Heliyon 10 (2024) e24452

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Bibliometric analysis of research trends on the combination of immune checkpoint inhibitors and PARP inhibitors in solid tumors

Yaqian Tan [a], Qi Song [b,*]

[a] Department of Pharmacy, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, China
[b] Department of Pharmacy, Affiliated Cancer Hospital & Institute of Guangzhou Medical University, Guangzhou, China

ARTICLE INFO

Keywords:
PARP inhibitors
Immunotherapy
Immune checkpoint inhibitors
Combination therapy
Solid tumors
Bibliometric analysis

ABSTRACT

Introduction: Immune checkpoint inhibitors (ICIs) has made significant achievements in the therapeutics of various tumor types, and recently growing evidence from preclinical studies and clinical trials has indicated that poly-ADP-ribose polymerase inhibitors (PARPi) are exhibiting encouraging synergism with ICIs. The aim of our current study is to explore the development pattern of literature related to the combined therapy of ICIs and PARPi in solid tumors from a bibliometric perspective.

Methods: Publications concerning the combination of ICIs and PARPi in solid tumors during 2008–2022 were extracted from the WOSCC database. VOSviewer and R-*bibliometrix* were applied to conduct bibliometrics.

Results: In total, 1113 articles were finally included. The USA was the most dominant country, and University of Texas MD Anderson Cancer Center was the most fruitful institute. Andreas Schneeweiss ranked first concerning the amount of publications in this research domain, and Timothy Yap had the most citations on this theme. The analysis of keyword co-occurrence indicated that research frontiers were shifted from the biological mechanisms of cell death to the combined strategy of ICIs and PARPi in clinical trials.

Conclusions: Our study comprehensively examined the publications on the combination of ICIs and PARPi in solid tumors from a bibliometric perspective. The research on this topic is in its rapid growth stage, and the USA is possessing an absolutely leading position in this field by its scientific accumulations and productivity. Moreover, the research frontiers have shifted from the mechanisms of ICIs and PARPi to their combined treatment in clinical application. In summary, our results demonstrated a comprehensive overview of the knowledge atlas and a valuable reference for the future investigations in this field.

1. Introduction

Immunotherapy has made substantial improvements in the therapeutics of various types of tumor during the past few decades [1–5]. In general, the underlying biological mechanism for immunotherapy is to enhance the immune system of the host in the elimination of cancer cells [6]. Immune checkpoint inhibitors (ICIs) are monoclonal antibodies against inhibitory checkpoint molecules which expressed on the cell membranes of antigen presenting cells and $CD4^+$ T cells [7,8]. With the rapid growth in the theory of

* Corresponding author.
E-mail address: songqi319@hotmail.com (Q. Song).

https://doi.org/10.1016/j.heliyon.2024.e24452
Received 9 September 2023; Received in revised form 13 December 2023; Accepted 9 January 2024
Available online 10 January 2024

immunotherapy, ICIs such as programmed death 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), have been broadly applied in the treatment of several solid cancer types [9–11]. The emerging clinical data has led to the approval of ICIs in a constantly increasing list of cancers, and is likely to change the current routine intervention measures for many types of cancers [12–19].

Recently, with the advancement of precision medicine, targeted therapy has drawn wide attention [20,21]. The accumulation of DNA damage is believed to be the hallmark of various cancers, and DNA damage repair (DDR) has become a basic strategy for targeted cancer therapy [22]. The poly (ADP-ribose) polymerase inhibitors (PARPi) have been discovered to display efficient outcomes in tumor cells with defects in DDR, especially breast cancer gene (BRCA)-positive and BRCA-negative cancers with homologous recombination deficiencies (HRD) [23–26]. In addition, PARPi sensitivity was found to be actively correlated with non-homologous end joining, which is the other pathway for DNA double-strand breaks repair aside from homologous recombination repair [27–31]. Moreover, the PI3-kinase pathway also has a major part in the application of PARPi as it involves in several DNA replication and cell cycle regulation processes [32,33]. From the perspective of clinical application, PARPi as a monotherapy in maintenance strategy, have shown considerable clinical impacts in various kinds of solid tumor, including ovarian cancers, breast cancers, and pancreatic cancers [34–37].

Despite the advances that have been witnessed in ICIs or PARPi alone, the weak points of the therapy, such as acquired resistance and immune escape, have also been observed in patients [38]. Interestingly, ICIs and PARPi represented a rational combination. For instance, the DNA damage mediated by PARPi can regulate the immune microenvironment of tumor cells through a series of cellular mechanisms that further support the susceptibility of tumor cells to ICIs [2,39]. Despite that there are currently no guidelines for the combined treatments of ICIs and PARPi, the combination therapy is proved to be promising and its effect has been verified in many clinical trials [40]. Specifically, majority of the clinical trials have examined that such combined strategies have tolerance for patients and are effective in several tumor types, including breast cancers [41–44], ovarian cancers [45,46], and prostate cancers [47]. However, there are several key issues remain to be solved in the follow-up study of this combination therapy: What is the benefit from combination treatment compared to monotherapy? Is there an optimal dosage or dosing schedule for the combined treatment? What is the efficiency between different tumor types or different populations?

Hence, an inclusive summary of existing publications on the combined strategy of ICIs and PARPi in solid tumors is necessary to present the knowledge atlas of this field. Thus far, there are several reviews that summarized the knowledge of combined strategy of ICIs and PARPi [1–5]. However, the above reviews contain relatively little literature, and a comprehensive observation of this topic in a broader perspective, has not been reported. Bibliometrics, which can analyze a large number of literature at a macro level, has become a widely used analytical method in the medical field [48–50]. The quantitative analysis is a major highlight in bibliometrics, and the trajectory tracing function enables researchers to examine the networks of literature in multiple dimensions [50–54]. So far, no bibliometric analysis has been found concerning combined strategy of ICIs and PARPi in solid tumors. Therefore, we conducted a summarized bibliometric analysis on the relevant papers from 2008 to 2022, aiming to explore the framework and directions of this

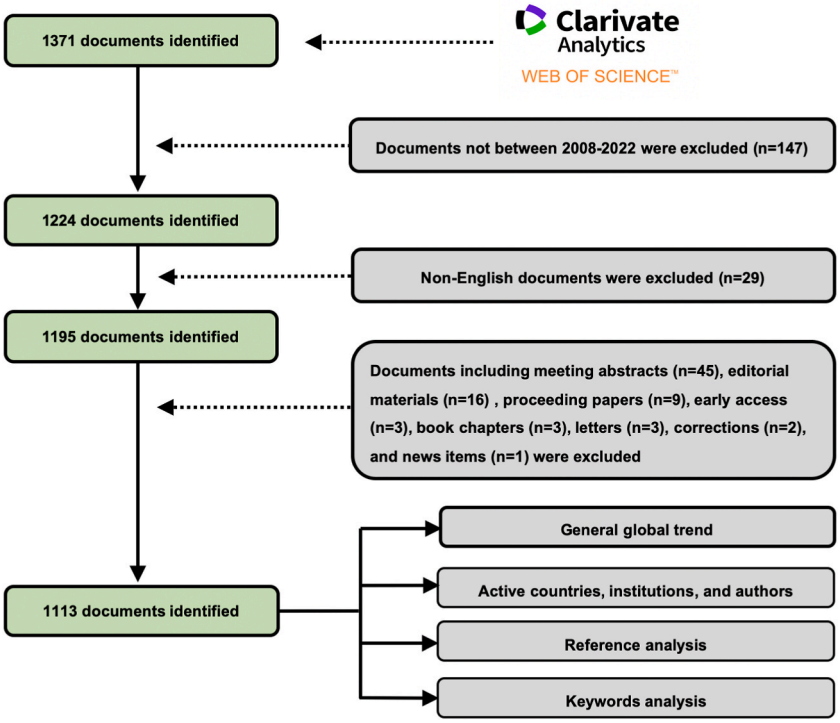

Fig. 1. Flowchart of literature collection and selection.

field. Our findings of the knowledge pattern will provide indicative references for future research in this theme.

2. Materials and methods

2.1. Data acquisition

Literature was extracted from the Web of Science Core Collection (WOSCC) database with edition limited to the Science Citation Index Expanded Edition. Data acquisition was performed on a single day (August 4th, 2023) to avoid bias caused by the frequent updates of the WOSCC database. The search terms were as follows: TS=(cancer* OR carcinoma* OR neoplasms* OR tumor* OR tumour* OR malignan*) AND TS=(*parib OR poly (ADP-ribose) polymerase inhibitor* OR PARP inhibitor* OR PARP*) AND TS=(immunotherap* OR immune checkpoint blockade* OR immune checkpoint inhibitor* OR PD-1 OR PD 1 OR Programmed Cell Death Protein 1 OR PD-L1 OR PD L1OR Programmed Death-Ligand 1 OR CTLA-4 OR CTLA 4 OR Cytotoxic T-Lymphocyte-Associated Protein 4). The period of studies was set to 2008–2022 encompassing 15 years. The language of the literature was confined to English, and the types of literature were set to articles and reviews (Fig. 1).

2.2. Bibliometric analysis

In this study, Microsoft Excel 2019, GraphPad Prism (version 9.3.1), VOSviewer (version 1.6.18), R-*bibliometrix* (version 4.1.0), and the platform for bibliometric visualization (http://bibliometric.com/) were applied for bibliometric analysis.

Tables were generated by Microsoft Excel 2019, and bar charts were generated by GraphPad Prism. The global cooperation networks were constructed using the bibliometrics website (http://bibliometric.com/). VOSviewer is a JAVA-based software with the functions of processing and presenting mass bibliometric data [55–60]. In this study, VOSviewer was used to generate the co-occurrence and co-authorship networks. The R-*bibliometrix* is an *R*-based software with the functions of systematic and comprehensive bibliometric analysis [59–63]. In the present study, R-*bibliometrix* was applied to construct bibliometric map of global output, collaborations, literature sources, and keywords.

3. Results

3.1. Analysis of general trend

In total, 1113 records were finally identified from the database. As displayed in Fig. 2, the yearly global production reflected a constantly ascending tendency (growth rate = 28.88 %). From 2008 to 2019, the annual output was less than 100, indicating a slow developing stage. The accelerating phase occurred in 2019 with 137 publications and 2669 citations. Subsequently, the annual output increased rapidly and peaked in 2022 with 287 publications and 10643 citations.

3.2. Analysis of countries

In total, 61 countries produced related publications during 2008–2022. Fig. 3A demonstrates the top 10 country in productions, and the USA has the largest amount of publications (n = 1606), followed by China (n = 714) and Italy (n = 482). Fig. 3B reveals that the USA, Italy, and China were the foremost countries in terms of total citations (USA: 16045, Italy: 3990, China:3803). As shown in Fig. 3C, the most frequent international collaboration was USA-UK (n = 41), followed by USA-Italy (n = 34), and USA-China (n = 29). Fig. 3D depicts the global cooperation networks of countries. The time trend visualization for country co-authorship networks are shown in Fig. 3E, and minimal number of publications was set to 5. The size of the node is used to indicate the output of the country, and the color of the node is used to indicate the academic activity of the country. For instance, South Korea was represented by a dark blue node, indicating that this country started earlier in this research field, whereas the dark red color for Brazil suggesting that

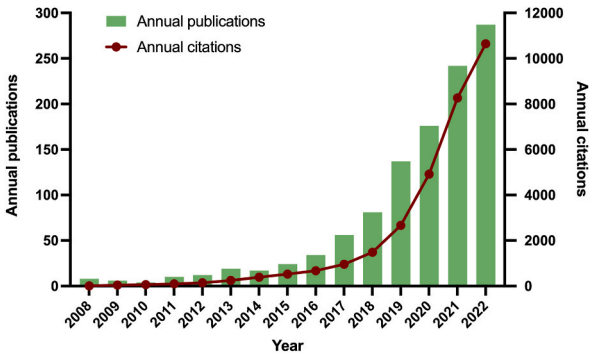

Fig. 2. Global trend of publications and citations from 2008 to 2022.

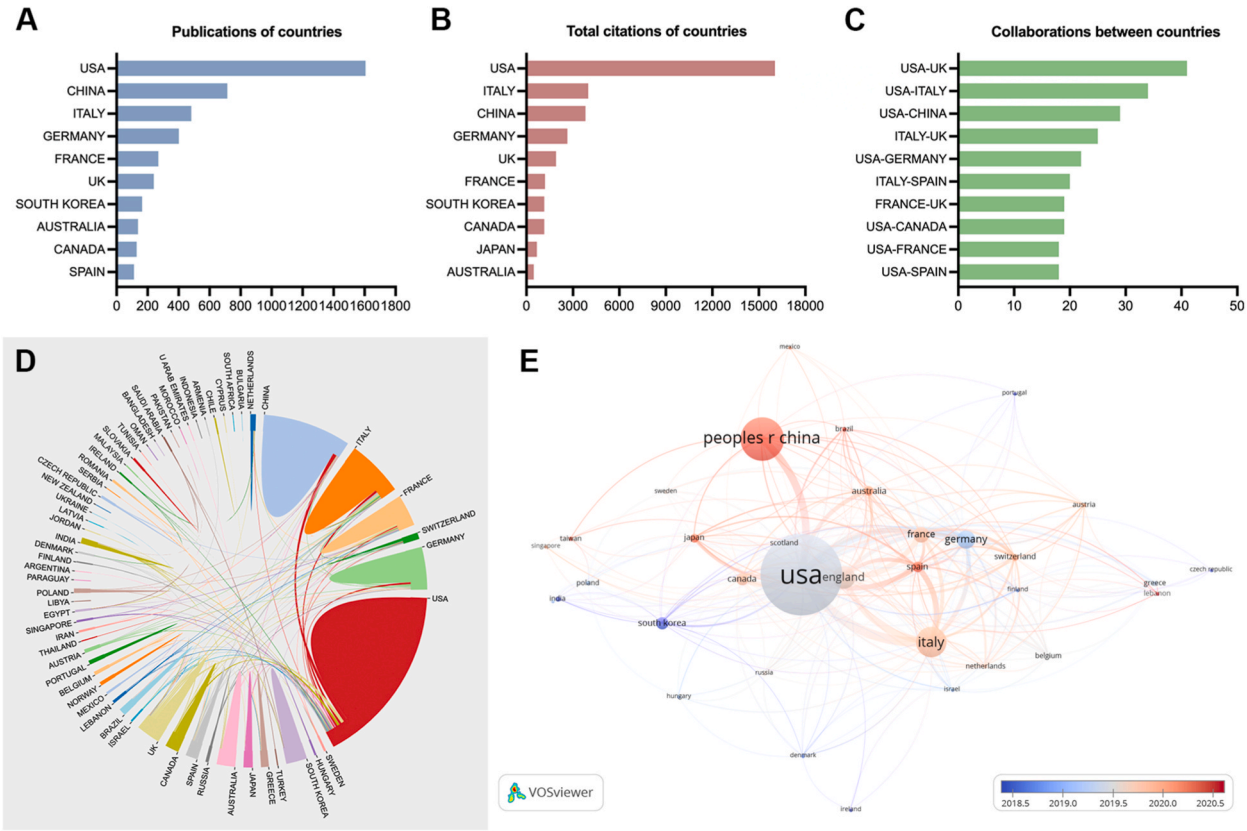

Fig. 3. Contributions of countries. **(A)** The top 10 countries in publications. **(B)** The top 10 countries regarding citations. **(C)** The top 10 collaborations between countries. **(D)** Global cooperative relationships between countries. **(E)** Chronological networks for country co-authorship.

researchers from Brazil have been more active in this field recently.

3.3. Analysis of institutions

In total, 1734 institutions were included in the bibliometric analysis. As displayed in Table 1, University of Texas MD Anderson Cancer Center ranked first regarding the number of documents (n = 147), followed by National Cancer Institute (n = 63), and Dana-Farber Cancer Institute (n = 59). Fig. 4A represents the chronological evolution of institution productions, and the minimum limit was set to 10 publications. National Cancer Institute showing in dark blue indicated an early-stage participation in this field. German Cancer Research Center was labeled in dark red, suggesting the high activity in recent years. Fig. 4B represents the degree of activity for institutions by the cooperation frequency heatmap. Dana-Farber Cancer Institute, University of Texas MD Anderson Cancer Center, and National Cancer Institute had the most frequent inter-institute cooperation.

Table 1
The top 10 active institutions contributing to research on the combined therapy of ICIs and PARPi in solid tumors.

Rank	Institution	Country	Publications	Total citations
1	University of Texas MD Anderson Cancer Center	USA	147	2010
2	National Cancer Institute	USA	63	1013
3	Dana-Farber Cancer Institute	USA	59	709
4	Harvard Medical School	USA	38	482
5	Fudan University	China	37	42
6	Johns Hopkins University	USA	30	69
7	IRCCS	Italy	28	20
8	Memorial Sloan Kettering Cancer Center	USA	27	86
9	Seoul National University	South Korea	27	15
10	China Medical University	China	26	371

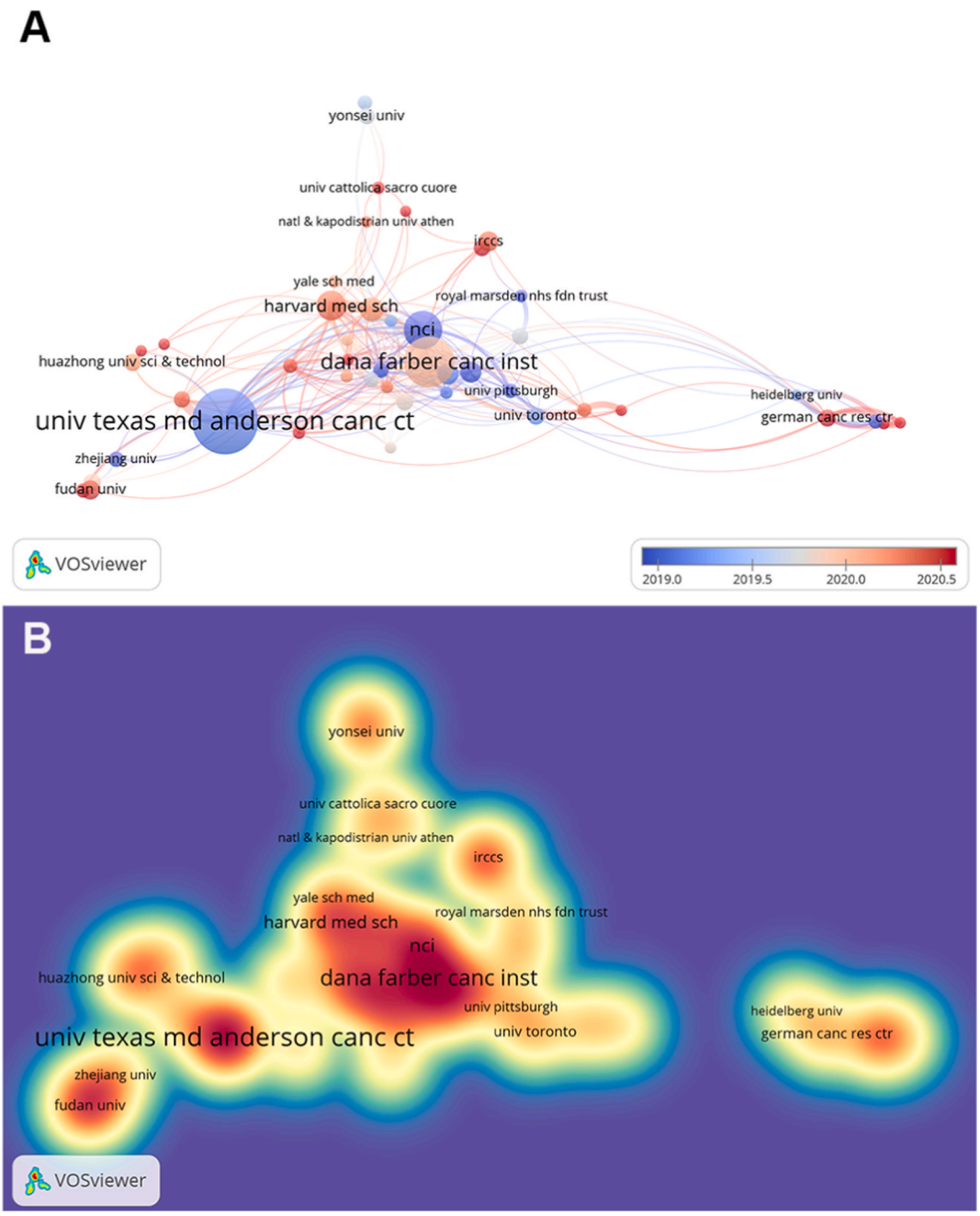

Fig. 4. Co-authorship networks for institutions. **(A)** Chronological networks for institution co-authorship. **(B)** Density map for institution co-authorship.

3.4. Analysis of authors

In this study, 6601 authors were identified in the analysis, and the most prolific authors in publications and citations are listed in Table 2 and Table 3. Andreas Schneeweiss was the author with the highest number of papers in this field (n = 14), followed by Timothy Yap (n = 12) and Gordon B. Mills (n = 12). From the perspective of total citations, Timothy Yap had the highest number of citations (n = 1398), followed by Gordon B. Mills (n = 1226) and Lauren Averett Byers (n = 1051). Fig. 5A displays the co-authorship network clusters between collaborative authors. For example, the size of the node for Andreas Schneeweiss suggesting his frequent collaborations with other authors, and the thickness of the connecting line between Andreas Schneeweiss and Peter A. Fasching indicating their close collaboration. Fig. 5B depicts the author co-authorship networks chronologically. For instance, Jung-Min Lee, which marked in dark blue, reflected the early-stage participation in this research field, whereas Francesco Massari, which started relatively

Table 2
The top 10 authors in publications related to the combined therapy of ICIs and PARPi in solid tumors.

Author	Publications	Institution	Country
Andreas Schneeweiss	14	University of Heidelberg	Germany
Timothy Yap	12	University of Texas MD Anderson Cancer Center	USA
Gordon B. Mills	12	Oregon Health and Science University	USA
Robert L. Coleman	10	University of Texas MD Anderson Cancer Center	USA
Jung-Min Lee	10	National Cancer Institute	USA
Domenica LoRusso	10	IRCCS	Italy
Emmanuel Antonarakis	9	University of Minnesota	USA
Joseph W. Kim	9	Yale School of Medicine	USA
Peter A. Fasching	9	University Hospital Erlangen	Germany
Tanja N. Fehm	9	Heinrich Heine University Düsseldorf	Germany

Table 3
The top 10 authors in citations related to the research of combined therapy of ICIs and PARPi in solid tumors.

Author	Total citations	Institution	Country
Timothy Yap	1389	University of Texas MD Anderson Cancer Center	USA
Gordon B. Mills	1226	Oregon Health and Science University	USA
Lauren Averett Byers	1051	University of Texas MD Anderson Cancer Center	USA
Jung-Min Lee	777	National Cancer Institute	USA
Amit Manulal Oza	709	Medicine at University of Toronto	Canada
Ursula A. Matulonis	624	Dana-Farber Cancer Institute	USA
Emmanuel Antonarakis	593	University of Minnesota	USA
Panagiotis A. Konstantinopoulos	593	Dana-Farber Cancer Institute	USA
Guang Peng	430	University of Texas MD Anderson Cancer Center	USA
Andreas Schneeweiss	394	University of Heidelberg	Germany

later in this field, was represented by a bright yellow node.

3.5. Analysis of journals

Papers relevant to the combined therapy of ICIs and PARPi in solid cancers were published in 403 journals in total. As shown in Table 4, the three leading journals in publications were *Cancers* (n = 80), *Cancer Treatment Reviews* (n = 33), and *Clinical Cancer Research* (n = 24). On the basis of Journal Citation Reports (JCR) 2022, half of the top ten most fruitful journals were Q1 journals, and the others were distributed in the Q2 region. The top 3 journals with respect to impact factor (IF) were *Annals of Oncology* (IF = 50.5), *Cancer Treatment Reviews* (IF = 11.8), and *Clinical Cancer Research* (IF = 11.5).

3.6. Analysis of references

A total of 50330 related references were detected. The impact of a study can be assessed by "local citation" in the peer field, and "global citation" in the general field [64,65]. The paper published in *Clinical Cancer Research* titled "PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression" had the highest local citation of 175 (Table 5), whereas the study published in *Nature Reviews Clinical Oncology* titled "Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease" had the highest global citation of 1494 (Table 6).

3.7. Analysis of keywords

Our current study extracted 2610 keywords from the documents, and the cluster visualization for keywords is displayed in Fig. 6A. The minimal keyword occurrence was set to 50 in order to provide a good readability of the graph, and keywords were assigned to 4 clusters by the co-occurrence network. The red cluster consisted of immunotherapy, open-label, double-blind, chemotherapy, ovarian cancer, and targeted therapy. The main focus of this cluster was clinical trials of immunotherapy. The major terms of the blue cluster included olaparib, PARP inhibitor, poly ADP-ribose polymerase, maintenance therapy, and breast cancer, in which the main focus of this cluster was PARPi and maintenance therapy. The green cluster was composed of expression, cancer, apoptosis, therapy, survival, and PD-L1. This cluster represented the potential mechanisms and applications of cell death. In the yellow cluster, tumor-infiltrating lymphocytes, pembrolizumab, anti-tumor activity, PD-1 expression, and phase-II were the main nodes included, and this cluster indicated the widely concerning role of tumor-infiltrating lymphocytes in immunotherapy. Fig. 6B shows the evolution of keywords according to the gradient of color. For example, the dark blue color for "apoptosis" indicating a research hotspot of the earlier stage, while "olaparib" marked in dark red suggesting that this keyword has recently become an active topic. Fig. 6C illustrates the frequency density map of keywords in which the most frequent hotspots included "immunotherapy", "chemotherapy", "open-label", "olaparib", and "PARP inhibitors". As shown in Fig. 6D–a three-field plot was generated in order to detect the attention received for keywords and

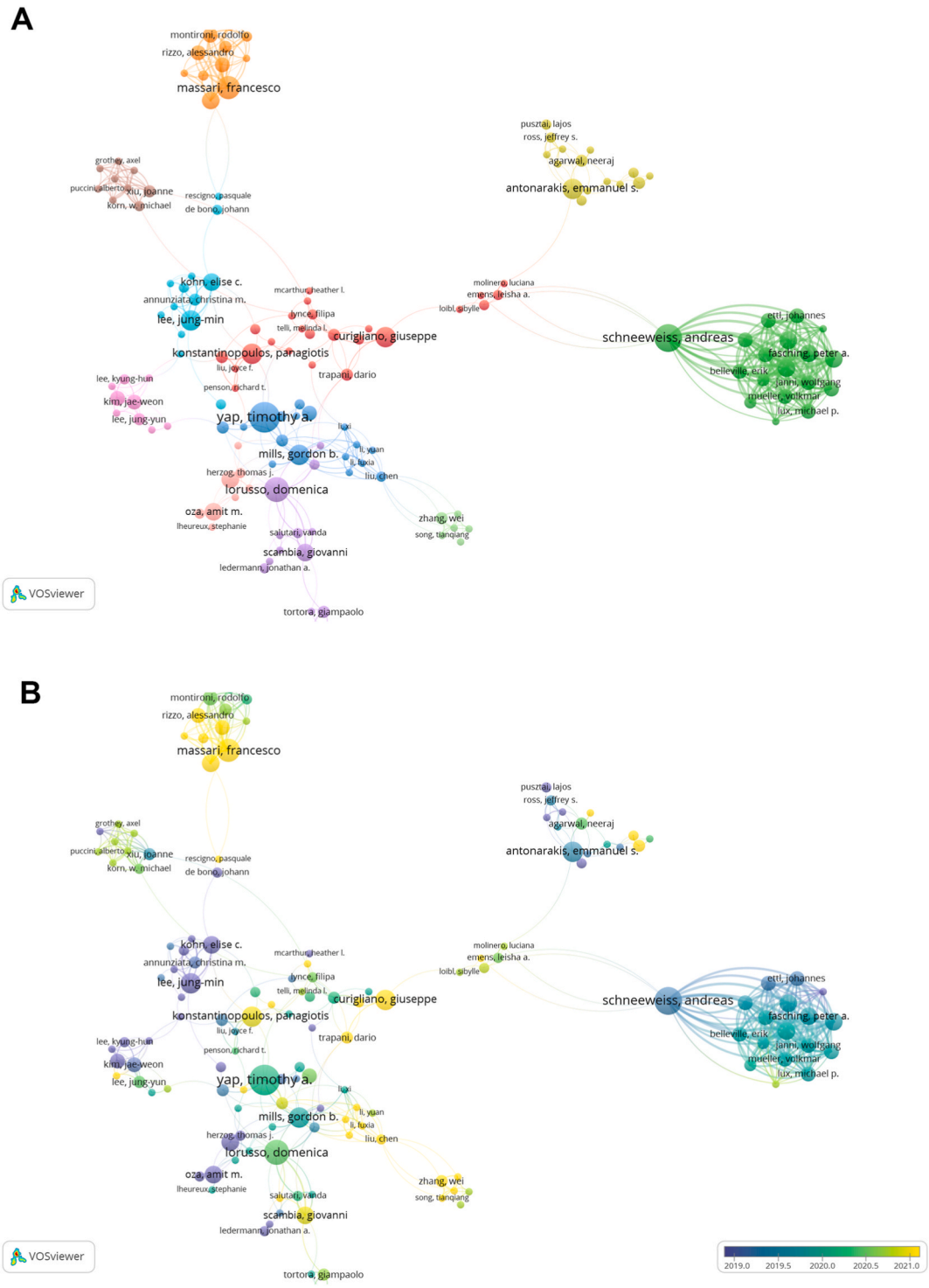

Fig. 5. Co-authorship networks for authors. **(A)** Clusters for author co-authorship. **(B)** Chronological networks for author co-authorship.

their relations at different stages. Before 2014, the main keywords included “apoptosis”, “cancer”, and “necroptosis”, indicating that the study focused on the mechanisms and applications of cell death in immunotherapy. From 2014 to 2018, researchers paid more attention to PARPi and their synergism with immunotherapy, including keywords such as “immunotherapy,” “breast neoplasms,” “olaparib,” “DNA repair,” and “PARP.” Since 2019, “immunotherapy,” “PARP inhibitors,” “ovarian neoplasms,” and “small cell lung cancer” have received continuous interest, suggesting that the combined treatment of immunotherapy and PARPi in ovarian cancer

Table 4
The top 10 most productive journals according to publications.

Rank	Journal	Publications	Total citations	IF (2022)	JCR region
1	*Cancers*	80	1141	5.2	Q2
2	*Cancer Treatment Reviews*	33	611	11.8	Q1
3	*Clinical Cancer Research*	24	403	11.5	Q1
4	*BMC Cancer*	22	263	3.8	Q2
5	*Current Treatment Options in Oncology*	20	407	4.3	Q2
6	*Frontiers in Oncology*	19	685	4.7	Q2
7	*International Journal of Molecular Sciences*	15	1314	5.6	Q1
8	*Annals of Oncology*	15	524	50.5	Q1
9	*Frontiers in Immunology*	14	138	7.3	Q1
10	*Current Oncology Reports*	13	154	4.7	Q2

Table 5
The top 10 local-cited documents.

Rank	Document	DOI	Local citations
1	Jiao SP, 2017, *Clin Cancer Res*	10.1158/1078-0432.CCR-16-3215	175
2	Shen JF, 2019, *Cancer Res*	10.1158/0008–5472.CAN-18-1003	89
3	Sen T, 2019, *Cancer Discov*	10.1158/2159–8290.CD-18-1020	73
4	Ding LY, 2018, *Cell Rep*	10.1016/j.celrep.2018.11.054	72
5	Pantelidou C, 2019, *Cancer Discov*	10.1158/2159–8290.CD-18-1218	70
6	Higuchi T, 2015, *Cancer Immunol Res*	10.1158/2326–6066.CIR-15-0044	69
7	Sato H, 2017, *Nat Commun*	10.1038/s41467-017-01883-9	63
8	Lee JM, 2017, *J Clin Oncol*	10.1200/JCO.2016.72.1340	59
9	Vinayak S, 2019, *Jama Oncol*	10.1001/jamaoncol.2019.1029	54
10	Domchek SM, 2020, *Lancet Oncol*	10.1016/S1470-2045 (20)30324-7	52

Table 6
The top 10 global-cited documents.

Rank	Document	DOI	Global citations
1	Bianchini G, 2016, *Nat Rev Clin Oncol*	10.1038/nrclinonc.2016.66	1494
2	Harbeck N, 2019, *Nat Rev Dis Primers*	10.1038/s41572-019-0111-2	1195
3	Mizrahi JD, 2020, *Lancet*	10.1016/S0140-6736 (20)30974-0	974
4	Lheureux S, 2019, *Ca-Cancer J Clin*	10.3322/caac.21559	635
5	Jiao SP, 2017, *Clin Cancer Res*	10.1158/1078-0432.CCR-16-3215	576
6	Pilie PG, 2019, *Nat Rev Clin Oncol*	10.1038/s41571-018-0114-z	567
7	Loibl S, 2021, *Lancet*	10.1016/S0140-6736 (20)32381-3	438
8	Sen T, 2019, *Cancer Discov*	10.1158/2159–8290.CD-18-1020	435
9	Sato H, 2017, *Nat Commun*	10.1038/s41467-017-01883-9	380
10	Morales JC, 2014, *Crit Rev Eukar Gene*	10.1615/critreveukaryotgeneexpr.2,013,006,875	347

was another hot topic in the field.

4. Discussion

4.1. General trends and structure

The amount of yearly global production is an intuitive indicator for the advancement of a specific research domain [66,67]. The growth trend of research on the combined therapy of ICIs and PARPi in solid tumors could be divided into two phases for the past 15 years. As displayed from the results, a slow growth phase during 2008–2019 was observed, with an annual output less than 100 and an average growth rate of 26.05 %. Subsequently, publications associated with the combination of ICIs and PARPi in solid tumors increased rapidly from 2019 to 2022 with an average growth rate of 36.23 %. This suggested that the underlying mechanisms of ICIs-PARPi interactions in oncology treatment are being uncovered, and emerging clinical applications have appeared. Furthermore, the steep rise in both publications and citations indicated that more researchers are investing and paying attention into this field. Therefore, we envision that the utility of ICIs-PARPi treatment in solid tumors will expand further in the coming years.

Based on our results in Fig. 3, the USA was significantly higher in all aspects compared to other countries, including publications, citations, and global cooperation. The USA constituted 31.95 % of all publications and 43.61 % of all citations worldwide. Basically, the distribution of institutions is consistent with the distribution of countries. The USA contributed 6 of the top 10 institutions, and covered the top 4 on the list in Table 1. These findings further suggested that the institutions from the USA contributed the most to the research in this area, which simultaneously gained deep academic accumulations that promoted the national academic status of this

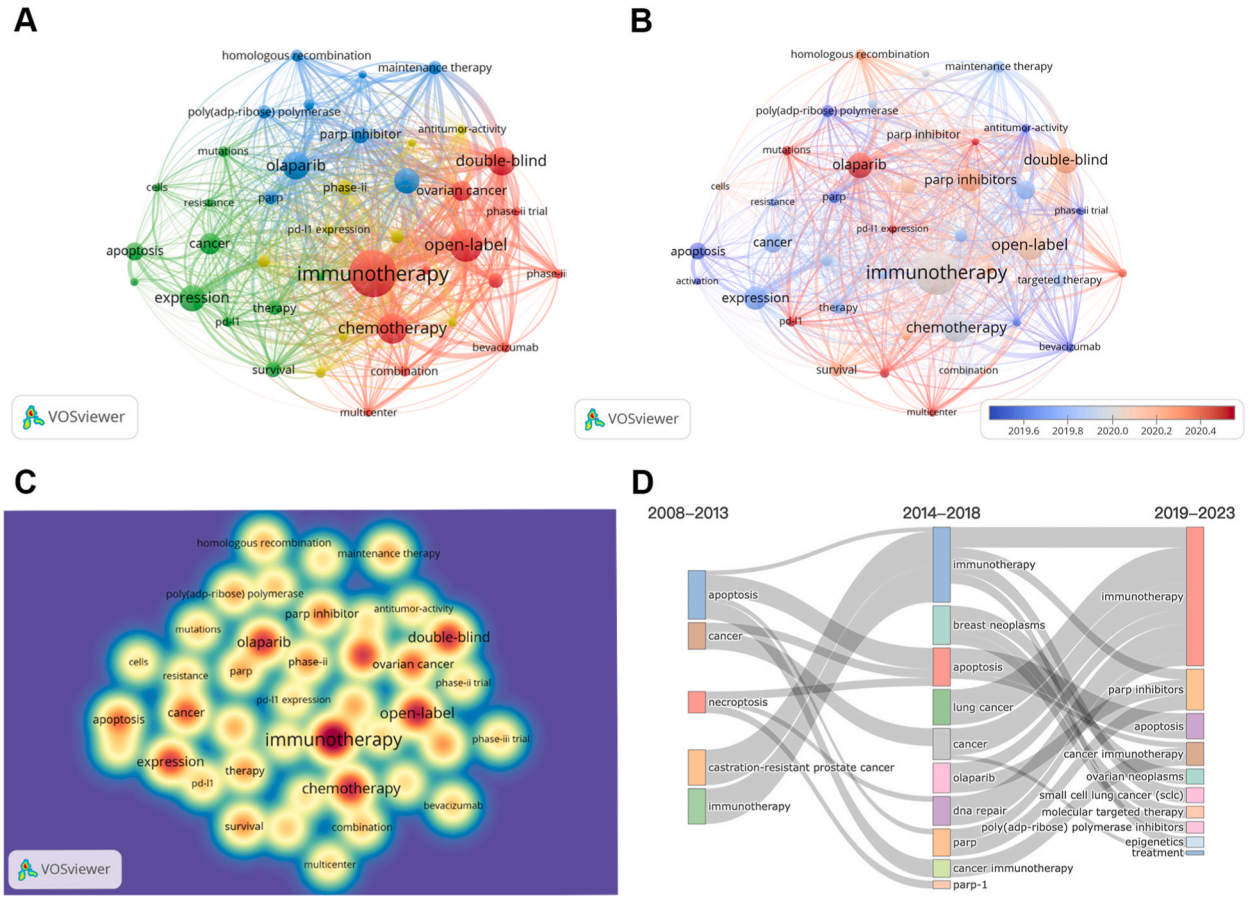

Fig. 6. Co-occurrence networks for keywords. **(A)** Clusters for keyword co-occurrence. **(B)** Chronological networks for keyword co-occurrence. **(C)** Density map for keyword co-occurrence. **(D)** The evolution of keywords over three time periods.

country. Notably, based on tables 2 and 3, we found that the majority of prolific authors on this topic were from institutions located in the USA. Moreover, University of Texas MD Anderson Cancer Center was a key player in this field with a great impact, possibly because of the outstanding researchers in the area (including Timothy Yap, Robert L. Coleman, Lauren Averett Byers, and Guang Peng) are working at this institution.

Together, based on these data, we believe that this research area will receive continuous attention in the coming years, and the USA is possessing an absolutely leading position in this research domain.

The academic influence of journals is commonly measured by the IF and JCR, and there are four zones divided by JCR according to the IF [68,69]. In regard to the top 10 journals related to the synergism of ICIs and PARPi, *Cancers* (80 publications) was the most productive journal, followed by *Cancer Treatment Reviews* (33 publications) and *Clinical Cancer Research* (24 publications). In addition, all the top 10 journals were either Q1 or Q2 journals, and the highest IF was 50.5 for *Annals of Oncology*. Therefore, these data revealed the significant impact and top quality of these journals, which will be valuable references for scholars finding the core journals in this field.

The most frequently cited references can supply fundamental guidance for researchers in this domain. There are two basic conceptions in bibliometrics, "local citation" and "global citation". Local citation refers to the degree of recognition in the similar fields, whereas global citation demonstrates the impact across disciplines [50,61,64,65]. Local citations are generally lower than global citations, and the difference between these two citations can enrich our understanding of the cited references as they reflect a more comprehensive situation of the academic impact [64,65]. In the current study, the most local-cited paper (175 local citations) titled "PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression", Shiping Jiao et al. focused on the interplay between PARPi and immunosuppression, and proved that the association between PARPi and PD-1/PD- L1 is an encouraging therapy in breast cancers. As for the paper with the highest global citation (1494 global citations) titled "Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease", Giampaolo Bianchini et al. reviewed the most promising therapeutic opportunities together with the relevant molecular findings, and provided a strong rationale for testing ICIs and targeted agents such as PARPi in triple-negative breast cancer.

Keyword co-occurrence analysis is a common approach to reflect the hotspots of the publications. Here, the historical structure of keywords was divided into three fields by the changes in research emphasis. The early hotspots of ICIs were apoptosis, necroptosis, and

castration-resistant prostate cancer, and gradually shifted to the effects of PARPi, ICIs, and clinical applications of both therapies. This suggested that this research field is expanding, and has been merged with other frontiers into clinical practice.

4.2. Evolution of research hotspots

4.2.1. Mechanism of function

ICIs has been proven to be potent in the therapeutics of multiple types of cancer and has achieved impressive clinical successes [1,2,70]. On the one hand, ICIs such as nivolumab, pembrolizumab, atezolizumab, durvalumab, and tremelimumab, have been approved in a constantly increasing list of cancers, including melanoma, non-small cell lung carcinoma, small cell lung carcinoma, gastric cancer, esophageal cancer, colorectal cancer, hepatocellular carcinoma, head and neck squamous cell carcinoma, and lymphoma [12–18]. On the other hand, several biomarkers, such as tumor mutation burden (TMB), tumor-infiltrating lymphocytes, and PD-L1 expression level, have been found to examine the clinical performance of ICIs [71]. Particularly, the TMB level (with TMB >10 mutations per megabase) was found to show better outcomes for ICIs performance in cancer of unknown primary [72]. However, some limitations were observed in patients treated with ICIs-based therapy, and the primary two reasons were unsatisfactory efficiency and toxic adverse effects produced [60–62].

PARPi have the ability to disrupt the repair process of DNA damage and induce synthetic lethality, particularly in tumor cells carrying defects in DDR, such as BRCA1/2 mutations [73–75]. Initially, the research emphasis of PARPi was on the combined therapy of PARPi with cytotoxic chemotherapy drugs, but the outcome was debatable considering the immoderate toxicity [76]. Subsequently, the potential anti-tumor effect of PARPi was determined in epithelial ovarian cancer with BRCA1/2 mutations [77,78]. In epithelial ovarian cancer, BRCA1/2 germline mutations are the strongest known genetic risk factors, and BRCA1/2 status was closely related to a greater expected survival of patients as BRCA1/2 carriers respond better than non-carriers to platinum-based chemotherapies [79]. At a later stage, PARPi response was demonstrated in breast cancers, pancreatic cancers, and prostate cancers [34,35,37,80–82]. More recently, clinical studies indicated that tumors without BRCA mutations were vulnerable to PARPi as well [83–86]. However, acquired resistance and limited efficacy were also observed in clinical practice aside from the advances of PARPi [87].

4.2.2. Combined strategy of ICIs and PARPi

Although ICIs and PARPi have made great contributions to the therapeutics of solid tumors, disadvantages such as acquired resistance, limited efficacy, and toxic adverse effects are commonly observed [34–37]. Thus, a demand for combining ICIs and PARPi has been raised, and the ultimate goal of the combined treatment is to enhance the efficacy while reducing the toxicity [88,89].

Extensive evidence focused on the underlying biological mechanisms suggested that combined therapy is an optimal choice for the therapeutic efficacy. It has been reported that interferons can be released by tumor cells as a signal amplifiers to immune cells under the context of PARPi, which leads to immune cell activation and recruitment [90,91]. Other evidence showed that PARPi are able to strengthen the ICIs response by inducing neoantigen release, increasing TMB, and upregulating PD-L1 expression [23,92,93]. More recent findings focused on the communication between DNA damage and tumor microenvironment inflammation reported that PARPi can elevate the level of anti-tumor immune cells in the tumor microenvironment [45,94,95]. Moreover, PARPi were reported to activate the cGAS-STING pathway which further induces anti-tumor immunity activated by ICIs in a BRCA-independent manner [96,97]. Other clinical models showed that PARPi can dose-dependently downregulate glycogen synthase kinase 3 (GSK3) and upregulate PD-L1, thereby inhibiting T-cell activation and inducing cancer cell apoptosis [5].

Preclinical studies in mouse models have shown promising anti-tumor effects that strongly support the combination of ICIs and PARPi, and further encourage the translation to humans [95]. Specifically, this double-agent strategy blocked tumor growth and prolonged survival time in breast cancers, lung cancers, colon cancers, and bladder cancers [98]. From the perspective of clinical trials, numerous studies have examined the PARPi-PD1 and PARPi-PDL1 combined strategies. Significant efficacies have been discovered mainly in tumors harboring BRCA mutations, including breast cancers [41–44], ovarian cancers [45,46], and prostate cancers [47], whereas investigations in gastrointestinal cancers showed moderate disease control rates [94,99]. Currently, there are insufficient data in studies concerning lung cancers [100,101] and urothelial cancers [102]. Thus, the effects are unclear in these two tumor types. Interestingly, in clinical trials, relatively less promising anti-tumor effects were noticed compared to those of the preclinical studies, which might indicate a limited translation of the outcomes from animals to humans. Hence, future investigations should focus on the selection of suitable models that can better transform preclinical data into clinical practice.

The combination of PARPi with CTLA-4 was less explored compared to PARPi-PD1 and PARPi-PDL1 combined strategies, possibly because of the undiscovered mechanisms of the PARPi-CTLA-4 pathway. An early preclinical study showed that the PARPi-CTLA-4 combination significantly prolonged the survival time in a majority of mice [103]. Another phase I clinical study combined olaparib and tremelimumab in BRCA-deficient ovarian cancer, and showed therapeutic effects as well as acceptable tolerability in patients [104].

4.2.3. Outlook

Although extensive results from clinical trials have proven the efficiency of combined treatment of ICIs and PARPi, this combination did not significantly improve the anti-tumor effects compared to the single agent of ICIs or PARPi. Therefore, future research should focus on the following aspects. First, improvement of the efficacy and safety of the combined therapy requires further evaluation in the future clinical studies, aiming to enhance the efficiency and decrease the chances of toxic adverse effects. For example, the development of selective PARPi in preclinical studies have demonstrated higher potency which may provide better clinical efficacy and broader spectrum of treatment [105,106]. Second, it is critical to screen and target the patient groups that benefit the most from

the combination therapy. Thus, research efforts should focus more on biomarkers that predict the outcome of patients, which is crucial to achieve precision medicine. Third, novel solutions of PARPi and/or ICIs resistance would be of great value for further investigations. For instance, proteomic technologies such as mass spectrometry and protein array analysis, have provided new therapeutic choices in ovarian cancer which can decrease the chance of drug resistance [107]. Finally, from the perspective of clinical applications, the optimal dose, duration, frequency, and the schedule of combination treatment should also be addressed.

5. Limitations

This study summarized the publications during 2008–2022 concerning combined therapy of ICIs and PARPi in solid tumors. Nevertheless, there exists some limitations that need to be noted. First of all, the written language of the published papers was restricted to English, and non-English studies in this field were thus not included. In addition, only the publications from WOSCC were collected, such that some relevant papers from other major databases (including PubMed, Google Scholar, and Scopus), were thereby lost. Moreover, data acquisition was restricted to the published papers from 2008 to 2022. Although the 15-year time span is considered to be long enough to reflect the development trends, some classic papers that formed the foundation of this field, and some of the very recent findings may be missing. Finally, there is a methodological limitation of bibliometrics that the analysis is relatively quantitative, thus novel strategies such as text mining and machine learning, could be considered for the qualitative analysis in the future bibliometric research [108,109].

6. Conclusion

In summary, the global studies on the combined therapy of ICIs and PARPi in solid tumors have developed rapidly in the past 15 years. The significant increase in annual publications indicated the growing importance of this topic. The USA ranked first with its leading position in the scientific productivity, as well as the distributions of productive authors and institutions. Keyword co-occurrence analysis indicated that research frontiers were shifted from mechanisms of cell death to the combined strategy of ICIs and PARPi in clinical trials. Therefore, our study explored the development pattern of research on this subject from a bibliometric perspective, and provided a comprehensive overview of research hotspots in this field.

Ethics declaration

Informed consent was not required for this study because no animal or human research data are generated.

Funding

This work was supported by the National Natural Science Foundation of China (No.82104223 and No. 82204372), Guangdong Basic and Applied Basic Research Foundation (No.2020A1515110008), Science and Technology Program of Guangzhou (No.202102021022 and No. 2023A04J0601), and Guangzhou Municipal Science and Technology Project for Medicine and Healthcare (No.20211A011044).

Data availability statement

The data sets analyzed in this study are available upon request from the corresponding author.

CRediT authorship contribution statement

Yaqian Tan: Writing – original draft, Software, Funding acquisition, Formal analysis, Data curation. **Qi Song:** Writing – review & editing, Writing – original draft, Funding acquisition, Formal analysis, Data curation, 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.

Acknowledgments

We thank Prof. Nees Jan van Eck, Prof. Ludo Waltman, Prof. Massimo Aria, and Prof. Corrado Cuccurullo, for the free access to VOSviewer and R-*bibliometrix*.

References

[1] P. Vikas, N. Borcherding, A. Chennamadhavuni, R. Garje, Therapeutic potential of combining PARP inhibitor and immunotherapy in solid tumors, Front. Oncol. 10 (2020), https://doi.org/10.3389/fonc.2020.00570.

[2] F. Peyraud, A. Italiano, Combined PARP inhibition and immune checkpoint therapy in solid tumors, Cancers 12 (6) (2020), https://doi.org/10.3390/cancers12061502.

[3] R.A. Stewart, P.G. Pilié, T.A. Yap, Development of PARP and immune-checkpoint inhibitor combinations, Cancer Res. 78 (24) (2018) 6717–6725, https://doi.org/10.1158/0008-5472.Can-18-2652.

[4] Z. Wu, P. Cui, H. Tao, S. Zhang, J. Ma, Z. Liu, et al., The Synergistic effect of PARP inhibitors and immune checkpoint inhibitors, Clin. Med. Insights Oncol. 15 (2021) 1179554921996288, https://doi.org/10.1177/1179554921996288.

[5] A. Revythis, A. Limbu, C. Mikropoulos, A. Ghose, E. Sanchez, M. Sheriff, et al., Recent insights into PARP and immuno-checkpoint inhibitors in epithelial ovarian cancer, Int. J. Environ. Res. Publ. Health 19 (14) (2022), https://doi.org/10.3390/ijerph19148577.

[6] P. Gotwals, S. Cameron, D. Cipolletta, V. Cremasco, A. Crystal, B. Hewes, et al., Prospects for combining targeted and conventional cancer therapy with immunotherapy, Nat. Rev. Cancer 17 (5) (2017) 286–301, https://doi.org/10.1038/nrc.2017.17.

[7] R. Bai, N. Chen, L. Li, N. Du, L. Bai, Z. Lv, et al., Mechanisms of cancer resistance to immunotherapy, Front. Oncol. 10 (2020) 1290, https://doi.org/10.3389/fonc.2020.01290.

[8] C. Robert, A decade of immune-checkpoint inhibitors in cancer therapy, Nat. Commun. 11 (1) (2020) 3801, https://doi.org/10.1038/s41467-020-17670-y.

[9] R.J. Motzer, C. Porta, M. Eto, T. Powles, V. Grünwald, T.E. Hutson, et al., Phase 3 trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) or everolimus (EVE) versus sunitinib (SUN) monotherapy as a first-line treatment for patients (pts) with advanced renal cell carcinoma (RCC) (CLEAR study), J. Clin. Oncol. 39 (6_suppl) (2021) 269, https://doi.org/10.1200/JCO.2021.39.6_suppl.269.

[10] T. Powles, E.R. Plimack, D. Soulières, T. Waddell, V. Stus, R. Gafanov, et al., Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial, Lancet Oncol. 21 (12) (2020) 1563–1573, https://doi.org/10.1016/s1470-2045(20)30436-8.

[11] B.I. Rini, E.R. Plimack, V. Stus, R. Gafanov, R. Hawkins, D. Nosov, et al., Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma, N. Engl. J. Med. 380 (12) (2019) 1116–1127, https://doi.org/10.1056/NEJMoa1816714.

[12] S.M. Ansell, A.M. Lesokhin, I. Borrello, A. Halwani, E.C. Scott, M. Gutierrez, et al., PD-1 blockade with nivolumab in relapsed or refractory hodgkin's lymphoma, N. Engl. J. Med. 372 (4) (2014) 311–319, https://doi.org/10.1056/NEJMoa1411087.

[13] H. Borghaei, L. Paz-Ares, L. Horn, D.R. Spigel, M. Steins, N.E. Ready, et al., Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer, N. Engl. J. Med. 373 (17) (2015) 1627–1639, https://doi.org/10.1056/NEJMoa1507643.

[14] R.L. Ferris, G. Blumenschein, J. Fayette, J. Guigay, A.D. Colevas, L. Licitra, et al., Nivolumab for recurrent squamous-cell carcinoma of the head and neck, N. Engl. J. Med. 375 (19) (2016) 1856–1867, https://doi.org/10.1056/NEJMoa1602252.

[15] R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H.J. Hammers, S. Srinivas, et al., Nivolumab versus everolimus in advanced renal-cell carcinoma, N. Engl. J. Med. 373 (19) (2015) 1803–1813, https://doi.org/10.1056/NEJMoa1510665.

[16] M. Reck, D. Rodríguez-Abreu, A.G. Robinson, R. Hui, T. Csőszi, A. Fülöp, et al., Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer, N. Engl. J. Med. 375 (19) (2016) 1823–1833, https://doi.org/10.1056/NEJMoa1606774.

[17] C. Robert, G.V. Long, B. Brady, C. Dutriaux, M. Maio, L. Mortier, et al., Nivolumab in previously untreated melanoma without BRAF mutation, N. Engl. J. Med. 372 (4) (2015) 320–330, https://doi.org/10.1056/NEJMoa1412082.

[18] Y. Wang, K. Zheng, H. Xiong, Y. Huang, X. Chen, Y. Zhou, et al., PARP inhibitor upregulates PD-L1 expression and provides a new combination therapy in pancreatic cancer, Front. Immunol. 12 (2021), https://doi.org/10.3389/fimmu.2021.762989.

[19] P. Solange, P.-A. Luis, S.H. Roy, R. Martin, Addressing CPI resistance in NSCLC: targeting TAM receptors to modulate the tumor microenvironment and future prospects, Journal for ImmunoTherapy of Cancer 10 (7) (2022) e004863, https://doi.org/10.1136/jitc-2022-004863.

[20] N. Jin, Y. Xia, Q. Gao, Combined PARP inhibitors and small molecular inhibitors in solid tumor treatment, Int. J. Oncol. 62 (2) (2023), https://doi.org/10.3892/ijo.2023.5476 (Review).

[21] P.G. Pilié, C. Tang, G.B. Mills, T.A. Yap, State-of-the-art strategies for targeting the DNA damage response in cancer, Nat. Rev. Clin. Oncol. 16 (2) (2019) 81–104, https://doi.org/10.1038/s41571-018-0114-z.

[22] R. Huang, P.K. Zhou, DNA damage repair: historical perspectives, mechanistic pathways and clinical translation for targeted cancer therapy, Signal Transduct Target Ther 6 (1) (2021) 254, https://doi.org/10.1038/s41392-021-00648-7.

[23] J. Murai, S.Y. Huang, B.B. Das, A. Renaud, Y. Zhang, J.H. Doroshow, et al., Trapping of PARP1 and PARP2 by clinical PARP inhibitors, Cancer Res. 72 (21) (2012) 5588–5599, https://doi.org/10.1158/0008-5472.Can-12-2753.

[24] C.E. Ström, F. Johansson, M. Uhlén, C.A.-K. Szigyarto, K. Erixon, T. Helleday, Poly (ADP-ribose) polymerase (PARP) is not involved in base excision repair but PARP inhibition traps a single-strand intermediate, Nucleic Acids Res. 39 (8) (2010) 3166–3175, https://doi.org/10.1093/nar/gkq1241.

[25] H. Farmer, N. McCabe, C.J. Lord, A.N.J. Tutt, D.A. Johnson, T.B. Richardson, et al., Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy, Nature 434 (7035) (2005) 917–921, https://doi.org/10.1038/nature03445.

[26] N.J. Curtin, C. Szabo, Poly(ADP-ribose) polymerase inhibition: past, present and future, Nat. Rev. Drug Discov. 19 (10) (2020) 711–736, https://doi.org/10.1038/s41573-020-0076-6.

[27] S. Boussios, C. Mikropoulos, E. Samartzis, P. Karihtala, M. Moschetta, M. Sheriff, et al., Wise management of ovarian cancer: on the cutting edge, J. Personalized Med. 10 (2) (2020) 41.

[28] S. Boussios, E. Rassy, M. Moschetta, A. Ghose, S. Adeleke, E. Sanchez, et al., BRCA mutations in ovarian and prostate cancer: bench to bedside, Cancers 14 (16) (2022), https://doi.org/10.3390/cancers14163888.

[29] R. Gupta, K. Somyajit, T. Narita, E. Maskey, A. Stanlie, M. Kremer, et al., DNA repair network analysis reveals shieldin as a key regulator of NHEJ and PARP inhibitor sensitivity, Cell 173 (4) (2018), https://doi.org/10.1016/j.cell.2018.03.050, 972-88.e23.

[30] S. Boussios, E. Rassy, S. Shah, E. Ioannidou, M. Sheriff, N. Pavlidis, Aberrations of DNA repair pathways in prostate cancer: a cornerstone of precision oncology, Expert Opin. Ther. Targets 25 (5) (2021) 329–333, https://doi.org/10.1080/14728222.2021.1951226.

[31] M.J. Metzger, B.L. Stoddard, R.J. Monnat Jr., PARP-mediated repair, homologous recombination, and back-up non-homologous end joining-like repair of single-strand nicks, DNA Repair 12 (7) (2013) 529–534, https://doi.org/10.1016/j.dnarep.2013.04.004.

[32] F. Aliyuda, M. Moschetta, A. Ghose, K. Sofia Rallis, M. Sheriff, E. Sanchez, et al., Advances in ovarian cancer treatment beyond PARP inhibitors, Curr. Cancer Drug Targets 23 (6) (2023) 433–446, https://doi.org/10.2174/1568009623666230209121732.

[33] H. Hiroki, K. Akahane, T. Inukai, T. Morio, M. Takagi, Synergistic effect of combined PI3 kinase inhibitor and PARP inhibitor treatment on BCR/ABL1-positive acute lymphoblastic leukemia cells, Int. J. Hematol. 117 (5) (2023) 748–758, https://doi.org/10.1007/s12185-022-03520-8.

[34] T. Golan, P. Hammel, M. Reni, E. Van Cutsem, T. Macarulla, M.J. Hall, et al., Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer, N. Engl. J. Med. 381 (4) (2019) 317–327, https://doi.org/10.1056/NEJMoa1903387.

[35] J.K. Litton, H.S. Rugo, J. Ettl, S.A. Hurvitz, A. Gonçalves, K.-H. Lee, et al., Talazoparib in patients with advanced breast cancer and a germline BRCA mutation, N. Engl. J. Med. 379 (8) (2018) 753–763, https://doi.org/10.1056/NEJMoa1802905.

[36] K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander, et al., Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer, N. Engl. J. Med. 379 (26) (2018) 2495–2505, https://doi.org/10.1056/NEJMoa1810858.

[37] M. Robson, S.-A. Im, E. Senkus, B. Xu, S.M. Domchek, N. Masuda, et al., Olaparib for metastatic breast cancer in patients with a germline BRCA mutation, N. Engl. J. Med. 377 (6) (2017) 523–533, https://doi.org/10.1056/NEJMoa1706450.

[38] P. Juncheng, A. Lafarge, G. Kroemer, M. Castedo, PARP1 inhibition elicits immune responses against non-small cell lung cancer, OncoImmunology 11 (1) (2022) 2111915, https://doi.org/10.1080/2162402x.2022.2111915.

[39] R.M. Chabanon, G. Muirhead, D.B. Krastev, J. Adam, D. Morel, M. Garrido, et al., PARP inhibition enhances tumor cell–intrinsic immunity in ERCC1-deficient non–small cell lung cancer, J. Clin. Investig. 129 (3) (2019) 1211–1228, https://doi.org/10.1172/JCI123319.

[40] C.W.S. Wanderley, T.S. Correa, M. Scaranti, F.Q. Cunha, R. Barroso-Sousa, Targeting PARP1 to enhance anticancer checkpoint immunotherapy response: rationale and clinical implications, Front. Immunol. 13 (2022), https://doi.org/10.3389/fimmu.2022.816642.

[41] S.M. Domchek, S. Postel-Vinay, S.A. Im, Y.H. Park, J.P. Delord, A. Italiano, et al., Olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast cancer (MEDIOLA): an open-label, multicentre, phase 1/2, basket study, Lancet Oncol. 21 (9) (2020) 1155–1164, https://doi.org/10.1016/s1470-2045(20)30324-7.
[42] J.-M. Lee, A. Cimino-Mathews, C.J. Peer, A. Zimmer, S. Lipkowitz, C.M. Annunziata, et al., Safety and clinical activity of the programmed death-ligand 1 inhibitor durvalumab in combination with poly (ADP-Ribose) polymerase inhibitor olaparib or vascular endothelial growth factor receptor 1-3 inhibitor cediranib in women's cancers: a dose-escalation, phase I study, J. Clin. Oncol. 35 (19) (2017) 2193–2202, https://doi.org/10.1200/jco.2016.72.1340.
[43] Z.I. Mitri, J. Vuky, K.A. Kemmer, M.A. Savin, S. Parmar, A.K. Kolodzie, et al., A phase II trial of olaparib and durvalumab in metastatic BRCA wild type triple-negative breast cancer, J. Clin. Oncol. 37 (15_suppl) (2019), https://doi.org/10.1200/JCO.2019.37.15_suppl.TPS1111. TPS1111-TPS.
[44] S. Vinayak, S.M. Tolaney, L.S. Schwartzberg, M.M. Mita, G.A.-L. McCann, A.R. Tan, et al., TOPACIO/Keynote-162: niraparib + pembrolizumab in patients (pts) with metastatic triple-negative breast cancer (TNBC), a phase 2 trial, J. Clin. Oncol. 36 (15_suppl) (2018) 1011, https://doi.org/10.1200/JCO.2018.36.15_suppl.1011.
[45] M. Friedlander, T. Meniawy, B. Markman, L. Mileshkin, P. Harnett, M. Millward, et al., Pamiparib in combination with tislelizumab in patients with advanced solid tumours: results from the dose-escalation stage of a multicentre, open-label, phase 1a/b trial, Lancet Oncol. 20 (9) (2019) 1306–1315, https://doi.org/10.1016/S1470-2045(19)30396-1.
[46] P.A. Konstantinopoulos, S.E. Waggoner, G.A. Vidal, M.M. Mita, G.F. Fleming, R.W. Holloway, et al., TOPACIO/Keynote-162 (NCT02657889): a phase 1/2 study of niraparib + pembrolizumab in patients (pts) with advanced triple-negative breast cancer or recurrent ovarian cancer (ROC)—results from ROC cohort, J. Clin. Oncol. 36 (15_suppl) (2018) 106, https://doi.org/10.1200/JCO.2018.36.15_suppl.106.
[47] F. Karzai, R.A. Madan, H. Owens, A. Hankin, A. Couvillon, L.M. Cordes, et al., Combination of PDL-1 and PARP inhibition in an unselected population with metastatic castrate-resistant prostate cancer (mCRPC), J. Clin. Oncol. 35 (15_suppl) (2017) 5026, https://doi.org/10.1200/JCO.2017.35.15_suppl.5026.
[48] C. Chen, R. Dubin, M.C. Kim, Emerging trends and new developments in regenerative medicine: a scientometric update (2000 – 2014), Expet Opin. Biol. Ther. 14 (9) (2014) 1295–1317, https://doi.org/10.1517/14712598.2014.920813.
[49] C. Chen, Searching for intellectual turning points: progressive knowledge domain visualization, Proc. Natl. Acad. Sci. USA 101 (suppl_1) (2004) 5303–5310, https://doi.org/10.1073/pnas.0307513100.
[50] C. Chen, M. Song, Visualizing a field of research: a methodology of systematic scientometric reviews, PLoS One 14 (10) (2019) e0223994, https://doi.org/10.1371/journal.pone.0223994.
[51] D. Stuart, Open bibliometrics and undiscovered public knowledge, Online Inf. Rev. 42 (3) (2018) 412–418, https://doi.org/10.1108/oir-07-2017-0209.
[52] A. Ninkov, J.R. Frank, L.A. Maggio, Bibliometrics: methods for studying academic publishing, Perspectives on Medical Education 11 (3) (2022) 173–176, https://doi.org/10.1007/s40037-021-00695-4.
[53] D.F. Thompson, C.K. Walker, A descriptive and historical review of bibliometrics with applications to medical sciences, Pharmacotherapy 35 (6) (2015) 551–559, https://doi.org/10.1002/phar.1586.
[54] P. Kokol, H. Blažun Vošner, J. Završnik, Application of bibliometrics in medicine: a historical bibliometrics analysis, Health Inf. Libr. J. 38 (2) (2021) 125–138, https://doi.org/10.1111/hir.12295.
[55] N.J. van Eck, L. Waltman, Software survey: VOSviewer, a computer program for bibliometric mapping, Scientometrics 84 (2) (2010) 523–538, https://doi.org/10.1007/s11192-009-0146-3.
[56] H. Arruda, E.R. Silva, M. Lessa, D. Proença Jr., R. Bartholo, VOSviewer and bibliometrix, J. Med. Libr. Assoc. 110 (3) (2022) 392–395, https://doi.org/10.5195/jmla.2022.1434.
[57] N.J. van Eck, L. Waltman, Citation-based clustering of publications using CitNetExplorer and VOSviewer, Scientometrics 111 (2) (2017) 1053–1070, https://doi.org/10.1007/s11192-017-2300-7.
[58] Y. Yu, Y. Li, Z. Zhang, Z. Gu, H. Zhong, Q. Zha, et al., A bibliometric analysis using VOSviewer of publications on COVID-19, Ann. Transl. Med. 8 (13) (2020) 816, https://doi.org/10.21037/atm-20-4235.
[59] D. Guleria, G. Kaur, Bibliometric analysis of ecopreneurship using VOSviewer and RStudio Bibliometrix, 1989–2019, Libr. Hi Technol. 39 (4) (2021) 1001–1024, https://doi.org/10.1108/LHT-09-2020-0218.
[60] D.O. Oyewola, E.G. Dada, Exploring machine learning: a scientometrics approach using bibliometrix and VOSviewer, SN Appl. Sci. 4 (5) (2022) 143, https://doi.org/10.1007/s42452-022-05027-7.
[61] M. Aria, C. Cuccurullo, bibliometrix: an R-tool for comprehensive science mapping analysis, J Informetrics 11 (2017) 959–975.
[62] H. Darvish, Bibliometric analysis using bibliometrix an R package, Journal of Scientometric Research 8 (2020) 156–160, https://doi.org/10.5530/jscires.8.3.32.
[63] R. Rodríguez-Soler, J. Uribe-Toril, J. De Pablo Valenciano, Worldwide trends in the scientific production on rural depopulation, a bibliometric analysis using bibliometrix R-tool, Land Use Pol. 97 (2020) 104787, https://doi.org/10.1016/j.landusepol.2020.104787.
[64] R.M. Batista-Canino, L. Santana-Hernández, P. Medina-Brito, A scientometric analysis on entrepreneurial intention literature: delving deeper into local citation, Heliyon 9 (2) (2023), https://doi.org/10.1016/j.heliyon.2023.e13046.
[65] N. Donthu, S. Kumar, D. Mukherjee, N. Pandey, W.M. Lim, How to conduct a bibliometric analysis: an overview and guidelines, J. Bus. Res. 133 (2021) 285–296, https://doi.org/10.1016/j.jbusres.2021.04.070.
[66] V. Durieux, P.A. Gevenois, Bibliometric indicators: quality measurements of scientific publication, Radiology 255 (2) (2010) 342–351, https://doi.org/10.1148/radiol.09090626.
[67] Y. Tan, Q. Song, Research trends and hotspots on the links between caveolin and cancer: bibliometric and visual analysis from 2003 to 2022, Front. Pharmacol. 14 (2023) 1237456, https://doi.org/10.3389/fphar.2023.1237456.
[68] T.H. Feeley, A bibliometric analysis of communication journals from 2002 to 2005, Hum. Commun. Res. 34 (3) (2008) 505–520, https://doi.org/10.1111/j.1468-2958.2008.00330.x.
[69] M. Bordons, M.T. Fernández, I. Gómez, Advantages and limitations in the use of impact factor measures for the assessment of research performance, Scientometrics 53 (2) (2002) 195–206, https://doi.org/10.1023/A:1014800407876.
[70] C.R. Parish, Cancer immunotherapy: the past, the present and the future, Immunol. Cell Biol. 81 (2) (2003) 106–113, https://doi.org/10.1046/j.0818-9641.2003.01151.x.
[71] J.J. Havel, D. Chowell, T.A. Chan, The evolving landscape of biomarkers for checkpoint inhibitor immunotherapy, Nat. Rev. Cancer 19 (3) (2019) 133–150, https://doi.org/10.1038/s41568-019-0116-x.
[72] E. Rassy, S. Boussios, N. Pavlidis, Genomic correlates of response and resistance to immune checkpoint inhibitors in carcinomas of unknown primary, Eur. J. Clin. Invest. 51 (9) (2021) e13583, https://doi.org/10.1111/eci.13583.
[73] R. Krishnakumar, W.L. Kraus, The PARP side of the nucleus: molecular actions, physiological outcomes, and clinical targets, Mol. Cell 39 (1) (2010) 8–24, https://doi.org/10.1016/j.molcel.2010.06.017.
[74] A. Ray Chaudhuri, A. Nussenzweig, The multifaceted roles of PARP1 in DNA repair and chromatin remodelling, Nat. Rev. Mol. Cell Biol. 18 (10) (2017) 610–621, https://doi.org/10.1038/nrm.2017.53.
[75] M. Rouleau, A. Patel, M.J. Hendzel, S.H. Kaufmann, G.G. Poirier, PARP inhibition: PARP1 and beyond, Nat. Rev. Cancer 10 (4) (2010) 293–301, https://doi.org/10.1038/nrc2812.
[76] M.S. Dhawan, I.H. Bartelink, R.R. Aggarwal, J. Leng, J.Z. Zhang, N. Pawlowska, et al., Differential toxicity in patients with and without DNA repair mutations: phase I study of carboplatin and talazoparib in advanced solid tumors, Clin. Cancer Res. 23 (21) (2017) 6400–6410, https://doi.org/10.1158/1078-0432.Ccr-17-0703.
[77] P.C. Fong, D.S. Boss, T.A. Yap, A. Tutt, P. Wu, M. Mergui-Roelvink, et al., Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers, N. Engl. J. Med. 361 (2) (2009) 123–134, https://doi.org/10.1056/NEJMoa0900212.

[78] T.A. Yap, S.K. Sandhu, P. Workman, J.S. de Bono, Envisioning the future of early anticancer drug development, Nat. Rev. Cancer 10 (7) (2010) 514–523, https://doi.org/10.1038/nrc2870.
[79] S. Shah, A. Cheung, M. Kutka, M. Sheriff, S. Boussios, Epithelial ovarian cancer: providing evidence of predisposition genes, Int. J. Environ. Res. Publ. Health 19 (13) (2022), https://doi.org/10.3390/ijerph19138113.
[80] M.R. Mirza, B.J. Monk, J. Herrstedt, A.M. Oza, S. Mahner, A. Redondo, et al., Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer, N. Engl. J. Med. 375 (22) (2016) 2154–2164, https://doi.org/10.1056/NEJMoa1611310.
[81] E. Pujade-Lauraine, J.A. Ledermann, F. Selle, V. Gebski, R.T. Penson, A.M. Oza, et al., Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial, Lancet Oncol. 18 (9) (2017) 1274–1284, https://doi.org/10.1016/s1470-2045(17)30469-2.
[82] R. Wesolowski, D.G. Stover, M.B. Lustberg, A. Shoben, M. Zhao, E. Mrozek, et al., Phase I study of veliparib on an intermittent and continuous schedule in combination with carboplatin in metastatic breast cancer: a safety and [18F]-Fluorothymidine positron emission tomography biomarker study, Oncol. 25 (8) (2020) e1158–e1169, https://doi.org/10.1634/theoncologist.2020-0039.
[83] R.L. Coleman, G.F. Fleming, M.F. Brady, E.M. Swisher, K.D. Steffensen, M. Friedlander, et al., Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer, N. Engl. J. Med. 381 (25) (2019) 2403–2415, https://doi.org/10.1056/NEJMoa1909707.
[84] J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, et al., DNA-repair defects and olaparib in metastatic prostate cancer, N. Engl. J. Med. 373 (18) (2015) 1697–1708, https://doi.org/10.1056/NEJMoa1506859.
[85] I. Ray-Coquard, P. Pautier, S. Pignata, D. Pérol, A. González-Martín, R. Berger, et al., Olaparib plus bevacizumab as first-line maintenance in ovarian cancer, N. Engl. J. Med. 381 (25) (2019) 2416–2428, https://doi.org/10.1056/NEJMoa1911361.
[86] A. Min, S.A. Im, PARP inhibitors as therapeutics: beyond modulation of PARylation, Cancers 12 (2) (2020), https://doi.org/10.3390/cancers12020394.
[87] S.M. Noordermeer, H. van Attikum, PARP inhibitor resistance: a tug-of-war in BRCA-mutated cells, Trends Cell Biol. 29 (10) (2019) 820–834, https://doi.org/10.1016/j.tcb.2019.07.008.
[88] M. Patel, S. Nowsheen, S. Maraboyina, F. Xia, The role of poly(ADP-ribose) polymerase inhibitors in the treatment of cancer and methods to overcome resistance: a review, Cell Biosci. 10 (1) (2020) 35, https://doi.org/10.1186/s13578-020-00390-7.
[89] A. Ribas, J.D. Wolchok, Cancer immunotherapy using checkpoint blockade, Science 359 (6382) (2018) 1350–1355, https://doi.org/10.1126/science.aar4060.
[90] S.F. Bakhoum, B. Ngo, A.M. Laughney, J.A. Cavallo, C.J. Murphy, P. Ly, et al., Chromosomal instability drives metastasis through a cytosolic DNA response, Nature 553 (7689) (2018) 467–472, https://doi.org/10.1038/nature25432.
[91] S.S. Ho, W.Y. Zhang, N.Y. Tan, M. Khatoo, M.A. Suter, S. Tripathi, et al., The DNA structure-specific endonuclease MUS81 mediates DNA sensor STING-dependent host rejection of prostate cancer cells, Immunity 44 (5) (2016) 1177–1189, https://doi.org/10.1016/j.immuni.2016.04.010.
[92] K.W. Mouw, M.S. Goldberg, P.A. Konstantinopoulos, A.D. D'Andrea, DNA damage and repair biomarkers of immunotherapy response, Cancer Discov. 7 (7) (2017) 675–693, https://doi.org/10.1158/2159-8290.Cd-17-0226.
[93] K. Nesic, M. Wakefield, O. Kondrashova, C.L. Scott, I.A. McNeish, Targeting DNA repair: the genome as a potential biomarker, J. Pathol. 244 (5) (2018) 586–597, https://doi.org/10.1002/path.5025.
[94] Y.-J. Bang, B. Kaufman, R. Geva, S.M. Stemmer, S.-H. Hong, J.-S. Lee, et al., An open-label, phase II basket study of olaparib and durvalumab (MEDIOLA): results in patients with relapsed gastric cancer, J. Clin. Oncol. 37 (4_suppl) (2019) 140, https://doi.org/10.1200/JCO.2019.37.4_suppl.140.
[95] S. Jiao, W. Xia, H. Yamaguchi, Y. Wei, M.K. Chen, J.M. Hsu, et al., PARP inhibitor upregulates PD-L1 expression and enhances cancer-associated immunosuppression, Clin. Cancer Res. 23 (14) (2017) 3711–3720, https://doi.org/10.1158/1078-0432.Ccr-16-3215.
[96] J. Shen, W. Zhao, Z. Ju, L. Wang, Y. Peng, M. Labrie, et al., PARPi triggers the STING-dependent immune response and enhances the therapeutic efficacy of immune checkpoint blockade independent of BRCAness, Cancer Res. 79 (2) (2019) 311–319, https://doi.org/10.1158/0008-5472.Can-18-1003.
[97] C. Pantelidou, O. Sonzogni, M. De Oliveria Taveira, A.K. Mehta, A. Kothari, D. Wang, et al., PARP inhibitor efficacy depends on CD8(+) T-cell recruitment via intratumoral STING pathway activation in BRCA-deficient models of triple-negative breast cancer, Cancer Discov. 9 (6) (2019) 722–737, https://doi.org/10.1158/2159-8290.Cd-18-1218.
[98] Z. Wang, K. Sun, Y. Xiao, B. Feng, K. Mikule, X. Ma, et al., Niraparib activates interferon signaling and potentiates anti-PD-1 antibody efficacy in tumor models, Sci. Rep. 9 (1) (2019) 1853, https://doi.org/10.1038/s41598-019-38534-6.
[99] H.L. Kindler, P. Hammel, M. Reni, E.V. Cutsem, T.M. Mercade, M.J. Hall, et al., Olaparib as maintenance treatment following first-line platinum-based chemotherapy (PBC) in patients (pts) with a germline BRCA mutation and metastatic pancreatic cancer (mPC): phase III POLO trial, J. Clin. Oncol. 37 (18_suppl) (2019), https://doi.org/10.1200/JCO.2019.37.18_suppl.LBA4. LBA4-LBA.
[100] B. Carney, S. Kossatz, B.H. Lok, V. Schneeberger, K.K. Gangangari, N.V.K. Pillarsetty, et al., Target engagement imaging of PARP inhibitors in small-cell lung cancer, Nat. Commun. 9 (1) (2018) 176, https://doi.org/10.1038/s41467-017-02096-w.
[101] N.Y. Gabrail, A. Bessudo, E.P. Hamilton, J.C. Sachdev, M.R. Patel, J.R. Ahnert, et al., IOLite: multipart, phase 1b, dose-finding study of the PD-1 inhibitor dostarlimab in combination with the PARP inhibitor niraparib ± bevacizumab (bev), or with platinum-based chemotherapy ± bev for advanced cancer, J. Clin. Oncol. 37 (15_suppl) (2019) 2560, https://doi.org/10.1200/JCO.2019.37.15_suppl.2560.
[102] T. Powles, D. Carroll, S. Chowdhury, G. Gravis, F. Joly, J. Carles, et al., An adaptive, biomarker-directed platform study of durvalumab in combination with targeted therapies in advanced urothelial cancer, Nat. Med. 27 (5) (2021) 793–801, https://doi.org/10.1038/s41591-021-01317-6.
[103] T. Higuchi, D.B. Flies, N.A. Marjon, G. Mantia-Smaldone, L. Ronner, P.A. Gimotty, et al., CTLA-4 blockade synergizes therapeutically with PARP inhibition in BRCA1-deficient ovarian cancer, Cancer Immunol. Res. 3 (11) (2015) 1257–1268, https://doi.org/10.1158/2326-6066.Cir-15-0044.
[104] S.F. Adams, O. Rixe, J.-H. Lee, D.J. McCance, S. Westgate, S.C. Eberhardt, et al., Phase I study combining olaparib and tremelimumab for the treatment of women with BRCA-deficient recurrent ovarian cancer, J. Clin. Oncol. 35 (15_suppl) (2017) e17052-e, https://doi.org/10.1200/JCO.2017.35.15_suppl.e17052.
[105] N.Y.L. Ngoi, E. Leo, M.J. O'Connor, T.A. Yap, Development of next-generation poly(ADP-ribose) polymerase 1-selective inhibitors, Cancer Journal 27 (6) (2021) 521–528, https://doi.org/10.1097/ppo.0000000000000556.
[106] X. Peng, W. Pan, F. Jiang, W. Chen, Z. Qi, W. Peng, et al., Selective PARP1 inhibitors, PARP1-based dual-target inhibitors, PROTAC PARP1 degraders, and prodrugs of PARP1 inhibitors for cancer therapy, Pharmacol. Res. 186 (2022) 106529, https://doi.org/10.1016/j.phrs.2022.106529.
[107] A. Ghose, S.V.N. Gullapalli, N. Chohan, A. Bolina, M. Moschetta, E. Rassy, et al., Applications of proteomics in ovarian cancer: dawn of a new era, Proteomes 10 (2) (2022) 16.
[108] Y. Zhang, C. Ling, A strategy to apply machine learning to small datasets in materials science, npj Comput. Mater. 4 (1) (2018) 25, https://doi.org/10.1038/s41524-018-0081-z.
[109] B.M. Lindgren, B. Lundman, U.H. Graneheim, Abstraction and interpretation during the qualitative content analysis process, Int. J. Nurs. Stud. 108 (2020) 103632, https://doi.org/10.1016/j.ijnurstu.2020.103632.