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A bibliometric and knowledge-map analysis of bispecific antibodies in cancer immunotherapy from 2000 to 2023

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ABSTRACT

Background: Bispecific antibody (BsAb)-based cancer immunotherapy has provided new avenues for the treatment of various malignancies. The approval of Blinatumomab has encouraged further investigation into these treatments, and a series of preclinical and clinical trials have been conducted, together with the publication of numerous articles. Here, the knowledge structure of BsAb-based cancer immunotherapy is summarized using bibliometric analysis to provide in-depth insight into current research trends and foci.

Methods: The studies included in the bibliometric analysis of BsAbs in cancer immunotherapy were retrieved from the online Web of Science Core Collection (WOSCC) database on April 16th, 2023. Visualization analysis was performed with the help of CtieSpace (version 6.2.2.msi [64-bit]), VOSviewer (version 1.6.19), R (version 4.2.1), and the Bibliometric analysis platform (R-based online data processing tool).

Results: A total of 1750 papers were identified. Analysis of annual publications and total citations indicated that publications have increased steadily over the past few decades. The USA, followed by Germany, had largest number of publications, making significant contributions to the field. The Memorial Sloan Kettering Cancer Center received the highest number of citations (n = 3769). However, its collaboration and cooperation with different institutions require further strengthening. *MAbs* and *Clinical Cancer Research* published the most papers, while *Blood* and *Cancer Research* were the most commonly co-cited journals. DM Goldenberg from the USA published the most articles with the highest H-index (34), and the most co-cited author (2137 citations) was PA Baeuerle; both these authors have distinguished achievements in this field. Analysis of co-cited references and keywords showed that the hotspots and research focus on the use of BsAbs for solid tumors have increased rapidly while the application of BsAb immunotherapy in hematologic malignancies has expanded significantly. The hot topics in the field included cytokine release syndrome, the efficacy and safety of BsAbs, resistance mechanisms, and the exploration and optimization of combination therapies.

Conclusion: Cancer immunotherapies based on BsAbs are a hot topic in research. Current studies focus on the construction and optimization of BsAb structure, as well as their combination with other treatment modalities to improve their efficacy and overcome resistance. Furthermore, it is expected that the ongoing investigation of BsAb-based immunotherapy for solid tumors will bear fruit with significant clinical application prospects in the near future.

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1. Introduction

Cancer immunotherapy involves the strengthening of the intrinsic immune response of the body to eliminate malignant cells, and has revolutionized conventional therapeutic strategies against advanced cancers and is considered a highly promising treatment for these diseases [1]. Recent decades have shown great progress in research into BsAbs and their application in immuno-oncology. Nisonoff et al. were the first to propose the concept of BsAbs in the early 1960s [2], but it took several decades before their basic research was transformed clinical application and drugs. In contrast to monoclonal antibodies (mAbs) which contain the antigen-binding site composed of the heavy- and light-chain variable domains of the immunoglobulin together with the Fc region that mediates effector functions such as complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, or antibody-dependent cellular phagocytosis [3], BsAbs have the specificities of two antibodies and bind two separate epitopes, thus strengthening antibody-antigen binding and offering significant potential for cancer immunotherapy applications. With evolving conceptual and technical innovations in recombinant antibody engineering and biology, BsAbs have opened a door to a new era of extensive groundbreaking discoveries, accompanied by commercialized technology platforms built by biotech and pharma companies to generate novel bio-therapeutics [3–9].

BsAbs are designed and manufactured using quadromas, chemical conjugation, or genetic engineering to recognize and bind unique epitopes either simultaneously or sequentially [10,11]. BsAbs possess a variety of antibody structural formats and derivatives, which can be classified into two different types according to the Fc domain, namely, the IgG like-format and non-IgG like-format [12–17]. The IgG like-format with an Fc region mediates binding to the FcRn, allowing recycling, and the presence of the Fc region increases the molecular weight of the antibody and prolongs its half-life in the serum. The non-IgG like-formats are beneficial in increasing tissue permeability [18]. The most promising formats include knobs-into-holes, (IgG)2, scFv-IgG, BiTE, DART, TandscFv, TandAb, Diabody, F(ab′)2, and ImmTAC. Different formats are also currently being explored [19,20]. Catumaxomab (Removab®), a triomab targeting EpCAM/CD3, was the first recombinant antibody approved by the European Union in 2009 as intraperitoneal therapy for malignant ascites. However, intravenous administration was not feasible and it mediated Fc-based off-target T cell activation in peripheral tissues, inducing fatal toxicity at low doses [21]. Although Catumaxomab was ultimately removed from the market in 2017, the impressive clinical results of Blinatumomab (CD3 × B lymphocyte antigen CD19), a bispecific T cell engager (BiTE), has rekindled interest in the field. Blinatumomab (MT103 or AMG 103) was approved for the treatment of relapsed/refractory (RR) B-precursor acute lymphoblastic leukemia (B-ALL) by the FDA in December 2014 [22]. It shows high efficacy and high response rates and is currently the subject of numerous clinical trials to expand its clinical indications in other hematological malignancies such as AML and multiple myeloma [23–27]. Furthermore, various bispecific T cell-recruiting antibodies derived from BiTEs are also under investigation for both hematological malignancies and solid tumors [7].

While BsAbs have shown excellent clinical efficacy and outcomes against hematological malignancies, their application for treating solid tumors presents difficulties, particularly in relation to the complex nature of suppressive tumor microenvironment (TME) and the absence of tumor-specific targets on certain tumor cells [28–32]. However, various strategies are being explored to further improve the antitumor efficacy of BsAb. These include 1) combining BsAbs with immune checkpoint inhibitors, 2) overcoming the immunosuppressive TME via cytokine modulation [33], 3) the use of BsAb-armed activated T cells (BAT), redirecting bystander T-cells to attack tumor cells [34], and 4) the combination of BsAb therapy with conventional antitumor therapy, such as chemotherapy, radiotherapy, and targeted therapy [35]. However, "on-target, off-tumor" adverse effects and undesired cytokine release induced by T cell recruiters are issues that require further assessment. Approaches to modulate target affinities and conditionally activate T cells upon target cell binding within the TME are currently under exploration to alleviate potential adverse effects, toxicity in non-targeted tissues, and hyper-immunity or the systemic immune response [36,37].

With advances in the identification of novel targets and biotechnology, BsAb therapy represents an important player in the field of cancer immunotherapy. However, the large number of publications on the topic makes it difficult for researchers to keep track of the latest research trends. Bibliometric analysis is an advanced scientometric methodology used for the quantitative and qualitative analysis of documents within a research field, and thus has significant advantages for conveying information [38]. To date, there are no comprehensive studies summarizing and analyzing the developmental trends in BsAb research. Therefore, the present study conducted a bibliometric analysis of BsAbs from 2000 to 2023 for a comprehensive insight into BsAb-based cancer immunotherapy, compiling information on countries, institutions, and authors, to provide information on the current research foci and trends.

2. Materials and methods

2.1. Data retrieval and extraction

The Science Citation Index Expanded (SCI-Expanded 1900-present) and Social Sciences Citation Index (SSCI 1900-present) in the Web of Science Core Collection (WoSCC, Clarivate Analytics) are the two most influential and comprehensive citation-based databases including extensive international academic journals and literature for bibliometric analysis. Here, all the BsAb-related publications were retrieved from the SCI-Expanded and SSCI of WoSCC databases, using the "Advanced search" function. Furthermore, BsAbs and cancer-related subjects were searched using entry terms from the Medical Subject Headings (MeSH) database of the United States National Library of Medicine, using Boolean operators and wildcard characters such as "*". Table 1 provides details of the screening strategy. The retrieval period was from 2000 to April 16, 2023, and document types (articles or reviews) in English were included. To avoid variations caused by daily updates to the databases, data extraction and export were completed within the same day. Two

researchers (WJ and HZ) independently retrieved the dataset from the WoSCC and screened the relevant documents' titles, abstracts, and full texts, excluding irrelevant articles. Ultimately, 1750 documents (1249 research and 484 reviews) were exported with the record content of "Plain text file" and "Full Record and Cited References" to extract data for further analysis. The flow chart of the screening process and data collection is shown in Fig. 1.

2.2. Statistical and bibliometric analysis

After the initial extraction of original data from SCI-Expanded and SSCI of WoSCC databases, the documents were imported into Citespace V (version 6.2.2.msi, Drexel University, USA) to remove duplicates and acquire relevant information, including NP and citations, publication years and types, H-index, G-index, countries/regions, affiliations, journals, authors, keywords, references, and research areas for quantitative and qualitative analysis with synonym substitution of partial fields. For descriptive statistical analysis, Origin Pro 2023, Microsoft Excel 2019, and R software (v 4.2.3.) were utilized. Furthermore, with the help of CtieSpace, VOSviewer (version 1.6.19, Leiden University, the Netherlands), and Bibliometrix (an online bibliometric analysis platform), scientific knowledge maps were analyzed and bibliometric information was visualized.

2.3. CtieSpace

CiteSpace, a Java-based science mapping application introduced by Professor Chaomei Chen, explores research hotspots and visually summarizes trends in specific research fields by data mining and forecasting future developmental prospects and research directions. Here, Citespace was utilized to 1) depict a co-authorship network of institutions, 2) provide a dual-map overlay of journals, 3) conduct a citation burst analysis of keywords and references, 4) conduct a co-citation network of references, and 5) construct a timeline view analysis of co-cited references. The applied parameters used were time period = 2000–2023, years per slice = 1, link retaining factor (3), node types = (institution, keyword, reference), and pruning = none. Other parameters were set as default.

2.4. VOSviewer

VOSviewer, developed by van Eck and Waltman, is a tool used for analyzing bibliometric networks based on co-authorship, co-occurrence, co-citation, or citation of items in the Java environment. It provides three types of visualization maps, namely, network, density, and overlay maps. Here, VOSviewer was primarily used for 1) citation analysis of documents and co-citation analysis of cited sources, 2) overlay visualization of targeted research fields, and 3) co-occurrence network of all keywords.

2.5. Bibliometrix

Bibliometrix is an online analytical platform for comprehensive literature analysis and visualization using Biblioshiny packages in R software. This tool extracted the arranged annual publication and data of countries, institutions, journals, or authors to quantify data and conduction visualization analyses.

3. Results

3.1. An overview of publications on BsAbs in cancer immunotherapy

A total number of 1750 (1249 research studies [71.37%] and 484 reviews [27.66%]) publications on BsAbs in cancer immunotherapy were extracted for bibliometric analysis following comprehensive retrieval and screening from the WoSCC database. These publications were from 49 countries/regions and 1777 institutions, 475 journals, involving 9550 authors, and included 57 389 cited references.

Table 1
Search strategies and details of search terms.

Searching Strategy	Terms
A	#1=(((((((TS=(Antibod*, Bispecific)) OR TS=(Bispecific Antibod*)) OR TS=(Bifunctional Antibod*)) OR TS=(Antibod*, Bifunctional)) OR TS=(Bispecific Monoclonal Antibod*)) OR TS=(Antibod*, Bispecific Monoclonal)) OR TS=(Monoclonal Antibod*, Bispecific)) OR TS=(bispecific T cell engager*)) OR TS=(Natural Killer cell engager*)
B	#2=((((((((((((((((((TS=(Neoplasms)) OR TS=(Tumor)) OR TS=(Neoplasm)) OR TS=(Tumors)) OR TS=(Neoplasia)) OR TS=(Neoplasias)) OR TS=(Cancer)) OR TS=(Cancers)) OR TS=(Malignant Neoplasm)) OR TS=(Malignancy)) OR TS=(Malignancies)) OR TS=(Malignant Neoplasms)) OR TS=(Neoplasm, Malignant)) OR TS=(Neoplasms, Malignant)) OR TS=(Benign Neoplasms)) OR TS=(Benign Neoplasm)) OR TS=(Neoplasms, Benign)) OR TS=(Neoplasm, Benign)
C	#1 AND #2

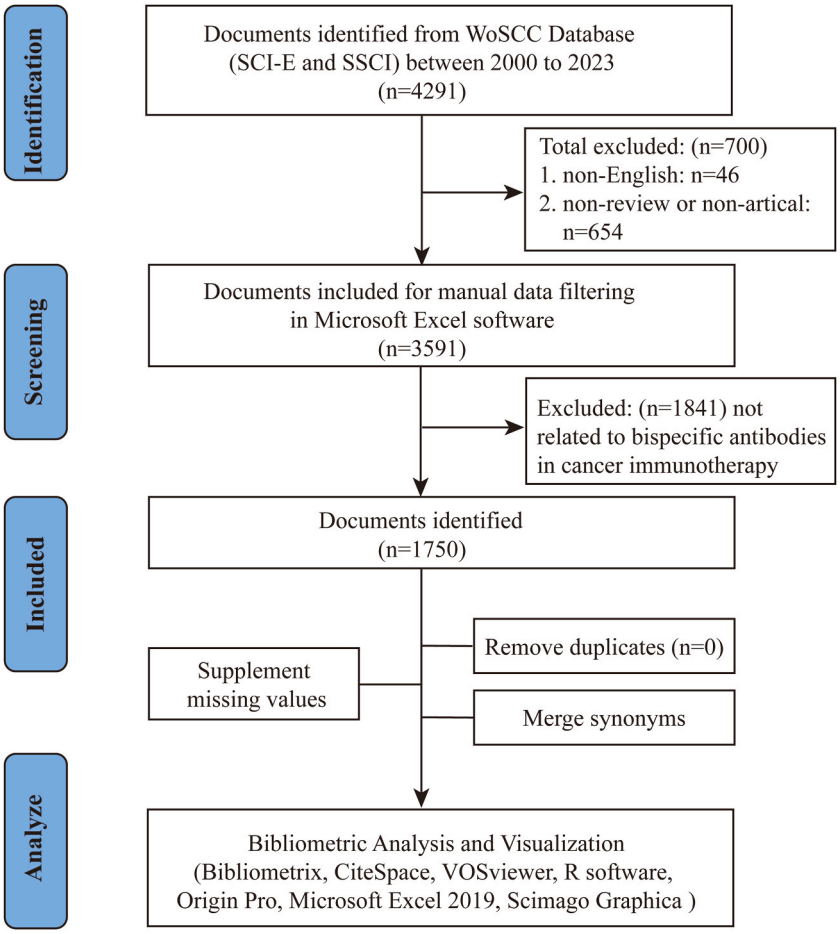

Fig. 1. Flowchart of article retrieval and data extraction for BsAb-based cancer immunotherapy.

3.2. Annual trends in publications

During the investigated period, the number of articles published each year showed a steady growth trend with an annual growth rate of 1.63%. Furthermore, the polynomial regression model constructed using Microsoft Office Excel 2019 indicated that the annual NP was well-fitted to the publication year with a correlation coefficient of $R^2 = 0.9494$ (Supplementary Figure S1), showing a

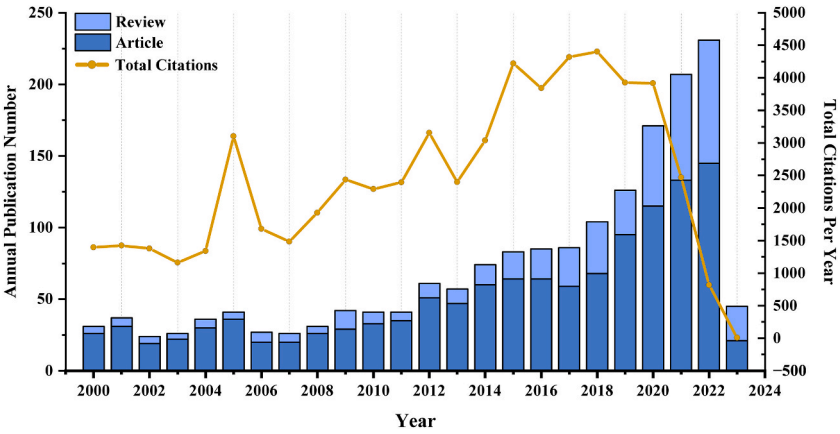

Fig. 2. Global trends in the number of publications and total citations per year for BsAb-based cancer immunotherapy over the past 20 years. The yellow line indicates the total number of citations of all publications each year.

statistically significant relationship between them. The cumulative total citations (TC) from the retrieved documents were 58,537 and the number of citations per document was 33.45 on average. The annual total citation curve presented a fluctuating upward trend with 3105 citations in 2005 and 2398 in 2012 while the NP was relatively low. The annual NP and TC are depicted in Fig. 2 and Table S1.

The quantitative analysis of publication and citation indicated that the research on BsAbs in cancer immunotherapy have received constant attention in recent years after a long exploration period.

3.3. Global contribution of countries and institutions to the field

3.3.1. Countries

During 2000–2023, 1750 documents on BsAb-based cancer immunotherapy were published by 49 countries/regions. Table 2 lists the 10 most productive countries with 88.17% (1543) of the total published data. The top 3 countries with the most publications were the USA (36.80%, n = 644), Germany (17.14%, n = 300), and China (14.74%, n = 258), covering a combined 68.69% (1202) of all publications. Furthermore, the USA was ranked 1st in terms of H-index (130), the TC frequency (23 804), and between centrality (BC = 0.64), indicating that it had a significant scientific impact in this field and played a vital role as an international communication bridge. Although the NP of the United Kingdom ranked last in the 10 countries with the most publications, the average number of article citations was the highest (67.5). The annual trends in the publications from the top 10 countries are shown in Fig. 3A and Supplementary Table S2. The Bibliometrix platform, Biblioshiny R packages, and Scimago Graphica were used for data analysis and visualization-map generation to elucidate international collaborations. Supplementary Figure S2 illustrates the multiple country publications (MCP) reflecting collaborations between different countries. Among the top 10 countries, the USA had the strongest collaborations with other countries (MCP = 120 and MCP-ratio = 0.186), while Switzerland had the strongest MCP-ratio of 0.550 (MCP = 22) with relatively low NP (40). The visualization network showing collaboration among countries is shown in Fig. 3B.

3.3.2. Institutions

A total of 1777 institutions contributed at least 1 paper related to BsAb-based cancer immunotherapy. Table S3 indicates the top 10 most productive research institutions. Six of the 10 institutions are located in the USA, 2 in Germany, and the rest are in China and Japan, respectively, with NP ranging from 40 (Sichuan University) to 83 (Memorial Sloan Kettering Cancer Center). The total link strength (TLS), calculated from the thickness of the lines linking the nodes, indicates the strength of collaborations between institutions. The TLS and the TC values of the top 10 institutions are displayed in a Sunburst Plot in Fig. 4A, while the annual productions over time are presented in Fig. 4B. The German Cancer Research Center, Memorial Sloan Kettering Cancer Center, and the Dresden University of Technology were ranked as the top three institutions with TLS values of 131, 100, and 93, respectively. The top three institutions with the highest TC values were the Memorial Sloan Kettering Cancer Center (3769), Minnesota University (3348), and the German Cancer Research Center (2306). No institutions had BC values > 0.1.

3.4. Journals and Co-cited journals

A total of 475 academic journals published articles on BsAbs in cancer immunotherapy. The top 10 journals and the most cited journals are listed in Table 3. Journal-level metrics, including the journal's impact factor (IF) and journal citation reports (JCR) quartile, were used to assess the influence of the journal using the most recent data indexed in the WSCC. *MAbs* (n = 66 papers), *Clinical Cancer Research* (n = 52 papers), and *Journal for Immunotherapy of Cancer* (n = 49 papers) were the journals with the most published articles, followed by *Frontiers in Immunology* (n = 47 papers) and *Cancers* (n = 43 papers). Furthermore, of the top 10 most productive journals, *Clinical Cancer Research* (IF = 13.801) had the highest IF (2021), followed by *Cancer Research* (IF = 13.312) and *Journal for Immunotherapy of Cancer* (IF = 12.485). Furthermore, 70% of the citing journals were classified into Q1 (top 25% of IF distribution), while the remaining three were Q2 (between the 25th and 50th quartiles). All the top 10 co-cited journals were co-cited over 1500 times, accounting for >29% of the TC, with *Blood* (7546 times, 6.64%) being the highest, *Cancer Research* (4642 times, 4.09%) and *Clinical Cancer Research* (4346 times, 3.83%) ranking 2nd and 3rd, respectively. Overall, 90% of these co-cited journals belonged to Q1 in the JCR, and 70% of cited journals had an IF > 10, with t*he New England Journal of Medicine* (IF = 176.082), *Science* (IF = 63.832), and *Journal of Clinical Oncology* (IF = 50.739) ranked as the top three. VOSviewer software was used to generate network visualization

Table 2
Top 10 most productive countries in BsAb-based cancer immunotherapy.

Rank	Country	Publications	Percentage	H-index	MCP	TC	TLS	centrality
1	USA	644	36.80%	130	120	23804	404	0.64
2	GERMANY	300	17.14%	121	87	15873	306	0.17
3	CHINA	258	14.74%	51	32	3798	97	0.13
4	NETHERLANDS	76	4.34%	50	33	2615	114	0.02
5	FRANCE	56	3.20%	48	17	1938	109	0.10
6	JAPAN	55	3.14%	29	5	933	36	0.00
7	ITALY	48	2.74%	27	16	815	76	0.13
8	SWITZERLAND	40	2.29%	45	22	1643	109	0.03
9	KOREA	33	1.89%	18	6	361	36	0.00
10	UNITED KINGDOM	33	1.89%	33	9	2229	113	0.11

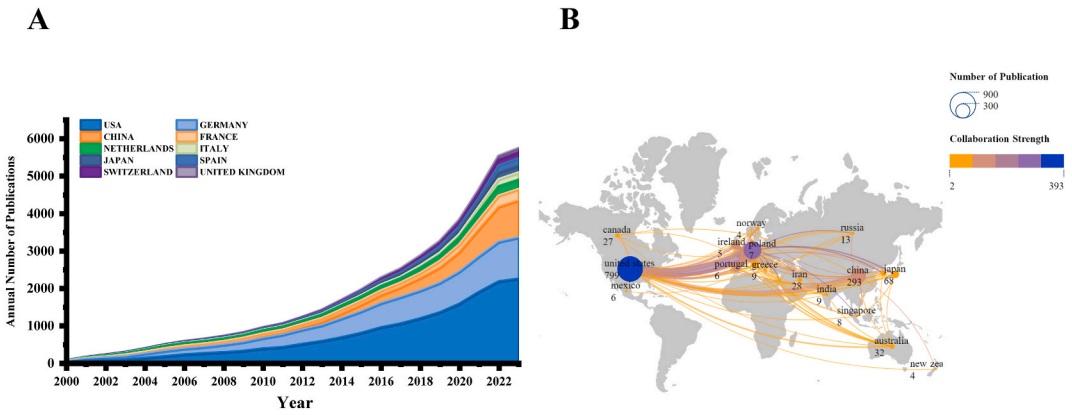

Fig. 3. **(A)** Trends of the numbers of annual cumulative publications in the top 10 countries/regions from 2000 to 2023. **(B)** The distribution of publications and collaborations, shown as a map visualization of the different countries, with the thickness and color of the lines reflecting the degree of collaboration between countries.

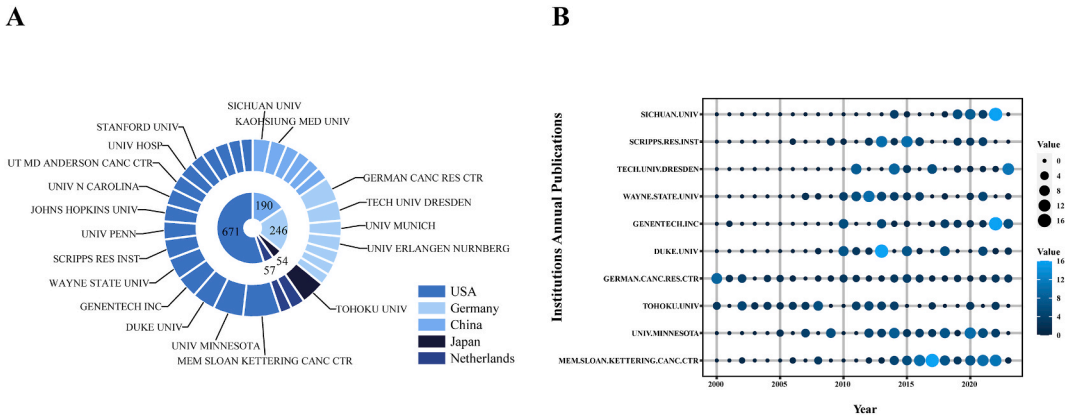

Fig. 4. **(A)** Sunburst plot showing institutions with over 25 publications; the figures in the inner ring reflect the total number of publications of the included institutions. **(B)** Distribution of the annual publication on BsAb-based cancer immunotherapy of the top 10 institutions (the node size and color represent the number of publications. The larger and the brighter the circle, the more publications in that year).

Table 3
Top 10 most productive journals and cited journals related to publication of research on BsAb-based cancer immunotherapy.

Rank	Journals	Counts	IF (2021)	JCR (2021)	Rank	Cited-Journals	Total citations	IF (2021)	JCR (2021)
1	MABS	66	6.44	Q2	1	BLOOD	7546	25.669	Q1
2	CLINICAL CANCER RESEARCH	52	13.801	Q1	2	CANCER RES	4642	13.312	Q1
3	JOURNAL FOR IMMUNOTHERAPY OF CANCER	49	12.485	Q1	3	CLIN CANCER RES	4346	13.801	Q1
4	FRONTIERS IN IMMUNOLOGY	47	8.787	Q1	4	J CLIN ONCOL	4254	50.739	Q1
5	CANCERS	43	6.575	Q1	5	J IMMUNOL	2883	5.43	Q2
6	MOLECULAR CANCER THERAPEUTICS	40	6.011	Q2	6	P NATL ACAD SCI USA	2659	10.7	Q1
7	CANCER IMMUNOLOGY IMMUNOTHERAPY	37	6.63	Q2	7	NEW ENGL J MED	2636	176.082	Q1
8	CANCER RESEARCH	37	13.312	Q1	8	INT J CANCER	1725	7.316	Q1
9	ONCOIMMUNOLOGY	29	7.723	Q1	9	MABS-AUSTIN	1636	6.44	Q2
10	INTERNATIONAL JOURNAL OF MOLECULAR SCIENCES	27	6.208	Q1	10	SCIENCE	1584	63.832	Q1

maps including citing journals with at least 5 publications and co-cited journals cited >200 times, including 83 citing journals and 87 co-cited journals (Figure S4A, S4B). The nodes in the maps represent citing journals or co-cited journals, while node sizes indicate the NP or the frequency of co-cited journal co-occurrence. The links between nodes represent the association between citation and co-

citation. The thickness of the links between the nodes reflects the co-occurrence strength of the co-cited journals, which can also be quantified using the TLS. Furthermore, the research fields in the published literature were visualized for comprehensive analysis (Fig. 5A), which indicated that the current focus is on oncology, biochemical research methods, and multidisciplinary sciences, with oncology the most researched of these.

Meanwhile, a dual-map overlay of academic journals was constructed using CiteSpace to depict the subject distribution. This represents an analysis of knowledge flow indicating the knowledge citations and co-citation evolutionary relationships between citing journals (or the research frontiers) and co-cited journals (or knowledge base). Fig. 5B indicates two main citation paths between the cited journals on the left and those on the right. Articles published in molecular, biological, and genetics journals were mainly cited by articles published in molecular, biological, and immunological and in medical and clinical fields (Fig. 5B).

3.5. Authors

The number of authors who published research on BsAbs in cancer immunotherapy was 9550, and the top 10 most active and co-cited authors are listed in Table S4. Among them, the top 3 most influential authors were from the USA. DM Goldenberg published the most in this research field (62 papers, 3345 citations), followed by RM Sharkey (44 papers, 2601 citations) and PA Baeuerle (43 papers, 5887 citations). The top 10 authors with the highest NP values are listed in Fig. 6A, and their publications over time are presented in Fig. 6B. Most authors started publishing in this field in 2002, and the publication trend was observed to be relatively flat. As Fig. 6B depicts, C. Klein became involved in this field in 2011 and has sustained output in recent years. VOSviewer was used to visualize the

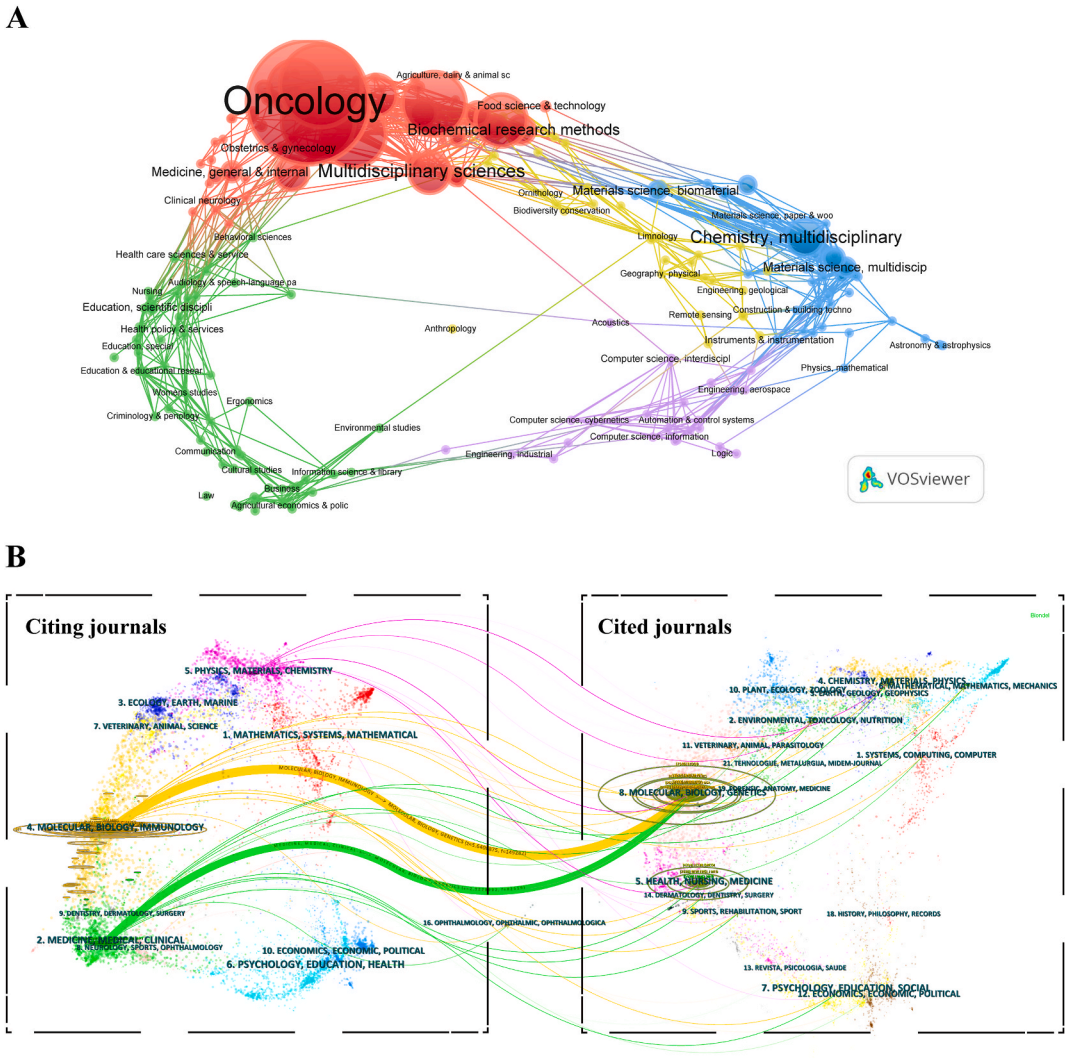

Fig. 5. **(A)** Superposition analysis of research fields. **(B)** Dual-map overlap of journals publishing articles on BsAb-based cancer immunotherapy, conducted by Citespace. The left part represents the citing journals and the right part represents the cited journals. The curves refer to the citation relationship.

collaborations of the authors in this field (Supplementary Figure S3A & S3B). Each node on the plot = one author, the node size = frequency of published articles, and the line thickness between nodes = co-occurrence relationship strength between authors. The figure shows that the authors with over 5 publications were clustered into 8 colors. PA Baeuerle, DM Goldenberg, and C. Klein were central to each cluster collaborative network. A total of 55 co-cited authors with a minimum of 100 co-occurrences were included (Figure S3B), and the authors are divided into 2 clusters: PA Baeuerle, RM Sharkey, and others (red); MS Topp and others (green).

3.6. Cited references

Reference analysis is a significant bibliometric indicator reflecting the basic knowledge map of the particular research field, of which co-cited references represent simultaneously cited references determined from citing documents, illustrating the association strength of references by measuring the co-citation frequency of the articles. Table S5 summarizes the basic information of the top 10 most co-cited references. These were mostly published in internationally renowned journals with high IF (7/10 Q1) and cited >100 citations. Furthermore, 40% of the articles had a high BC value of >0.1, indicating a strong role as a bridge in the association of references.

Moreover, a temporal timeline visualization network of co-cited references was constructed by CiteSpace (Fig. 7) to reflect variations in the hotspot over time and the interrelationships of the articles via clustering and time-slicing techniques. With the parameter set as period = 2000–2023 and a time slice of 1 year, 490 nodes along with 2437 links were included into 7 clusters based on a major research topic of the reference. In the timeline view, the Weighted Mean Silhouette S value was 0.9114, indicating excellent homogeneity of these clustering. Immuno-conjugate (Cluster #1) and pre-targeting (Cluster #4) were relatively early hotspots that gradually gave way to the research hotspots of multiple myeloma (Cluster #2), EpCAM (Cluster #3), and HER3 (Cluster #5). Recently, solid tumors (Cluster #0), BCMA (Cluster #6), and PD-L1 (Cluster #7) have been the most productive hotspots.

Citation burst references are articles that show a sudden increase in citations over a relatively short period, and this parameter is used to identify high-value research papers. Supplementary Figure S5 indicates the top 25 references with the strongest citation bursts. The blue line represents the research timeline, and the red sections indicate the durations of the citation bursts over time. Fifteen references (60%) with citation bursts were found between 2013 and 2023, indicating the most frequently cited papers within the previous 10 years, and suggesting that the field of cancer immunotherapy with BsAbs may continue to receive constant attention. The top 3 references with the strongest citation bursts were "Tumor regression in cancer patients by very low doses of a T cell-engaging antibody" (Strength: 43.90; Publication Year: 2008), "Bispecific antibodies: a mechanistic review of the pipeline" (Strength: 38.22; Publication Year: 2019), and "Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival" (Strength: 33.83; Publication Year: 2011). Currently, articles with the greatest values are still cited frequently, and it is speculated that research on BsAbs-based cancer immunotherapy will remain a hotspot over the next few years.

3.7. Keyword Co-occurrence, clusters, and evolution

Keywords represent the condensed and refined core content of research. The BsAb-based cancer immunotherapy research hotspots and frontiers were assessed analysis of the co-occurrence frequencies of keywords and clustering of keywords. After merging and replacing synonymous keywords, the top 20 co-occurrence keywords with the highest frequencies were extracted (Table S6), and 61 of the 5742 keywords were ultimately included in the analysis with the minimum time of occurrences parameter setting of 50 (Fig. 8A).

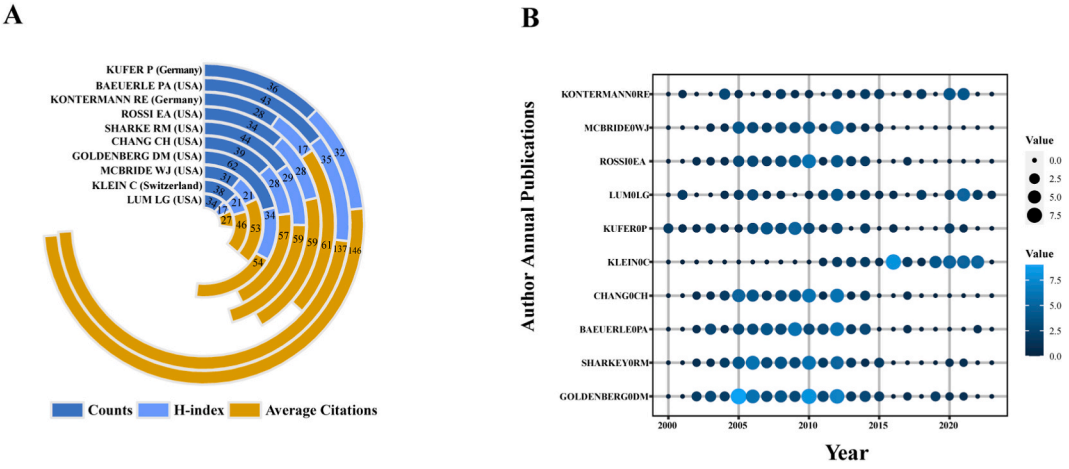

Fig. 6. **(A)** Pie and doughnut chart of counts, H-indices, and average citations of the 10 most productive authors. **(B)** Annual publications of the 10 most productive authors in the field of BsAb-based cancer immunotherapy (the node size and color represent the number of publications. The larger and the brighter the circle, the more publications in that year).

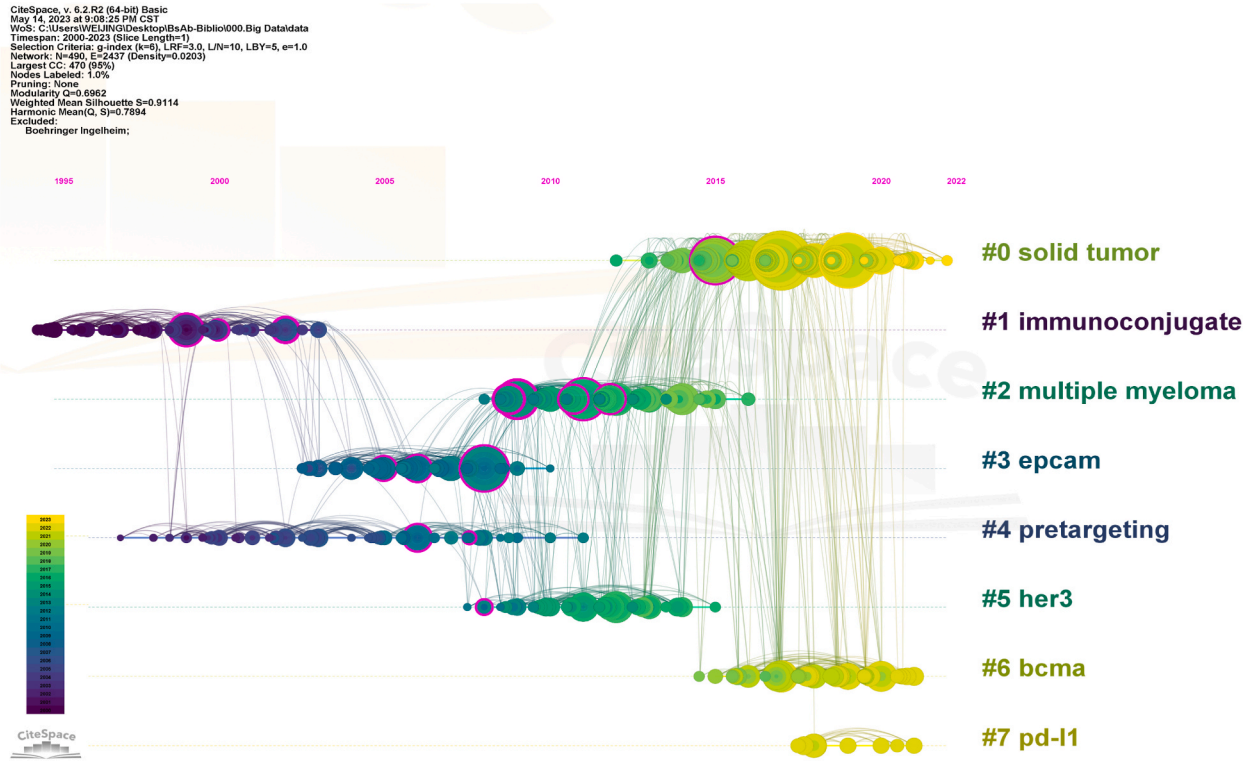

Fig. 7. Timeline view of seven clusters of co-cited references related to BsAb-based cancer immunotherapy. The node size represents the citation frequency of the references. The links between the nodes indicate co-citation relationships.

The most frequently co-occurring keywords were BsAbs (n = 784), followed by MAbs (n = 514), immunotherapy (n = 429), neoplasms (n = 393), and expression (n = 312).

The visualized network map showed clustering of the 61 selected keywords into 4 subgroups with specific colors, indicating 4 critical research directions. In cluster 1 (red nodes, 22 items), keywords focused on screening and binding antibody targets, such as expression, antigen, receptor, binding, and blockade. Cluster 2 (green nodes, 14 items) keywords were associated with the application

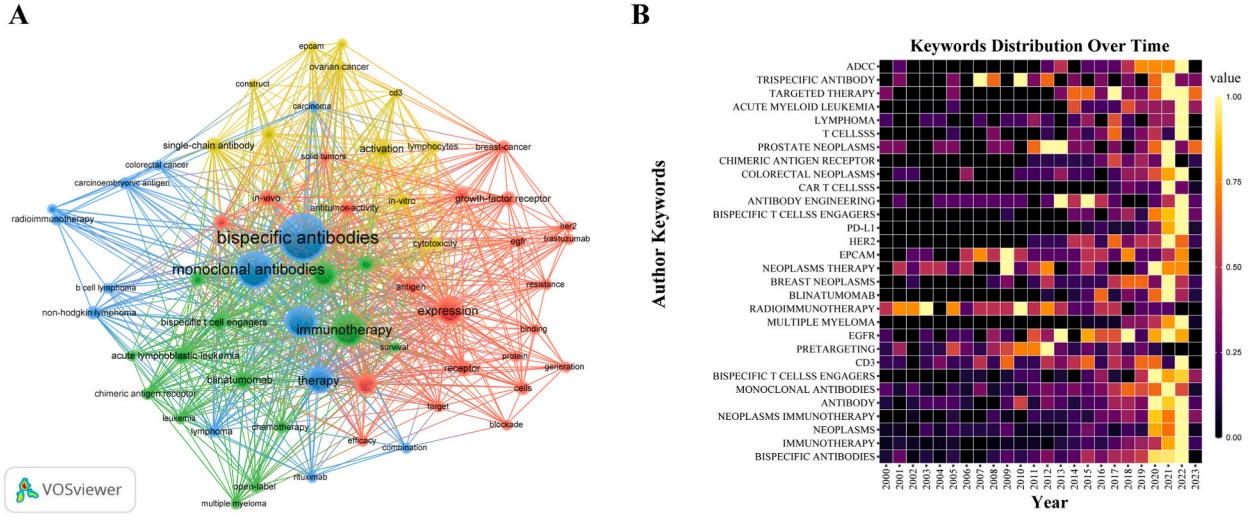

Fig. 8. **(A)** Network visualization of keywords with co-occurrence frequencies >50, with 61 nodes included in the visualization analysis. Nodes with different colors represent the keywords classified into different clusters. The size of the nodes indicates their frequency of occurrence. **(C)** Heatmap showing the annual top 30 keywords related to BsAb-based cancer immunotherapy from 2000 to 2023. The keyword frequency is proportional to the brightness of the color and is quantified between 0 and 1.

of BsAbs in hematologic malignancies, including “acute lymphoblastic-leukemia”, “acute myeloid-leukemia”, “multiple myeloma”, “bispecific t-cell engagers”, and “Blinatumomab”. Cluster 3 (blue nodes, 14 items) indicated the application of BsAbs in the treatment of solid neoplasms, such as “carcinoembryonic antigen”, “carcinoma”, “colorectal cancer”, “neoplasms”, and “radio-immunotherapy”. The keywords of cluster 4 (yellow nodes, 11 items) were linked with the construction and safety analysis of BsAbs in cancer immunotherapy, such as “construct”, “cytotoxicity”, and “single-chain antibody”. Supplementary Figure S6A depicts the visualization of keywords over time. The keyword’s color is based on the average publication year, where blue nodes represent the earliest keywords and yellow nodes indicate keywords that have appeared in recent years. Most yellow nodes were concentrated in clusters 1 and 2. The primary yellow keywords included “open-label” (2020.37), “blockade” (2019.75), “multiple myeloma” (2019.51), “Blinatumomab” (2019.25), “chimeric antigen receptor” (2019.17), “resistance” (2018.69), “bispecific t cell engagers” (2018.61), “HER 2” (2018.21), “acute myeloid-leukemia” (2018.13), and “efficacy” (2017.87). The distribution of the top 30 keywords over time was also quantitatively analyzed according to their frequency of appearance over a year. The frequency intensity was quantified between 0 and 1, which is more intuitive to visualize the annual trends in the popularity of a keyword (Fig. 8B).

A timeline for keywords that occurred frequently in association with BsAb immunotherapy over time is presented in Supplementary Figure S6B. The keywords were grouped into 7 sub-clusters to indicate their evolutionary track with #0 (acute lymphoblastic leukemia) representing the earliest and largest cluster, ranking 1st. For BsAb-based cancer immunotherapy, “bortezomib”, “daratumumab”, “dexamethasone”, “1st line treatment”, “nivolumab”, and “tumor-associated macrophages” represent the most recently used keywords, with steady progression. Furthermore, keywords in the fields of #1 (HER2), #2 (cancer immunotherapy), #3 (therapy), #4 (bispecific antibodies), #5 (monoclonal antibody), and #6 (malignant ascites) have long been research hotspots since the early days of the field.

3.8. Keyword citation burst analysis

The top 25 keywords with the strongest citation bursts are listed in Fig. 9, ranked by the year the citation burst began and extracted via a minimum duration of 2 years from 2000 to 2023. The initial keywords with strong citation bursts included “non-Hodgkin’s lymphoma”, “monoclonal antibody”, “fragments”, “carcinoma”, “single chain fv”, and “B cell lymphoma”. Of these, the burst strength of “monoclonal antibody” (2000–2011) and “non-Hodgkin’s lymphoma” (2003–2011) exceeded 12. The keywords with the strongest citation bursts during the last five years were “multiple myeloma”, “cytokine release syndrome”, “resistance”, “open label”, “tumor microenvironment”, and “T cell engager”, with the burst of the most of these still ongoing. These keywords demonstrate that the safety and efficacy of BsAbs in cancer immunotherapy are currently the primary research directions and hotspots.

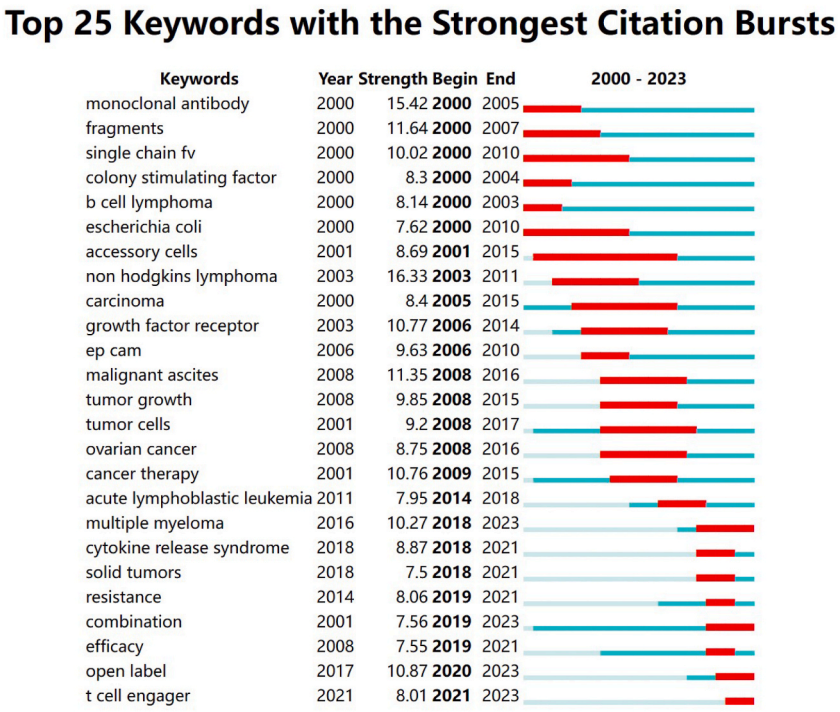

Fig. 9. Top 25 keywords with the strongest citation bursts in BsAb-based cancer immunotherapy from 2000 to 2023.

4. Discussion

Since the original proposal of the concept of BsAbs by Nisonoff et al., in 1960, the field has attracted scientists with increasing attention paid to the design and construction of the architectures of BsAbs. Currently, there are more than 100 BsAb formats, as have been described in high-quality review articles, with about one-quarter of these subsequently commercialized to establish mature technology platforms for generating novel BsAbs recognizing different targets [39–41]. In the field of tumor immunotherapy, the development and application of BsAbs is in full swing nowadays with the increasing understanding of the importance of reinvigorating and strengthening the pre-existing immune system, with numerous preclinical and clinical trials currently underway [4]. Thus, the present bibliometric analysis of BsAbs in cancer immunotherapy was performed to assist in summarizing the research context of this field, allowing a rapid grasp of the research frontiers of the field among the increasing proliferation of research information.

Initially, 1750 publications were identified and incorporated into preliminary statistical analyses. Based on the trends of annual NP and TC shown in Fig. 2, it is apparent that the topic of BsAbs has gained substantial attention and popularity in recent years, with 50.5% of the overall articles published in the last five years (2018–2023). This greatly renewed interest and further exploration of the field of BsAbs in cancer immunotherapy has led to a rapid increase in the number of research papers published, with the annual number of published articles exceeding 200 for the first time in 2021.

4.1. Countries, institutions, and authors

In general, the number of published papers can reflect the investment and attention of countries, institutions, and authors in a certain research field, while collaborative analysis indicates the global research trends in the study of BsAbs in cancer immunotherapy. The annual number of countries publishing research on BsAbs has shown steady growth over the past decades, indicating the increasing importance of the research field in these countries. Overall, the USA occupied an important global leadership position with interrelationships between institutions indicating considerable research strength. These countries are not only pursuing NPs but are also invested in the production of high-quality papers, which can be seen in the total number of citations, the high H-index, and other indicators. The collaboration networks of countries or institutions indicated that BsAb-based immunotherapy has not only attracted attention from researchers worldwide but has also led to the promotion of academic exchanges across borders (Fig. 3B). Despite the presence of international transboundary collaborations, the degree of collaboration requires further strengthening from the perspective of the overall number of collaborative publications. It is undeniable that financial support is a critical factor in the support of scientific research output. In addition to research institutions, pharmaceutical companies have also been involved in research & development (R&D), adding further impetus to the research field [42].

In terms of author contributions, the analysis showed that the three most productive researchers were all from the USA and they were also ranked among the top 10 most co-citated authors (Table S4). Dr DM Goldenberg and his team have been working in the field of antibody-targeted therapy over the years and also have closely collaborated with Dr RM Sharkey. From the design and construction of mAbs in the early stages to the exploration of the application of bi/multi-specific antibodies in anti-cancer immunotherapy in later stages [43,44], they have advanced the field considerably and pushed the work forward into clinical application. Dr PA Baeuerle is another researcher whose teamwork has focused on the exploration of BiTE, establishing a vital foundation for the use of activated T-cells in adaptive immunity to kill tumor cells. Besides, Dr Baeuerle is also the researcher with the highest number of co-citations, followed by Dr P Kufer who has been co-cited more than 1500 times, indicating the widespread attention paid to their work and the importance of their findings. The top 10 most co-cited authors are mainly from the USA and Germany, reflecting the national economic input and degree of emphasis, and their importance in the advancement of scientific research.

Peer-reviewed journals are critical for the transmission of scientific information, providing researchers with information on cutting-edge advances in relevant fields and contributing to the establishment of high-quality journals for the submission and review of articles via journal analysis or journal co-citation analysis. In addition to the NP, the IF, JCR, and TC are also important indicators for evaluating the academic value of journals. As shown in Table 3, most of these journals are professional journals, mainly focusing on molecular biotechnology and biotherapy, oncology, and translational medicine. Furthermore, most of these journals focus specifically on tumor immunity, demonstrating the significance of immunotherapy in tumor treatment. Journal co-citation analysis provides knowledge reserve and interdisciplinary research connections. *Blood, Cancer Research, Clinical Cancer Research*, and the *Journal of Clinical Oncology* were journals with TLS over 4000, illustrating that research papers related to BsAb-based cancer immunotherapy are published in journals with high citation numbers and significant academic value.

Moreover, analysis of the research fields covered by these journals (Fig. 5A) and journal citations, it is apparent that the BsAbs research field is not only currently focused on tumor immunotherapy but also on the comprehensive development of multi-discipline participation, integrating knowledge from medicine and biology, as well as science and engineering, to enhance the transformation of basic biomedical research to clinical medicine.

4.2. Knowledge base: co-cited references

The analysis of co-cited references, reflecting the degree of relevance between papers and constituting the knowledge base of a certain research area, is indispensable for researchers to grasp the important achievements and progress in a field and evaluate the academic impact of specific studies. Highly co-cited references represent influential papers that advance the field significantly. The detailed information on the co-cited references is summarized in Table S5. This shows that most of these papers are randomized controlled clinical trials published in high-quality journals. In the following section, we will give a detailed description of these studies

in the field of BsAb-based cancer immunotherapy.

The progress of translating the concepts of BsAbs into clinical applications has been relatively sluggish, with technical innovations in antibody engineering playing an important role in the process. For instance, the production of a bispecific heterodimeric IgG antibody by quadroma technology was the first attempt to construct a BsAb [45]. However, this was associated with problems in the pairing of random heavy and light chains, resulting in low protein production of the desired functional BsAbs. Subsequently, the 'knobs-into-holes' (KiH) genetic engineering approach was developed to solve this problem, effectively facilitating the construction and purification of heterodimer antibodies [46]. After optimizing the construction strategy to overcome issues such as low yields, unrelated byproducts, and cumbersome purification procedures, a recombinant bispecific single-chain variable antibody (CD3 antigen x CD19 antigen) comprising two different single-chain Fv fragments was generated to stimulate the recruitment of CD3-T cells to CD19-positive lymphoma. This bispecific molecule exhibited rapid induction of strong anti-tumor cytotoxicity at very low concentrations and 2:1 effector-target cell ratios without the need for cytokine pre-stimulation of T cells cytokine. This was a significant breakthrough in antibody immunotherapy, and led to the application of BsAbs to the treatment of non-Hodgkin's lymphoma [47]. Subsequently, many preclinical and clinical trials were conducted to verify the efficacy and safety of CD3xCD19 BiTE (blinatumomab: AMG103/MT103/MEDI-538) before its approval by the drug regulatory agency [48,49]. After investigating the clinical safety and efficacy of increasing doses of Blinatumomab for the treatment of non-Hodgkin's B-cell lymphoma in patients who had relapsed after receiving standard therapies, a study reported that Blinatumomab was effective in lysing tumor cells at low doses through the recruitment of T cells, leading to tumor regression at a 0.06 mg dose of the drug [50]. Meanwhile, the use of Blinatumomab has also been explored in chemotherapy-refractory minimal residual disease (MRD) in B-acute lymphoblastic leukemia (ALL) patients [51]. Ultimately, based on the therapeutic benefit shown by a single-arm trial evaluating the efficacy of Blinatumomab in adult patients with relapsed or refractory ALL, the FDA accelerated its approval for clinical application [22]. Numerous studies were carried out to explore the application of Blinatumomab to other types of tumors and compare the efficacy of Blinatumomab versus chemotherapy for patients with advanced ALL [52,53]. Besides, the structure and construction of BiTE shows extraordinary lysis potency by engaging polyclonal T cells to target tumor cells, resulting in significant interest in exploring the mechanisms underlying these actions. Detailed analysis of the structures of immune synapses using laser-scanning confocal microscopy showed that BiTE triggered the cytolytic T cell synapses while ignoring MHC class I expression, which represents a major means of immune evasion by tumor cells in vivo [54]. Moreover, three review papers were included. One of these reviewed the principles and challenges of BiTE [55]. With the continuous development of genetic engineering and associated technology, numerous formats of BsAbs have been designed and constructed in the past decades. Ulrich Brinkmann and Roland E. Kontermann have provided a comprehensive overview of the different BsAbs formats for specific applications, providing a better understanding of the progress in industry [7]. With the increasing participation of researchers and established commercialized technology platforms, more and more BsAbs are undergoing clinical development, which are essential stages before their transformation to clinical application. The last review summarized the mechanistic perspective and R&D pipelines of the current BsAb landscape [4]. Furthermore, CiteSpace was used to conduct reference analysis based on the strongest citation bursts from 2000 to 2023 (Figure S5). The first reference of the first burst, "Bispecific antibodies in cancer therapy", was published in 2000, with the burst continuing to 2004. This paper is a literature review that elaborates on BsAb-depended immune effectors against tumors and summarizes the current clinical progress in the BsAb field.

Notably, while the bursts associated with most references are over, the bursts of three references remain in an ongoing outbreak status, indicating these three studies had significant academic value and will receive constant attention in the next few years. According to the reference clustering analysis, the directions of the research field have altered from the early topics of immunoconjugates, pre-targeting, EpCAM, HER3, and multiple myeloma to solid tumors, BCMA, and PD-L1.

4.3. Keywords co-occurrence

Keyword co-occurrence, keyword bursts, and cluster analysis are also useful and intuitive approaches to identify popular research topics. The combined analysis of the frequencies and the overlay visualization map of co-occurrence keywords revealed that high-frequency words are at the forefront of research, with changes seen in the emerging research trends in recent years, allowing researchers to grasp the dynamic trends in specific research fields. As shown in Fig. 8B, keywords such as "EpCAM", "Radioimmunotherapy", and "pre-targeting" showed greater heat values in the early years of the field. More recently, the popularity of most keywords has increased over the last 10 years, especially during the last five years; these keywords are mainly associated with bi/multispecific antibodies, tumor immunotherapy, BiTE, chimeric antigen receptor, and immune checkpoint inhibitors [56]. Moreover, with the breakthrough of immune checkpoint inhibitors (ICIs) in the field of tumor immunotherapy, exploring the use of ICIs together with BsAbs has become the hotspot of current research, including the selection of target antigens and exploration of the curative effects of using BsAbs in combination with ICIs, revealed by the keyword timeline graph analysis [57]. Additionally, keywords with strongest burst strengths can also predict burgeoning frontier topics and reflect the evolution of research focus over time. In the last five years, two keywords, namely, "solid tumors" and "cytokine release syndrome", both showed ongoing bursts until 2021, while the citation burst keywords of "multiple myeloma", "resistance", "efficacy", "combination", "chemotherapy", and "open label" were in a continuous burst, suggesting that these topics are potential continuous hotspots in the future.

Multiple myeloma (MM) remains an incurable hematologic malignancy, even though considerable progress has been made in therapeutic approaches in the past decades. After the early use of allogeneic hematopoietic stem cell transplant (allo-HSCT), immunotherapies have been shown to be effective in a subset of patients, and different MAbs, such as daratumumab, elotuzumab, and isatuximab (anti-CD38), were successively approved for the treatment of MM [58–60]. Despite improved outcomes with stronger responses and longer survival after these new treatments, MM remains incurable and there are numerous cancer immunotherapies

under exploration, including BsAbs, to break the deadlock. Teclistamab (TECVAYLI®), a humanized B-cell maturation antigen (BCMA) x CD3 DuoBody® BsAb, was approved by the FDA in October 2022 for the treatment of adult patients with recurring and refractory MM, who have undergone at least four prior lines of therapy. This is the first BiTE to be conditionally approved for MM, based on the milestone clinical trial MajesTEC-1(NCT03145181, NCT04557098) [61]. Patients were found to have consistently better clinical outcomes with improved health-related quality of life in the first-in-human, open-label, single-arm, multi-center, phase I/II trial [62–64]. The preclinical and clinical exploration of other BCMA BsAbs is ongoing [65].

Based on the trailblazing progress in hematological malignancies with the breakthrough of Blinatumomab, BsAbs have also gained significant momentum in investigations for treating solid tumors. Nonetheless, the problems of adverse effects, such as cytotoxicity and cytokine release syndrome, still exist in the anti-tumor application of BsAbs. Furthermore, the remarkable efficacy of BsAbs observed in the hematological field has not been replicated in patients with solid tumors, where both reduced efficacy and resistance are observed. Multiple factors, such as the heterogeneous expression of target antigens, the complexity of the immunosuppressive TME, and low T lymphocyte infiltration, might be responsible for the unique treatment challenges in solid tumors. However, numerous strategies are under exploration to improve the short-term perspective, such as the identification and development of novel tumor targets, the construction of BsAbs with higher activity, the establishment of more advanced antibody design platforms, the exploration of antidrug antibodies (ADC), and the combination of different treatment approaches. Meanwhile, these treatment strategies require extensive clinical trials to furnish rigorous evidence supporting the curative effect of improved therapeutic strategies in future clinical applications.

4.4. Strengths and limitations

This study is the first to conduct a comprehensive analysis of the global progress and hotspots in the overall research field of BsAb-based cancer immunotherapy. The study analyzed research published during the past 20 years using bibliometric visualization, thus providing a significant guide for both clinicians and basic researchers. Furthermore, various forms of bibliometric software were utilized to conduct the literature analysis, allowing more comprehensive and credible multiple-dimensional results. Nevertheless, the study has some limitations. These are 1), although WoSCC is considered one of the most applicable databases for bibliometric analyses, it is possible that some potentially important studies indexed in other databases, such as PubMed, Embase, Scopus, and Ovid, might have been missed, 2), only articles published in English were included, which may have caused study bias, 3), Data on the BsAbs in cancer immunotherapy currently under clinical trials should also be included for higher credibility, 4), The value of recently published high-quality studies may have been underrated in terms of citations due to the shorter time.

5. Conclusions

In summary, the BsAb field in cancer immunotherapy has evolved continuously over the past few decades and has great potential for further research. This bibliometric analysis provides insight into historical developmental trends, research advances over the years, and current hotspots in BsAb-based cancer immunotherapy by comprehensively summarizing the research data, thus assisting researchers in future studies. It was revealed that a breakthrough is required for the use of BsAb-based cancer immunotherapy for solid tumors, which could be achieved by collaboration and support in multipartite fields. Research on BsAb-based cancer immunotherapy research is currently in the process of transfer from basic research to translational medicine for potential clinical applications. Therefore, more rigorous clinical trials are required to evaluate the preclinical efficacy and safety of BsAbs. Furthermore, professionals need to explore the mechanisms of resistance to BsAb treatment, and assess the optimization of treatment strategies and the use of BsAbs in combination with chemotherapy, antiangiogenic therapy, radiotherapy, and targeted therapy to improve sensitivity and specificity and limit adverse therapeutic effects. The results of the investigation suggested the potential advantages of the formation of multinational and multi-platform collaborations to promote innovation and progress in BsAb-based cancer immunotherapy.

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Data availability statement

The data associated with this study has been retrieved and downloaded from The Public available Database, and the data included in article/supp. material/referenced in this article is available which can be obtained from the corresponding author if necessary.

Ethics approval and consent to participate

Informed consent was not required for this study because the data extracted to conduct bibliometric analysis was directly retrieved from database without human and animal intervention.

CRediT authorship contribution statement

Jing Wei: Writing – original draft, Visualization, Software, Data curation. **Huilan Zheng:** Methodology, Data curation. **Shuang Dai:** Visualization, Validation, Supervision. **Ming Liu:** Writing – review & editing, Conceptualization.

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.

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Not applicable.

Abbreviations

BsAbs	Bispecific antibodies
WOSCC	Web of Science Core Collection
USA	The United States
mAbs	monoclonal antibodies
BiTE	Bispecific T cell engager
B-ALL	B- cell precursor acute lymphoblastic leukemia
TME	tumor microenvironment: NP: number of publications
SCI-Expanded	The Science Citation Index Expanded
SSCI	Social Sciences Citation Index
TC	total citations
MCP	multiple country publications
IF	impact factor
JCR	journal citation reports
EpCAM	epithelial cell adhesion molecule
R&D	research & development
BCMA	B-cell maturation antigen
ADC	antidrug antibodies

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