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ORIGINAL RESEARCH

A Visual Analysis of the Research Dynamics in Resistance to EGFR Inhibitors for NSCLC

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Purpose: Activating mutations in epidermal growth factor receptor (EGFR) have been identified as key predictive biomarkers for the customized treatment with EGFR tyrosine kinase inhibitors (TKIs) in non-small cell lung cancer (NSCLC), aiding in improving patient response rates and survival. However, resistance challenges the efficacy of these treatments, with limited understanding of post-resistance therapeutic strategies. A deep understanding of the biology and resistance mechanisms of EGFR-mutant NSCLC is crucial for developing new treatment approaches. This study, through bibliometric analysis, summarizes the trends in research on resistance to EGFR-TKIs.

Methods: Research papers on NSCLC with EGFR inhibitor resistance were collected from the Web of Science Core Collection (WoSCC). The analysis utilized bibliometric tools like CiteSpace, VOSviewer, and other platforms for comprehensive analysis and visualization of the outcomes.

Results: The WoSCC database contains a total of 5866 documents on resistance to EGFR-TKIs treatment, including 4727 articles (93.48%) and 1139 reviews (6.52%), spanning 81 countries and regions, 4792 institutions, with the involvement of 23,594 authors. Since 2016, there has been a significant increase in publications in this field. China has the highest publication output, while the United States has the highest citation count for papers. Harvard University leads in terms of the number of publications. Among the top ten journals with the highest output, Clinical Cancer Research has the highest impact factor at 11.5, with 90% of the journals classified in Q1 or Q2. Rafael Rosell is one of the most influential authors in this field, ranking second in publication volume and fourth in citation count. Research on EGFR-TKIs resistance mainly focuses on genetic testing, resistance mechanisms, and post-resistance treatment strategies.

Conclusion: This study provides researchers with a reliable basis and guidance for finding authoritative references, understanding research trends, and exploring potential directions.

Keywords: NSCLC, EGFR mutation, EGFR-TKIs, bibliometric analysis, hot SPOTS

Introduction

Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer, accounting for about 85% of cases. It primarily includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.[1] The EGFR is a transmembrane glycoprotein with tyrosine kinase activity that plays a crucial role in physiological processes such as cell growth, proliferation, and differentiation through its phosphorylation. EGFR gene mutations are the most common driver gene mutations in NSCLC. Their primary mechanism of action is to regulate tumor cell proliferation, angiogenesis, and tumor cell invasion and metastasis by binding to extracellular ligands and undergoing homologous or heterologous dimerization.[2,3]

Especially in the Chinese NSCLC population, the proportion of EGFR mutations is 28.2%, and in lung adenocarcinoma, this proportion rises to 50.2%.[4] The emergence of EGFR tyrosine kinase inhibitors (TKIs) has changed the standard treatment paradigm for patients with advanced EGFR mutation-positive NSCLC. TKIs have been evaluated and recommended as a first-line treatment option for patients with EGFR mutation-positive NSCLC by current treatment

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guidelines, including the National Comprehensive Cancer Network (NCCN).[5] Compared to traditional platinum-based chemotherapy, first- and second-generation EGFR-TKIs as first-line treatment for advanced NSCLC with classic EGFR mutations (deletions in EGFR exon 19 or L858R point mutations in exon 21) significantly improve median progression-free survival (mPFS) but not overall survival (OS).[6–8] Approximately 50%-60% of patients treated with first- or second-generation EGFR-TKIs as first-line therapy will develop secondary T790M resistance mutations.[9] Third-generation EGFR-TKIs can inhibit both EGFR-sensitive mutations and T790M resistance mutations, significantly increasing mPFS by about 10 months compared to first/second-generation EGFR-TKIs in patients with EGFR-sensitive mutations.[10–12] In the FLAURA study, Osimertinib achieved a statistically and clinically significant improvement in OS, extending it to 38.6 months (compared to 31.8 months in the control group, p=0.046). The results of the FLAURA2 study (comparing the efficacy and safety of Osimertinib in combination with chemotherapy versus Osimertinib monotherapy as first-line treatment), presented at the 2023 World Congress of lung cancer (WCLC), officially initiated the chapter on first-line combination therapy with third-generation EGFR-TKIs. Compared to Osimertinib monotherapy, combination chemotherapy extended median PFS by nearly 9 months, reducing the risk of disease progression by 38% (25.5 months vs 16.7 months, HR 0.62, p<0.0001).[13] Unfortunately, resistance caused by unconventional mutations in the EGFR gene and components of the signaling pathway continues to emerge. In addition to the common secondary (T790M) and tertiary (C797S) mutations, other EGFR mutations (such as L718Q, L796S, and L792H mutations, as well as exon 20 insertions), MET amplification, mutations in the phosphatidylinositol 4.5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), HER2 amplification, oncogene fusions, and alterations in cell cycle-related genes have been observed.[14]

Managing resistance in patients remains a challenge in current clinical diagnosis and treatment. There is an urgent need for better strategies to combat the inevitable molecular targeted resistance associated with EGFR inhibitors. Extensive research is currently underway to investigate the resistance to EGFR inhibitors. However, a comprehensive analysis of the existing literature regarding this topic has not been conducted thus far. Against this backdrop, we employ bibliometric analysis to delve into the research frontiers and hotspots of EGFR inhibitor resistance. This quantitative analysis method helps track the research profiles of different countries, institutions, and researchers, and describes the literature and keywords in the related field.[15–17] Throughout the exploration process, we have thoroughly investigated the evolution trajectory and progress of key research areas in this domain from 2004 to 2023, revealing emerging topics of interest and directing the forthcoming research efforts in this area.

Materials and Methods

Data Collection

The database selected for bibliometric analysis was the Web of Science Core Collection (WoSCC).[18,19] We conducted a search on January 1, 2024, within WoSCC, targeting articles related to resistance after treatment with EGFR-TKIs spanning the period from 2004 to December 31, 2023. Search strategy was based on the advanced search option with the following strategy: (((((((TS=(egfr)) OR TS=(ErbB Receptors)) OR TS=(Receptors, ErbB)) OR TS=(ErbB Receptor)) OR TS=(Receptor, ErbB)) OR TS=(Receptor, ErbB-1)) OR TS=(Receptor, ErbB 1)) OR TS=(Epidermal Growth Factor Receptor)) OR TS=(Receptor, Epidermal Growth Factor) AND ((((((((((TS=(Non-small cell lung cancer)) OR TS=(Carcinoma, Non-Small-Cell Lung)) OR TS=(Carcinoma, Non-Small Cell Lung)) OR TS=(Carcinomas, Non-Small-Cell Lung)) OR TS=(Lung Carcinoma, Non-Small-Cell)) OR TS=(Lung Carcinomas, Non-Small-Cell)) OR TS=(Non-Small-Cell Lung Carcinomas)) OR TS=(Non-Small -Cell Lung Carcinoma)) OR TS=(Non-Small Cell Lung Carcinoma)) OR TS=(Carcinoma, Non-Small Cell Lung)) OR TS=(Non-Small Cell Lung Carcinoma)) OR TS=(Non-small Cell Lung Cancer) AND TS=(Resistance). The literature screening for this study is based on the following inclusion criteria: (1) Full-text publications related to resistance after treatment with EGFR-TKIs; (2) Both articles and review manuscript categories are written in English; (3) Articles were published between January 1, 2004, and December 31, 2023. The exclusion criteria are as follows: (1) Topics not related to resistance after treatment with EGFR-TKIs; (2) Articles that are conference abstracts, news, briefings. The plain text versions of the papers were exported. Plain text versions of the selected papers were exported, and the publication selection process was illustrated in Figure 1. Additionally, ethical consent was not required for this study, as it did not involve animals or experiments.

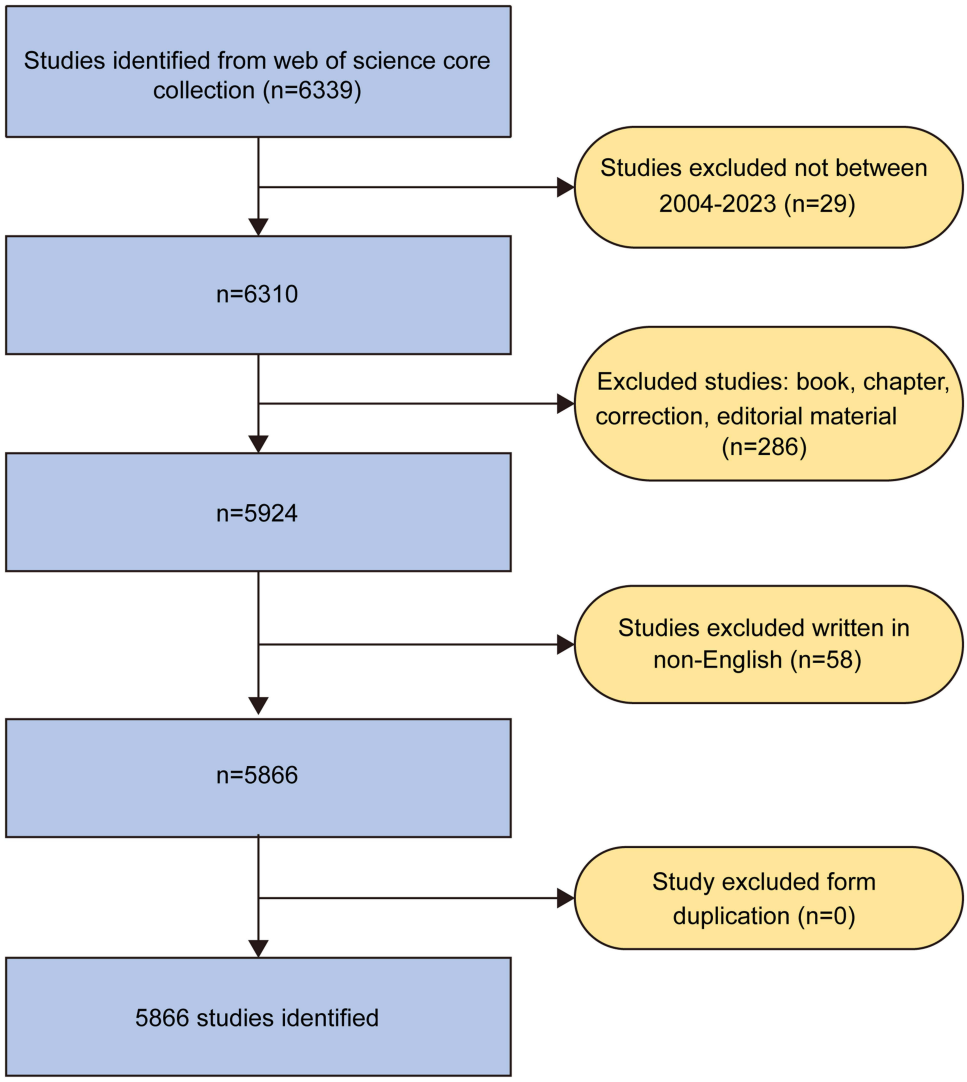

Figure 1 Flowchart of the process of publication selection.

Data Analysis and Visualization

Data categorization was performed utilizing Microsoft Excel 2021 (available at https://www.microsoftstore.com.cn/), while graphical representations were generated via the "bibliometrix" package within the R programming environment (accessible at https://cran.r-project.org/web/packages/bibliometrix/). The analysis encompassed the quantification of the total number of publications, the aggregate citation count, the Hirsch index, and the impact factor.[20,21]

The bibliometric software VOS viewer version 1.6.18 (available at https://www.vosviewer.com/) was employed for the construction of bibliometric maps, facilitating the visualization of clustering, overlay, and density perspectives.[21] These maps were generated based on varying parameters such as distances, node sizes, and densities, which represent different bibliometric indicators. Specifically, the node size reflects either the number of publications or the co-occurrence frequency of various bibliometric entities including authors, institutions, and keywords, with larger nodes denoting higher frequency or research prominence. Nodes pertaining to distinct clusters are differentiated by unique color codings. The total link strength metric quantifies the cumulative strength of connections of a particular node with all other nodes in the network. In this analysis, VOS viewer facilitated the examination of co-occurrence relationships among several dimensions: (i) authors, (ii) countries/regions, (iii) institutions, (iv) keywords, and (v) clusters of keywords, thereby providing comprehensive insights into the collaborative and thematic structures within the dataset.

CiteSpace version 6.1.6R facilitates the generation of visual knowledge maps, which are comprised of nodes and links, where each link signifies a co-occurrence relationship between nodes, and the thickness represents the connection strength.[22] This configuration was instrumental in this study for identifying pronounced citation bursts and delineating their respective timelines, thereby highlighting key moments of accelerated interest or pivotal shifts within the researched domain.

Results

Summary

The Results show that from January 1, 2004, to December 31, 2023, there were a total of 5866 documents related to resistance after EGFR treatment in the WoSCC database, including 4727 (93.48%) articles and 1139 reviews (6.52%). The literature involves 81 countries and regions, 4792 institutions, and 23,594 authors. Since 2004, the number of papers published annually has slowly increased (Figure 2A). This trend is divided into three stages: from 2004 to 2009, the growth was slow, with fewer than 100 papers published annually, indicating less attention to this field by researchers. From 2010 to 2015, the number of

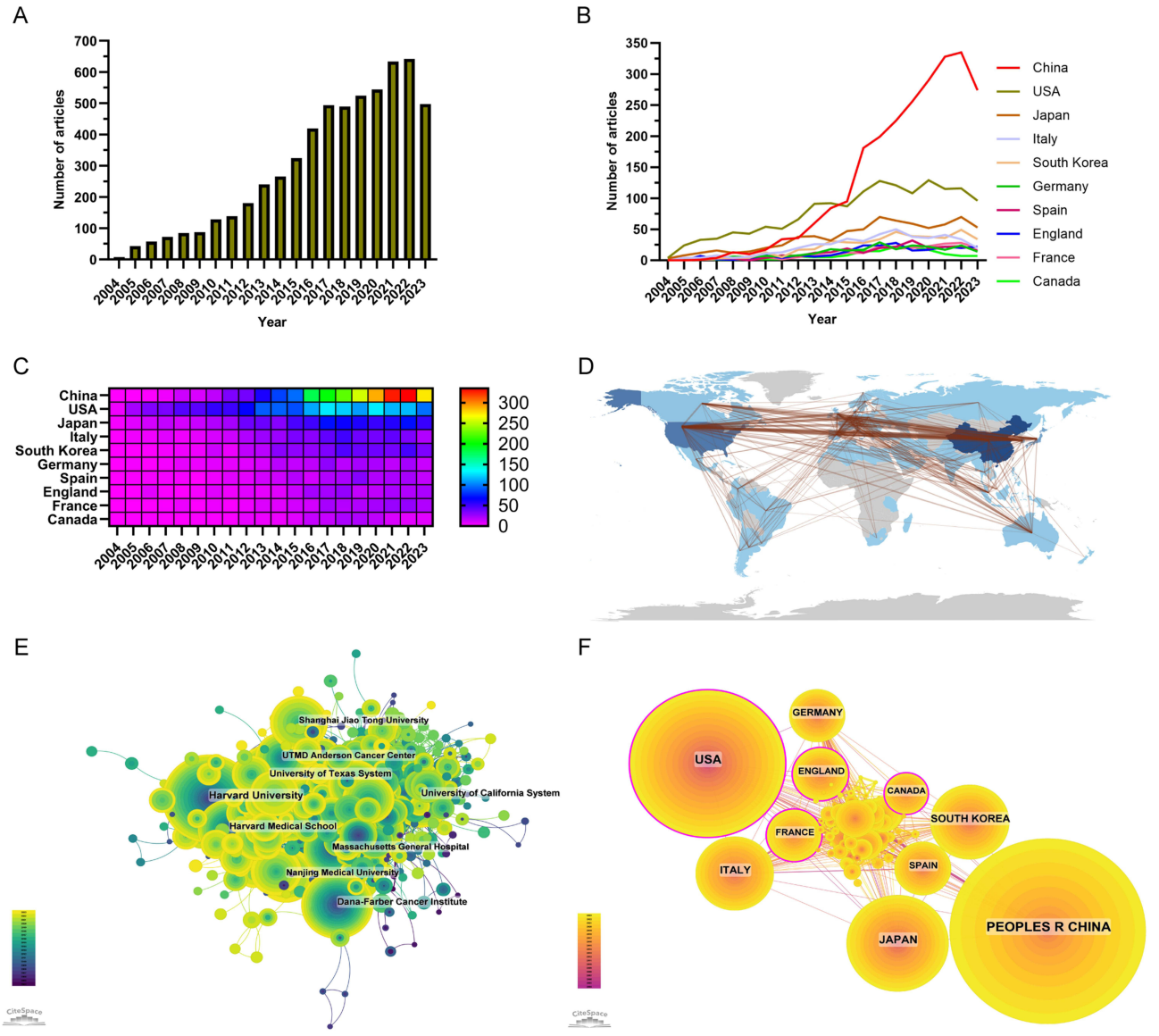

Figure 2 Comprehensive analysis of global EGFR inhibitor resistance research: Trends,Collaborations, and Leading Contributors (2004–2023). (**A**) The annual number of publications on EGFR inhibitor resistance from January 1, 2004 to December 31, 2023. (**B** and **C**) Line chart (**B**) and heatmap (**C**) of the annual publication volume of the top 10 countries in the past two decades. (**D**)World map of country cooperation. (**E** and **F**) CiteSpace network of countries or regions (**E**) and institutions (**F**) associated with EGFR inhibitor resistance from NSCLC based on the collaboration analysis.

publications gradually increased, suggesting that as the use of targeted drugs increased, this field gradually entered the researchers' view. After 2016, the number of publications rapidly increased and peaked in 2022, indicating that after 2016, with the use of third-generation EGFR-TKIs, this area received widespread attention.

Countries and Institutions

Research on resistance to EGFR-TKIs treatment has been conducted in 81 countries and regions. The annual publication volume of the top 10 countries over the past decade is displayed here, with the top 5 countries in this field being China, the United States, Japan, Italy, and South Korea (Figure 2B and 2C). Among them, China's publication volume accounts for 41.46% of the total, far exceeding that of other countries.

Among the top ten countries/regions in terms of the number of publications, the United States has the highest citation count at 139,554 (Table 1), far exceeding all other countries/regions. Its citation/publication ratio (90.09) ranks fourth among all countries/regions. China, with the highest number of publications (2432), ranks second in terms of citation count (69,389), but its citation/publication ratio (28.53) is relatively low, indicating that the overall quality of its published papers is generally lower.

We found that the collaboration between China and the United States, the two countries with the highest output, is close (Figure 2D). Globally, the United States has close collaborations with countries like Italy and the United Kingdom, while China has closer collaborations with Japan, Spain, and South Korea (Figure 2E). China's large volume of publications and high citation frequency indicate its leading position in this domain. In recent years, the rapid increase in the number of publications from countries like South Korea and Japan may be related to their collaboration with China. 4792 institutions have systematically published articles on resistance after EGFR treatment. Among the top ten institutions by publication volume, 7 are from the United States and 3 are from China (Table 2, Figure 2F). Harvard University has published the most documents (347 papers, 62,449 citations, 179.97 citations per paper). Harvard Medical

Table 1 The Top 10 Productive Countries Related to EGFR Inhibitor Resistance from NSCLC

Rank	Country/region	Article counts	centrality	Percentage (%)	Citation	Citation per publication
1	China	2432	0.02	41.46	69,389	28.53
2	USA	1549	0.15	26.41	139,554	90.09
3	Japan	741	0.07	12.63	38,950	52.56
4	Italy	451	0.06	7.69	26,440	58.63
5	South korea	429	0.09	7.31	32,753	76.35
6	Germany	249	0.06	4.24	18,930	76.02
7	Spain	241	0.09	4.11	21,812	90.51
8	England	234	0.20	3.99	29,440	125.81
9	France	222	0.19	3.78	18,051	81.31
10	Canada	149	0.13	2.54	14,691	98.60

Table 2 The Top 10 Institutions Published Literature Related to EGFR Inhibitor Resistance from NSCLC

Rank	Institution	Country	Number of studies	Total citations	Average citation
1	Harvard University	USA	347	62,449	179.97
2	Harvard Medical SchoolDana-Farber Cancer Institute	USA	204	34,645	169.83
3	Harvard Medical School	USA	193	36,086	186.97
4	University of Texas System	USA	192	19,276	100.40
5	University of California System	USA	187	17,174	91.84
6	Massachusetts General Hospital	USA	149	35,281	236.79
7	UTMD Anderson Cancer Center	USA	145	14,965	103.21
8	Nanjing Medical University	China	132	2593	19.64
9	Shanghai Jiao Tong University	China	130	3693	28.41
10	Chinese Academy of Medical Sciences Peking Union Medical College	China	128	3478	27.17

School Dana-Farber Cancer Institute ranks second (204 papers, 34,645 citations, 169.83 citations per paper), and Harvard Medical School ranks third (193 papers, 36,086 citations, 186.97 citations per paper). Further analysis reveals that domestic institutions tend to collaborate more with units within their own country, hence we call for strengthening cooperation between domestic and international institutions to break down academic barriers.

Journal

The top 10 most productive and cited journals were identified and showed using a density map (Table 3, Figure 3A). "Lung Cancer" is the journal with the most published papers in this field, with 265 articles accounting for 4.52%. It is followed by "Clinical Cancer Research" with 166 articles (2.83%), "Frontiers in Oncology" with 158 articles (2.69%), and 'Oncotarget' with 157 articles (2.68%). Among the top ten most productive journals, 'Clinical Cancer Research' has the highest impact factor of 11.5. Furthermore, 90% of these journals are classified in the Q1 or Q2 quartile, indicating their high quality and influence in the field. The influence of a journal is determined by how often it is co-cited, indicating whether the journal has been recognized in academia.

The journal with the highest number of co-citations is "Clinical Cancer Research" (4797 times), followed by "The New England Journal of Medicine" (NEJM) with 4604 times and "Journal of Clinical Oncology" with 4397 times. Among the top 10 journals with the most co-citations, NEJM has 4604 citations, and its impact factor is the highest among the top 10 journals, at 158.5. In the set of journals with the most co-citations, all journals are in the Q1/Q2 quartile, indicating their high relevance and quality in the field (Table 4, Figure 3B).

The distribution of topics in academic publications is displayed through a dual-map overlay (Figure 3C). The colored trajectories represent citation relationships, with citing journals on the left and cited journals on the right. Based on the display results, we identified two main colored citation paths: research published in journals in the molecular/biology/immunology field is primarily cited by research published in the molecular/biology/genetics field, and research published in the medicine/medical/clinical field is mainly cited by research published in the molecular/biology/genetics field.

Authors and Co-Citing Authors

Among all authors who have published on resistance after EGFR treatment, Table 5 lists the top 10 authors by the number of publications. The top 10 authors together have published 535 papers, accounting for 9.12% of all papers in this area. Park, Keunchil has published the most research papers, with 62 publications, followed by Rosell, Rafael (61 papers) and Wu, Yi-Long (54 papers). Further analysis reveals that among the top 10 ranked authors, 4 are from South Korea, 3 from China, 2 from Japan, and 1 from Spain. The VOSviewer tool visually represented the network among authors, highlighting the formation of core author groups across different institutions/countries, indicating a propensity for collaboration within these groups (Figure 3D).

Furthermore, A total of 179 authors have been cited more than 50 times, indicating their research has high prestige and impact (Figure 3E). The largest node is related to the author with the highest number of co-citations, including

Table 3 The Top 10 Productive Journals Related to EGFR Inhibitor Resistance from NSCLC

Rank	Journal	Article counts	Percentage (5866)	IF	Quartile in category
1	Lung cancer	265	4.52	5.3	Q2
2	Clinical cancer research	166	2.83	11.5	Q1
3	Frontiers in oncology	158	2.69	4.7	Q2
4	Oncotarget	157	2.68	5.2	Q2
5	Cancers	143	2.44	5.2	Q2
6	Journal of thoracic oncology	135	2.30	20.4	Q1
7	Clinical lung cancer	133	2.27	3.6	Q2
8	Thoracic cancer	100	1.70	2.9	Q3
9	Translational lung cancer research	93	1.59	4.0	Q2
10	Oncotargets and therapy	88	1.50	4.0	Q2

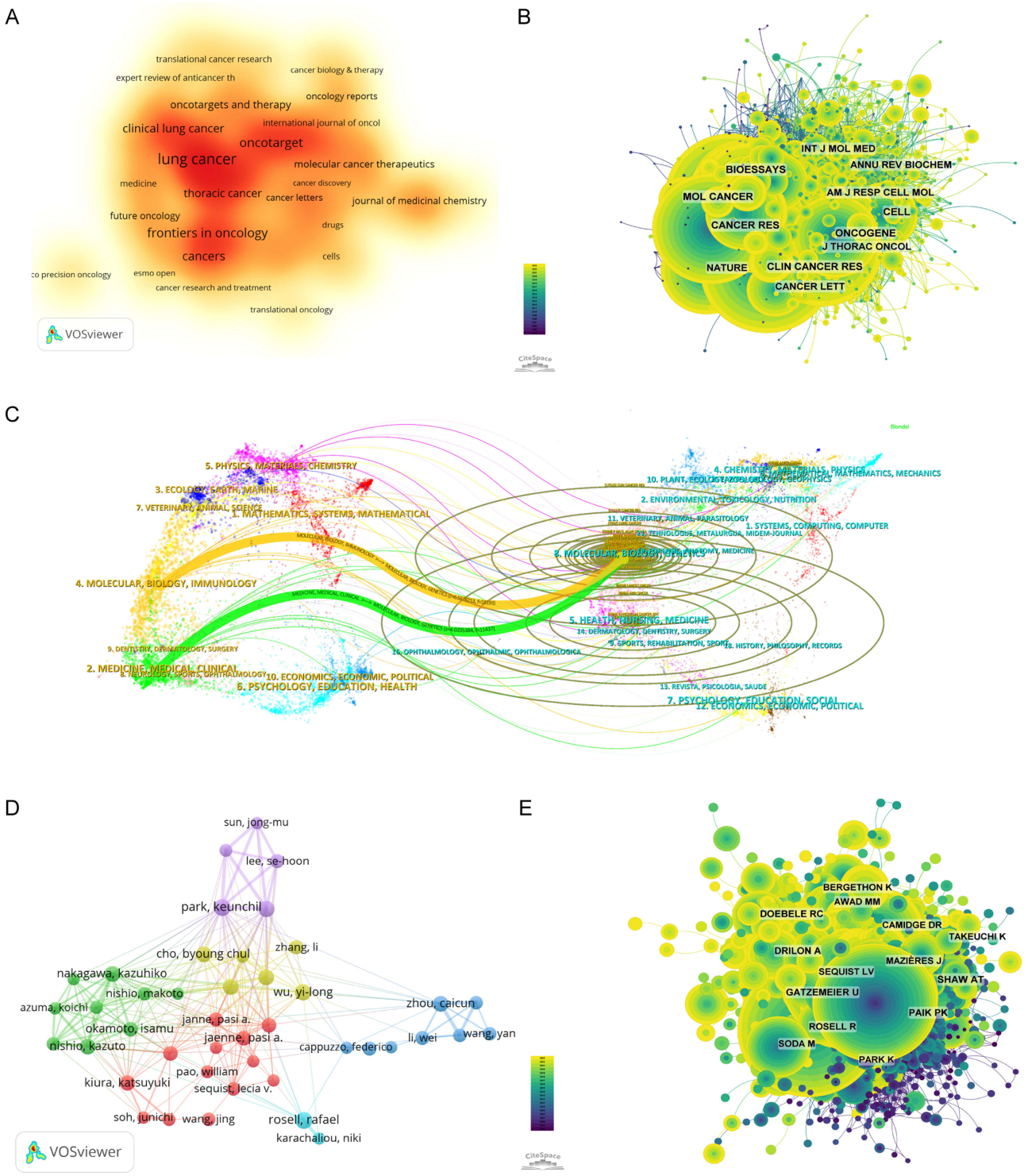

Figure 3 Exploring the landscape of EGFR inhibitor resistance in NSCLC: Publication Density, Journal Networks, and Author Collaborations. (**A**) Density map of magazine issuance in the field of EGFR inhibitor resistance from NSCLC. (**B**) Network map showing the co-cited journals in regard to EGFR inhibitor resistance from NSCLC. (**C**) The dual-map overlay of journals related to EGFR inhibitor resistance from NSCLC. The colored tracks indicate citation links, with citing journals on the left and cited journals on the right. (**D**) Author's collaborative web chart showing the authors with the most publications and their cooperation related to EGFR inhibitor resistance from NSCLC. (**E**) Author co-citation network map illustrating the top 10 most co-cited authors.

SEQUIST LV (2031 citations), MOK TS (1834 citations), and PAO W (1776 citations). Further analysis reveals that Rosell, Rafael, who ranks second in terms of publication volume and fourth in citation count, is one of the most representative authors in this field.

Table 4 The Top 10 Co-Cited Journals Associated with EGFR Inhibitor Resistance from NSCLC

Rank	Cited Journal	Co-Citation	IF (2020)	Quartile in category
1	CLIN CANCER RES	4797	11.5	Q1
2	NEW ENGL J MED	4604	158.5	Q1
3	J CLIN ONCOL	4397	45.4	Q1
4	J THORAC ONCOL	3734	20.4	Q1
5	CANCER RES	3732	11.2	Q1
6	LUNG CANCER	3317	5.3	Q2
7	LANCET ONCOL	3146	51.1	Q1
8	ANN ONCOL	2860	50.5	Q1
9	P NATL ACAD SCI USA	2805	11.1	Q1
10	SCIENCE	2708	56.9	Q1

Table 5 Top 10 Most Prolific and Co-Cited Authors in the Field of EGFR Inhibitor Resistance from NSCLC

Rank	Author	Count	Location	Rank	Co-cited author	Citation
1	Park, Keunchil	62	South Korea	1	SEQUIST LV	2031
2	Rosell, Rafael	61	Spain	2	MOK TS	1834
3	Wu, Yi-Long	54	China	3	PAO W	1776
4	Ahn, Myung-Ju	53	South Korea	4	ROSELL R	1614
5	Kim, Dong-Wan	52	South Korea	5	ENGELMAN JA	1502
6	Nishio, Kazuto	52	Japan	6	LYNCH TJ	1449
7	Yang, James Chih-hsin	52	China	7	KOBAYASHI S	1328
8	Zhou, Cai-Cun	51	China	8	PAEZ JG	1284
9	Cho, Byoung Chul	49	South Korea	9	YU HA	1278
10	Nakagawa, Kazuhiko	49	Japan	10	MITSUDOMI T	1158

Co-Citation of References

Using a one-year time slice from 2004 to 2023, the co-citation reference network comprises 2125 nodes and 12,624 links (Figure 4A). According to the top 10 articles by co-citation count (Table 6),[12] the article titled "Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer" published in the NEJM (IF=158.5) is the most co-cited reference, with Jean-Charles Soria as the first author. Osimertinib is an orally administered third-generation EGFR-TKI that selectively inhibits both EGFR-TKI sensitizing mutations and the EGFR T790M resistance mutation. The mPFS with Osimertinib was significantly longer than with standard EGFR-TKIs (18.9 months vs 10.2 months; hazard ratio for disease progression or death, 0.46; 95% confidence interval, 0.37 to 0.57; P<0.001), indicating that Osimertinib as a first-line treatment for EGFR mutation-positive advanced NSCLC has superior efficacy to standard EGFR-TKIs, with similar safety and a lower rate of serious adverse events. This article established the significant therapeutic position of third-generation EGFR-TKI as a continuation treatment after resistance to first-generation EGFR-TKI and as a breakthrough in the treatment of resistance with third-generation EGFR-TKI, leading the trend in scientific research.

Through co-citation reference clustering and temporal clustering analysis (Figure 4B), we observed the evolution of research hotspots and trends within the field. Initially, the focus was predominantly on Gefitinib (cluster0) and Vandetanib (cluster9), which played significant roles in the early application of EGFR-TKI therapy. As research progressed, mid-term hotspots shifted towards Osimertinib (cluster1), Crizotinib (cluster3), and HGF (cluster8), indicating that with a deeper understanding of targets such as EGFR mutations and ALK fusion genes, therapeutic strategies and research focuses evolved accordingly.

In recent years, as research has deepened, topics such as Osimertinib Resistance (cluster2), Afatinib (cluster4), Liquid Biopsy (cluster5), MET Amplification (cluster6), Immunotherapy (cluster7), Mobocertinib (cluster10), TP53 (cluster11),

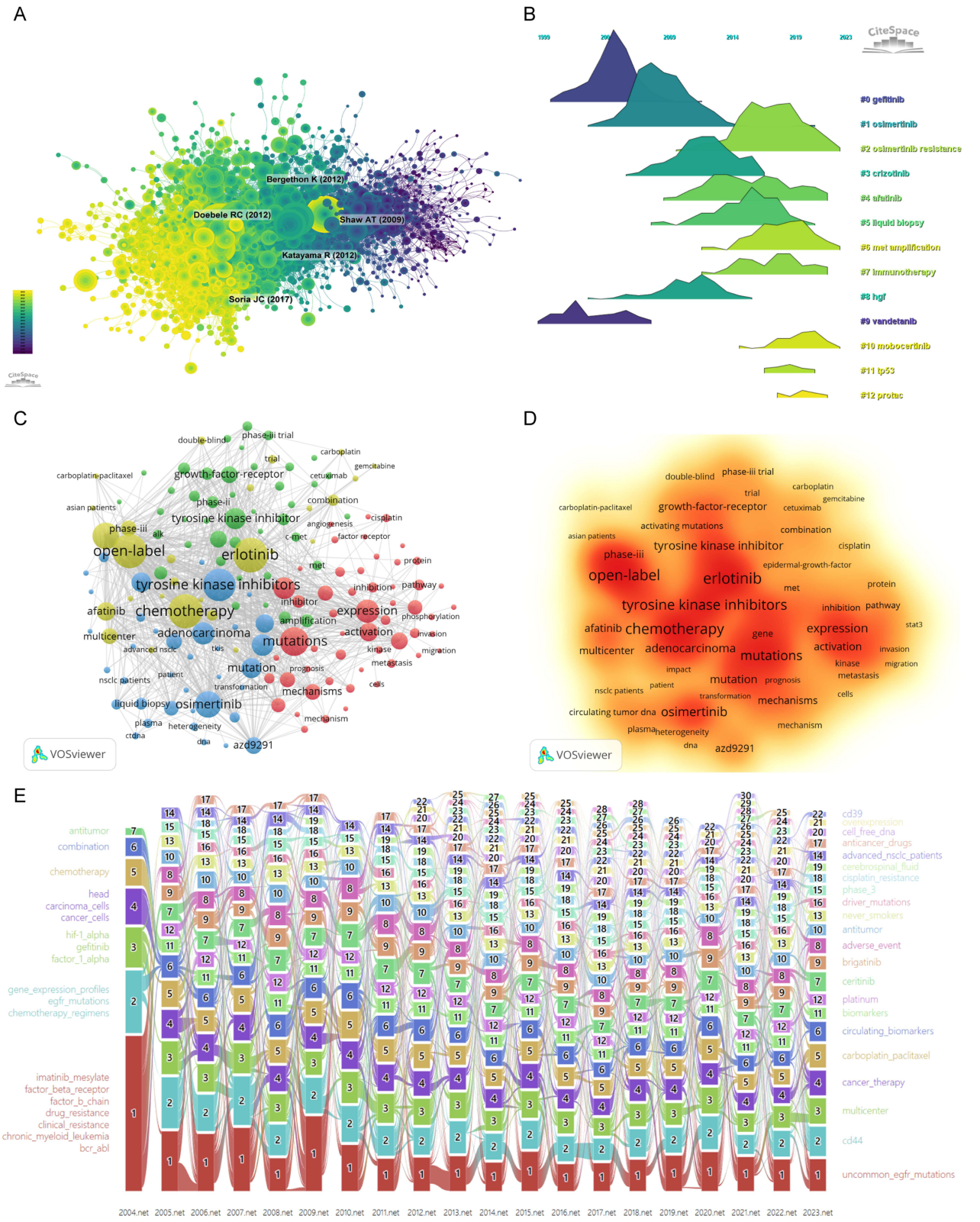

Figure 4 Evolution and impact in research: Analyzing Co-cited Literature, Keywords, and Trends in Scientific Publications (2004–2023).) (**A**) Co-cited literature network map. (**B**) Co-cited literature volcano chart based on the time from 2004 to 2023. (**C**) Network diagram depicting the high-frequency keyword. (**D**) Keyword Density Map. (**E**) Keywords: 2004–2023 alluvial diagram. X-axis: Time slices. Y-axis: Module count. Numbering: The order of modules on each time slice, sorted by the number of nodes.

Table 6 The Top 10 Centralities of Co-Cited References Related to EGFR Inhibitor Resistance from NSCLC

Rank	Title	Journal IF (2021)	Author(s)	Total citations
1	Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer.[12]	NEW ENGLAND JOURNAL OF MEDICINE (IF=158.5)	Soria JC	809
2	Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer.[23]	NEW ENGLAND JOURNAL OF MEDICINE (IF=158.5)	Mok TS	604
3	AZD9291 in EGFR Inhibitor-Resistant Non-Small-Cell Lung Cancer.[24]	NEW ENGLAND JOURNAL OF MEDICINE (IF=158.5)	Janne, P. A.	526
4	Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised Phase 3 trial.[25]	LANCET ONCOLOGY (IF=51.1)	Rosell R	482
5	Analysis of Tumor Specimens at the Time of Acquired Resistance to EGFR-TKI Therapy in 155 Patients with EGFR-Mutant Lung Cancers.[26]	CLINICAL CANCER RESEARCH (IF=11.5)	Yu HA	438
6	Cancer Statistics, 2021.[27]	CA-A CANCER JOURNAL FOR CLINICIANS (IF=254.7)	Siegel RL	430
7	Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC.[28]	NEW ENGLAND JOURNAL OF MEDICINE (IF=158.5)	Ramalingam SS	387
8	Acquired EGFR C797S mutation mediates resistance to AZD9291 in non-small cell lung cancer harboring EGFR T790M.[29]	NATURE MEDICINE (IF=82.9)	Thress KS	385
9	AZD9291, an Irreversible EGFR TKI, Overcomes T790M-Mediated Resistance to EGFR Inhibitors in Lung Cancer.[30]	CANCER DISCOVERY (IF=29.1)	Cross DAE	382
10	Gefitinib or Carboplatin-Paclitaxel in Pulmonary Adenocarcinoma.[31]	NEW ENGLAND JOURNAL OF MEDICINE (IF=158.5)	Mok TS	355

and PROTAC (cluster12) have emerged as hot topics and trends in the field. These hotspots not only reflect in-depth Discussions on resistance mechanisms to known targets but also showcase the potential applications of new technologies (such as liquid biopsy), new therapies (such as immunotherapy and PROTAC technology), and the discovery and research of new targets (such as MET amplification, TP53 mutations). Furthermore, the study of Osimertinib resistance highlights the new challenge of overcoming resistance with the continuous advancement of therapeutic drugs. Overall, these clustering analysis results hint at the dynamic evolution of lung cancer treatment research and potential future directions, including further exploration of resistance mechanisms, development of new targets, and application of new therapies.

Keyword Analysis

By analyzing keywords, we can swiftly grasp the current state and development trends within a field. After removing irrelevant keywords, we constructed a network of 159 keywords that appeared at least 26 times, resulting in four distinct clusters (Table 7, Figure 4C and 4D). The first group (red) contains 53 keywords, including “Expression”, “Mutations”, “Receptor”, “Mechanisms”, “Potent”, “Kinase”, “inhibition”, “sensitivity”, “Protein”, “EMT”, “Migration”, “Prognosis”, “Statistics”, “Mutant” reflecting a focus on molecular mechanisms and gene expression in cancer research. The second group (green) consists of 42 keywords related to targeted therapy, such as “C-Met”, “Tyrosine Kinase Inhibitor”, “Never-

Table 7 The Top 10 Most Frequent and Centralized Keywords Related to EGFR Inhibitor Resistance from NSCLC

Rank	Keyword	Counts	Rank	Keyword	Counts
1	Erlotinib	1218	11	Lung cancer	570
2	Open-label	1185	12	Tyrosine kinase inhibitor	550
3	Chemotherapy	1175	13	Mutation	502
4	Tyrosine kinase inhibitors	1072	14	EGFR mutation	472
5	Mutations	889	15	Activation	435
6	1st-line treatment	777	16	Afatinib	429
7	Osimertinib	773	17	Survival	428
8	Expression	631	18	AZD9291	371
9	Adenocarcinoma	594	19	Growth	371
10	Therapy	572	20	Targeted therapy	364

Smokers", "KRAS", "HER2", "Antitumor-Activity", "Cetuximab", "Gene Copy Number", "T790M Mutations", "Copy Number", "ALK", "BRAF", "Crizotinib" focusing on research into targeted treatments and specific gene mutations. The third group (blue) includes 37 keywords like "Osimertinib", "Therapy", "AZD9291", "Plasma", "Liquid Biopsy", "Heterogeneity", "ctDNA", "Brain Metastases", "Case Report", "Resistance Mechanisms", "Biomarker", "Survival", "Evolution" mainly focusing on research into new drugs, biomarkers, and resistance mechanisms. The fourth group (yellow) contains 27 keywords, such as "Chemotherapy", "Open-Label", "Erlotinib", "Afatinib", "Multicenter", "Nivolumab", "Docetaxel", "Efficacy", "Phase-III", "Immunotherapy", "Trial", "Double-blind", "Combination" focusing on clinical trials, drug efficacy, and treatment strategies. This analysis indicates that the area of EGFR-TKI resistance research is evolving towards more refined exploration of molecular mechanisms, optimization of targeted treatments, strategies to overcome resistance mechanisms, and the application of new biomarkers.

Emerging Trends and New Developments

Interconnected keywords can form specific research modules, which may continuously diverge or converge over time, leading to the emergence of new research trends. In the past two decades, some keywords have demonstrated lasting influence, becoming stable directions in the field of research, while others have emerged as new hotspots, and some have gradually faded from the research landscape. Data from 2004 to 2023 reveals that the keywords contained in Module 1 have formed the largest research tributary (marked in red), indicating that this module may be the most enduring research module (Figure 4E). This suggests that the most common direction in EGFR-TKI research is focused on studies of uncommon EGFR mutations. The use of platinum-based double chemotherapy following EGFR-TKI treatment is a classical regimen, particularly suitable for patients who develop EGFR amplification or secondary EGFR mutations, leading to resistance after EGFR-TKI therapy. Currently, authoritative guidelines both domestically and internationally, such as NCCN and CSCO, recommend a platinum-containing chemotherapy regimen for patients resistant to EGFR-TKI.[32] This treatment regimen has a mPFS of approximately 5 months.[33,34] Moreover, for patients resistant to EGFR-TKI, ongoing clinical studies are exploring the combination of other mechanisms for treatment. These studies include quadruple therapy regimens based on chemotherapy, such as chemotherapy combined with PD-1 and anti-angiogenesis drugs, chemotherapy combined with EGFR-cMET dual antibody and third-generation EGFR-TKI, as well as triple therapy regimens, like chemotherapy combined with PD-1 and third-generation EGFR-TKI. The progress of these studies may provide new directions and insights for finding effective strategies to treat resistance to EGFR-TKI.

Additionally, we have mapped out all keywords from the top 6 modules of 2023. Module 1, named "Uncommon EGFR Mutation" encompasses 13 keywords such as "Positive Solid Tumors", "Antibody−Drug Conjugates", "Tyrosine Kinase Inhibitor Resistance" (Figure 5A). This indicates that research into specific EGFR mutations and their treatment methods remains a focal area for NSCLC, especially in seeking new strategies to overcome resistance. Module 2, named "CD44" includes 16 keywords like "Cancer Stem Cells", "DNA Methylation", "Apoptosis" (Figure 5B), suggesting an interest in targeting cancer stem cells as a treatment strategy, given their crucial role in tumor formation, recurrence, and resistance. Module 3, named "Multicenter" gathers 18 keywords such as "Afatinib", "Osimertinib", "Chemotherapy" (Figure 5C), indicating that multicenter studies are focusing on the effects of various cancer treatments, including targeted therapies for specific molecular markers. Module 4, named "Cancer Therapy" collects 16 keywords including "Pyrimidine Derivatives", "C797S Resistance", "Circular RNA" (Figure 5D), reflecting the exploration of new methods in cancer treatment, particularly in overcoming known resistance mechanisms. Module 5, named "Carboplatin Paclitaxel" includes 6 keywords such as "Clinical Impact", "TP53 Mutations", "Circulating Tumor DNA" (Figure 5E), showing interest in the effects and biomarkers of the classic chemotherapy combination of carboplatin and paclitaxel under specific genetic backgrounds. Module 6, named "Circulating Biomarkers" encompasses 8 keywords including "Antibody−Drug Conjugate", "Exon 20 Insertion", "Leptomeningeal Metastases" (Figure 5F), highlighting the potential value of circulating biomarkers in cancer diagnosis, treatment monitoring, and prognosis assessment.

Citation burst refers to a significant increase in the number of citations of a publication within a certain period. In this analysis, among the 50 most reliable citation bursts from 2004 to 2023, 48 were published in the last 20 years (Figure 6), highlighting the active and ongoing importance of research in the field of EGFR treatment resistance during this period.

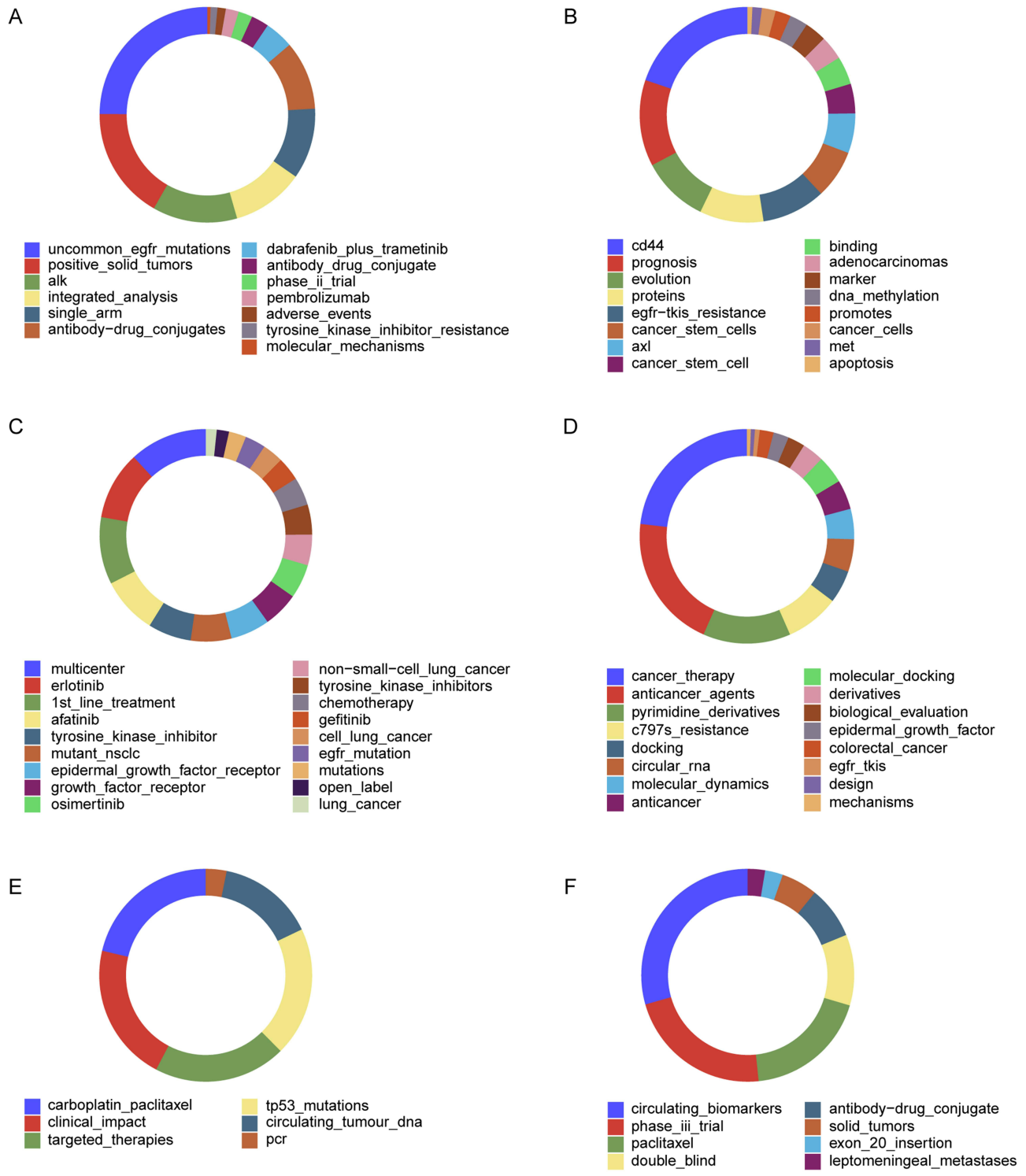

Figure 5 Keywords of the Top 6 Modules of 2023. (**A-F**): Module 1–6.

The fact that 8 papers are currently at their citation peak indicates that certain aspects of EGFR resistance research remain hot topics, suggesting that this area is likely to continue receiving significant attention in the future.

Keyword burst analysis reveals themes that are rapidly gaining attention within a research field. In this case, the 50 most prominent burst keywords represent the current hotspots and potential future directions of research in the EGFR treatment resistance (Figure 7). For example, studies on "Osimertinib Resistance" and "Exon 14 Mutation" show that

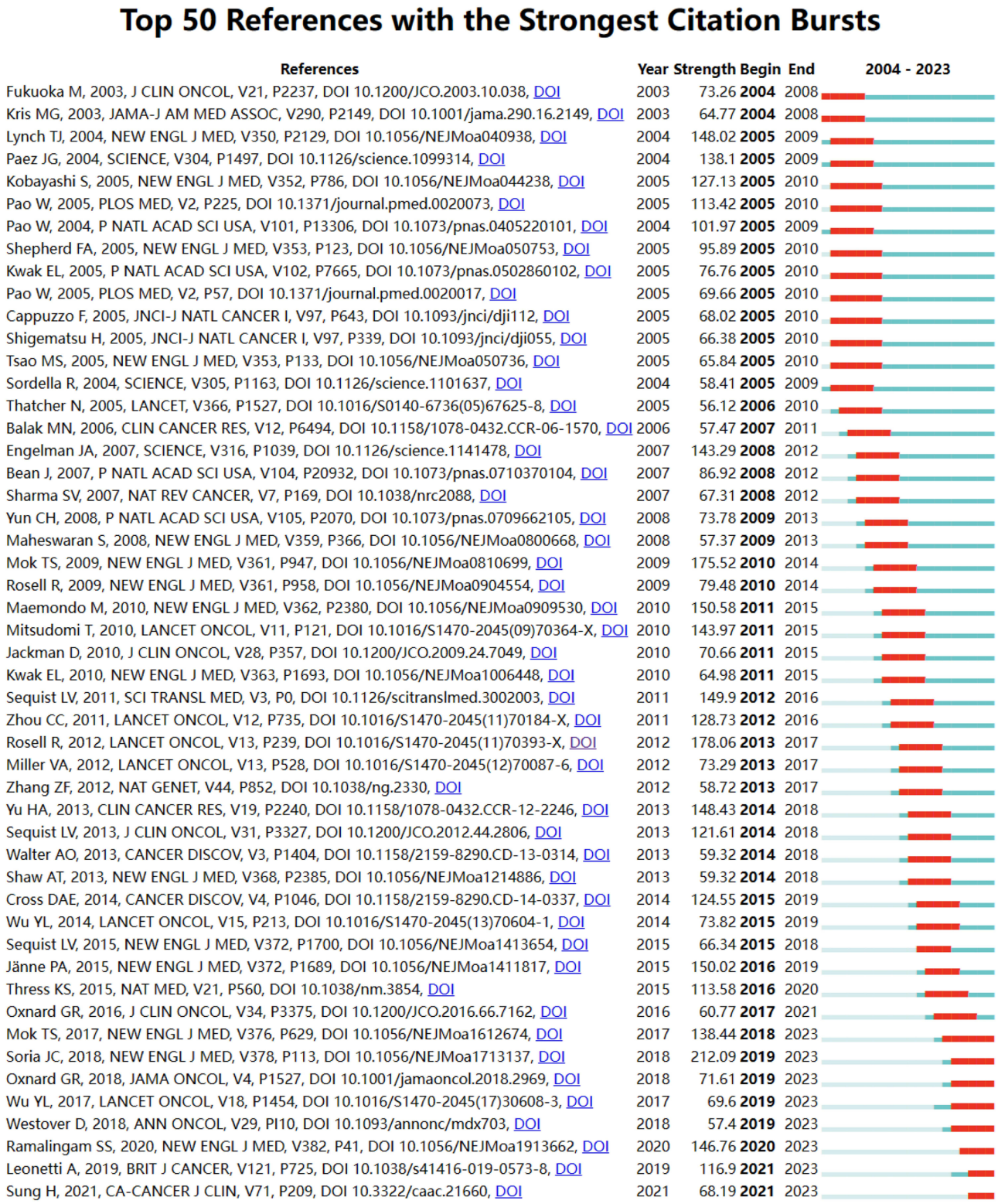

Figure 6 References burst analysis from 2004 to 2023. Blue lines indicate the timeline, and the red sections on the blue timeline represent the start year, the end year, and the burst duration.

researchers are exploring mechanisms and solutions for resistance caused by specific genetic mutations. "Tumor Microenvironment" and "Immune Checkpoint Inhibitors" emphasize the potential of immunotherapy in overcoming resistance, particularly how the tumor microenvironment can be modulated to enhance therapeutic effectiveness. The

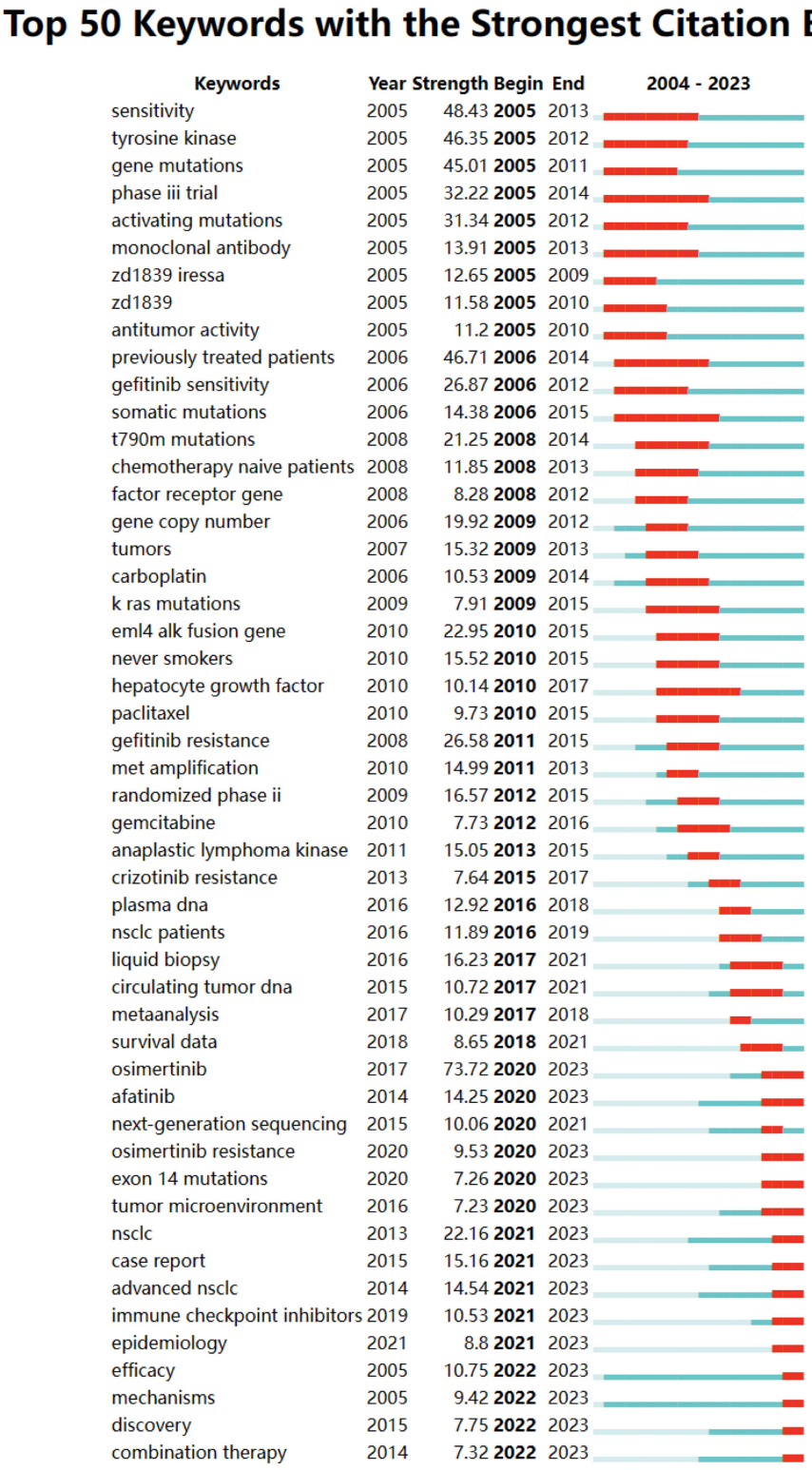

Figure 7 Keywords burst analysis from 2004 to 2023. Blue lines indicate the timeline, and the red sections on the blue timeline represent the start year, the end year, and the burst duration.

emergence of "Epidemiology" points to an interest in researching the incidence, distribution, and influencing factors of resistance. Discussions on "Combination therapy" indicate that researchers are seeking to overcome resistance by combining different types of treatments, such as effectively integrating chemotherapy, targeted therapy, and immunotherapy.

Discussion

This study outlines the trends and focuses of resistance development in NSCLC patients after EGFR-TKI treatment, highlighting three main directions of interest:

On the Diagnostic Level

For advanced EGFR-mutant NSCLC patients, re-biopsy after treatment progression to assess resistance mechanisms and potential histological transformation is crucial for formulating subsequent treatment plans. The acquisition of tissue samples is particularly important, as they can be used to identify molecular variants associated with resistance and confirm any histological transformation.[35] When tissue samples are not obtainable, ctDNA (Circulating Tumor DNA) testing in blood serves as a viable alternative, although its limited sensitivity may lead to false-negative results.[36] Moreover, compared to traditional single-gene testing, Next-Generation Sequencing (NGS) technology has the ability to detect a broader range of genes and loci at both DNA and RNA levels, offering more possibilities for uncovering resistance mechanisms and guiding further treatment.

Finally, with ongoing technological innovations, new methods such as single-cell sequencing will enhance the sensitivity and accuracy of detection, aiding in a better understanding of tumor heterogeneity and providing more precise treatment options for patients.

On the Mechanistic Level

Regarding the mechanisms of acquired resistance to the most commonly used third-generation EGFR-TKI, Osimertinib, they can primarily be classified into five categories: (1) MET pathway-related resistance. MET gene amplification is the most common, activating alternative signaling pathways to bypass EGFR inhibition.[37] Reports indicate that the proportion of MET gene amplification after first-line and second-line treatment resistance to Osimertinib is approximately 7% to 17% and 5% to 50%, respectively.[38,39] Overexpression of the MET protein is also a possible mechanism leading to resistance, with 29% of Osimertinib-resistant patients exhibiting high levels of MET protein overexpression in the SAVANNAH study.[40,41] (2) EGFR Pathway-Dependent Resistance. The C797X mutation is one of the significant mechanisms of resistance to Osimertinib. Osimertinib primarily works by forming a covalent bond with the C797 residue in the ATP-binding domain, exerting an irreversible inhibitory effect on sensitive EGFR mutations and the T790M mutation. Therefore, the C797 residue is a susceptible site for the development of Osimertinib resistance.[30] In the FLAURA study, after first-line resistance to Osimertinib, the occurrence rates of L718Q and S768I mutations were 2% and 1%, respectively;[42] in the AURA3 study, after second-line resistance to Osimertinib, the occurrence rate of the L792X mutation was 3%, and the occurrence rates of G796X, L718Q, and exon 20 insertion mutations were 1% each.[43] Other reported rare EGFR mutation sites include L798I, L844V, L692V, E709K, V802I/F, V834L, E758D, F712L, T854A, V843I, V726M, G824D, L747P.[13] In relevant studies, the occurrence rates of EGFR amplification after first-line and second-line resistance to Osimertinib were approximately 4% to 12%, and 6% to 15%, respectively.[38,44,45] (3) Histological Type Transformation. The occurrence rate is about 2% to 15%.[46] Previous research has shown that mutations in the RB1 and TP53 genes are associated with the transformation of EGFR-mutant lung adenocarcinoma to SCLC.[47] (4) Other oncogene abnormalities related to resistance to third-generation EGFR-TKIs include: 1) Driver gene abnormalities such as HER2, KRAS, BRAF, RET, ALK, or NTRK;[42,43,48–53] 2) PIK3CA, FGFR, and cell cycle gene disorder.[54–56] (5) Currently, the resistance mechanisms remain unclear for 40% of patients after Osimertinib treatment, necessitating further investigation.[42,43]

The complexity of EGFR-TKI resistance mechanisms arises from a multitude of molecular and cellular interactions, collectively leading to treatment failure and disease progression. To thoroughly address or effectively prevent resistance issues, a deep understanding of the molecular basis of resistance is required. This includes, but is not limited to, gene mutations, activation of signaling pathways, and changes in the intracellular and extracellular environment. The key lies in the integrated application of multidisciplinary approaches, encompassing molecular biology, genetics, pharmacology, and clinical medicine, to unveil the complete picture and inherent mechanisms of resistance. Moreover, early monitoring and identification of resistance development are crucial for preventing resistance, allowing for the early detection of treatment failure signs and timely adjustment of treatment plans.

On the Treatment Level

After patients develop resistance to EGFR-TKIs, subsequent treatment strategies should be formulated based on a comprehensive consideration of the resistance progression pattern, mechanisms of resistance, evidence-based medicine, clinical availability of drugs, and the patient's physical and financial situation.

Firstly, combination therapy integrates existing means. For patients with oligoprogressive disease, it is recommended to combine EGFR-TKI with local treatments (such as radiation therapy, surgery, ablation, etc).[57–59] For those with extensive progression, a more diverse consideration of chemotherapy drugs, targeted agents, anti-angiogenic drugs, and immunotherapies is necessary to effectively strategize treatment.[33,34,60,61]

After patients develop resistance to EGFR-TKIs, subsequent treatment strategies should be formulated based on a comprehensive consideration of the resistance progression pattern, mechanisms of resistance, evidence-based medicine, clinical availability of drugs, and the patient's physical situation.

First-generation EGFR-TKIs can reversibly bind to the ATP-binding pocket of EGFR, selectively targeting exon 19 deletions or the L858R mutation in exon 21. Second-generation TKIs were designed and developed to address T790M resistance, covalently binding to EGFR and irreversibly inhibiting ATP binding. Third-generation TKIs also have an irreversible mode of action but exhibit higher selectivity for the T790M mutation. In recent years, scientists have proposed various pharmacochemical strategies to treat NSCLC patients resistant to third-generation TKIs. Early results from clinical trials of fourth-generation drugs under development have shown encouraging initial outcomes (Figure 8).

This next generation of TKIs includes both allosteric and ATP-competitive EGFR inhibitors, based on different chemical structures. The development of mutant-selective allosteric inhibitors is a promising strategy to overcome resistance to FDA-approved TKIs. Unlike ATP-competitive TKIs, these inhibitors specifically bind to the allosteric pocket of EGFR, accessible only with specific mutations like L858R, L858R/T790M, and L861Q. These mutations destabilize the inactive state of EGFR, exposing the allosteric pocket and allowing inhibitor binding, which stabilizes the inactive conformation and prevents kinase activation.[62] Early allosteric inhibitor EAI001 showed promising mutant-selective activity.[63] Its structure binds the allosteric pocket in a unique way, stabilizing the inactive form of EGFR. Further modifications led to EAI045, with higher potency and selectivity, but both EAI001 and EAI045 are ineffective as

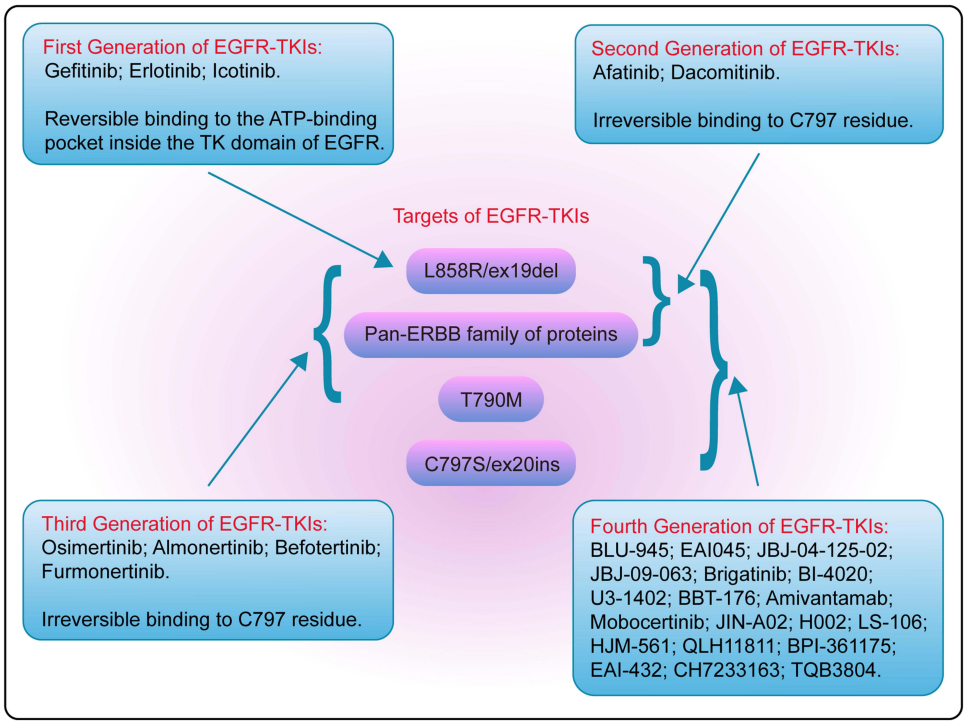

Figure 8 Names, indications and rationale of four Generations of EGFR-TKIs.

single agents due to EGFR dimerization. Combining EAI045 with cetuximab, which disrupts EGFR dimers, showed potential but caused side effects due to non-mutant specificity.[64] Further structural modifications led to more effective allosteric inhibitors like JBJ-04-125-02 and JBJ-09-063, used as monotherapy or in combination with Osimertinib, these inhibitors exhibit improved potency and selectivity. However, they have also faced challenges in patient-derived models due to EGFR dimer levels and resistance mutations affecting the allosteric pocket.

Secondly, regarding ATP-Competitive Reversible TKIs, these compounds share an anilinopyrimidine scaffold, essential for interacting with the ATP-binding pocket. Brigatinib, discovered in 2016, is a notable TKI designed to inhibit ALK, ROS1, and FLT3.[65,66] It also shows promise against triple-mutant EGFR L858R/T790M/C797S, especially when combined with cetuximab.[67–69] Brigatinib selectively binds to the ATP-binding pocket, establishing a bidentate hydrogen bond with the backbone amide of M793, a key feature for effective inhibition.[70] In a clinical retrospective study, 60% complete response and 100% disease control rate were achieved among 5 NSCLC patients with EGFR-Del19 /T790M/C797S treated with the combination of Brigatinib and Cetuximab, which is significantly higher than the control group receiving cisplatin chemotherapy.[69] Various Brigatinib derivatives, including TQB3804, BPI-361175, HS-10375, and DAJH-1050766, have been approved to enter clinical trial stages, along with URP1444.[71,72]

Regarding N-(Pyridin-2-yl)pyrimidin-4-amine derivatives, BLU-945 showed high in vivo antitumor activity in resistant NSCLC models and enhanced efficacy when combined with Osimertinib. However, it is less effective against the ex19Del mutation and is being developed for first-line combination therapy.[73] CH7233163, another TKI with a N-(pyridin-2-yl)pyrimidin-4-amine scaffold, effectively inhibits EGFR triple mutants and shows high selectivity and low toxicity, making it a promising candidate to overcome resistance.[74]

Other promising fourth-generation TKIs in early clinical evaluation include BI-4020, a macrocyclic TKI with an aminobenzimidazole scaffold, which is highly selective against EGFR Del19/T790M/C797S and L858R/T790M/cis-C797S mutations. A 2019 study reported that BI-4020 induced strong regression in all 10 tumor models, with all mice showing good tolerance to this treatment.[75]

Finally, it is worth mentioning that Mobocertinib has filled a clinical treatment gap, bringing hope for survival to patients with advanced NSCLC with EGFR exon 20 insertion mutations. Globally, 114 patients who had previously received platinum-based chemotherapy were enrolled, achieving an overall response rate of 28%, with a median duration of response extended to 8 months. The median progression-free survival increased to 3 months, and the median overall survival improved to 20.2 months.[76] Additionally, Amivantamab (JNJ-61186372), a bispecific antibody targeting EGFR-MET, has been approved for patients with advanced NSCLC with EGFR exon 20 insertion mutations who have failed prior platinum-based chemotherapy. Besides targeting the resistant EGFR-20ins mutation, there are also reports of Amivantamab being used in cases with L858R/T790M/C797S triple mutations, where patients showed rapid and durable responses.[77]

Regarding to NSCLC treatment, there is a hopeful anticipation for more clinical trials in the future aimed at providing new treatment options for patients in dire need of help. Given the complexity of the human body and significant individual differences, future clinical trial designs must be more precise and scientific, ensuring a more thorough and comprehensive trial process. Simultaneously, the development of new drugs should focus on a holistic approach, exploring diverse therapeutic mechanisms to address the challenge of resistance. This should not only include innovations in targeted therapy and immunotherapy but also improvements to traditional chemotherapy drugs and the development of novel drug delivery systems to reduce side effects, enhance patient safety, and improve quality of life.

Conclusion

Although our study employed the principles of bibliometrics to conduct a comprehensive analysis of the resistance to EGFR-TKI treatment, revealing the research trends and hotspots in this field, we must also acknowledge some limitations in our research process. First, our literature collection was confined to the WoSCC database, which may introduce publication bias since some significant studies could be published in other databases or in non-English formats. Such restrictions might lead to a certain degree of inaccuracy in our analysis results. Moreover, bibliometric analysis itself lacks a universally accepted set of execution standards, which could inevitably introduce a degree of subjective judgment into the analysis process.

Despite these limitations, our study still offers valuable insights into resistance issue after EGFR-TKI treatment, helping to grasp the development trajectory and current hot topics in this domain. Future research could address these limitations by expanding the literature collection scope and using cross-verification methods across multiple databases. Additionally, introducing stricter analysis standards and methods could help reduce the impact of subjective bias, aiming for more comprehensive and accurate research outcomes. Furthermore, researchers are encouraged to adopt an open mindset when conducting bibliometric analyses, considering research findings from different areas and cultural backgrounds, thereby providing a richer and more diverse perspective for scientific research.

Abbreviations

TKIs, Tyrosine kinase inhibitors; NSCLC, Non-Small Cell Lung Cancer; EGFR, Epidermal Growth Factor Receptor; EGFR-TKIs, Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors; NCCN, National Comprehensive Cancer Network; mPFS, Median Progression-Free Survival; OS, Overall Survival; WoSCC, Web Of Science Core Collection; PD-1, Programmed Cell Death Protein 1; PD-L1, Programmed Cell Death 1 Ligand 1; ICIs, Immune Checkpoint Inhibitors; NGS, Next-Generation Sequencing; ctDNA, Circulating Tumor DNA; ADC, Antibody-Drug Conjugate; TROP2, Trophoblast Cell-Surface Antigen 2; RP2D, Recommended Phase 2 Dose; MTD, Maximum Tolerated Dose.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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