodes, several authors started this research mainly in 2010–2015 (Fig. 5B). Press Oliver W, Goldenberg David M, and Klein Christian were the three highest ranked researchers, published more than 45 articles Table 3A. The authors with over 4000 citations are listed in Table 4. The list includes White CA (citation = 5047), Grillo Lopez AJ (citation = 4847), Coiffier B (citation = 5117), and Gaulard P (citation = 4565), which indicate their considerable contributions in this field.

Over time, six thousand sixty-three articles on CD20-targeting antibody therapy in lymphoma were also cited. Citespace generated a co-citation network of articles, and the top 10 citation articles were marked on the map (Fig. 6 A) (Table 5). The most co-cited reference was published by a clinical trial published by McLaughlin P in 1998 [17], followed by a clinical trial published by Coiffier B in 2002 [18], and another clinical trial published by Czuczman M S in 1999 [19].

Citation bursts of a reference mean it is cited frequently in a period. The top 50 most robust citation bursts are shown in Fig. 6B. The

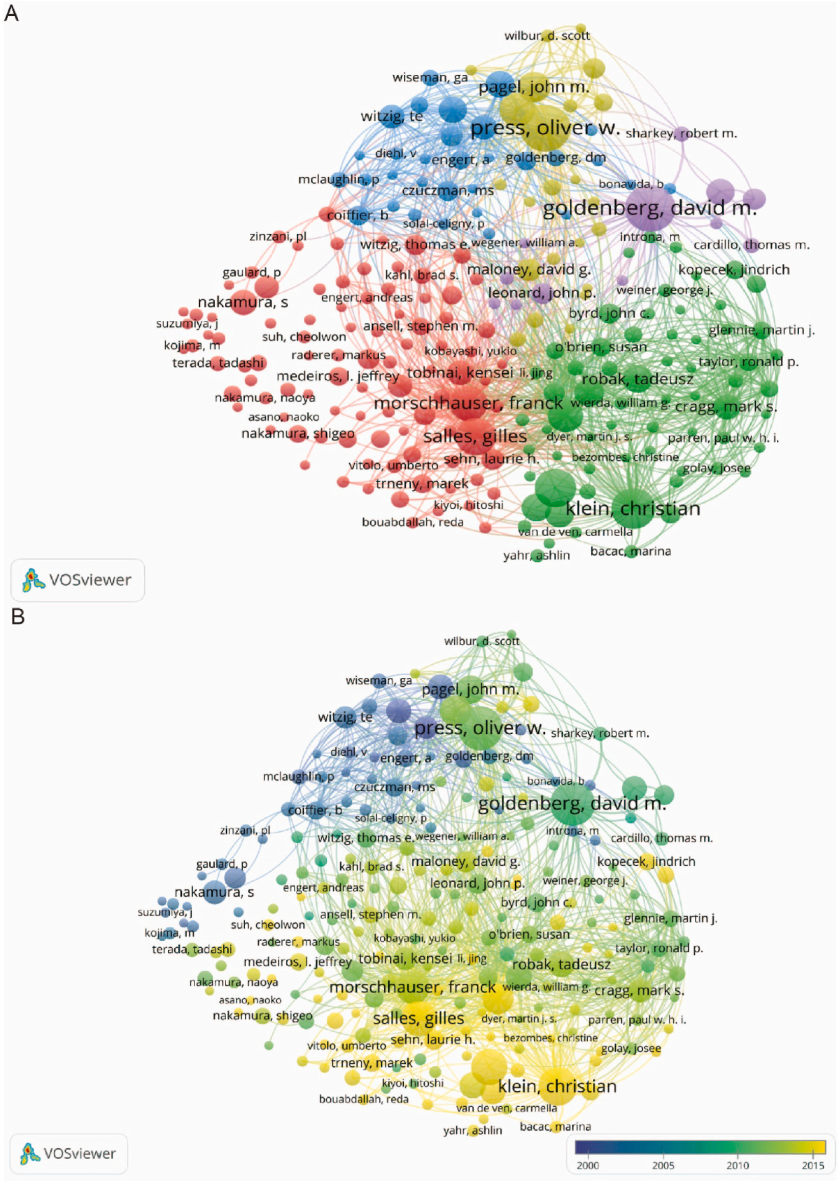

Fig. 5. Visualization map of co-authorship of authors A: network visualization of authors on CD20-targeting antibody therapy in lymphoma. B: time-dependent overlay visualization of authors on CD20-targeting antibody therapy in lymphoma.

Table 3
Pivotal authors of documents of CD20-targeting antibody therapy in lymphoma.

NO.	Author	Affiliation	H-index	Total link strength	documents	citations
1	Press, Oliver W	Fred Hutchinson Cancer Center , USA	54	84362	55	2498
2	Goldenberg, David M	Penn State Health , USA	88	83907	55	1726
3	Klein, Christian	Roche Holding , Switzerland	49	90486	47	2298
4	Cairo, Mitchell s	Westchester Medical Center , USA	68	29532	44	404
5	Salles, Gilles	Univ Lyon , France	94	105639	43	3079
6	Morschhauser, Franck	CHU Lille, France	53	83051	40	2949
7	Gopal, Ajay K	Fred Hutchinson Cancer Center,	44	54845	38	2234
8	Cartron, Guillaume	CHU de Montpellier, France	25	102704	37	1721
9	Pagel, John M	Swedish Cancer Institute, USA	46	50631	34	1930
10	Robak, Tadeusz	Med Univ Lodz, Poland	59	59530	31	1933

Table 4
The authors with total citations of over 4000.

15	White, CA	Atlanta VA Medical Center, USA	22	60331	29	5047
19	Grillo-lopez, AJ	POB 3797, USA	42	59197	27	4847
34	Coiffier, B	CHU Lyon, France	94	60752	21	5117
114	Gaulard, P	Universite Paris-Est-Creteil-Val-de-Marne (UPEC), France	63	10654	13	4565

citation burstiness of these references was evenly distributed from 1999 to 2016. The articles with the strongest burstiness (strength = 111.94) were published by McLaughlin P, in 1998, with citation bursts from 1999 to 2003. From the above analysis, the articles on CD20-targeting antibody therapy in lymphoma mainly focus on clinical research.

3.5. Publication distribution among journals

A total of 6663 articles were published in 1026 journals and 250 journals with more than five articles. Blood was the most popular journal, receiving 534 articles; Leukemia & Lymphoma ranked second (n = 259), followed by Journal of Clinical Oncology (n = 174). Although the Journal of Clinical Oncology was not the journal with the highest total citations, it obtained the highest citation per paper (n = 139.2701) (Table 6). From the network visualization analysis, Blood, Leukemia & Lymphoma, and Journal of Clinical Oncology were the most popular journals in this research field (Fig. 7A). Current research has recently been reported in journals that have never published articles on this research field, such as Frontier in immunology, blood advances, oncoimmunology, etc. (Fig. 7B). Besides, a dual-map overlay of journals reveals that articles on CD20-targeting antibody therapy in lymphoma published in molecular, biology, immunology and medicine, medical, and clinical were cited by articles published in molecular, biology, immunology and health, nursing, medicine journals (Fig. 7C).

3.6. Hotspot and emerging trends from keywords analysis

VOSviewer was used for keywords co-occurrence and cluster analysis. A total of 7154 keywords were extracted, of which 522 appeared more than five times and 257 appeared more than ten times. The overlay visualization of co-occurrence keywords can provide high-frequency keywords, which may reveal the hotspots in the current research field. As shown in Fig. 8A, rituximab was the highest frequency keyword with 1159 co-occurrences, followed by lymphoma and non-Hodgkin's lymphoma. The keywords were classified into four clusters, represented by four colors (red, green, blue, and yellow). Time-dependent overlay visualization could reveal the emerging trend in this field. The keywords for targeted drugs include obinutuzumab, ibrutinib, idelalisib, venetoclax, immune checkpoint inhibitors, and therapy methods including car-t, cancer immunotherapy, cellular therapy, atomic force microscopy. While emerging molecules involving myc, PD-1, cd3, and cd45 (Fig. 8B).

From the above research, rituximab remained the research hotspot. It is a significant turning point in the treatment of lymphoma and leads the progress of the whole oncology department in precision and targeted treatment. Moreover, many antibody drugs, such as new generation CD20 antibodies (Obinutuzumab), inhibitors for BCL-2/PI3k/BTK, and therapy methods, such as immunotherapy, and cellular therapy, have greatly enriched the treatment of tumors.

3.7. Combined therapy with obinutuzumab and PD1 inhibitor is synergistic in lymphoma cells

The co-occurrence analysis of key terms in DLBCL treatment research demonstrates a frequent simultaneous consideration of 'CD20 antibodies' and 'PD1 inhibitors'. This suggests a close association between these treatment methods. Obinutuzumab, exemplifying the new generation of CD20 antibodies, has been engineered to amplify therapeutic effectiveness and circumvent drug resistance. Similarly, Nivolumab, a prototypical PD1 inhibitor, exhibits significant efficacy in DLBCL treatment [20,21]. This study combines the new generation CD20 antibody- Obinutuzumab with PD1 inhibitor-nivolumab for lymphoma therapy. As shown in Fig. 9, Obinutuzumab treatment could induce cell apoptosis; when combined with PD1 inhibitor, the apoptosis rate could significantly increase (Fig. 9).

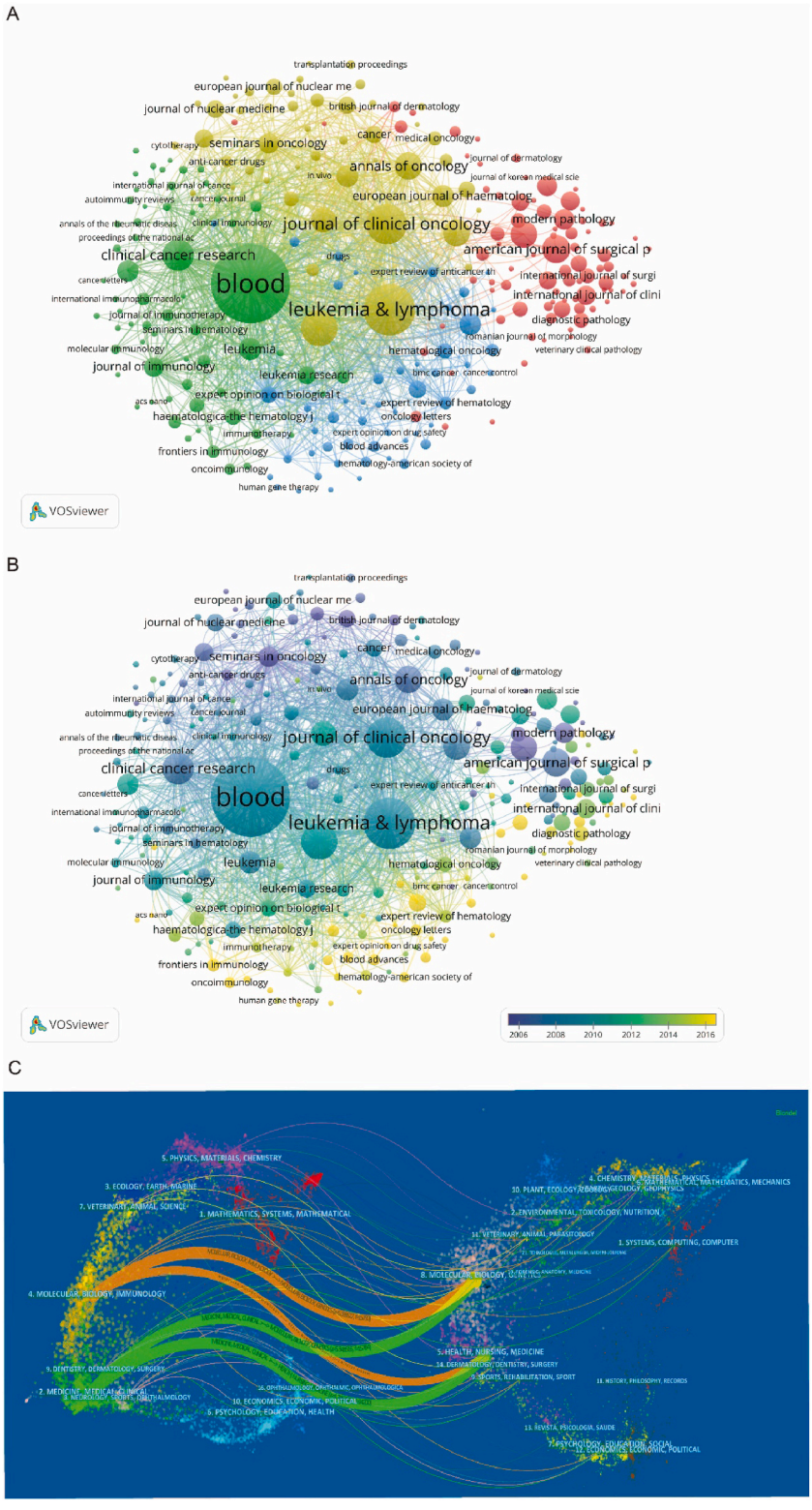

Fig. 6. Journal analysis on CD20-targeting antibody therapy in lymphoma. A: network visualization of journals B: time-dependent overlay visualization of journals C: dual-map overlay of journals. Notes: left side as citing journals, and right side as cited journals, the orange and green path means citations relationship. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 5
Top 10 citation reference.

Citation counts	References	Article type
259	McLaughlin P, 1998, J CLIN ONCOL, 16, 2825	Clinical trial
197	Coiffier B, 2002, NEW ENGL J MED, 346, 235	Clinical trial
183	Czuczman MS, 1999, J CLIN ONCOL, 17, 268	Clinical trial
152	Coiffier B, 1998, BLOOD, 92, 1927	Clinical trial
133	Maloney DG, 1997, BLOOD, 90, 2188	Clinical trial
103	Witzig TE, 2002, J CLIN ONCOL, 20, 2453	Clinical trial
95	Colombat P, 2001, BLOOD, 97, 101	Clinical trial
89	Cartron G, 2002, BLOOD, 99, 754	Clinical trial
89	Shan D, 1998, BLOOD, 91, 1644	Article
87	Marcus R, 2005, BLOOD, 105, 1417	Clinical trial

Table 6
Top 10 journals for publications.

Rank	Journal	Documents	Citations	Average citation	JCR/IF
1	Blood	535	37978	70.98692	Q1/22.113
2	Leukemia & Lymphoma	259	4702	18.15444	Q3/3.28
3	Journal of Clinical Oncology	174	24233	139.2701	Q1/44.544
4	British Journal of Hematology	145	5397	37.22069	Q1/6.998
5	Clinical Cancer Research	113	6545	57.92035	Q1/12.531
6	American Journal of Surgical Pathology	94	5444	57.91489	Q1/6.394
7	Annals of Oncology	90	3631	40.34444	Q1/32.976
8	International Journal of Hematology	87	1077	12.37931	Q3/2.49
9	American Journal of Clinical Pathology	85	2957	34.78824	Q3/2.493
10	Haematologica	77	2314	30.05195	Q1/9.941

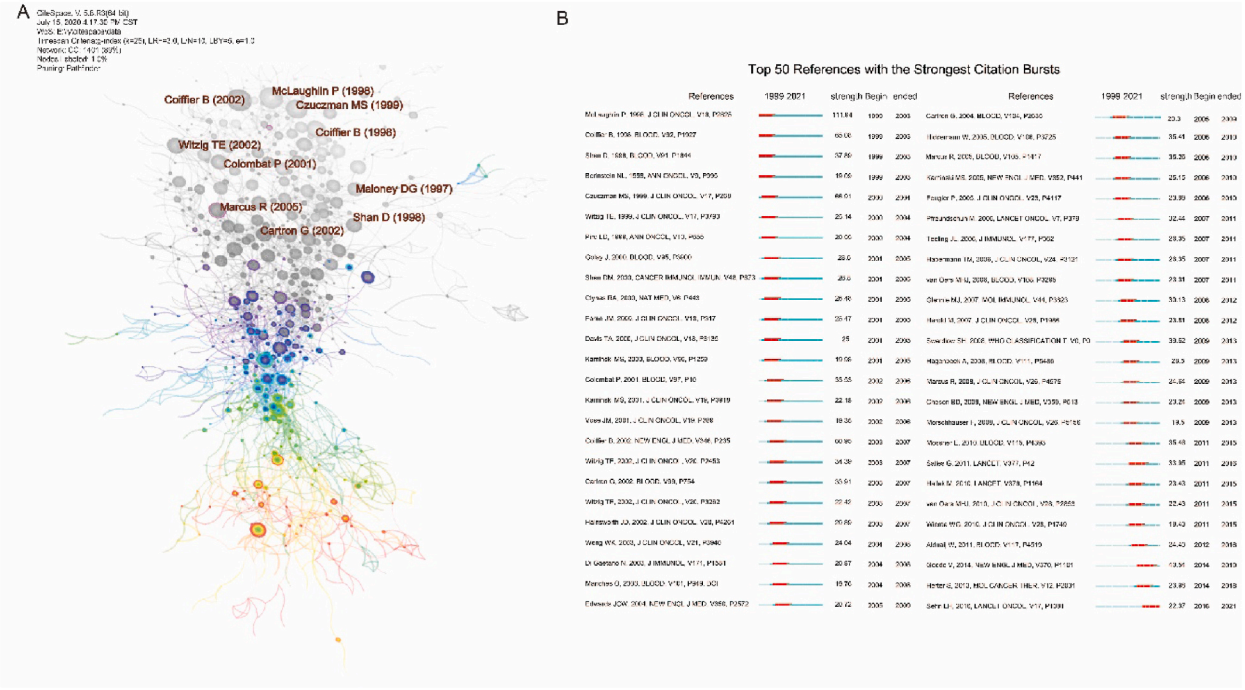

Fig. 7. Reference analysis on CD20-targeting antibody therapy in lymphoma. A: visualization of ten references with the highest citations. B: the top 50 references with the most robust bursts of citations.

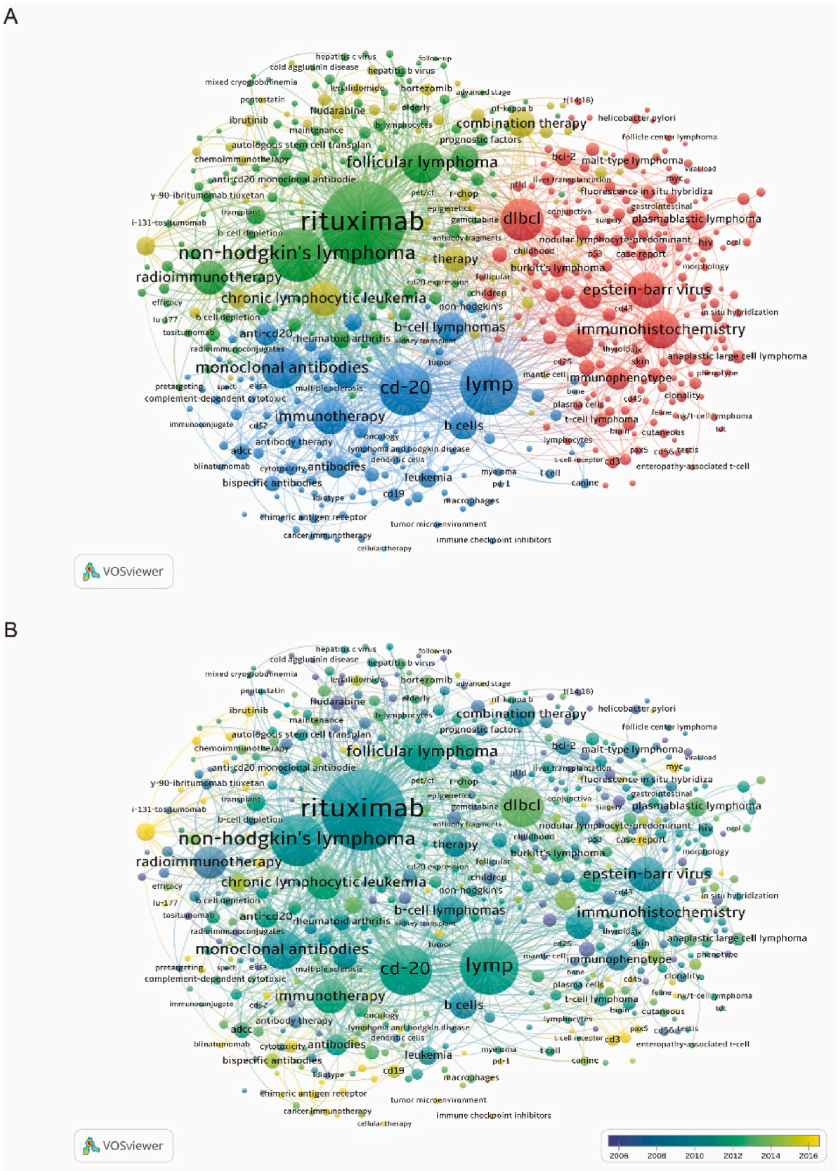

Fig. 8. Keywords analysis on CD20-targeting antibody therapy in lymphoma A: network visualization of journals B: time-dependent overlay visualization of journals C: dual-map overlay of journals. Notes: left side as citing journals, and right side as cited journals, the orange and green path means citations relationship. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

4. Discussion

4.1. General information

This study retrieved 6663 CD20-targeting antibody therapy in lymphoma articles from the WOSCC database until May 31, 2022. The current study involves 1026 journals by 30991 authors from 104 countries and 5990 institutions.

The annual number and trend of articles reflect this field's development speed and research progress [22,23]. As shown in Fig. 1A–B that the overall growth pattern of publications was steadily increasing, which indicated that current research might enter a plateau. Besides, after being adjusted to be a tendency line, the growth pattern of current publications from 1999 to 2002 was inclined to fit an exponential trend rather than a linear equation according to the correlation coefficient of 0.9492 of its exponential equation $y = 117.91e0.224\times$. Not every distribution of publications conforms to Price's Law in any period. The growth patterns of publications are impacted by many aspects [24]. However, the citation has been growing. From the annual numbers and citations analysis, the current research may develop steadily, but it still receives considerable attention from scholars.

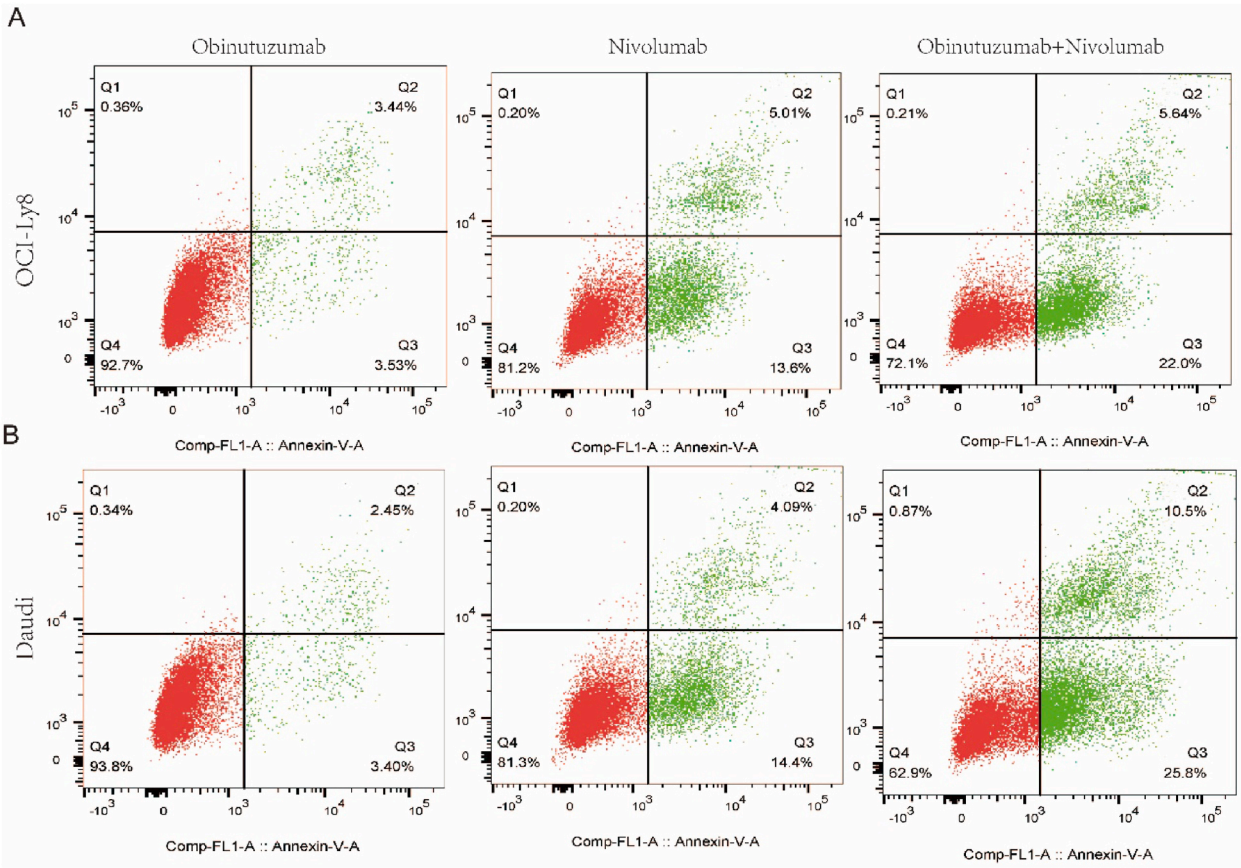

Fig. 9. Obinutuzumab combined with PD1 inhibitors acts synergistically for lymphoma. A: Cell apoptosis analysis for OCI-Ly8 cells. B: Cell apoptosis analysis for Daudi cells.

The distribution of publications across different countries has been unbalanced and restricted by several factors, such as economic development and investment in scientific research. Centrality is an index to measure the importance of a node in the network, which is mainly used to measure the value of the bridge function of the node in the entire network structure [25].

The USA was the most prolific country and obtained the highest centrality value, which was regarded as an essential turning point that may lead to transformative discoveries [26,27]. Although the number of publications of Italy and the UK was not ranked in the top 3 productive countries, their node was colored purple round, indicating that they were influential countries in this field. Noticeably, the publications in China were increasing rapidly in 2008 (Fig. 1C). It may conclude that more Chinese researchers are equipped to engage in this field and conduct more research. Besides, there are active collaborations among the USA, France, Germany, UK, Japan, and China, indicating that CD20-targeting antibody therapy in lymphoma research has gained interest mainly in USA, western countries, and the USA was the main collaborating center.

Are there differences among institutions in the current study? Fig. 4C and D, Table 2 showed that the University of Texas MD Anderson Cancer Center, University Washington, and Mayo Clinic were the top productive institutions, implying their notable contributions to this research field. Importantly, all the top 10 productive institutions came from the USA, which confirmed its leading role in current fields.

Highlighting the contributions of influential researchers can help scholars move along the road and provide further directions and guidelines [28]. In this study, Press, Oliver W, and Goldenberg, David M published the most papers, while White, CA had the most co-citations. Salles, Gilles, and Coiffier, B had the highest H-index value, indicating their powerful influence in this research field. The network of authors provides information about potential collaborators and influential research groups.

Journals analysis showed that Blood was the most popular journal. Although the Journal of Clinical Oncology was not the journal with the highest total citations, it obtained the highest citation per paper (n = 139.2701). Besides, a dual-map overlay of journals reveals that articles on CD20-targeting antibody therapy in lymphoma published in molecular, biology, immunology and medicine, medical, and clinical were cited by articles published in molecular, biology, immunology and health, nursing, and medical journals. The connection between different research fields enhances the understanding of different specialties and promotes their development. Both primary and clinical research are involved in the current research field, which means the clinical translational application of this research had a considerable achievement.

4.2. The hotspots and frontiers

Co-occurrence keywords/terms can reflect the hotspots of research fields. In this bibliometrics, high-frequency keywords of current research included rituximab, non-Hodgkin's lymphoma, diffuse large b cell lymphoma, Epstein-Barr virus, immunohistochemistry, monoclonal antibodies, etc. Non-Hodgkin lymphoma accounts for 90 % of lymphoma, while Hodgkin's accounts for 10 %. At the same time, non-Hodgkin's lymphoma is further divided into B-cell and T-cell/natural killer (NK) cell types. Most non-Hodgkin's lymphoma in the clinic is B-cell type [17,29]. Generally, the CD20 antigen is expressed in over 90 % of B-cell lymphoma; it is regarded as an effective therapy for B-cell lymphoma. Diffuse large B-cell lymphoma (DLBCL), an aggressive B-cell lymphoma, accounts for 25–30 % of non-Hodgkin's lymphoma [9]. Although generation CD20 antibodies were applied in the clinic, rituximab is likely to maintain a position within the therapeutic armamentarium of its successful clinical use in long history [30].

Furthermore, keywords analysis also found that Epstein-Barr virus (EBV) was related to our research. EBV was discovered more than 50 years and is regarded to be a human tumor virus according to its tumorigenic role in a diverse range of tumors, such as lymphoma and Nasopharyngeal carcinoma [31–33]. EBV infection led to the development of cancers may attribute to its infection of T cells, B cells, and epithelial cells [34]. To study EBV is to explore the pathogenesis of lymphoma. In terms of lymphoma types, DLBCL would be the hotspots of this research, while pathogenesis of lymphoma was also the research highlight according to knowledge structure.

According to the time-dependent overlay map of keywords, emerging keywords about targeted drugs, therapy methods, molecules including obinutuzumab, ibrutinib, idelalisib, venetoclax, immune checkpoint inhibitors, car-t, cancer immunotherapy, cellular therapy, atomic force microscopy, combination therapy, myc, PD-1, cd3, cd45. CD20 targeting monoclonal antibody therapy changed the treatment landscape of lymphoma, especially for b-cell-derived [35]. However, patients with double-hit lymphoma transformed lymphomas, and early relapses will become refractory to standard therapies and have limited alternatives for cure [36].

Therefore, generating other targeting drugs as alternative therapies or combination therapies which have greatly enriched the treatment of lymphoma. Besides, the top three citation references revealed that clinical trials of rituximab or rituximab plus CHOP for lymphoma treatment were the hotspot research. Interesting, the most reference was also the reference with the most powerful citation bursts, which was published by Mclaughlin P in 1998. In this research, an anti-CD20 antibody was applied in the treatment of patients with relapsed low-grade or follicular lymphoma, and the effects after treatment and the side effects during treatment were analyzed. Compared with chemotherapy, toxicity was mild, and the response rate was 48 %. This article provides essential information for follow-up clinical research [17].

The success of rituximab promotes the development of other anti-CD20 monoclonal antibodies. This study examines the advancements in next-generation CD20 antibodies for B-cell lymphoma treatment, focusing on the development and clinical application of innovative anti-CD20 monoclonal antibodies, including ublituximab, ofatumumab, and obinutuzumab. Ofatumumab and ublituximab, as newer generation CD20-targeted antibodies, offer promising options for B-cell lymphoma therapy. Ofatumumab, a fully humanized CD20 monoclonal antibody, demonstrates high affinity for CD20 and potential efficacy in certain refractory or relapsed conditions. Ublituximab, a third-generation antibody, exhibits enhanced antigen binding and increased immune-mediated cytotoxicity. Among these, obinutuzumab has undergone the most extensive research and has demonstrated superior efficacy compared to rituximab in randomized pivotal trials, particularly in chronic lymphocytic leukemia and indolent non-Hodgkin lymphoma [37,38]. The phase 3 GALLIUM trial underscored obinutuzumab-based immunochemotherapy's significant improvement in progression-free survival over rituximab-based therapy for follicular lymphoma [39]. Current research is exploring novel combination therapies incorporating obinutuzumab for DLBCL. According to our analysis, the combined Obinutuzumab and PD1 inhibitor is synergistic in lymphoma. Results showed that combining these two drugs would significantly improve the therapy of lymphoma cells, which is consistent with the research tendency.

The current study revealed that CD20-targeting antibody therapy in lymphoma research was mainly focused on clinical research. The most researched type of lymphoma was DLBCL, and rituximab remains the center position within therapeutic drugs. Furthermore, the pathogenesis of lymphoma was also a popular topic in current research. Research in frontier areas concentrates on integrating CD20 antibody therapies with other treatment modalities, including chemotherapy, radiotherapy, and immunotherapy. The integration of CD20 monoclonal antibody with chemoradiotherapy is now the established protocol for certain B-cell lymphomas, particularly in Diffuse Large B-Cell Lymphoma (DLBCL) for stages I/II without a large mass. The recommended treatment is either 3–4 cycles of the R–CHOP regimen plus Involved Site Radiation Therapy (ISRT) or 6 cycles of the R–CHOP regimen with or without ISRT. In frontline therapy for stages III and IV, participation in clinical trials is primarily recommended, or alternatively, 6–8 cycles of R–CHOP chemotherapy. Additionally, the synergy of CD20 monoclonal antibody with immune checkpoint inhibitors (such as Hu5F9-G4, Pembrolizumab, Atezolizumab, Nivolumab, and Lenalidomide) has demonstrated enhanced efficacy in treating non-Hodgkin lymphomas, notably DLBCL [20,40–45]. This efficacy, stemming from the augmented ability of the immune system to target cancer cells, has led to increased treatment response rates and extended progression-free survival, especially in patients exhibiting specific biomarkers like PD-L1. These findings highlight the growing importance and potential of immunotherapy in lymphoma treatment.

This study entailed an extensive analysis of three reviews with similar themes. The first review encapsulated a range of monoclonal antibody therapies for large B-cell lymphoma, encompassing naked antibodies, radioimmunoconjugates, and antibody-drug conjugates, and evaluated their clinical efficacy and safety [46]. The second review concentrated on the evolution and utilization of anti-CD20 monoclonal antibodies in B-cell malignancies treatment. It provided an in-depth examination of the molecular structure, mechanism of action, and clinical outcomes of various antibodies, including rituximab and obinutuzumab [47]. The third review delved into the advancements in monoclonal antibody therapies for DLBCL, particularly focusing on novel therapies beyond rituximab, assessing their effectiveness and safety in treating DLBCL, notably in relapsed or refractory cases [48]. A distinctive feature of this

study is the inaugural application of bibliometric methods to thoroughly analyze CD20-targeted antibody treatment of lymphoma. This approach unveiled research trends and hotspots, and pinpointed pivotal studies and teams in the field. Contrary to prior research, this paper amalgamates a comprehensive literature review with original experiments investigating the synergistic effects of CD20 antibodies and PD1 inhibitors. This novel empirical evidence and deeper insight into lymphoma treatment strategies address a previously unexplored aspect in this domain. Compared with the traditional reviews, our results provide researchers with richer objective information, knowledge, and insight.

5. Conclusions

In conclusion, the articles for CD20-targeting antibody therapy in lymphoma were entered into the plateau, but the citations were increasing along with the time, which indicated that it had received extensive attention from several scholars. Furthermore, efforts were applied to elucidate the mechanism and effectiveness of CD20-targeting antibodies in treating lymphoma. Future research hotspots will focus on alternative therapy, such as CAR-T, immune checkpoint inhibitors, and combination therapy for higher therapeutic effects. We hope these research results will provide helpful references and direction for further research.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding authors.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82260365, 82372315). Hunan Provincial Innovation Foundation For Postgraduate (CX20230296), Basic Research Program of Qinghai Province - Applied Basic Research Program (2023-ZJ-716).

CRediT authorship contribution statement

Xin Wu: Conceptualization, Data curation. **Xiaoying Sun:** Writing – original draft. **Woding Deng:** Funding acquisition, Investigation. **Rong Xu:** Software, Supervision. **Qiangqiang Zhao:** Validation, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviation

CD20	membrane spanning 4-domains A1
WOSCC	Web of Science Core Collection
CAR-T	Chimeric Antigen Receptor T-cell, a type of immunotherapy
PDL1/PD1	Programmed Death-Ligand 1/Programmed Cell Death Protein 1
SCI	Science Citation Index
DLBCL	Diffuse Large B-cell Lymphoma
EBV	Epstein-Barr Virus
R–CHOP	Rituximab, Cyclophosphamide, Hydroxydaunorubicin (Doxorubicin), Oncovin (Vincristine), and Prednisone
ISRT	Involved-Site Radiation Therapy

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e34068.

References

[1] A. Du, X. Wu, Y. Gao, B. Jiang, J. Wang, et al., m6A Regulator-mediated Methylation Modification patterns and tumor microenvironment infiltration characterization in acute myeloid leukemia, Front. Immunol. 12 (2021) 789914.
[2] D. Jiang, X. Wu, X. Sun, W. Tan, X. Dai, et al., Bone mesenchymal stem cell-derived exosomal microRNA-7-5p inhibits progression of acute myeloid leukemia by targeting OSBPL11, J Nanobiotechnology 20 (1) (2022) 29.
[3] X. Wu, X. Zhang, W. Feng, H. Feng, Z. Ding, et al., A targeted Erythrocyte membrane-encapsulated drug-delivery system with anti-osteosarcoma and anti-osteolytic effects, ACS Appl. Mater. Interfaces 13 (24) (2021) 27920–27933.
[4] Z. Wu, X. Zhang, D. Chen, Z. Li, X. Wu, et al., N6-Methyladenosine-Related LncRNAs are potential remodeling Indicators in the tumor microenvironment and prognostic Markers in osteosarcoma, Front. Immunol. 12 (2021) 806189.
[5] Wu Xin, Li Shiqin, Chen Dongjie, Zheng Guiping, Zhaohua Zhang, et al., An inflammatory response-related gene signature associated with immune status and prognosis of acute myeloid leukemia, Am J Transl Res (2022).
[6] A.L. Smith, A.P. Eiken, S.A. Skupa, D.Y. Moore, L.T. Umeta, et al., A novel triple-action inhibitor targeting B-cell receptor signaling and BRD4 demonstrates preclinical activity in chronic lymphocytic leukemia, Int. J. Mol. Sci. 23 (12) (2022).
[7] S.H.C.E. Serdlow, N.L. Harris, et al., WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, fourth ed., IARC Press, Lyon (France), 2008.
[8] National Institute of Health NCICsfs. Available at: www.seer.cancer.gov/statfacts/html. Accessed May 8. 2016.
[9] E.N. Mugnaini, N. Ghosh, Lymphoma, Prim Care 43 (4) (2016) 661–675.
[10] C. Chung, Current targeted therapies in lymphomas, Am. J. Health Syst. Pharm. 76 (22) (2019) 1825–1834.
[11] F. Jakab, Z. Zavodszky, I. Sugar, T. Ughy, Changes in heparin level in experimental liver transplantation in dog, Acta Chir. Hung. 29 (1) (1988) 15–20.
[12] M.A.O. Santos, M.M. Lima, CD20 role in pathophysiology of Hodgkin's disease, Rev. Assoc. Med. Bras. 63 (9) (2017) 810–813, 1992.
[13] S.H. Shao, Y. Wang, X.Y. Dai, Y.J. Xiao, J.J. Guan, et al., [CD20-positive T cell lymphoma: clinicopathological features of five cases], Zhonghua Bing Li Xue Za Zhi 49 (10) (2020) 1021–1026.
[14] S. Yang, Y. Ba, G. Jiang, [Clinical analysis of 11 cases of CD20 positive extranodal NK/T cell lymphoma], Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 35 (5) (2021) 436–440.
[15] J.R. Blase, D. Frame, T.F. Michniacki, K. Walkovich, Case Report: use of obinutuzumab as an alternative monoclonal anti-CD20 antibody in a patient with refractory immune Thrombocytopenia complicated by rituximab-induced serum sickness and anti-rituximab antibodies, Front. Immunol. 13 (2022) 863177.
[16] C.L. Freeman, L. Sehn, Anti-CD20 directed therapy of B cell lymphomas: are new agents really better? Curr. Oncol. Rep. 20 (12) (2018) 103.
[17] P. McLaughlin, A.J. Grillo-Lopez, B.K. Link, R. Levy, M.S. Czuczman, et al., Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program, J. Clin. Oncol. 16 (8) (1998) 2825–2833.
[18] B. Coiffier, E. Lepage, J. Briere, R. Herbrecht, H. Tilly, et al., CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma, N. Engl. J. Med. 346 (4) (2002) 235–242.
[19] M.S. Czuczman, A.J. Grillo-Lopez, C.A. White, M. Saleh, L. Gordon, et al., Treatment of patients with low-grade B-cell lymphoma with the combination of chimeric anti-CD20 monoclonal antibody and CHOP chemotherapy, J. Clin. Oncol. 17 (1) (1999) 268–276.
[20] I.V. Madabhavi, S. Revannasiddaiah, M.S. Sarkar, M.G. Modi, Sanctuary site central nervous system relapse-refractory DLBCL responding to nivolumab and lenalidomide, Oral Oncol. 93 (2019) 122–124.
[21] N. Jain, J. Senapati, B. Thakral, A. Ferrajoli, P. Thompson, et al., A phase 2 study of nivolumab combined with ibrutinib in patients with diffuse large B-cell Richter transformation of CLL, Blood Adv 7 (10) (2023) 1958–1966.
[22] Y. Song, F. Zhao, W. Ma, G. Li, Hotspots and trends in liver kinase B1 research: a bibliometric analysis, PLoS One 16 (11) (2021) e0259240.
[23] J. Zhang, L. Song, L. Xu, Y. Fan, T. Wang, et al., Knowledge domain and emerging trends in Ferroptosis research: a bibliometric and knowledge-map analysis, Front. Oncol. 11 (2021) 686726.
[24] X. Huang, Z. Yang, J. Zhang, R. Wang, J. Fan, et al., A bibliometric analysis based on web of science: current Perspectives and potential trends of SMAD7 in oncology, Front. Cell Dev. Biol. 9 (2021) 712732.
[25] D. Ma, B. Yang, B. Guan, L. Song, Q. Liu, et al., A bibliometric analysis of Pyroptosis from 2001 to 2021, Front. Immunol. 12 (2021) 731933.
[26] C. Chen, Searching for intellectual turning points: progressive knowledge domain visualization, Proc. Natl. Acad. Sci. U.S.A. 101 (Suppl 1) (2004) 5303–5310.
[27] C. Chen, Z. Hu, S. Liu, H. Tseng, Emerging trends in regenerative medicine: a scientometric analysis in CiteSpace, Expet Opin. Biol. Ther. 12 (5) (2012) 593–608.
[28] K. Kodonas, A. Fardi, C. Gogos, N. Economides, Scientometric analysis of vital pulp therapy studies, Int. Endod. J. 54 (2) (2021) 220–230.
[29] M.R. Smith, Non-Hodgkin's lymphoma, Curr. Probl. Cancer 20 (1) (1996) 6–77.
[30] G. Salles, M. Barrett, R. Foa, J. Maurer, S. O'Brien, et al., Rituximab in B-cell hematologic malignancies: a review of 20 Years of clinical experience, Adv. Ther. 34 (10) (2017) 2232–2273.
[31] J. Wang, J. Ge, Y. Wang, F. Xiong, J. Guo, et al., EBV miRNAs BART11 and BART17-3p promote immune escape through the enhancer-mediated transcription of PD-L1, Nat. Commun. 13 (1) (2022) 866.
[32] L.S. Young, L.F. Yap, P.G. Murray, Epstein-Barr virus: more than 50 years old and still providing surprises, Nat. Rev. Cancer 16 (12) (2016) 789–802.
[33] L. Yuan, S. Li, Q. Chen, T. Xia, D. Luo, et al., EBV infection-induced GPX4 promotes chemoresistance and tumor progression in nasopharyngeal carcinoma, Cell Death Differ. 29 (8) (2022) 1513–1527.
[34] E. Grywalska, J. Rolinski, Epstein-Barr virus-associated lymphomas, Semin. Oncol. 42 (2) (2015) 291–303.
[35] D. Modi, B. Potugari, J. Uberti, Immunotherapy for diffuse large B-cell lymphoma: current landscape and future directions, Cancers 13 (22) (2021).
[36] J.C. Chavez, F.L. Locke, CAR T cell therapy for B-cell lymphomas, Best Pract. Res. Clin. Haematol. 31 (2) (2018) 135–146.
[37] W. Hiddemann, A.M. Barbui, M.A. Canales, P.K. Cannell, G.P. Collins, et al., Immunochemotherapy with obinutuzumab or rituximab for previously untreated follicular lymphoma in the GALLIUM study: influence of chemotherapy on efficacy and safety, J. Clin. Oncol. : Official Journal of the American Society of Clinical Oncology 36 (23) (2018) 2395–2404.
[38] J.C. Strefford, M. Nowicka, C. Hargreaves, C. Iriyama, K.V. Latham, et al., Prognostic impact of germ-line *FCGR2A* (H131R), *FCGR3A* (F158V), and *FCGR2B* (I232T) single nucleotide polymorphisms in lymphoma patients treated with obinutuzumab or rituximab in combination with chemotherapy: results from the phase III GALLIUM and GOYA clinical trials, Blood 132 (2018) 6.
[39] C. Pott, E. Hoster, B. Kehden, M. Unterhalt, M. Herold, et al., Minimal residual disease response at end of induction and during maintenance correlates with updated outcome in the phase III GALLIUM study of obinutuzumab- or rituximab-based immunochemotherapy in previously untreated follicular lymphoma patients, Blood 132 (2018) 4.
[40] R. Advani, I. Flinn, L. Popplewell, A. Forero, N.L. Bartlett, et al., CD47 blockade by Hu5F9-G4 and rituximab in non-hodgkin's lymphoma, N. Engl. J. Med. 379 (18) (2018) 1711–1721.
[41] S.M. Ansell, M.B. Maris, A.M. Lesokhin, R.W. Chen, I.W. Flinn, et al., Phase I study of the CD47 blocker TTI-621 in patients with relapsed or refractory hematologic malignancies, Clin. Cancer Res. 27 (8) (2021) 2190–2199.
[42] C. Ho, A.K. Gopal, B.G. Till, M. Shadman, R.C. Lynch, et al., Pembrolizumab with R-CHOP in previously untreated DLBCL: sustained, high efficacy, and safety with long-term follow-up, Clin Lymphoma Myeloma Leuk (2023).
[43] S.D. Smith, B.G. Till, M.S. Shadman, R.C. Lynch, A.J. Cowan, et al., Pembrolizumab with R-CHOP in previously untreated diffuse large B-cell lymphoma: potential for biomarker driven therapy, Br. J. Haematol. 189 (6) (2020) 1119–1126.
[44] L. Wang, L.R. Li, K.H. Young, New agents and regimens for diffuse large B cell lymphoma, J. Hematol. Oncol. 13 (1) (2020) 175.
[45] A. Younes, J.M. Burke, B.D. Cheson, C.S. Diefenbach, S. Ferrari, et al., Safety and efficacy of atezolizumab with rituximab and CHOP in previously untreated diffuse large B-cell lymphoma, Blood Adv 7 (8) (2023) 1488–1495.

[46] M. Novo, E. Santambrogio, P.M.M. Frascione, D. Rota-Scalabrini, U. Vitolo, Antibody therapies for large B-cell lymphoma, Biol. Targets & Ther. 15 (2021) 153–174.
[47] C. Klein, C. Jamois, T. Nielsen, Anti-CD20 treatment for B-cell malignancies: current status and future directions, Expet Opin. Biol. Ther. 21 (2) (2021) 161–181.
[48] S.G. Papageorgiou, T.P. Thomopoulos, A. Liaskas, T.P. Vassilakopoulos, Monoclonal antibodies in the treatment of diffuse large B-cell lymphoma: moving beyond rituximab, Cancers 14 (8) (2022).