HUMAN VACCINES & IMMUNOTHERAPEUTICS
2025, VOL. 21, NO. 1, 2464379
https://doi.org/10.1080/21645515.2025.2464379

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

OPEN ACCESS Check for updates

Research hotspots and trends of immunotherapy and melanoma: A bibliometric analysis during 2014–2024

Zixuan Jia[a,b], Youao Zhang[a,c], Luyan Cao[d], Jieyan Wang[a], and Hui Liang[a]

[a]Department of Urology, People's Hospital of Longhua, Shenzhen, Guangdong, China; [b]School of Chinese Medicine, Southern Medical University, Guangzhou, China; [c]The First School of Clinical Medicine, Nanfang Hospital, Southern Medical University, Guangzhou, China; [d]Institute of Health and Wellbeing, University of Glasgow, Glasgow, Scotland

ABSTRACT

Over the last decade, the increasing global prevalence of melanoma has sparked growing interest in immunotherapies, which show significant potential against this form of skin cancer. This research aims to offer a framework to guide future studies and inspire new research directions. In this study, we used the Web of Science Core Collection to collect papers on immunotherapy and melanoma published between 2014 and 2024. With Excel and visualization tools like VOSviewer, COOC 13.2, Citespace, and Bibliometrix (R-Tool of R-Studio), we analyzed the data to spot trends and new focuses in the research. Our findings indicate a substantial surge in research activity concerning immunotherapy and melanoma between 2014 and 2024. The USA and China emerged as leading contributors, engaging in extensive and close collaborative efforts with European counterparts. Furthermore, seven of the top 10 research institutions are located in the USA, with the MD Anderson Cancer Center in Texas being the most productive. In addition, the Journal of Cancer Immunotherapy is the journal with the most articles published in the field. Professor Georgina V. Long from the Melanoma Institute at the University of Sydney was one of the most productive scholars. Keyword analysis shows that immune checkpoint inhibitors, tumor microenvironment and targeted therapies are key areas of interest for the research community. This paper uses bibliometric analysis to outline research trends and key points in immunotherapy and melanoma from 2014 to 2024, which helps understand the current research and guides future research directions.

ARTICLE HISTORY
Received 4 October 2024
Revised 22 January 2025
Accepted 5 February 2025

KEYWORDS
Melanoma; immunotherapy; immune checkpoint inhibitors; tumor microenvironment; targeted therapy

Introduction

In recent years, the global incidence of malignant melanoma has shown a concerning upward trend. According to GLOBOCAN, the year 2022 saw over 320,000 new cases of melanoma worldwide, with approximately 60,000 fatalities attributed to this disease.[1] As the most aggressive form of skin cancer, melanoma poses a significant threat to human health and life.[2]

Melanoma originates from melanocytes, which are predominantly located in the skin but can also be found in various other parts of the body, including the eyes, ears, meninges, gastrointestinal tract, and mucous membranes of the mouth, genitals, and sinuses. Since the 1950s, the incidence of cutaneous melanoma among Caucasians has been escalating, with the majority of cases linked to ultraviolet radiation (UVR) exposure, both from natural sunlight and indoor tanning.[3–5] Research indicates that UV irradiation can elicit addiction-like responses in humans and preclinical models, a phenomenon believed to be mediated by beta-endorphin production.[6] It is estimated that over 75% of cutaneous melanomas in Caucasians are triggered by the mutagenic effects of UV light.[3,6,7] Interestingly, melanoma is less common in nonwhite populations, with lower incidence rates among Hispanics and Asians, and the lowest rates observed in the black population.[8–10] Metastatic spread is the primary cause of melanoma-related deaths, typically beginning with lymph node involvement and subsequently spreading to the lungs.[11] However, the introduction of effective systemic therapies has led to an 18% decrease in mortality rates among white people in high-income countries within just three years.[12] Moreover, checkpoint immunotherapy, particularly in adjuvant settings, has set new benchmarks for neoadjuvant therapy.[13] Significant advancements in surgical trials have also revolutionized the practice of lymph node dissection for resectable melanoma.[14,15] Despite these advancements, there has been no observed reduction in mortality rates among nonwhite or lower socioeconomic status populations; instead, an increase in melanomas with poor prognoses has been noted.[16]

Immunotherapy, particularly immune checkpoint inhibitors (ICIs) such as PD-1 and CTLA-4 inhibitors, has emerged as a promising therapeutic strategy, demonstrating significant efficacy through the stimulation of the body's immune response against tumors. Additionally, adoptive cell transfer (ACT) and nanovaccines have garnered considerable attention for their therapeutic potential. ACT has shown promising anti-tumor effects by genetically modifying T cells to target melanoma cells.[17] Vaccine therapy, due to its effective and long-lasting anti-tumor effects, is a focal point of research.[18] However, subunit vaccines, which include molecular adjuvants and cancer-associated antigens or

CONTACT Jieyan Wang 993368974@qq.com; Hui Liang lianghui8689@smu.edu.cn Department of Urology, People's Hospital of Longhua, No.38 Jinglong Jianshe Road, Shenzhen, Guangdong, 518109, China

cancer-specific neoantigens, have shown limited clinical benefit in cancer patients, primarily due to inefficient vaccine delivery.[19] In contrast, the application of nanotechnology in melanoma treatment has shown considerable promise, particularly in enhancing drug delivery and targeting. Nanoparticles' (NPs) ability to deliver drugs precisely to cancer cells is a significant approach in cancer treatment, as their unique biological properties enable them to target cancer cells with precision while minimizing harm to healthy tissue.[20]

Melanoma, recognized for its aggressive nature, and the potential of immunotherapy are currently at the forefront of medical research. A thorough investigation into this field is crucial for the development of more precise and effective treatment strategies, with the ultimate goal of reducing the incidence and mortality rates of melanoma. This paper aims to provide an in-depth visual analysis of the literature on melanoma and immunotherapy using CiteSpace and VOSviewer. This approach will facilitate a more comprehensive understanding of the current state and future trajectory of the field, thereby fostering the emergence of innovative research directions and ideas.

Material and methods

Data retrieval strategy, data extraction, and cleaning

The focal point of this paper is the intersection of immunotherapy and melanoma research. Our data source was the esteemed Web of Science Core Collection, an expansive and authoritative repository encompassing over 12,000 peer-reviewed journals. For our study, we specifically utilized the SCI-Expanded (SCI-E) database within the Web of Science Core Collection. Our search strategy was executed through an advanced search, employing the following query: TS=(melanoma OR melanocarcinoma) OR TI=(melano* OR melanoma OR melanocarcinoma) OR AB=(melano* OR melanoma OR melanocarcinoma) AND TS=("immunotherapies" OR "immunotherapy" OR "immunotherapeutic" OR "immune therapy" OR "immunity therapy" OR "immunization therapy" OR "immunotherapy treatment" OR "immunological therapy"). The search was conducted for the period from January 1, 2014, to July 1, 2024, yielding a total of 16,013 documents. After rigorously excluding duplicates, conference abstracts, letters, and other non-peer-reviewed materials, we curated a collection of primarily full papers and reviews. Through meticulous examination of the title, abstract, and keywords, we ultimately assembled a dataset comprising 13,947 articles for our analysis.

Scientometric analysis methods

The 13,947 articles were meticulously exported in plain text format to facilitate comprehensive analysis. Employing a suite of analytical tools, including Excel 2019 and visualization software such as VOSviewer, COOC13.2, Citespace, Bibliometrix (an R-Tool within R-Studio), HistCite, and Pajek, we conducted a multifaceted analysis. This encompassed overall trend analysis, synonym consolidation, frequency assessments, and the computation of total local citation scores (TLCS) for countries/regions, institutions, and authors. Additionally, we performed cluster analysis on co-occurrence matrices, citation analysis, and two-mode matrix analysis. The burst detection in keyword mapping was instrumental in uncovering the research hotspots and identifying the cutting-edge directions in the field of immunotherapy and melanoma.

Results

Annual analysis of publication

Figure 1 illustrates a remarkable exponential growth in the research domain of immunotherapy and melanoma between 2014 and 2024. Initially, in 2014, the field was marked by a modest 592 publications, signifying a relatively nascent interest in the subject matter. However, this figure witnessed a steady annual ascent, culminating in a peak of 1,785 papers in 2021. Moreover, the cumulative count of papers exhibits a persistent upward trajectory, escalating from 592 in 2014 to a substantial 13,947 by 2024. This upward trend mirrors the burgeoning knowledge and research advancements accumulated over the past decade, underscoring the intensifying research momentum in this field. Such a surge in scholarly output offers a wealth of resources and insights, serving as a valuable foundation for future investigative endeavors.

Country/Region, institution, author and journal frequency analysis

The frequency analysis of country/region distribution, as delineated in Table 1, reveals that the USA stands at the forefront of academic contributions to the field of immunotherapy and melanoma, boasting the highest volume of scientific papers published on a global scale. Delving into the institutional landscape, the University of Texas MD Anderson Cancer Center emerges as the most dynamic research entity, with a significant impact in this domain. Considering individual scholarly contributions, Professor Georgina V. Long from the Melanoma Research Institute at the University of Sydney is recognized as the most distinguished researcher, with an impressive body of work that has significantly advanced the field. Among the journals, the Journal for Immunotherapy of Cancer, Cancers, and Frontiers in Immunology secure the top three positions, underscoring their pivotal roles in random-oncology and cancer biology research. It is noteworthy that the top 10 journals are all dedicated to exploring the foundational principles and practical applications of immunotherapy, investigating molecular mechanisms, and conducting research on specific cancer types. This comprehensive focus reflects the multifaceted nature of cancer research, indicative of the depth and breadth of scholarly inquiry in this area. Furthermore, the fact that eight of these 10 journals are classified within the JCR Q1 category is a testament to the high caliber and international reach of research in immunotherapy and melanoma.

Country/Region, institution, author, and journal TLCS analysis

The Total Local Citation Score (TLCS) serves as a quantitative indicator of the citation frequency within the entire corpus of relevant literature, thereby gauging the scholarly influence of a country, institution, or individual on a specific subject matter (Table 2). In the context of institutional contributions, the USA

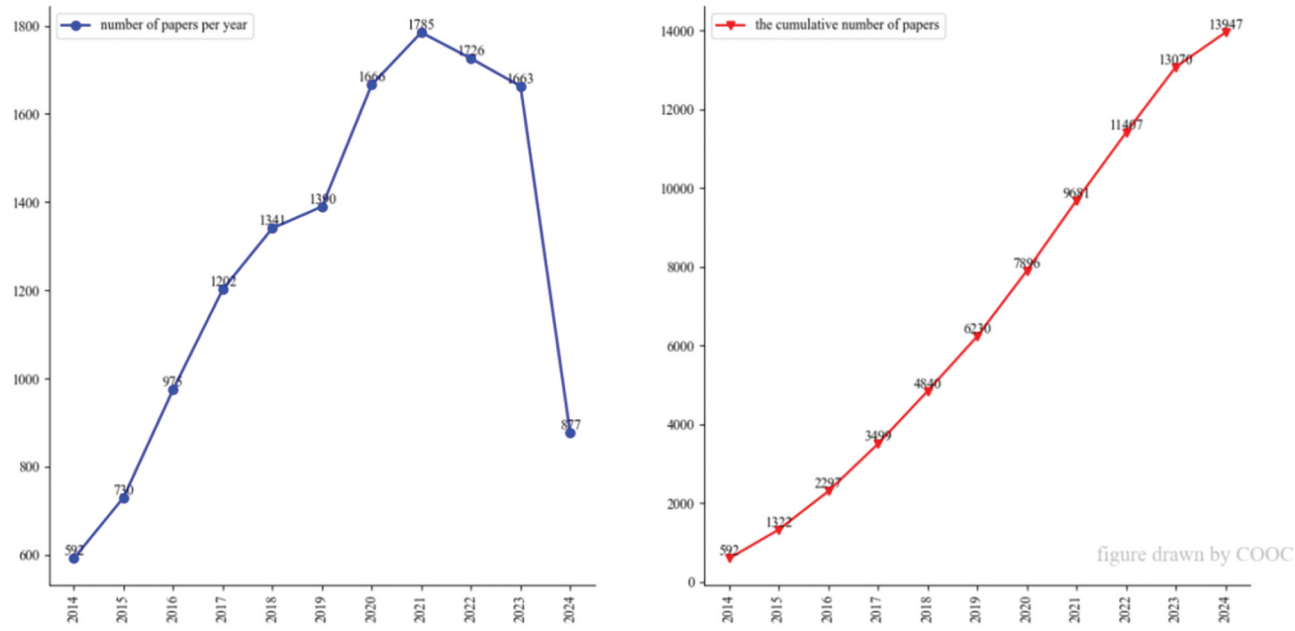

Figure 1. Trends in the literature related to immunotherapy and melanoma over the past 10 years.

Table 1. Top 10 countries/regions, institutions, authors and journals.

Rank	Country/ Region	Count	Institution	Count	Author	Count	Journal	Count	2022 Impact Factor/ JCR quartile
1	USA	5897	Univ Texas Md Anderson Canc Ctr	567	Long, Georgina V.	165	Journal for Immunotherapy of Cancer	608	10 .3/Q1
2	China	3035	Harvard Med Sch	436	Ascierto, Paolo A.	160	Cancers	578	4.5/Q1
3	Italy	1183	Mem Sloan Kettering Canc Ctr	369	Menzies, Alexander M.	118	Frontiers in Immunology	573	5.7/Q1
4	Germany	1181	Univ Sydney	304	Schadendorf, Dirk	107	Oncoimmunology	374	6.5/Q1
5	France	904	Dana Farber Canc Inst	277	Johnson, Douglas B.	99	Frontiers in Oncology	334	3.5/Q2
6	England	773	Massachusetts Gen Hosp	275	Robert, Caroline	97	Cancer Immunology Immunotherapy	301	4.6/Q1
7	Australia	748	NCI	265	Dummer, Reinhard	97	Clinical Cancer Research	229	10 .0/Q1
8	Netherlands	614	Univ Pittsburgh	237	Scolyer, Richard A.	88	International Journal of Molecular Sciences	229	4.9/Q1
9	Japan	611	H Lee Moffitt Canc Ctr & Res Inst	231	Wolchok, Jedd D.	86	Melanoma Research	212	1.5/Q4
10	Switzerland	568	Mayo Clin	200	Carlino, Matteo S.	86	Cancer Immunology Research	206	8.1/Q1

Table 2. Top 10 TLCS countries/regions, institutions, authors and journals.

Rank	Country/Region	TLCS	Institution	TLCS	Author	TLCS	Journal	TLCS	2023 Impact Factor/JCR quartile
1	USA	44321	Mem Sloan Kettering Canc Ctr	8614	Ribas, Antoni	4639	Nature	3277	50.5/Q1
2	France	9027	Univ Texas MD Anderson Canc Ctr	7402	Robert, Caroline	4287	Clinical Cancer Research	3235	10 .0/Q1
3	Australia	7663	Dana Farber Canc Inst	5895	Long, Georgina V.	4184	Science	2961	44.7/Q1
4	Germany	7508	Univ Sydney	5494	Hodi, F. Stephen	3463	Lancet Oncology	2867	41.6/Q1
5	Netherlands	5985	Univ Calif Los Angeles	5398	Wolchok, Jedd D.	3393	Annals of Oncology	2371	56.7/Q1
6	Italy	5274	Massachusetts Gen Hosp	4708	Menzies, Alexander M.	2709	Journal of Clinical Oncology	2262	42.1/Q1
7	UK	4980	Harvard Med Sch	4469	Wargo, Jennifer A.	2670	Cell	2189	45.5/Q1
8	China	4412	NCI	3539	Postow, Michael A.	2408	European Journal of Cancer	2159	7.6/Q1
9	Switzerland	4189	Netherlands Canc Inst	3310	Schadendorf, Dirk	2329	Cancer Immunology Research	1949	8.1/Q1
10	Canada	3937	Gustave Roussy	3099	Gajewski, Thomas F.	2303	Nature Medicine	1939	58.7/Q1

asserts its dominance in the TLCS hierarchy, with seven of the leading institutions hailing from the USA, and Memorial Sloan Kettering Cancer Center securing the premier position. This underscores the USA's formidable presence and global leadership in the realm of immunotherapy and melanoma research. Regarding journal impact, Nature, Clinical Cancer Research, and Science claim the top spots in the TLCS rankings. These prestigious academic journals are pivotal not only as conduits for disseminating scientific findings but also as mirrors reflecting the international academic community's heightened interest in melanoma and immunotherapy research. It is particularly noteworthy that Professor Antoni Ribas from UCLA is a standout in the author TLCS rankings. His elevated TLCS value is a testament to his profound impact and scholarly contributions to the field, further validating that his research has garnered extensive recognition and citation within the scientific community.

Institutions, authors, and countries/regions, analysis of cooperation

Figure 2a delineates the geographic landscape of international research collaborations, with a pronounced emphasis on the robust academic interactions between the USA and Europe. This pattern underscores the expansive and profound collaborative frameworks that have been established between these regions in the field of immunotherapy and melanoma research. At the institutional level, as depicted in Figure 2b, the robust linkages between the University of Texas MD Anderson Cancer Center and Memorial Sloan Kettering Cancer Center are particularly noteworthy. These connections signify a high degree of collaborative synergy between these two preeminent cancer research hubs, particularly in the context of joint research initiatives. Furthermore, intricate collaborative relationships are evident among institutions such as Harvard Medical School, Dana-Farber Cancer Institute, and Brigham and Women's Hospital. These alliances are indicative of a dense network of academic cooperation that spans across these esteemed centers. The close-knit collaborative network among individual professors, as illustrated in Figure 2c, is particularly striking. Prominent figures like Professors Georgina V. Long, Alexander M. Menzies, Richard A. Scolyer, and Matteo S. Carlino are represented by their frequent collaborative efforts, which are indicative of a high

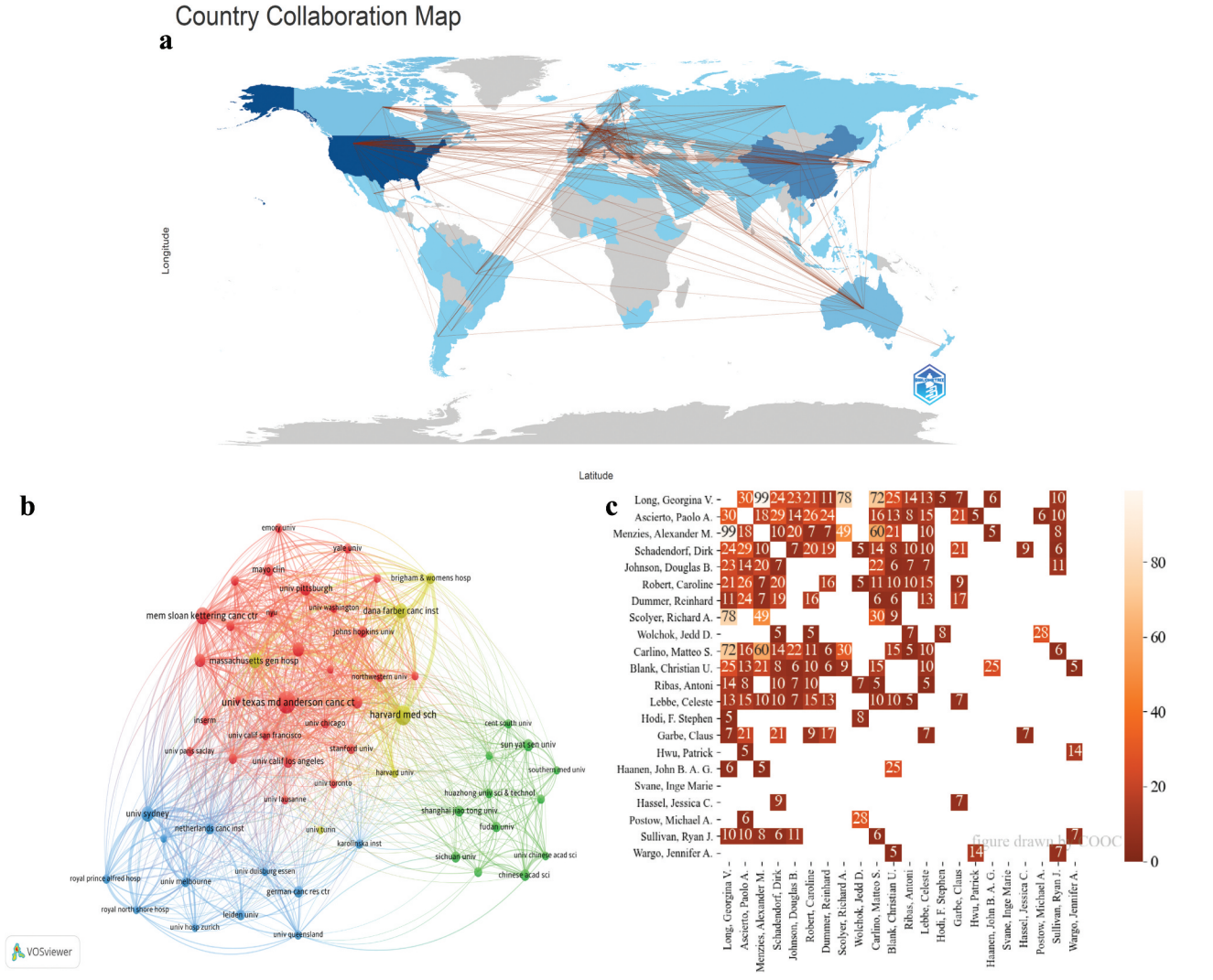

Figure 2. (a) Country collaboration map in the field of immunotherapy and melanoma. Lines represent the collaboration of the countries. (b) Immunotherapy and melanoma relevant institutions cluster analysis. Each node represents an institution, and the size of the circle is proportional to the number of articles published by that institution. The higher the centrality of a node, the more times it appears in the shortest path of the whole network, and the greater its influence and significance. Node connections show correlation strength, and more connections indicate more cooperation. (c) Author Collaboration Matrix.

level of academic discourse and team collaboration. Their collective work has significantly bolstered the field with a potent force of collaborative innovation.

To advance international collaboration in melanoma immunotherapy, we recommend that global research institutions join forces to create a dedicated global research platform. This platform would integrate resources, share data and research findings, and facilitate knowledge exchange. For example, top institutions from the U.S. and Europe could establish virtual labs to conduct collaborative projects online, breaking geographical barriers. Additionally, medical institutions worldwide should collaborate on clinical trials, sharing patient data and trial results. This transnational approach would accelerate the validation of new therapies, shorten the development cycle for innovative drugs, and ultimately bring earlier benefits to patients.

Citation analysis

Usage rate analysis of citations in 180 days

The 180-day usage count is a metric that captures the extent to which an article has addressed the information-seeking behaviors of users, as indicated by actions such as accessing the full text via publisher links or bookmarking the article's metadata for future reference. While a high usage count does not directly correlate with a high citation count, it does signify the currency and relevance of the research, as the academic community often gravitates toward the latest scholarly outputs (Table 3). Conversely, the enduring citation of established literature can lead to a resurgence in usage, underscoring the enduring value of foundational works. The 180-day usage count is particularly indicative of the current research trends and emerging areas of interest. The "180-day" timeframe is defined relative to the date on which we accessed the publications, specifically July 1, 2024. Within this recent period, the articles that garnered the highest usage were a review authored by Liu, Jian, and colleagues, featured in the Journal of Hematology & Oncology in 2022, an article by Lv, Bingzhe, et al., published in Frontiers in Immunology in 2022, and another article by Rui, Rui, et al., also in Frontiers in Immunology, but in 2023. These publications have clearly resonated with the current research community, reflecting the immediate and impactful nature of their contributions to the field.

Local citation score (LCS) analysis of citations

The Local Citation Score (LCS) denotes the total number of citations that a piece of literature has garnered within the corpus of relevant articles, offering a more concentrated measure of its scholarly impact and recognition within its thematic context compared to individual article citations (Table 4). Consequently, LCS presents a more nuanced analytical lens for our discourse. The articles that have achieved the highest LCS rankings are as follows: a seminal work by Topalian, Suzanne L., and coauthors, featured in the Journal of Clinical Oncology in 2014; a pivotal study by Zaretsky, Jesse M., and colleagues, published in the New England Journal of Medicine in 2016; and a landmark article by Robert, Caroline, et al., which appeared in The Lancet. These publications have notably shaped the discourse within their respective fields, as evidenced by their prominent LCS standings.

Citation map, burst citation and co-citation analysis

Utilizing Bibliometrix, we constructed a visualization of the cross-citation dynamics among the most frequently cited articles, as depicted in Figure 3a. This graphical representation elucidates the intricate web of interconnections and citations that exist between these scholarly works. The citation map facilitates the identification of pivotal nodes of connectivity, which are bifurcated into citation hubs and cited literature epicenters. The citation hubs are characterized by the articles that have amassed the highest number of citations within the high LCS group, signifying their status as authoritative and foundational contributions to the discipline. Conversely, the cited literature epicenters are the high LCS articles that extensively reference other works, offering an encompassing perspective on the domain. As illustrated in Figure 3a, the central node of the citation network analysis is the pioneering article authored by Zaretsky JM et al., which appeared in the New England Journal of Medicine in 2016. This publication has

Table 3. Ranking of the top 10 highest 180 days usage.

Rank	Year	Title	Journal	First Author	Usage count
1	2022	Cancer Vaccines as Promising Immuno-Therapeutics: Platforms and Current Progress	Journal of Hematology & Oncology	Liu, Jian	182
2	2022	Immunotherapy: Reshape The Tumor Immune Microenvironment	Frontiers in Immunology	Lv, Bingzhe	155
3	2023	Cancer Immunotherapies: Advances and Bottlenecks	Frontiers in Immunology	Rui, Rui	146
4	2021	mRNA Vaccine for Cancer Immunotherapy	Molecular Cancer	Miao, Lei	123
5	2020	Engineering Macrophages for Cancer Immunotherapy and Drug Delivery	Advanced Materials	Xia, Yuqiong	122
6	2022	Immune Checkpoint Inhibitors in Cancer Therapy	Current Oncology	Shiravand, Yavar	118
7	2024	A Smart DNA Hydrogel Enables Synergistic Immunotherapy and Photodynamic Therapy of Melanoma	Angewandte Chemie-International Edition	Yang, Sen	109
8	2023	Dietary Tryptophan Metabolite Released by Intratumoral *Lactobacillus Reuteri* Facilitates Immune Checkpoint Inhibitor Treatment	Cell	Bender, Mackenzie J	108
9	2020	The Human Tumor Microbiome Is Composed of Tumor Type-Specific Intracellular Bacteria	Science	Nejman, Deborah	108
10	2021	Therapeutic Cancer Vaccines	Nature Reviews Cancer	Saxena, Mansi	106

Table 4. Ranking of the top 10 LCS cited references.

Rank	Year	Title	Journal	First Author	LCS
1	2014	Survival, Durable Tumor Remission, and Long-Term Safety in Patients with Advanced Melanoma Receiving Nivolumab	Journal of Clinical Oncology	Topalian, Suzanne L.	619
2	2016	Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma	New England Journal of Medicine	Zaretsky, Jesse M.	551
3	2014	Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a andomized dose-comparison cohort of a phase 1 trial	Lancet	Robert, Caroline	531
4	2017	Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy	Cell	Sharma, Padmanee	504
5	2018	Cancer immunotherapy using checkpoint blockade	Science	Ribas, Antoni	474
6	2018	Immune-Related Adverse Events Associated with Immune Checkpoint Blockade	New England Journal of Medicine	Postow, Michael A.	449
7	2015	Talimogene Laherparepvec Improves Durable Response Rate in Patients with Advanced Melanoma	Journal of Clinical Oncology	Andtbacka, Robert H. I.	447
8	2017	An immunogenic personal neoantigen vaccine for patients with melanoma	Nature	Ott, Patrick A.	443
9	2015	Melanoma-intrinsic β-catenin signaling prevents anti-tumor immunity	Nature	Spranger, Stefani	425
10	2014	Cancer Immunotherapy Based on Mutation-Specific CD4+T Cells in a Patient with Epithelial Cancer	Science	Tran, Eric	416

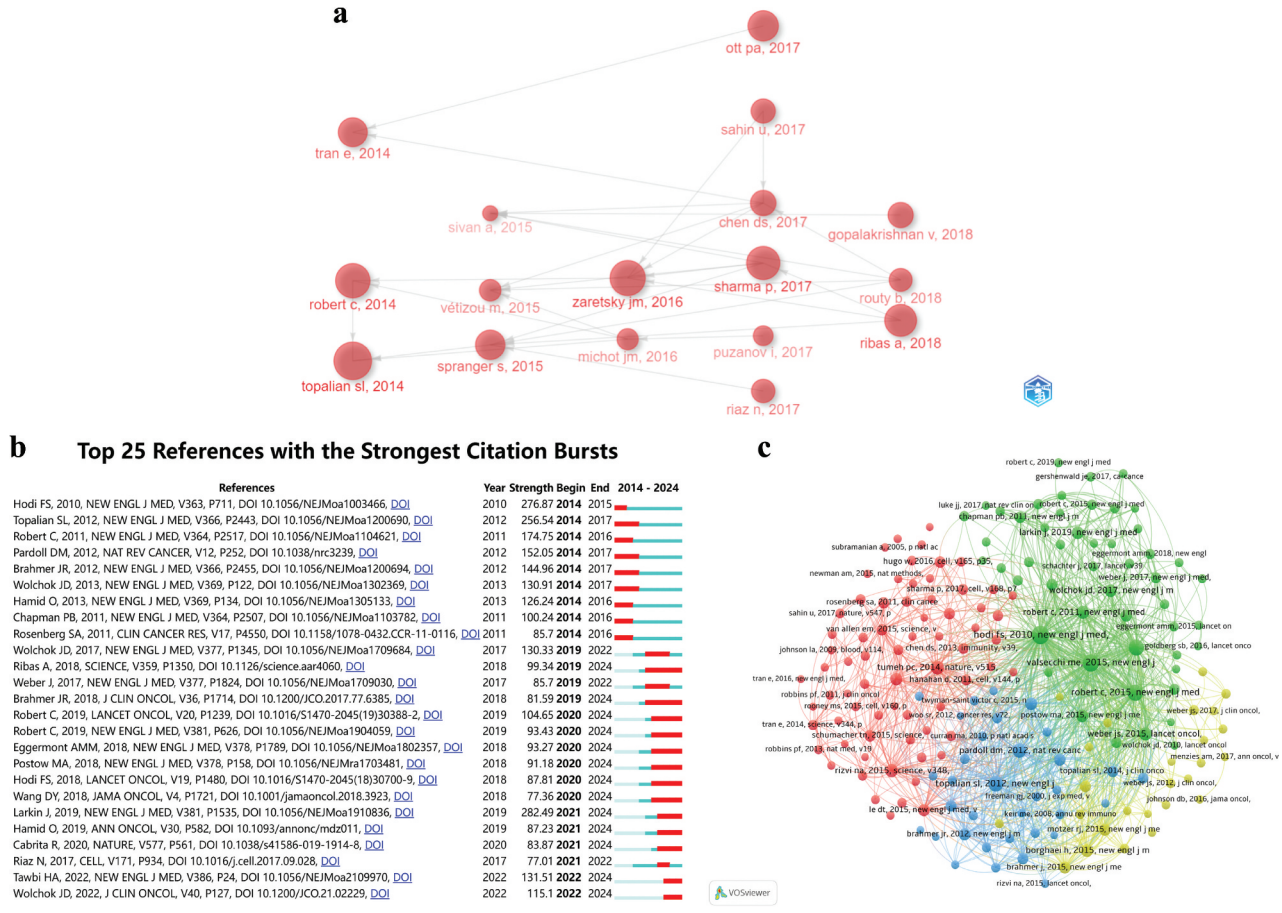

Figure 3. (a) Relationship graph of high cited articles, the connecting lines represent the citations between them. Sizes of nodes mean citations of documents. (b) The top 25 references involving the strongest citation burst in immunotherapy and melanoma, sorted by year of origin, the blue bars mean the reference had been published, the red bars represent citation burstness. (c) Co-citation network analysis of academic papers based on VOSviewer.

emerged as a prominent landmark in the field due to its profound scholarly merit and influence, catalyzing a wealth of subsequent research and discourse.

Furthermore, employing CiteSpace, we have chronologically cataloged the top 25 references that exhibit the most significant citation bursts, as showcased in Figure 3b. Assessed by their burst strength scores, the articles by Larkin J et al., published in 2019, and Hodi FS et al., published in 2010, both in the New England Journal of Medicine, stand out as having the most pronounced citation surges. These publications have not only garnered considerable attention but also sparked substantial scholarly interest and discussion within the field, underscoring their pivotal roles in shaping current research trajectories.

References that accrue citations over time are indicative of prevailing scholarly trends and anticipate future research trajectories. Figure 3c presents a co-citation analysis, skillfully crafted with VOSviewer. The intensity of the co-citation connections is directly proportional to the frequency with which the articles are jointly cited, signifying a higher degree of thematic similarity. Within the visualization of Figure 3c, nodes of varying hues correspond to distinct research topics or related fields. Notably, red nodes predominantly denote studies in the realm of cancer immunotherapy, with a particular emphasis on ICIs and anti-PD-1/PD-L1 therapeutic strategies. Green nodes encompass areas such as cancer genomics and the intricacies of the tumor microenvironment. Blue nodes delve into the molecular biological mechanisms and genetic underpinnings of cancer. Furthermore, yellow nodes encapsulate a variety of cross-disciplinary or integrative research elements. The interplay and overlap among these thematic nodes mirror the intricate and multifaceted nature of contemporary melanoma and immunotherapy research. This co-citation map not only offers a snapshot of the research hotspots and prevailing trends within the field but also illuminates potential avenues for collaborative efforts and prospective research pathways.

Keywords analysis

Keywords frequency and co-occurrence analysis

Employing the COOC13.2 tool for keyword extraction and synonym integration, Figure 4a displays the 50 most frequently occurring keywords, reflecting the research field's focal points, trending topics, and cutting-edge trends. It also highlights the core issues that are of greatest concern to researchers. Recognizing the potential relationships between these keywords, we conducted a co-occurrence frequency analysis, which is visualized in Figure 4b. The keywords are primarily grouped into four thematic areas: the yellow section emphasizes the centrality of immunotherapy mechanisms, with terms like "pd-l1," "checkpoint inhibitor," and "immune checkpoint;" the green section focuses on cancer vaccine research, including "cancer immunotherapy," "tumor microenvironment," and "vaccine;" the red section is dedicated to melanoma discussions, with "melanoma," "immunotherapy," and "cancer" being prominent; and the blue section specializes in ICIs, featuring "ICIs," "ipilimumab," and "pembrolizumab." Figure 4c presents a timeline of keyword appearances from 2019 to 2021, with the yellow color indicating a rapidly evolving field and the emergence of new keywords. Notable keywords such as ICIs, microenvironment, prognosis, and uveal melanoma represent the current hotspots in the field. The co-occurrence of keywords at a higher frequency in the literature indicates a stronger relationship within the knowledge structure, reflecting researchers' preferences for specific conceptual combinations in theoretical framework construction. Analyzing these patterns provides insights into interdisciplinary intersections and potential future research directions. Figure 4d's three-field diagram illustrates the linkages between the top 18 most prolific authors, the top 19 keywords, and the top 13 journals. The size of each region

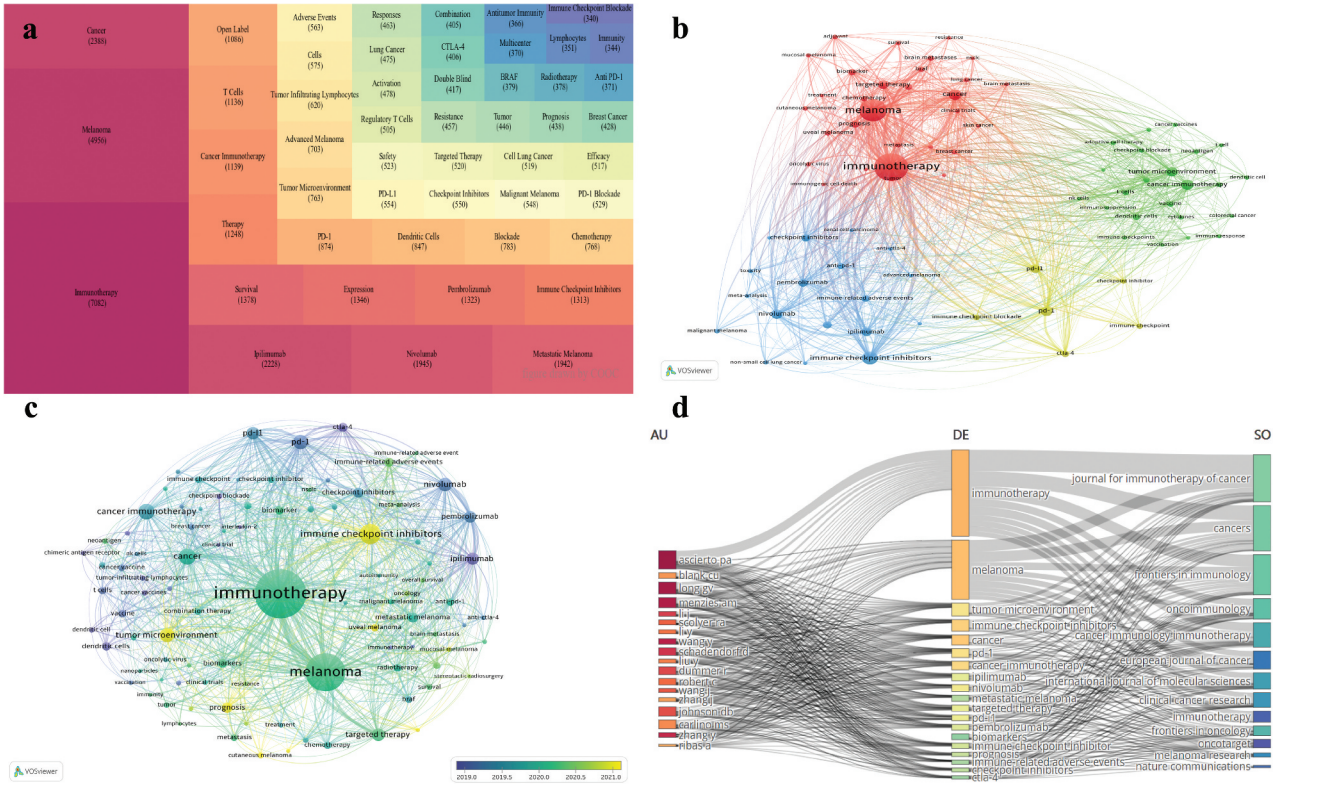

Figure 4. (a) the top 50 most frequent keywords within the field of immunotherapy and melanoma. (b) Cluster diagram of keyword co-occurrence analysis network. (c) Co-occurrence network analysis graph of keywords, different colors represent different mean published years. (d) it shows a three-field diagram about highly productive authors, journals, and keywords.

reflects the linear density of published articles, indicating the strength of relationships. This graph offers a clear view of each author's research direction and the thematic focus of journals, with the size of each region directly corresponding to the strength of the links between elements. This visualization aids in understanding the specialization and research focus of authors and the editorial orientation of academic journals.

Keywords cluster analysis

Cluster analysis, an invaluable analytical instrument, offers a multidimensional and profound lens through which to dissect the internal architecture and evolutionary trajectory of a research topic. By leveraging specialized software such as Citespace, COOC 13.2, and Bibliometrix, we have conducted a meticulous categorization and elucidation of keywords. The analytical outcomes epitomized in Figure 5 exemplify the efficacy of this approach. In particular, Figure 5a showcases a segmentation of the data into five principal thematic clusters: #0 cancer immunotherapy, #1 targeted therapy, #2 tumor microenvironment, #3 nivolumab, and #4 PD-1 blockade. These clusters encapsulate the central themes within the research landscape. Figure 5b employs a cosine matrix method to distill and synthesize keywords with a higher frequency of occurrence, thereby distinctly outlining four predominant research avenues. This method illuminates the interconnectedness of keywords and the thematic coherence, introducing an innovative perspective for comprehending pivotal issues within the field. Furthermore, utilizing Bibliometrix, we have honed in on six distinct clusters, as depicted in Figure 5c. Each cluster represents a constellation of closely affiliated bibliographic themes, collectively weaving a rich tapestry of interlinked knowledge strands within the research domain. This granular classification allows for a more nuanced understanding of the research's thematic diversity and its evolving scholarly discourse.

Keywords, time analysis

Utilizing Citespace and COOC13.2 software, we have crafted Figure 6 to illustrate the temporal evolution of research topics within the field. In Figure 6a, each circle symbolizes a keyword, with its size being indicative of the keyword's frequency. The analysis is anchored in the year of each keyword's initial emergence in our dataset; once identified, the reference year for a keyword remains constant, even if it reoccurs in later publications. Consequently, the figure only displays the year of a keyword's debut. Should a keyword reemerge in subsequent years, its frequency is cumulatively incremented at the position corresponding to its first appearance, leading to a proportional enhancement in its visibility. This method effectively addresses the visual complexity of overlapping keywords. Figure 6a, plotted with COOC software, provides a dynamic view of the research topic's progression over time. Additionally, the study delves into the temporal dynamics of keywords, as depicted in Figure 6b, to gain further insights into the melanoma and immunotherapy research trends. Figure 6c employs light blue shading to denote periods of keyword stability, suggesting a period of consolidation within the research theme, while dark blue areas indicate "slight mutations" in keywords. These mutations suggest the germination or growth of new concepts that, while not yet dominant, signal an emerging

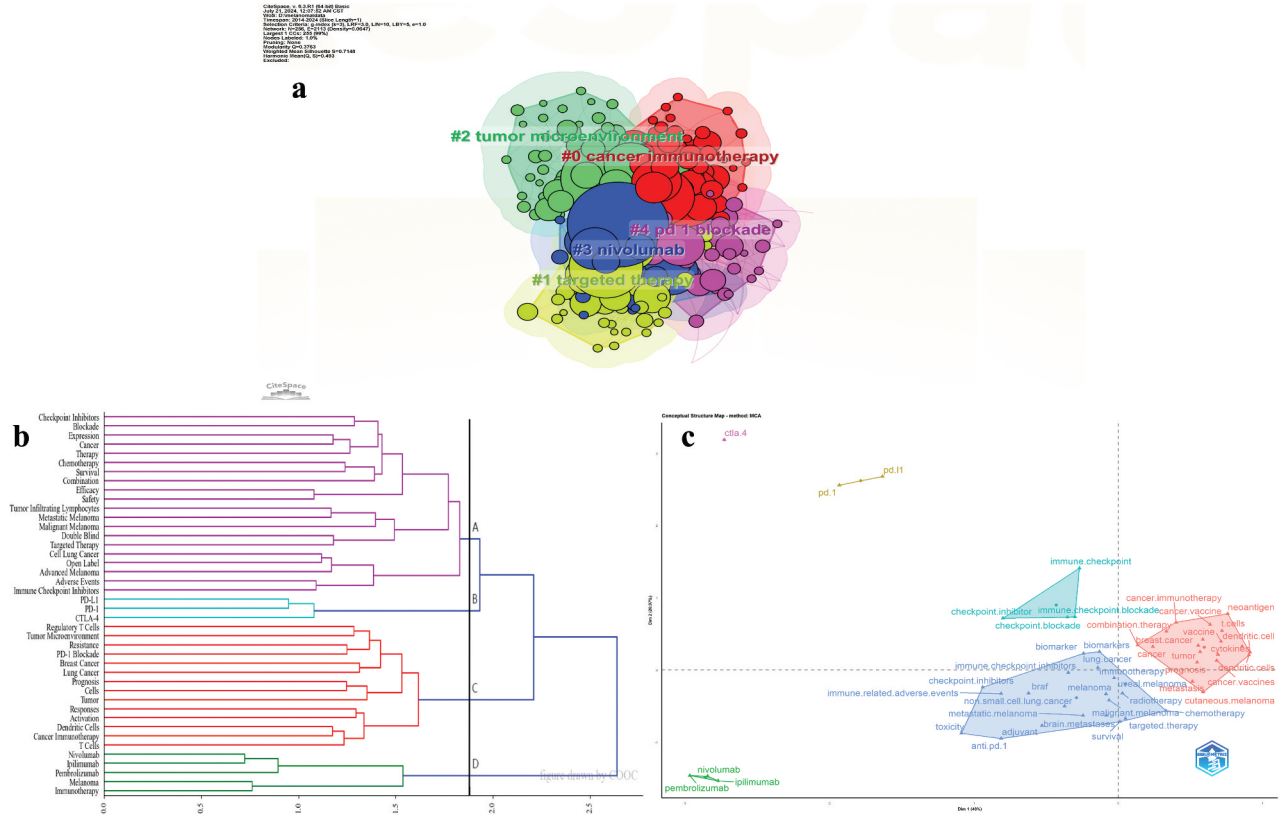

Figure 5. (a) Cluster analysis of keywords in the field of immunotherapy and melanoma. (b) Immunotherapy and melanoma related keywords classification dendrogram. (c) Conceptual structure map using method MCA. Different colors mean different clusters.

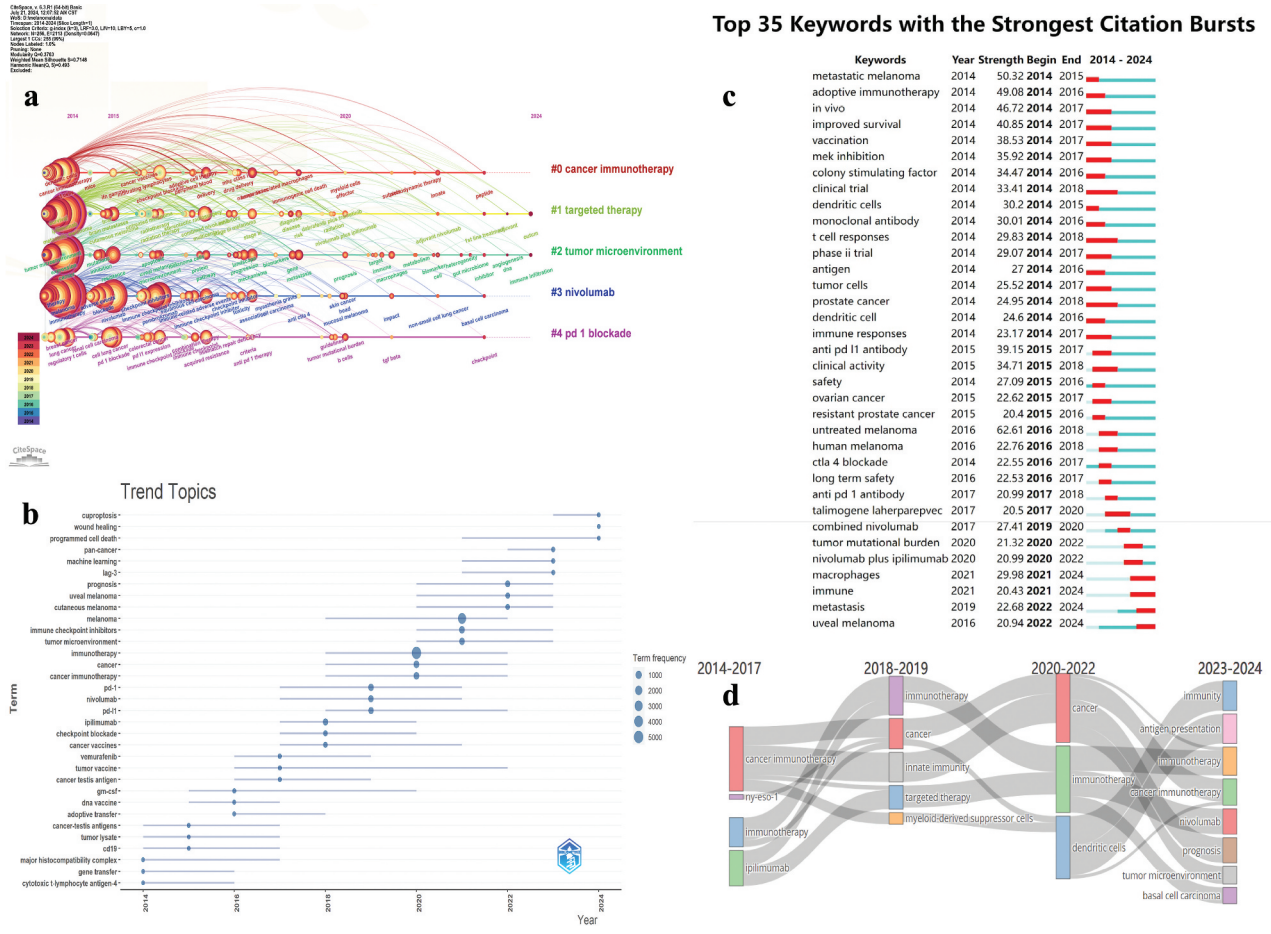

Figure 6. (a) Evolution of research topics over time. (b) Evolution of keywords over time. (c) The 35 keywords with the strongest citation burst in immunotherapy and melanoma. (d) it further illustrates the migration path of the keywords.

trend. The presence of red signifies a period of abrupt keyword transformation, often indicative of a paradigm shift in research direction, catalyzed by groundbreaking discoveries or technological advancements. Figure 6d extends this analysis by mapping the migration trajectories of keywords across various time points, facilitating the tracing of research concepts' lineage and evolution. This visualization aids in anticipating the potential focal points and future trajectories of research, offering a roadmap for upcoming scholarly endeavors in the domain.

Discussion

General information

In this research, we conducted an extensive bibliometric analysis of the literature pertaining to Immunotherapy & Melanoma spanning the years 2014 to 2024. By employing VOSviewer and CiteSpace for data visualization, we unveiled the evolutionary trends and identified the research frontiers and hotspots within the field. The analysis revealed a consistent upward trajectory in both citations and publications, indicative of the burgeoning interest and advancements in immunotherapy and melanoma research. The USA and China emerged as the leading contributors, demonstrating significant scholarly output and fostering extensive and close collaborative ties with European nations. Notably, seven of the top 10 institutions, as ranked by Total Link Strength (TLS), are based in the USA, with Texas MD Anderson Cancer Center standing out as the most prolific. The Journal for Immunotherapy of Cancer was identified as the preeminent journal in the field in terms of publication frequency. It is particularly striking that the top 10 journals are collectively dedicated to exploring the foundational research and practical applications of immunotherapy, delving into molecular mechanisms, and conducting research on specific cancer types. This comprehensive focus mirrors the multifaceted depth and breadth of research within the domain, highlighting the concerted efforts to advance understanding and treatment strategies in immunotherapy and melanoma.

Professor Georgina V. Long from the Melanoma Institute Australia at the University of Sydney has emerged as a leading authority in the field due to her outstanding research contributions. Her latest study demonstrated that pembrolizumab significantly improved overall survival in patients with unresectable advanced melanoma compared to ipilimumab, confirming that pembrolizumab offers long-term survival benefits in advanced melanoma.[21] In 2022, a review by Jian Liu and colleagues in the Journal of Hematology & Oncology became the most frequently

utilized literature, offering a comprehensive overview of cancer vaccine mechanisms and development platforms, and summarizing advancements in their clinical trials, thus serving as a crucial resource for future vaccine development.[22] Despite its recent publication, this article's high usage underscores its substantial impact on melanoma research, reflecting its quality and the valuable insights it provides to the research community. Another seminal article, published in the Journal of Clinical Oncology in 2014 by Suzanne L. Topalian et al., holds the highest Local Citation Score. It demonstrated that nivolumab treatment for advanced, treatment-resistant melanoma patients resulted in overall survival durations comparable to other similar patient populations, with the added benefit of durable responses that persisted post-therapy discontinuation and a favorable long-term safety profile.[23] These findings solidify nivolumab's reputation as an effective and safe therapeutic option, with profound implications for melanoma treatment strategies. The citation analysis also spotlights a groundbreaking 2016 article by Zaretsky JM et al. in the New England Journal of Medicine, which identified that acquired resistance to PD-1 blockade immunotherapy in melanoma patients is linked to defects in interferon receptor signaling and antigen presentation pathways.[24] This article has catalyzed significant academic interest and has spurred considerable follow-up research, contributing to the evolution of therapies targeting drug resistance mechanisms. From a keyword perspective, "Immunotherapy" and "Melanoma" have been central to the research discourse, with the frequency of their appearance over time indicating burgeoning research hotspots and trends. In recent years, "ICIs," "tumor microenvironment," and "targeted therapy" have risen as fresh areas of interest. Since 2021, there has been a notable focus on the interplay between melanoma and macrophages, immune responses, metastasis, and uveal melanoma, marking these as cutting-edge frontiers in melanoma research. The sustained research interest in these areas signals an ongoing fervor in the field.

These advancements not only hold significant scientific and clinical importance but also provide new directions for future therapeutic strategies, especially in the areas of biomarker research, optimization of combination therapies, and in-depth exploration of drug resistance mechanisms. They push the boundaries of medical science and bring hope for improving patients' quality of life and extending survival.

Analysis of research hotspots and frontiers

The examination of trending keywords and topics is an indispensable tool for researchers, enabling them to stay informed about the latest research trends and innovative breakthroughs within their domain. Amidst the current information deluge, the sheer volume of data and scholarly literature presents formidable challenges. Through the discernment of trending keywords and topics, researchers are equipped to efficiently sift through the noise to identify the most pertinent and significant information. This strategic approach allows them to remain at the forefront of their field, maintaining a pulse on the evolving landscape of scientific inquiry. The representative contents involved in the following hotspots and frontiers are shown in Figure 7.

Immunotherapy and immunomodulation

The genesis of immunotherapy can be traced back to the early observations of surgeon William Coley, who correlated postoperative infections in cancer patients with enhanced clinical outcomes. Over the century since these initial insights, a variety of immunotherapies have been sanctioned for oncological treatment, including BCG, interferon alpha, and interleukin 2 (IL-2). Notably, IL-2 has exemplified the potential for cytokines to substantially manage advanced metastatic cancers like melanoma and renal cell carcinoma by expanding T cell populations, underscoring the pivotal role of adaptive immunity in tumor regulation and paving the way for innovative immunotherapeutic approaches.[25] As the inaugural immunotherapy approved for melanoma treatment, IL-2 invigorates a range of immune cells, including cytotoxic T-cells, B-cells, macrophages, and natural killer (NK) cells. High-dose IL-2 (HD IL-2), administered intravenously at 8-hour intervals, has exhibited dose-dependent antitumor efficacy in animal models, a feat that lower-dose IL-2 regimens have not been able to replicate.[26] However, the brief half-life of IL-2 necessitates frequent, high-dose administrations, which can engender severe side effects. These may include capillary leakage syndrome – necessitating intensive care in approximately half of the patients – as well as lymphocyte infiltration into tissues, manifesting as chills, nausea, fluid retention, hypertension, and alterations in mental status.[27–29] Despite these challenges, IL-2 remains a milestone in immunotherapy, highlighting its therapeutic potential and the need for advancements to mitigate its side effects.

The landscape of cancer treatment has been profoundly transformed by the discovery of immune checkpoints. ICIs operate by obstructing these checkpoints, thereby enabling tumor suppression. They function through antibodies that target, either individually or in concert, the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death 1 (PD-1), and LAG-3 pathways. CTLA-4 is a protein that emerges post T-cell activation, binding to B7 molecules on antigen-presenting cells to transmit an inhibitory signal that dampens T-cell activation.[30] The inhibitory role of PD-1 is facilitated by the tyrosine phosphatase SHP-2, which downregulates signaling molecules downstream of the T cell receptor (TCR), consequently curbing the cytotoxic T cell response against tumors.[31–33] Lymphocyte activation gene 3 (LAG-3), a cell surface molecule expressed on immune cells including T cells, negatively modulates T cell proliferation and the functionality of effector T cells. Notably, LAG-3 is upregulated in a variety of tumor types, including melanoma, suggesting its potential as a therapeutic target.[34–36] These advancements have not only expanded the arsenal against cancer but also underscore the complexity of the immune system's interaction with cancer cells.

The USA Food and Drug Administration (FDA) has approved several ICIs, marking a significant milestone in cancer therapy. Ipilimumab, an antibody against CTLA-4, pioneered this class by being the first to receive approval for

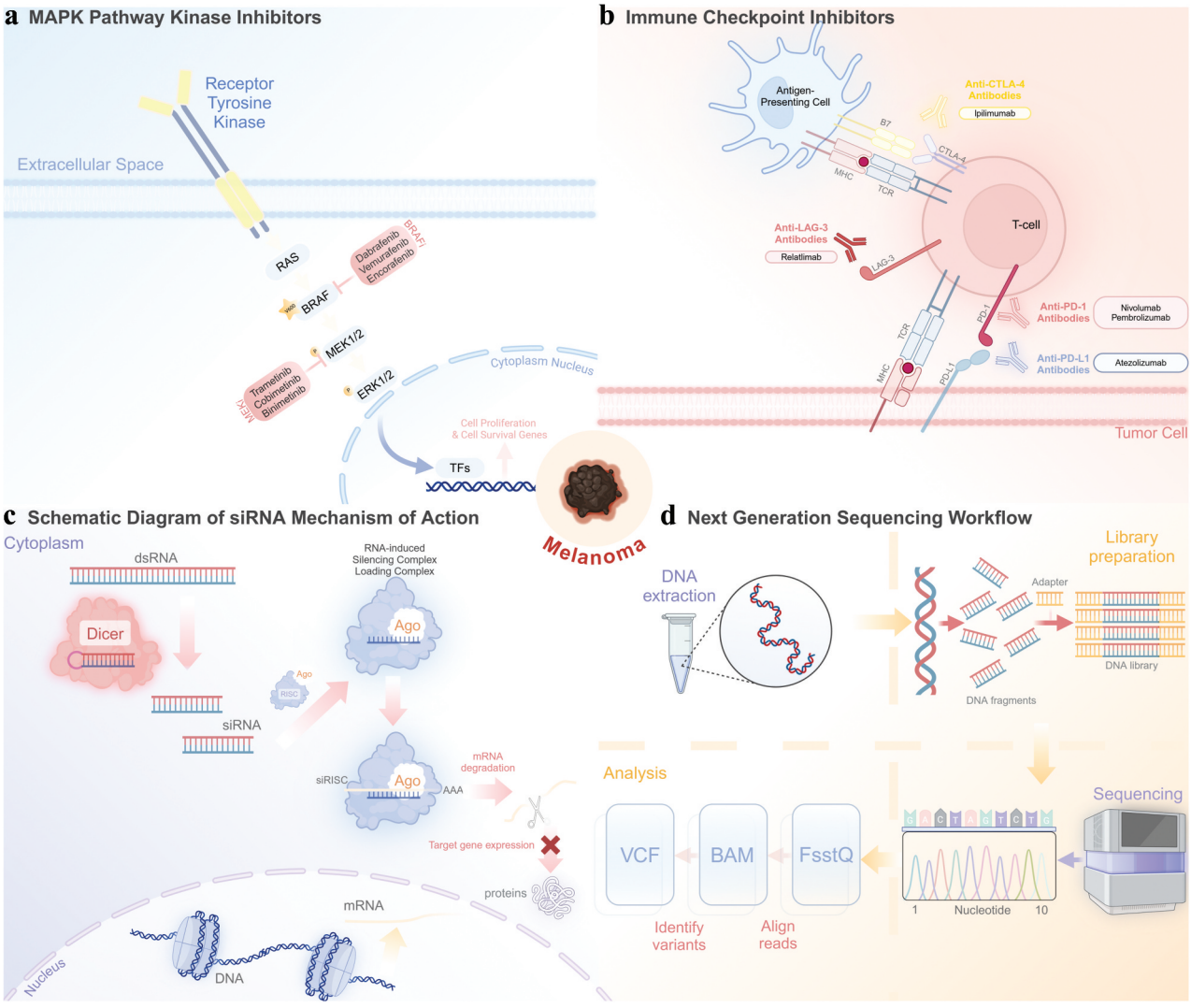

Figure 7. Comprehensive map of melanoma treatment mechanisms and gene analysis: Including MAPK pathway kinase inhibitors, immune checkpoint inhibitors, siRNA mechanism of action, and next generation sequencing workflow.

treating advanced melanoma. Subsequently, Pembrolizumab and Nivolumab, both of which target the PD-1 pathway, have also been sanctioned for melanoma treatment. The FDA further extended its approval to include the combination therapy of Ipilimumab and Nivolumab for advanced melanoma patients.[37] The promise of immunotherapy lies in its potential to elicit long-lasting responses, capitalizing on T cells' ability to remember their targets and to mount polyclonal responses that tumors would find challenging to evade. However, the challenges of primary resistance and the development of resistance after an initial response have become significant hurdles in checkpoint blockade therapy.[38] C. Robert et al., in a pivotal study based on randomized controlled trials, determined that for patients with unresectable or metastatic melanoma carrying BRAF V600E or V600K mutations, treatment with dabrafenib in combination with trametinib yielded superior long-term survival outcomes compared to first-line anti-PD-1 ICIs.[39] Pembrolizumab has shown enduring antitumor activity and a favorable tolerability profile in advanced melanoma patients, demonstrating long-term survival advantages over Ipilimumab.[40,41] Recent research has indicated that Relatlimab, a LAG-3 inhibitor, when combined with Nivolumab, significantly enhances progression-free survival in patients with untreated metastatic or unresectable melanoma. These findings reinforce the therapeutic potential of dual immune checkpoint inhibition in melanoma treatment.[42] Additionally, Cabrita, R et al. discovered that TLS plays a crucial role in the melanoma immune microenvironment and augments the efficacy of immunotherapy by inducing a distinctive T-cell phenotype. Consequently, the characterization of TLS gene expression may serve as a promising biomarker for predicting patient responsiveness to immunotherapy.[43] These advancements underscore the dynamic evolution of immunotherapeutic strategies and their growing impact on clinical outcomes for melanoma patients.

While immune checkpoint blockade therapy has demonstrated superior efficacy, it has also been associated with a spectrum of inflammatory responses, known as immune-related adverse events (irAEs).[44] The gastrointestinal tract, endocrine system, skin, and liver are frequently implicated in these adverse events.[45] Typically, these irAEs are manageable, but there are instances where drug discontinuation or the administration of immunosuppressive agents becomes necessary to mitigate symptoms.

Looking ahead, future research endeavors should focus on a profound investigation into the intricate mechanisms underlying these adverse events. Establishing an international registry system to aggregate data from practical applications would be a strategic step forward. By fostering multidisciplinary collaboration, the goal is to refine treatment strategies to enhance patient outcomes. Further exploration into the etiology of adverse events will not only shed light on their complex nature but also pave the way for the crafting of more targeted and precise treatment protocols.

Targeted therapies and molecular biology

In the realm of targeted therapy and molecular biology, significant strides have been made in the development of therapies that address specific genetic mutations, thanks to an expanding comprehension of the molecular underpinnings of tumorigenesis. Tumors arise when genetic aberrations perturb the regulatory mechanisms governing growth, culminating in unchecked cell proliferation. The mitogen-activated protein kinase (MAPK) signaling cascade, encompassing components such as RAS, RAF, ERK, and MEK, plays a pivotal role in the transduction of extracellular signals that preserve the equilibrium between cell proliferation and apoptosis (Figure 7). Perturbations within the MAPK pathway, such as mutations, can precipitate unbridled cellular growth, thereby initiating carcinogenesis. This pathway is frequently deregulated in melanoma and is recognized as a key driver mutation.[46] The targeting of these mutations has opened up new avenues for personalized and precision medicine, offering hope for more effective and tailored cancer treatments.

Mutations in the BRAF gene (v-RAF murine sarcoma viral oncogene homolog B1) represent the most frequent alterations within the MAPK signaling pathway, often leading to its hyperactivation. The high prevalence of BRAF mutations in cutaneous melanomas, coupled with the intricate network of kinases and proteins under its influence, underscores its potential as a critical therapeutic target. This insight has spurred the development of a suite of pharmacological inhibitors aimed at various oncological indications.[47] Sorafenib, an oral small-molecule kinase inhibitor, marked a milestone as the inaugural drug to enter clinical trials for metastatic melanoma.[48] It exerts a broad spectrum of anticancer effects, primarily through the inhibition of autophosphorylation of diverse receptor tyrosine kinases.[49] However, sorafenib as a monotherapy has shown very limited anti-tumor efficacy in advanced melanoma.[50–52] Subsequent Phase III clinical trials have shown that the combination of sorafenib with chemotherapeutic agents did not significantly improve patient survival rates.[53] In contrast, vemurafenib, a selective BRAF inhibitor designed to target the BRAF V600E mutation, has demonstrated remarkable efficacy. Clinical trials have reported response rates exceeding 50% in patients with metastatic melanoma possessing the BRAF V600E mutation, concomitantly leading to a significant improvement in overall patient survival.[54,55] These promising outcomes culminated in the FDA's approval of vemurafenib in 2011 for the treatment of unresectable or metastatic melanoma characterized by the BRAF V600E mutation.[56] This approval signifies a pivotal advancement in personalized medicine, highlighting the importance of genetic profiling in dictating treatment strategies for melanoma.

Furthermore, MEK, an important component of the MAPK signaling pathway, is frequently activated in melanomas harboring BRAF mutations. The combination of MEK inhibitors with BRAF inhibitors can reduce the toxicity associated with BRAF inhibitor monotherapy and help prevent drug resistance.[57] The synergistic application of MEK inhibitors with BRAF inhibitors, such as trametinib and cobimetinib, has demonstrated promising improvements in treatment efficacy. Trametinib, a potent MEK inhibitor, has been lauded for its clinical trial outcomes, which indicated a more favorable median progression-free survival of 4.8 months and a superior 6-month survival rate of 81% when compared to traditional chemotherapy drugs like dacarbazine or paclitaxel.[58] This led to the FDA's approval of trametinib in 2013 as the inaugural MEK inhibitor for the treatment of BRAF-mutated metastatic melanoma in patients previously untreated with a BRAF inhibitor.[57] The combined regimen of trametinib and dabrafenib not only demonstrated increased progression-free survival benefits but also reduced the mortality risk by 29%. This combination also alleviated the incidence of certain adverse events like rash and photosensitivity, albeit with a concomitant rise in fever cases. Given these substantial therapeutic advancements, the FDA endorsed the combination therapy of dabrafenib and trametinib in 2014 for the treatment of metastatic or unresectable BRAF V600E/K-mutated malignant melanoma. However, this combination therapy also introduced a spectrum of side effects associated with MEK inhibition, including retinopathy, a decrease in left ventricular ejection fraction, and elevated creatine phosphokinase levels.[59] These considerations emphasize the need for vigilant monitoring and management in the application of these targeted therapies.

Moreover, gene-editing technologies have shown potential applications in the treatment of melanoma. Although they are currently still in the preclinical research phase, with ongoing technological advancements and increased translational studies, these technologies hold promise for offering new strategies and directions in melanoma therapy.[60] For instance, a study utilized CRISPR/Cas9 to knockout CD133, discovering that this manipulation led to a decrease in matrix metalloproteinase MMP2/MMP9 levels and a reduction in cell invasiveness. This finding implies that CD133 significantly contributes to melanoma's invasive and metastatic capabilities, positioning it as a promising therapeutic target.[61] Researchers have also pinpointed genes such as SLC9A5, BIRC3, and SMAD3 through genome-wide CRISPR screening and subsequent experimental validation, revealing that these genes foster melanoma proliferation and resistance to BRAF inhibitors. This research enhances our comprehension of melanoma cell biology and uncovers novel vulnerabilities that may pave the way for the development of enduring therapies through precise interventions. Notably, the integrated AhR-SMAD3 signaling pathway has emerged as a potential key driver of melanoma growth and recurrence, presenting new avenues for therapeutic targeting.[62] These advancements underscore the burgeoning potential of gene editing in unraveling the complexities of melanoma and crafting tailored treatment strategies.

These advancements indicate that adopting a precision medicine strategy, which involves pinpointing specific genetic aberrations within tumors and subsequently tailoring the most fitting targeted treatment plans, has emerged as a pivotal direction in melanoma management. Nevertheless, alongside these strides, challenges persist, particularly regarding the development of drug resistance and the need for improved predictive models to determine which patients are likely to respond favorably to specific therapeutic interventions. As the research frontier continues to expand, the scientific community anticipates the emergence of additional innovative treatment modalities. These are expected to further enhance the treatment landscape and, ultimately, the clinical outcomes for individuals afflicted with melanoma. The ongoing pursuit of knowledge in this domain holds the promise of transforming the future of melanoma care, offering renewed hope for improved survival rates and quality of life for patients.

New technologies and drug delivery

The crux and primary challenge in gene therapy revolves around achieving efficient gene delivery. Therapeutic genes must navigate a complex path, evading the reticuloendothelial system (RES) upon entering circulation and overcoming numerous obstacles to reach the cytoplasm or nucleus of target cells.[63] Consequently, it is imperative to meticulously evaluate the key mechanisms and challenges at each stage to devise more potent gene delivery methods that minimize side effects.

In this regard, researchers have crafted an array of strategies. One such approach involves the local delivery of IL-2 via adenoviral gene therapy, which has shown low systemic toxicity and impressive complete remission rates, ranging from 51% to 62.5%.[64,65] Additionally, the utilization of nanoparticles for IL-2 delivery presents a promising avenue to mitigate the toxicity associated with high-dose IL-2. For instance, biodegradable polycationic vectors that deliver IL-2 have been demonstrated to suppress tumor growth in mice, accompanied by heightened activation and infiltration of CD8+, CD4+ T cells, and NK cells within the tumor microenvironment.[65] A particularly promising recent advancement is TransCon IL-2 β/γ, a long-acting prodrug with a half-life exceeding 30 hours. This prodrug facilitates a sustained release of IL-2 analogs that closely resemble endogenous IL-2 in terms of sequence, size, and potency at the IL-2 Rβ/γ receptor. It is capable of stimulating the proliferation and cytotoxic activity of CD8+ T cells, NK cells, and γδ T cells.[66]

Nucleic acid-based therapeutics, including small interfering RNAs (siRNAs), antisense oligonucleotides (ASOs), and aptamers, have emerged as promising molecular agents in cancer therapy. These agents possess distinctive therapeutic potential due to their capacity for precise recognition and modulation of specific target genes. When siRNAs are transported to their site of action via carrier complexes, they achieve gene silencing by selectively promoting the degradation of target protein mRNAs through RNA interference (RNAi) mechanisms.[67] For instance, targeting the microphthalmia-associated transcription factor (Mitf) through lipid-mediated transfection of siRNA has been shown to effectively trigger apoptosis and diminish melanoma cell viability in a B16 melanoma model.[68] ASOs represent another avenue for modulating gene expression, as they curtail the translation of target proteins by stimulating RNase H endonuclease activity and obstructing ribosomes at specific sequences within target mRNAs.[69] A case in point is AP-12009 (Trabedersen), an ASO that targets the angiogenic factor TGF-β2, which has advanced into a Phase I clinical trial for adult patients with advanced tumors characterized by excessive TGF-β2 production.[70] Furthermore, aptamers, identified through SELEX (Systematic Evolution of Ligands by Exponential enrichment) technology, can bind specifically to target molecules, impede protein-protein interactions, or be internalized by engaging cell-surface receptors, thereby functioning as vehicles for the delivery of other therapeutic agents.[71] An exemplar is the DNA aptamer LL4A, which, with high affinity and stability, targets vemurafenib-resistant melanoma cells by binding to the transmembrane protein CD63—a player in the activation of NF-κB and MAPK signaling pathways that contribute to vemurafenib resistance.[72]

Diagnostics and personalized medicine

Remarkable strides have been achieved in the molecular diagnosis of melanoma, primarily driven by breakthroughs in genomics, transcriptomics, and innovative technologies such as liquid biopsy. Genomic analysis, particularly facilitated by next-generation sequencing (NGS), has been instrumental in pinpointing specific mutations and genomic aberrations associated with melanoma. NGS enables a comprehensive assessment of multiple melanoma-associated genes in a single assay, streamlining the detection of mutations in pivotal genes like BRAF, NRAS, and c-KIT.[73] Although NGS is predominantly utilized as a research tool at present, its relevance in diagnostic applications is projected to escalate as more clinically relevant mutations are uncovered and targeted therapies are developed. Advancements in single-cell transcriptomics have unlocked the ability to dissect the tumor microenvironment in melanoma with unprecedented detail. This method has shed light on cellular dynamics and interactions within the tumor, illuminating the intricacies of melanoma progression and providing insights into potential therapeutic responses. By discerning diverse cellular subtypes and their transcriptional profiles, single-cell transcriptomics enhances our grasp of tumor heterogeneity, which is crucial for predicting therapeutic outcomes, particularly in the advanced stages of melanoma.[74] Moreover, this approach elucidates the mechanisms underlying responses and resistance to treatments, including ICIs. Furthermore, liquid biopsies are emerging as a valuable non-invasive diagnostic tool. They detect circulating tumor DNA in the bloodstream, offering a window into the tumor's genetic landscape. This minimally invasive method can track treatment responses and disease progression, serving as a complement to traditional diagnostic methods.[73] The integration of these cutting-edge techniques is set to revolutionize melanoma diagnosis and management, ushering in an era of more personalized and effective treatment strategies.

Melanoma biomarkers encompass a spectrum of indicators, ranging from serum proteins and genetic mutations to pathological findings and imaging data. The application of molecular biomarkers is becoming increasingly vital for early diagnosis, accurate staging, and predicting treatment responses in

melanoma. The BRAF V600E mutation, a well-characterized driver mutation, is responsive to BRAF inhibitors and serves as a biomarker for early diagnosis, staging, and treatment response prediction.[75–77] Conversely, NRAS mutations, while less prevalent, are significant and are correlated with poorer survival outcomes in patients with stage IV melanoma.[78–80] C-KIT mutations, although not strongly linked to histologic subtype or tumor stage, show a higher prevalence in the elderly, in limbal mucosal melanoma subtypes, and in areas of chronic sun damage.[81–85] On another note, female patients with elevated levels of plasma membrane calcium-transporting ATPase 4 (PMCA4) exhibit longer progression-free survival, and high PMCA4 expression in cutaneous melanoma is associated with a more favorable prognosis, particularly following PD-1 blockade therapy.[86] The tumor mutational burden (TMB) in melanoma is garnering attention for its potential to predict the efficacy of ICIs. A high TMB may suggest greater treatment effectiveness, indicating an enhanced capacity of the immune system to detect and eradicate tumors.[87–89] Gene expression profiling (GEP), such as the Decision-Dx Melanoma™ test, assesses the risk of melanoma recurrence and metastasis by examining the expression patterns of specific genes within the primary tumor, thereby informing clinical decision-making.[90,91] Moreover, the gut microbiome can influence cancer development by fostering either a pro- or anti-inflammatory environment. In melanoma, the gut microbiota's composition impacts the response to ICI therapy.[92] Enhanced microbial diversity, especially the presence of certain subspecies of Ruminococcaceae, is linked to better anti-PD-1 treatment efficacy and increased CD8+ T-cell infiltration. In contrast, specific anaplastic Bacteroidetes species may mitigate the risk of ICI-induced colitis.[93]

Investigations into personalized vaccines for melanoma have emerged as a prominent area of focus within the realm of tumor immunotherapy. These vaccines are meticulously designed to correspond with the distinct genetic aberrations present in an individual's tumor, thereby zeroing in on the unique tumor-specific antigens that arise from these mutations. The pioneering application of an RNA mutant vaccine in melanoma therapy was spearheaded by Ugur Sahin et al., showcasing the clinical viability, safety, and tumor-inhibiting activity of RNA neoepitope vaccines. This work has underscored the potential for extending personalized medicine to encompass a wider array of patients, marking a significant stride in the field.[94] Preliminary human trials have demonstrated that such personalized vaccines are adept at invigorating patients' immune responses against cancer. Clinical trials of neoantigen vaccines in melanoma have confirmed their safety and their capacity to elicit specific immune reactions against these singular tumor antigens.[94–97] The overarching objective is to assess the clinical efficacy of these vaccines, with a particular emphasis on their synergistic potential when combined with other immunotherapeutic approaches, such as ICIs. This combined strategy is anticipated to amplify the immune system's response to melanoma, offering a more potent and tailored therapeutic avenue.[98] The prospect of integrating these customized vaccines with existing immunotherapies holds promise for the future of melanoma treatment, heralding a new era of precision immunotherapy.

Overall, through the use of bibliometric analysis methods, we have provided a comprehensive research framework in the field of melanoma immunotherapy. This framework reveals key research directions, such as immune checkpoint inhibitors, tumor microenvironment, and personalized vaccines. It also analyzes the patterns of international collaboration and significant research achievements. Additionally, we explored the potential of emerging technologies, like gene editing and liquid biopsies, in precision treatment, providing directions and references for future research. The multidimensional visualization analysis methods offer an important reference framework for researchers in this field, further advancing the development of melanoma immunotherapy.

Limitations

Our study faces some inherent limitations. The data was exclusively sourced from the Web of Science Core Collection database, which, while comprehensive and reliable, may have led to the omission of studies not indexed there. Additionally, by focusing on English-language literature and reviews, we might have missed non-English studies and works in progress, potentially skewing our results. Despite these constraints, our findings, closely aligned with recent statistics, offer valuable insights into the melanoma and immunotherapy research landscape.

Conclusion

In this analysis, we employed bibliometric methods to examine the trajectory, key discussions, and pioneering investigations in melanoma and immunotherapy research from the past 10 years. Influential journals, including Nature, Clinical Cancer Research, and Science, have significantly shaped discourse in this domain, with experts like Antoni Ribas and Caroline Robert leading the way. Current research gravitates toward ICIs, the tumor microenvironment, and targeted therapy strategies.

Looking ahead, as our grasp of melanoma biology and immunotherapeutic potentials grows alongside technological innovations, the field anticipates a wave of inventive treatment options. These are anticipated to drive personalized approaches to melanoma therapy, aiming to heighten treatment efficacy and reduce associated side effects. We aspire for this study to equip scholars with informative resources, fuel the field's rapid evolution, and assist readers in attaining a scientifically grounded, objective, and well-rounded perspective. With ongoing research, we are optimistic that future developments will yield more efficacious therapies, ultimately enhancing the prognosis for individuals battling melanoma.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by Special Fund Project for Science and Technology Innovation Strategy of Guangdong Province (Grant number pdjh2023b0107), National College Students Innovation and Entrepreneurship Training Program (Grant number 202212121008),

Shenzhen Science and Technology Planning Project (No. JCYJ20220530165014033), Medical research project of Shenzhen Longhua Medical Association (2023LHMA10) and Shenzhen Medical Key Discipline (No. MKD202007090201), Special Fund for Science and Technology Innovation in Longhua District, Shenzhen (11501A20240704D87ABF8).

Notes on contributors

Jieyan Wang, MD, Researcher in the Urology Department at Longhua District People's Hospital of Shenzhen.

Hui Liang, Chief Physician, MD, Master's Supervisor, Postdoctoral Cooperative Supervisor, currently serves as the Director and Academic Leader of the Urology Department at Longhua District People's Hospital of Shenzhen. He specializes in the clinical diagnosis and treatment of various common urological diseases and has presided over and participated in multiple National Natural Science Foundation projects as well as provincial and municipal scientific research projects. His clinical and research work has been widely recognized by peers and patients.

Data availability statement

The datasets generated during the current study are available in the Web of Science (http://www.webofknowledge.com.)

Ethical approval and consent to participate

The data are all from the public database Web of Science, which does not involve ethical issues.

References

1. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229–263. Epub 2024/04/04. doi: 10.3322/caac.21834. PubMed PMID: 38572751.
2. Xing J, Li Y, Chen Y, Han Y. A novel inflammatory response-related signature predicts the prognosis of cutaneous melanoma and the effect of antitumor drugs. World J Surg Oncol. 2022;20(1):263. Epub 2022/08/19. doi: 10.1186/s12957-022-02726-8. PubMed PMID: 35982458; PubMed Central PMCID: PMCPMC9389732.
3. Chang C, Murzaku EC, Penn L, Abbasi NR, Davis PD, Berwick M, Polsky D. More skin, more sun, more tan, more melanoma. Am J Public Health. 2014;104(11):e92–9. Epub 2014/09/12. doi: 10.2105/ajph.2014.302185. PubMed PMID: 25211764; PubMed Central PMCID: PMCPMC4202947.
4. Cust AE, Armstrong BK, Goumas C, Jenkins MA, Schmid H, Hopper JL, Kefford RF, Giles GG, Aitken JF, Mann GJ, et al. Sunbed use during adolescence and early adulthood is associated with increased risk of early-onset melanoma. Intl J Cancer. 2011;128(10):2425–2435. Epub 2010/07/30. doi: 10.1002/ijc.25576. PubMed PMID: 20669232; PubMed Central PMCID: PMCPMC2993823.
5. Long GV, Swetter SM, Menzies AM, Gershenwald JE, Scolyer RA. Cutaneous melanoma. Lancet. 2023;402(10400):485–502. Epub 2023/07/28. doi: 10.1016/s0140-6736(23)00821-8. PubMed PMID: 37499671.
6. Islami F, Marlow EC, Thomson B, McCullough ML, Rumgay H, Gapstur SM, Patel AV, Soerjomataram I, Jemal A. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States, 2019. CA Cancer J Clin. 2024;74(5):405–432. Epub 2024/07/11. doi: 10.3322/caac.21858. PubMed PMID: 38990124.
7. Arnold M, de Vries E, Whiteman DC, Jemal A, Bray F, Parkin DM, Soerjomataram I. Global burden of cutaneous melanoma attributable to ultraviolet radiation in 2012. Int J Cancer. 2018;143(6):1305–1314. Epub 2018/04/17. doi: 10.1002/ijc.31527. PubMed PMID: 29659012.
8. Goldenberg A, Vujic I, Sanlorenzo M, Ortiz-Urda S. Melanoma risk perception and prevention behavior among African-Americans: the minority melanoma paradox. Clin Cosmet Investig Dermatol. 2015;8:423–429. Epub 2015/09/09. doi: 10.2147/ccid.S87645. PubMed PMID: 26346576; PubMed Central PMCID: PMCPMC4531028.
9. Kaliki S, Shields CL. Uveal melanoma: relatively rare but deadly cancer. Eye (Lond). 2017;31(2):241–257. Epub 2016/12/03. doi: 10.1038/eye.2016.275. PubMed PMID: 27911450; PubMed Central PMCID: PMCPMC5306463.
10. Hu DN, Yu GP, McCormick SA, Schneider S, Finger PT. Population-based incidence of uveal melanoma in various races and ethnic groups. Am J Ophthalmol. 2005;140(4):.e612.1–.e612.8. Epub 2005/10/18. doi: 10.1016/j.ajo.2005.05.034. PubMed PMID: 16226513.
11. Di Raimondo C, Lozzi F, Di Domenico PP, Campione E, Bianchi L. The diagnosis and management of cutaneous metastases from melanoma. Int J Mol Sci. 2023;24(19):14535. Epub 2023/10/14. doi:10.3390/ijms241914535. PubMed PMID: 37833981; PubMed Central PMCID: PMCPMC10572973.
12. Berk-Krauss J, Stein JA, Weber J, Polsky D, Geller AC. New systematic therapies and trends in cutaneous melanoma deaths among US whites, 1986-2016. Am J Public Health. 2020;110(5):731–733. Epub 2020/03/20. doi: 10.2105/ajph.2020.305567. PubMed PMID: 32191523; PubMed Central PMCID: PMCPMC7144422.
13. Patel SP, Othus M, Chen Y, Wright GP Jr, Yost KJ, Hyngstrom JR, Hu-Lieskovan S, Lao CD, Fecher LA, Truong T-G, et al. Neoadjuvant–adjuvant or adjuvant-only pembrolizumab in advanced melanoma. N Engl J Med. 2023;388(9):813–823. Epub 2023/03/02. doi: 10.1056/NEJMoa2211437. PubMed PMID: 36856617; PubMed Central PMCID: PMCPMC10410527.
14. Faries MB, Thompson JF, Cochran AJ, Andtbacka RH, Mozzillo N, Zager JS, Jahkola T, Bowles TL, Testori A, Beitsch PD, et al. Completion dissection or observation for sentinel-node metastasis in melanoma. N Engl J Med. 2017;376(23):2211–2222. Epub 2017/06/08. doi: 10.1056/NEJMoa1613210. PubMed PMID: 28591523; PubMed Central PMCID: PMCPMC5548388.
15. Leiter U, Stadler R, Mauch C, Hohenberger W, Brockmeyer NH, Berking C, Sunderkötter C, Kaatz M, Schatton K, Lehmann P, et al. Final analysis of DeCOG-slt trial: no survival benefit for complete lymph node dissection in patients with melanoma with positive sentinel node. J Clin Oncol. 2019;37(32):3000–3008. Epub 2019/09/27. doi: 10.1200/jco.18.02306. PubMed PMID: 31557067.
16. Chen ML, de Vere Hunt IJ, John EM, Weinstock MA, Swetter SM, Linos E, de Vere Hunt IJ. Differences in thickness-specific incidence and factors associated with cutaneous melanoma in the US from 2010 to 2018. JAMA Oncol. 2022;8(5):755–759. Epub 2022/03/25. doi: 10.1001/jamaoncol.2022.0134. PubMed PMID: 35323844; PubMed Central PMCID: PMCPMC8949752.
17. Shan Z, Liu F. Advances in immunotherapy for mucosal melanoma: harnessing immune checkpoint inhibitors for improved treatment outcomes. Front Immunol. 2024;15:1441410. Epub 2024/09/05. doi: 10.3389/fimmu.2024.1441410. PubMed PMID: 39234260; PubMed Central PMCID: PMCPMC11373357.
18. Li J, Li J, Peng Y, Du Y, Yang Z, Qi X. Dendritic cell derived exosomes loaded neoantigens for personalized cancer immunotherapies. J Control Release. 2023;353:423–433. Epub 2022/12/06. doi: 10.1016/j.jconrel.2022.11.053. PubMed PMID: 36470333.
19. Zhu G, Zhang F, Ni Q, Niu G, Chen X. Efficient nanovaccine delivery in cancer immunotherapy. ACS Nano. 2017;11(3):2387–2392. Epub 2017/03/10. doi: 10.1021/acsnano.7b00978. PubMed PMID: 28277646.

20. Chaturvedi VK, Singh A, Singh VK, Singh MP. Cancer nanotechnology: a new revolution for cancer diagnosis and therapy. Curr Drug Metab. 2019;20(6):416–429. Epub 2018/09/20. doi: 10.2174/1389200219666180918111528. PubMed PMID: 30227814.
21. Long GV, Carlino MS, McNeil C, Ribas A, Gaudy-Marqueste C, Schachter J, Nyakas M, Kee D, Petrella TM, Blaustein A, et al. Pembrolizumab versus ipilimumab for advanced melanoma: 10-year follow-up of the phase III KEYNOTE-006 study. Ann Oncol. 2024;35(12):1191–1199. Epub 2024/09/22. doi: 10.1016/j.annonc.2024.08.2330. PubMed PMID: 39306585.
22. Liu J, Fu M, Wang M, Wan D, Wei Y, Wei X. Cancer vaccines as promising immuno-therapeutics: platforms and current progress. J Hematol Oncol. 2022;15(1):28. Epub 2022/03/20. doi: 10.1186/s13045-022-01247-x. PubMed PMID: 35303904; PubMed Central PMCID: PMCPMC8931585.
23. Topalian SL, Sznol M, McDermott DF, Kluger HM, Carvajal RD, Sharfman WH, Brahmer JR, Lawrence DP, Atkins MB, Powderly JD, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014;32(10):1020–1030. Epub 2014/03/05. doi: 10.1200/jco.2013.53.0105. PubMed PMID: 24590637; PubMed Central PMCID: PMCPMC4811023.
24. Zaretsky JM, Garcia-Diaz A, Shin DS, Escuin-Ordinas H, Hugo W, Hu-Lieskovan S, Torrejon DY, Abril-Rodriguez G, Sandoval S, Barthly L, et al. Mutations associated with acquired resistance to PD-1 blockade in melanoma. N Engl J Med. 2016;375(9):819–829. Epub 2016/07/20. doi: 10.1056/NEJMoa1604958. PubMed PMID: 27433843; PubMed Central PMCID: PMCPMC5007206.
25. Ribas A, Wolchok JD. Cancer immunotherapy using checkpoint blockade. Science. 2018;359(6382):1350±. doi:10.1126/science.aar4060. PubMed PMID: WOS:000428043600036.
26. Tarhini AA, Agarwala SS. Cutaneous melanoma: available therapy for metastatic disease. Dermatol Ther. 2006;19(1):19–25. Epub 2006/01/13. doi: 10.1111/j.1529-8019.2005.00052.x. PubMed PMID: 16405566.
27. Karp SE. Low-dose intravenous bolus interleukin-2 with interferon-alpha therapy for metastatic melanoma and renal cell carcinoma. J Immunother. 1998;21(1):56–61. Epub 1998/02/11. doi: 10.1097/00002371-199801000-00007. PubMed PMID: 9456437.
28. Sanlorenzo M, Vujic I, Posch C, Dajee A, Yen A, Kim S, Ashworth M, Rosenblum MD, Algazi A, Osella-Abate S, et al. Melanoma immunotherapy. Cancer Biol Ther. 2014;15(6):665–674. Epub 2014/03/22. doi: 10.4161/cbt.28555. PubMed PMID: 24651672; PubMed Central PMCID: PMCPMC4049781.
29. Smith FO, Downey SG, Klapper JA, Yang JC, Sherry RM, Royal RE, Kammula US, Hughes MS, Restifo NP, Levy CL, et al. Treatment of metastatic melanoma using interleukin-2 alone or in conjunction with vaccines. Clin Cancer Res. 2008;14(17):5610–5618. Epub 2008/09/04. doi: 10.1158/1078-0432.Ccr-08-0116. PubMed PMID: 18765555; PubMed Central PMCID: PMCPMC2656367.
30. Chambers CA, Kuhns MS, Egen JG, Allison JP. CTLA-4-mediated inhibition in regulation of T cell responses: mechanisms and manipulation in tumor immunotherapy. Annu Rev Immunol. 2001;19(1):565–594. Epub 2001/03/13. doi: 10.1146/annurev.immunol.19.1.565. PubMed PMID: 11244047.
31. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012;12(4):252–264. doi:10.1038/nrc3239. PubMed PMID: WOS:000302134900010.
32. Baumeister SH, Freeman GJ, Dranoff G, Sharpe AH. Coinhibitory pathways in immunotherapy for cancer. Annu Rev Immunol. 2016;34(1):539–573. Epub 2016/03/02. doi: 10.1146/annurev-immunol-032414-112049. PubMed PMID: 26927206.
33. Ribas A. Adaptive immune resistance: how cancer protects from immune attack. Cancer Discov. 2015;5(9):915–919. Epub 2015/08/15. doi: 10.1158/2159-8290.Cd-15-0563. PubMed PMID: 26272491; PubMed Central PMCID: PMCPMC4560619.
34. Durham NM, Nirschl CJ, Jackson CM, Elias J, Kochel CM, Anders RA, Drake CG. Lymphocyte activation gene 3 (LAG-3) modulates the ability of CD4 T-cells to be suppressed in vivo. PLoS One. 2014;9(11):e109080. Epub 2014/11/06. doi: 10.1371/journal.pone.0109080. PubMed PMID: 25372844; PubMed Central PMCID: PMCPMC4220939 Squibb, Compugen and Roche/Genentech. CGD is a co-inventor on a patent entitled: "Manipulation of Regulatory T Cells Using LAG-3 Antibodies, Genes, Agonists and Antagonists", filing case number: C04255. This patent is currently un-licensed. This does not alter the authors' adherence to PLOS ONE policies on sharing data and materials.
35. Workman CJ, Cauley LS, Kim IJ, Blackman MA, Woodland DL, Vignali DA. Lymphocyte activation gene-3 (CD223) regulates the size of the expanding T cell population following antigen activation in vivo. J Immunol. 2004;172(9):5450–5455. Epub 2004/04/22. doi: 10.4049/jimmunol.172.9.5450. PubMed PMID: 15100286.
36. Hemon P, Jean-Louis F, Ramgolam K, Brignone C, Viguier M, Bachelez H, Triebel F, Charron D, Aoudjit F, Al-Daccak R, et al. MHC class II engagement by its ligand LAG-3 (CD223) contributes to melanoma resistance to apoptosis. J Immunol. 2011;186(9):5173–5183. Epub 2011/03/29. doi: 10.4049/jimmunol.1002050. PubMed PMID: 21441454.
37. Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, Chau I, Ernstoff MS, Gardner JM, Ginex P, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2018;36(17):1714–1768. doi:10.1200/jco.2017.77.6385. PubMed PMID: WOS:000434770500011.
38. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, adaptive, and acquired resistance to cancer immunotherapy. Cell. 2017;168(4):707–723. doi:10.1016/j.cell.2017.01.017. PubMed PMID: WOS:000396277600019.
39. Robert C, Grob JJ, Stroyakovskiy D, Karaszewska B, Hauschild A, Levchenko E, Chiarion Sileni V, Schachter J, Garbe C, Bondarenko I, et al. Five-year outcomes with dabrafenib plus trametinib in metastatic melanoma. N Engl J Med. 2019;381(7):626–636. doi:10.1056/NEJMoa1904059. PubMed PMID: WOS:000481462800008.
40. Robert C, Ribas A, Schachter J, Arance A, Grob J-J, Mortier L, Daud A, Carlino MS, McNeil CM, Lotem M, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol. 2019;20(9):1239–1251. doi:10.1016/s1470-2045(19)30388-2. PubMed PMID: WOS:000484364700041.
41. Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, Wolchok JD, Hersey P, Joseph R, Weber JS, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol. 2019;30(4):582–588. doi:10.1093/annonc/mdz011. PubMed PMID: WOS:000468283900014.
42. Tawbi HA, Schadendorf D, Lipson EJ, Ascierto PA, Matamala L, Castillo Gutiérrez E, Rutkowski P, Gogas HJ, Lao CD, De Menezes JJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386(1):24–34. Epub 2022/01/06. doi: 10.1056/NEJMoa2109970. PubMed PMID: 34986285; PubMed Central PMCID: PMCPMC9844513.
43. Cabrita R, Lauss M, Sanna A, Donia M, Larsen MS, Mitra S, Johansson I, Phung B, Harbst K, Vallon-Christersson J, et al. Tertiary lymphoid structures improve immunotherapy and survival in melanoma. Nature. 2020;577(7791):561–565. doi:10.1038/s41586-019-1914-8. PubMed PMID: WOS:000509200100023.
44. Postow MA, Sidlow R, Hellmann MD, Longo DL. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018;378(2):158–168. doi:10.1056/NEJMra1703481. PubMed PMID: WOS:000419971600009.
45. Weber JS, Hodi FS, Wolchok JD, Topalian SL, Schadendorf D, Larkin J, Sznol M, Long GV, Li H, Waxman IM, et al. Safety profile of nivolumab monotherapy: a pooled analysis of patients with advanced melanoma. J Clin Oncol. 2017;35(7):785–792. Epub

2017/01/10. doi: 10.1200/jco.2015.66.1389. PubMed PMID: 28068177.
46. Shajari N, Baradaran B, Tohidkia MR, Nasiri H, Sepehri M, Setayesh S, Aghebati-Maleki L. Advancements in melanoma therapies: from surgery to immunotherapy. Curr Treat Opt Oncol. 2024;25(8):1073–1088. doi:10.1007/s11864-024-01239-8. PubMed PMID: WOS:001277862000003.
47. Zhang J, Joshua AM, Li Y, O'Meara CH, Morris MJ, Khachigian LM. Targeted therapy, immunotherapy, and small molecules and peptidomimetics as emerging immunoregulatory agents for melanoma. Cancer Lett. 2024;586:216633. doi:10.1016/j.canlet.2024.216633.
48. Cerchia C, Lavecchia A. Small molecule drugs and targeted therapy for melanoma: current strategies and future directions. Curr Med Chem. 2017;24(21):2312–2344. Epub 2017/04/18. doi: 10.2174/0929867324666170414163937. PubMed PMID: 28413965.
49. Wilhelm S, Carter C, Lynch M, Lowinger T, Dumas J, Smith RA, Schwartz B, Simantov R, Kelley S. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. Nat Rev Drug Discov. 2006;5(10):835–844. Epub 2006/10/04. doi: 10.1038/nrd2130. PubMed PMID: 17016424.
50. Eisen T, Ahmad T, Flaherty KT, Gore M, Kaye S, Marais R, Gibbens I, Hackett S, James M, Schuchter LM, et al. Sorafenib in advanced melanoma: a phase II randomised discontinuation trial analysis. Br J Cancer. 2006;95(5):581–586. Epub 2006/08/02. doi: 10.1038/sj.bjc.6603291. PubMed PMID: 16880785; PubMed Central PMCID: PMCPMC2360687.
51. Hauschild A, Agarwala SS, Trefzer U, Hogg D, Robert C, Hersey P, Eggermont A, Grabbe S, Gonzalez R, Gille J, et al. Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. J Clin Oncol. 2009;27(17):2823–2830. Epub 2009/04/08. doi: 10.1200/jco.2007.15.7636. PubMed PMID: 19349552.
52. Mangana J, Levesque MP, Karpova MB, Dummer R. Sorafenib in melanoma. Expert Opin Investig Drugs. 2012;21(4):557–568. Epub 2012/03/08. doi: 10.1517/13543784.2012.665872. PubMed PMID: 22394203.
53. Flaherty KT, Lee SJ, Zhao F, Schuchter LM, Flaherty L, Kefford R, Atkins MB, Leming P, Kirkwood JM. Phase III trial of carboplatin and paclitaxel with or without sorafenib in metastatic melanoma. J Clin Oncol. 2013;31(3):373–379. Epub 2012/12/19. doi: 10.1200/jco.2012.42.1529. PubMed PMID: 23248256; PubMed Central PMCID: PMCPMC4878104 are found at the end of this article.
54. Bollag G, Tsai J, Zhang J, Zhang C, Ibrahim P, Nolop K, Hirth P. Vemurafenib: the first drug approved for braf-mutant cancer. Nat Rev Drug Discov. 2012;11(11):873–886. Epub 2012/10/13. doi: 10.1038/nrd3847. PubMed PMID: 23060265.
55. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–2516. Epub 2011/06/07. doi: 10.1056/NEJMoa1103782. PubMed PMID: 21639808; PubMed Central PMCID: PMCPMC3549296.
56. Kim G, McKee AE, Ning YM, Hazarika M, Theoret M, Johnson JR, Xu QC, Tang S, Sridhara R, Jiang X, et al. FDA approval summary: vemurafenib for treatment of unresectable or metastatic melanoma with the BRAFV600E mutation. Clin Cancer Res. 2014;20(19):4994–5000. Epub 2014/08/07. doi: 10.1158/1078-0432.Ccr-14-0776. PubMed PMID: 25096067.
57. Grimaldi AM, Simeone E, Festino L, Vanella V, Strudel M, Ascierto PA. MEK Inhibitors in the treatment of metastatic melanoma and solid tumors. Am J Clin Dermatol. 2017;18(6):745–754. Epub 2017/05/26. doi: 10.1007/s40257-017-0292-y. PubMed PMID: 28537004.
58. Akinleye A, Furqan M, Mukhi N, Ravella P, Liu D. MEK and the inhibitors: from bench to bedside. J Hematol Oncol. 2013;6(1):27. Epub 2013/04/17. doi: 10.1186/1756-8722-6-27. PubMed PMID: 23587417; PubMed Central PMCID: PMCPMC3626705.
59. Subbiah V, Baik C, Kirkwood JM. Clinical development of BRAF plus MEK inhibitor combinations. Trends Cancer. 2020;6(9):797–810. Epub 2020/06/17. doi: 10.1016/j.trecan.2020.05.009. PubMed PMID: 32540454.
60. Rahimi A, Esmaeili Y, Dana N, Dabiri A, Rahimmanesh I, Jandaghian S, Vaseghi G, Shariati L, Zarrabi A, Haghjooy Javanmard S, et al. A comprehensive review on novel targeted therapy methods and nanotechnology-based gene delivery systems in melanoma. Eur J Pharm Sci. 2023;187:106476. Epub 2023/05/27. doi: 10.1016/j.ejps.2023.106476. PubMed PMID: 37236377.
61. Simbulan-Rosenthal CM, Haribabu Y, Vakili S, Kuo LW, Clark H, Dougherty R, Alobaidi R, Carney B, Sykora P, Rosenthal DS, et al. Employing CRISPR-Cas9 to generate CD133 synthetic lethal melanoma stem cells. Int J Mol Sci. 2022;23(4):2333. Epub 2022/02/27. doi:10.3390/ijms23042333. PubMed PMID: 35216449; PubMed Central PMCID: PMCPMC8877091.
62. Gautron A, Bachelot L, Aubry M, Leclerc D, Quéméner AM, Corre S, Rambow F, Paris A, Tardif N, Leclair HM, et al. CRISPR screens identify tumor-promoting genes conferring melanoma cell plasticity and resistance. EMBO Mol Med. 2021;13(5):e13466. Epub 2021/03/17. doi: 10.15252/emmm.202013466. PubMed PMID: 33724679; PubMed Central PMCID: PMCPMC8103100.
63. Harris E, Elmer JJ. Optimization of electroporation and other non-viral gene delivery strategies for T cells. Biotechnol Prog. 2021;37(1):e3066. Epub 2020/08/19. doi: 10.1002/btpr.3066. PubMed PMID: 32808434.
64. Boyd KU, Wehrli BM, Temple CL. Intra-lesional interleukin-2 for the treatment of in-transit melanoma. J Surg Oncol. 2011;104(7):711–717. Epub 2011/07/12. doi: 10.1002/jso.21968. PubMed PMID: 21744347.
65. Radny P, Caroli UM, Bauer J, Paul T, Schlegel C, Eigentler TK, Weide B, Schwarz M, Garbe C. Phase II trial of intralesional therapy with interleukin-2 in soft-tissue melanoma metastases. Br J Cancer. 2003;89(9):1620–1626. Epub 2003/10/30. doi: 10.1038/sj.bjc.6601320. PubMed PMID: 14583759; PubMed Central PMCID: PMCPMC2394422.
66. Rosen DB, Kvarnhammar AM, Laufer B, Knappe T, Karlsson JJ, Hong E, Lee Y-C, Thakar D, Zúñiga LA, Bang K, et al. TransCon IL-2 β/γ: a novel long-acting prodrug with sustained release of an IL-2Rβ/γ-selective IL-2 variant with improved pharmacokinetics and potent activation of cytotoxic immune cells for the treatment of cancer. J Immunother Cancer. 2022;10(7):e004991. Epub 2022/07/12. doi:10.1136/jitc-2022-004991. PubMed PMID: 35817480; PubMed Central PMCID: PMCPMC9274542.
67. Dana H, Chalbatani GM, Mahmoodzadeh H, Karimloo R, Rezaiean O, Moradzadeh A, Moradzadeh A, Mazraeh A, Marmari V, Rashno MM, et al. Molecular mechanisms and biological functions of siRNA. Int J Biomed Sci. 2017;13(2):48–57. Epub 2017/08/22. PubMed PMID: 28824341; PubMed Central PMCID: PMCPMC5542916. 10.59566/IJBS.2017.13048.
68. Obeid MA, Aljabali AAA, Rezigue M, Amawi H, Alyamani H, Abdeljaber SN. Use of nanoparticles in delivery of nucleic acids for melanoma treatment. Methods Mol Biol. 2021;2265:591–620. Epub 2021/03/12. doi: 10.1007/978-1-0716-1205-7_41. PubMed PMID: 33704742.
69. Bertrand JR, Pottier M, Vekris A, Opolon P, Maksimenko A, Malvy C. Comparison of antisense oligonucleotides and siRNAs in cell culture and in vivo. Biochem Biophys Res Commun. 2002;296(4):1000–1004. Epub 2002/08/30. doi: 10.1016/s0006-291x(02)02013-2. PubMed PMID: 12200148.
70. Le BT, Raguraman P, Kosbar TR, Fletcher S, Wilton SD, Veedu RN. Antisense oligonucleotides targeting angiogenic factors as potential cancer therapeutics. Mol Ther Nucleic Acids. 2019;14:142–157. Epub 2018/12/31. doi: 10.1016/j.omtn.2018.11.007. PubMed PMID: 30594893; PubMed Central PMCID: PMCPMC6307321.
71. Nimjee SM, White RR, Becker RC, Sullenger BA. Aptamers as therapeutics. Annu Rev Pharmacol Toxicol. 2017;57(1):61–79. Epub 2017/01/08. doi: 10.1146/annurev-pharmtox-010716-

104558. PubMed PMID: 28061688; PubMed Central PMCID: PMCPMC6035745.
72. Li H, Liu J, Xiao X, Sun S, Zhang H, Zhang Y, Zhou W, Zhang B, Roy M, Liu H, et al. A novel aptamer LL4A specifically targets vemurafenib-resistant melanoma through binding to the CD63 protein. Mol Ther Nucleic Acids. 2019;18:727–738. Epub 2019/11/15. doi: 10.1016/j.omtn.2019.10.005. PubMed PMID: 31726389; PubMed Central PMCID: PMCPMC6859286.
73. Garbe C, Amaral T, Peris K, Hauschild A, Arenberger P, Basset-Seguin N, Bastholt L, Bataille V, Del Marmol V, Dréno B, et al. European consensus-based interdisciplinary guideline for melanoma. Part 1: diagnostics: update 2022. Eur J Cancer. 2022;170:236–255. Epub 2022/05/16. doi: 10.1016/j.ejca.2022.03.008. PubMed PMID: 35570085.
74. Quek C, Bai X, Long GV, Scolyer RA, Wilmott JS. High-dimensional single-cell transcriptomics in melanoma and cancer immunotherapy. Genes (Basel). 2021;12(10):1629. Epub 2021/10/24. doi:10.3390/genes12101629. PubMed PMID: 34681023; PubMed Central PMCID: PMCPMC8535767.
75. Long GV, Menzies AM, Nagrial AM, Haydu LE, Hamilton AL, Mann GJ, Hughes TM, Thompson JF, Scolyer RA, Kefford RF, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol. 2011;29(10):1239–1246. Epub 2011/02/24. doi: 10.1200/jco.2010.32.4327. PubMed PMID: 21343559.
76. Ny L, Hernberg M, Nyakas M, Koivunen J, Oddershede L, Yoon M, Wang X, Guyot P, Geisler J. BRAF mutational status as a prognostic marker for survival in malignant melanoma: a systematic review and meta-analysis. Acta Oncol. 2020;59(7):833–844. Epub 2020/04/15. doi: 10.1080/0284186x.2020.1747636. PubMed PMID: 32285732.
77. Wolfe AR, Chablani P, Siedow MR, Miller ED, Walston S, Kendra KL, Wuthrick E, Williams TM. BRAF mutation correlates with worse local–regional control following radiation therapy in patients with stage III melanoma. Radiat Oncol. 2021;16(1):181. Epub 2021/09/20. doi: 10.1186/s13014-021-01903-5. PubMed PMID: 34537078; PubMed Central PMCID: PMCPMC8449455.
78. Ellerhorst JA, Greene VR, Ekmekcioglu S, Warneke CL, Johnson MM, Cooke CP, Wang L-E, Prieto VG, Gershenwald JE, Wei Q, et al. Clinical correlates of NRAS and BRAF mutations in primary human melanoma. Clin Cancer Res. 2011;17(2):229–235. Epub 2010/10/27. doi: 10.1158/1078-0432.Ccr-10-2276. PubMed PMID: 20975100; PubMed Central PMCID: PMCPMC3022950.
79. Jakob JA, Bassett RL Jr., Ng CS, Curry JL, Joseph RW, Alvarado GC, Rohlfs ML, Richard J, Gershenwald JE, Kim KB, et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. Cancer. 2012;118(16):4014–4023. Epub 2011/12/20. doi: 10.1002/cncr.26724. PubMed PMID: 22180178; PubMed Central PMCID: PMCPMC3310961.
80. Dummer R, Schadendorf D, Ascierto PA, Arance A, Dutriaux C, Di Giacomo AM, Rutkowski P, Del Vecchio M, Gutzmer R, Mandala M, et al. Binimetinib versus dacarbazine in patients with advanced nras-mutant melanoma (NEMO): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(4):435–445. Epub 2017/03/13. doi: 10.1016/s1470-2045(17)30180-8. PubMed PMID: 28284557.
81. Carvajal RD, Antonescu CR, Wolchok JD, Chapman PB, Roman RA, Teitcher J. KIT as a therapeutic target in metastatic melanoma. Jama. 2011;305(22):2327–2334. Epub 2011/06/07. doi: 10.1001/jama.2011.746. PubMed PMID: 21642685; PubMed Central PMCID: PMCPMC3986039.
82. Hodi FS, Corless CL, Giobbie-Hurder A, Fletcher JA, Zhu M, Marino-Enriquez A, Friedlander P, Gonzalez R, Weber JS, Gajewski TF, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol. 2013;31(26):3182–3190. Epub 2013/06/19. doi: 10.1200/jco.2012.47.7836. PubMed PMID: 23775962; PubMed Central PMCID: PMCPMC4878082 are found at the end of this article.
83. Wei X, Mao L, Chi Z, Sheng X, Cui C, Kong Y, Dai J, Wang X, Li S, Tang B, et al. Efficacy evaluation of imatinib for the treatment of melanoma: evidence from a retrospective study. Oncol Res. 2019;27(4):495–501. Epub 2018/08/05. doi: 10.3727/096504018x15331163433914. PubMed PMID: 30075827; PubMed Central PMCID: PMCPMC7848371.
84. Guo J, Carvajal RD, Dummer R, Hauschild A, Daud A, Bastian BC, Markovic SN, Queirolo P, Arance A, Berking C, et al. Efficacy and safety of nilotinib in patients with kit-mutated metastatic or inoperable melanoma: final results from the global, single-arm, phase II TEAM trial. Ann Oncol. 2017;28(6):1380–1387. Epub 2017/03/23. doi: 10.1093/annonc/mdx079. PubMed PMID: 28327988; PubMed Central PMCID: PMCPMC5452069.
85. Guo J, Si L, Kong Y, Flaherty KT, Xu X, Zhu Y, Corless CL, Li L, Li H, Sheng X, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-kit mutation or amplification. J Clin Oncol. 2011;29(21):2904–2909. Epub 2011/06/22. doi: 10.1200/jco.2010.33.9275. PubMed PMID: 21690468.
86. Hegedüs L, Livingstone E, Bánkfalvi Á, Viehof J, Enyedi Á, Bilecz Á, Győrffy B, Baranyi M, Tőkés A-M, Gil J, et al. The prognostic relevance of PMCA4 expression in melanoma: gender specificity and implications for immune checkpoint inhibition. Int J Mol Sci. 2022;23(6):3324. Epub 2022/03/26. doi:10.3390/ijms23063324. PubMed PMID: 35328746; PubMed Central PMCID: PMCPMC8949876.
87. Forschner A, Battke F, Hadaschik D, Schulze M, Weißgraeber S, Han CT, Kopp M, Frick M, Klumpp B, Tietze N, et al. Tumor mutation burden and circulating tumor DNA in combined CTLA-4 and PD-1 antibody therapy in metastatic melanoma – results of a prospective biomarker study. J Immunother Cancer. 2019;7(1):180. Epub 2019/07/14. doi: 10.1186/s40425-019-0659-0. PubMed PMID: 31300034; PubMed Central PMCID: PMCPMC6625062 support from Roche, Novartis, BMS, Pierre-Fabre, received speaker fees from Cegat, Roche, Novartis, BMS, MSD. TA received travel support from Novartis. TE served as consultant to Roche, Novartis, MSD, BMS, Pierre-Fabre; received speaker fees from Roche, Novartis, BMS, MSD. CG reports grants and personal fees from Novartis, BMS, Roche, personal fees from MSD. Personal fees from Amgen, Philogen, LEO, Incyte, outside the submitted work. DD received travel support from BMS. No competing interests were declared by the other authors.
88. Huang T, Chen X, Zhang H, Liang Y, Li L, Wei H, Sun W, Wang Y. Prognostic role of tumor mutational burden in cancer patients treated with immune checkpoint inhibitors: a systematic review and meta-analysis. Front Oncol. 2021;11:706652. Epub 2021/08/17. doi: 10.3389/fonc.2021.706652. PubMed PMID: 34395281; PubMed Central PMCID: PMCPMC8358612.
89. Marcus L, Fashoyin-Aje LA, Donoghue M, Yuan M, Rodriguez L, Gallagher PS, Philip R, Ghosh S, Theoret MR, Beaver JA, et al. FDA approval summary: pembrolizumab for the treatment of tumor mutational burden–high solid tumors. Clin Cancer Res. 2021;27(17):4685–4689. Epub 2021/06/05. doi: 10.1158/1078-0432.Ccr-21-0327. PubMed PMID: 34083238; PubMed Central PMCID: PMCPMC8416776.
90. Bollard SM, Casalou C, Potter SM. Gene expression profiling in melanoma: a view from the clinic. Cancer Treat Res Commun. 2021;29:100447. Epub 2021/08/28. doi: 10.1016/j.ctarc.2021.100447. PubMed PMID: 34450405.
91. Grossman D, Okwundu N, Bartlett EK, Marchetti MA, Othus M, Coit DG, Hartman RI, Leachman SA, Berry EG, Korde L, et al. Prognostic gene expression profiling in cutaneous melanoma: identifying the knowledge gaps and assessing the clinical benefit. JAMA Dermatol. 2020;156(9):1004–1011. Epub 2020/07/30. doi: 10.1001/jamadermatol.2020.1729. PubMed PMID: 32725204; PubMed Central PMCID: PMCPMC8275355.
92. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, Karpinets TV, Prieto PA, Vicente D, Hoffman K, Wei SC, et al. Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. Science. 2018;359(6371):97–103. Epub

2017/11/04. doi: 10.1126/science.aan4236. PubMed PMID: 29097493; PubMed Central PMCID: PMCPMC5827966.

93. Dubin K, Callahan MK, Ren B, Khanin R, Viale A, Ling L, No D, Gobourne A, Littmann E, Huttenhower C, et al. Intestinal microbiome analyses identify melanoma patients at risk for checkpoint-blockade-induced colitis. Nat Commun. 2016;7 (1):10391. Epub 2016/02/03. doi: 10.1038/ncomms10391. PubMed PMID: 26837003; PubMed Central PMCID: PMCPMC4740747.
94. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M, Bukur V, Tadmor AD, Luxemburger U, Schrörs B, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature. 2017;547(7662):222–226. Epub 2017/07/06. doi: 10.1038/nature23003. PubMed PMID: 28678784.
95. Carreno BM, Magrini V, Becker-Hapak M, Kaabinejadian S, Hundal J, Petti AA, Ly A, Lie W-R, Hildebrand WH, Mardis ER, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science. 2015;348(6236):803–808. Epub 2015/04/04. doi: 10.1126/science.aaa3828. PubMed PMID: 25837513; PubMed Central PMCID: PMCPMC4549796.
96. Hu Z, Leet DE, Allesøe RL, Oliveira G, Li S, Luoma AM, Liu J, Forman J, Huang T, Iorgulescu JB, et al. Personal neoantigen vaccines induce persistent memory T cell responses and epitope spreading in patients with melanoma. Nat Med. 2021;27 (3):515–525. Epub 2021/01/23. doi: 10.1038/s41591-020-01206-4. PubMed PMID: 33479501; PubMed Central PMCID: PMCPMC8273876.
97. Ott PA, Hu Z, Keskin DB, Shukla SA, Sun J, Bozym DJ, Zhang W, Luoma A, Giobbie-Hurder A, Peter L, et al. An immunogenic personal neoantigen vaccine for patients with melanoma. Nature. 2017;547(7662):217–221. Epub 2017/07/06. doi: 10.1038/nature22991. PubMed PMID: 28678778; PubMed Central PMCID: PMCPMC5577644.
98. Kim HJ, Kim YH. Molecular frontiers in melanoma: pathogenesis, diagnosis, and therapeutic advances. Int J Mol Sci. 2024;25(5):2984. Epub 2024/03/13. doi:10.3390/ijms25052984. PubMed PMID: 38474231; PubMed Central PMCID: PMCPMC10931637.