Treatment of advanced-stage non-small cell lung cancer: Current progress and a glimpse into the future (Review)

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Abstract. Before the twentieth century, patients with advanced lung cancer had limited treatment options and chemotherapy was the primary form of treatment, with an overall survival often <0.5 years. However, with advances in society and medical technology, the treatment approaches for advanced non-small cell lung cancer (NSCLC) have markedly changed. Traditional chemotherapy has been gradually replaced by targeted therapy and immunotherapy, leading to the emergence of various new therapeutic options that offer patients more personalized and precise care. This raises the question of what the future holds for the treatment of NSCLC. This review provides a comprehensive analysis of the latest breakthroughs in targeted therapies, immunotherapies, and drugs for antibody-drug conjugates (ADCs), highlights advances in multimodal combination therapy strategies, and explores the causes of resistance and the challenges that exist in overcoming it. In particular, this review provides unique insights into key directions for future research in NSCLC, such as personalised treatment strategies and biomarker exploration based on multi-omics data, aiming to provide new inspiration for clinical decision-making and research.

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Abbreviations: NSCLC, non-small-cell lung cancer; ICIs, immune checkpoint inhibitors; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; RET, rearranged during transfection; NTRK, neurotrophic tyrosine receptor kinase; EGFR, epidermal growth factor receptor; MET, mesenchymal-epithelial transition factor; BRAF, v-raf murine sarcoma viral oncogene homolog B1; KRAS G12C, kirsten rat sarcoma viral oncogene homolog G12C; CNS, central nervous system; ORR, objective response rate; ADCs, antibody-drug conjugates; mPFS, median progression-free survival; mOS, median overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; CTLA-4, cytotoxic t-lymphocyte-associated protein 4; CAR-T, chimeric antigen receptor T-cell; TILs, tumor-infiltrating lymphocytes; HLA-I, human leukocyte antigen class I; NLR, neutrophil-to-lymphocyte ratio; TME, tumor microenvironment; TMB, tumor mutational burden; TIGIT, T-cell immunoreceptor with Ig and ITIM domains

Key words: NSCLC, treatment, summarize, review, perspective

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1. Introduction

Diagnosis and treatment of advanced solid tumors, among which lung and breast cancers feature the most rapid development, have been greatly improved owing to the advances of modern oncology. Over the past two decades, the discovery of treatable driver mutations and the development of immune checkpoint inhibitors (ICIs) have led to various breakthroughs in treating non-small-cell lung cancer (NSCLC). One such breakthrough is the development of targeted therapies based on treatable driver mutations, while a second one is the employment of immunotherapies based on ICIs. Unlike anti-angiogenic therapeutic drugs that have their unique mechanisms of action and are widely used in clinical practice, vascular-targeted drugs still cannot be used as first- or second-line treatments alone. Vascular-targeted drugs are used in combination with other treatments for added benefit, thereby they are associated with a modest breakthrough. The next breakthrough in advanced lung cancer treatment could be the adoption of precise and multidisciplinary combination therapies.

Through a rigorous investigation and summary of current NSCLC treatments, the aim of the present study is to provide clinicians with a comprehensive reference on current and upcoming treatment options, focusing on some key mutations and promising emerging treatments, as well as providing an outlook on the future direction of lung cancer treatment.

2. Comprehensive management of NSCLC

Disease staging and incidence frequency of lung cancer are critical research topics, particularly because the current trends indicate a shift in demographics and disease management. Lung cancer staging is based on the TNM staging system, which classifies tumors according to their size (T), lymph node involvement (N) and distant metastasis (M). The newly published ninth edition of the TNM staging system for lung cancer is an important guide for the diagnosis, treatment and prognostic assessment of lung cancer (1). The major changes to the TNM staging system include further subdivision of stage N2 into N2a and N2b, and further subdivision of stage M1c into M1c1 and M1c2. These changes are intended to more accurately predict patient prognosis and guide treatment decisions. Current statistics indicate that stage I lung cancer (early stage, tumor is small and has not spread) accounts for ~48.6%, stage II (locally progressive) accounts for 12.2%, stage III (regionally advanced, extended to adjacent lymph nodes) accounts for 11.2%, while stage IV (advanced or has developed distant metastasis) accounts for 28% (2). Due to the lack of early symptoms of lung cancer, several patients at the time of their diagnosis are already in the advanced stage, resulting in a lost opportunity for surgery and poor overall prognosis (3).

Patients with lung cancer can have activating mutations that may drive tumor growth. These mutations can be identified through a range of molecular diagnostic techniques. These methods include traditional tissue biopsy-based approaches such as Sanger sequencing, fluorescence *in situ* hybridization, reverse-transcription quantitative PCR, immunohistochemistry, as well as more comprehensive next-generation sequencing (4). Additionally, liquid biopsy techniques, which analyze circulating tumor DNA or circulating tumor cells in the blood, provide a minimally invasive and repeatable option for patients unable to undergo tissue biopsy (5,6). Among these methods, PCR-based technologies such as the amplification refractory mutation system and digital PCR are frequently used to detect specific gene mutations due to their high sensitivity and specificity. Upon advances in technology, emerging methods such as exosome-based detection are also offering new perspectives for genetic testing in lung cancer. Physicians select the most appropriate testing method based on the specific condition of the patient, sample availability, testing sensitivity and specificity requirements, as well as economic considerations, to guide treatment strategies effectively (7).

In addition, with the continuous advancements in lung cancer treatment options, interdisciplinary collaboration has become increasingly important. Advanced lung cancer involves numerous complexities and patients often exhibit varying responses to different treatment options. By assembling a multidisciplinary team, including oncologists, radiologists, surgeons, pathologists and other healthcare professionals, not only can the accuracy of diagnosis be improved, but a more comprehensive perspective can be offered in the development of treatment strategies. This approach addresses the individual needs of patients more thoroughly; therefore, establishing an efficient multidisciplinary team is crucial for improving the survival rates and quality of life for patients with lung cancer (8,9).

3. Existing treatment paradigm for NSCLC

Over the past two decades, breakthroughs in the treatment of NSCLC have included the widespread adoption of targeted therapy, immunotherapy, anti-vascular therapy and personalized treatment strategies, significantly improving patient survival and quality of life (Fig. 1). Among all the treatments, chemotherapy is the most toxic and even paclitaxel, which has significantly improved tumor treatment, can cause adverse reactions such as allergic reactions (10). The advent of albumin-bound paclitaxel and paclitaxel polymer micelles are advancements in the field of chemotherapy; however, they are also associated with adverse effects such as alopecia, peripheral nerve toxicity and impaired cardiac function (11). Subsequent clinical selection of chemotherapeutic agents is based on case types for individualized treatment.

Since 2004, lung cancer treatment has entered the era of targeted therapy. Targeted therapy is a precise treatment that focuses on specific targets, allowing patients with treatable target mutations to achieve high efficacy and relatively low toxicity. Gefitinib is the first tyrosine kinase inhibitor (TKI) approved for use in advanced NSCLC, marking the beginning of the era of targeted therapy (12). At that time, clinicians discovered that higher efficacy could be achieved in specific populations by administering oral doses of a targeted drug with much lower toxicity than traditional chemotherapy. This efficient and less toxic treatment option quickly replaced chemotherapy. Since then, nearly 10 pathways, including anaplastic lymphoma kinase (ALK) fusion, ROS proto-oncogene 1, receptor tyrosine kinase (ROS1) fusion and rearranged during transfection (RET) fusion, have been discovered and new drugs have been developed, bringing survival benefits to several patients (13).

A decade ago, for patients with negative-driving genes, long-term survival was in stark contrast with those with positive mutations due to a lack of effective treatment options. Focusing on the tumor itself, the development of kinase inhibitors has reached a bottleneck, and even neurotrophic tyrosine receptor kinase (NTRK) fusion with a mutation rate of only ~3% has been widely studied (14). Finding effective therapeutic targets, such as EGFR, that benefit a large proportion of the population is challenging. However, ICIs focusing on the tumor microenvironment (TME) have significantly changed the treatment landscape for patients with driver-negative genes (15). In 2013, Nivolumab, as the first ICI, was approved for marketing. Since then, immunotherapy has experienced a development path from backline to first-line, from advanced to locally advanced to early, and from single agent to combination.

Bevacizumab is the first drug developed based on the concept of antiangiogenesis. The ECOG-4599 study and BEYOND study have successfully established bevacizumab combined with chemotherapy as a first-line treatment (16,17).

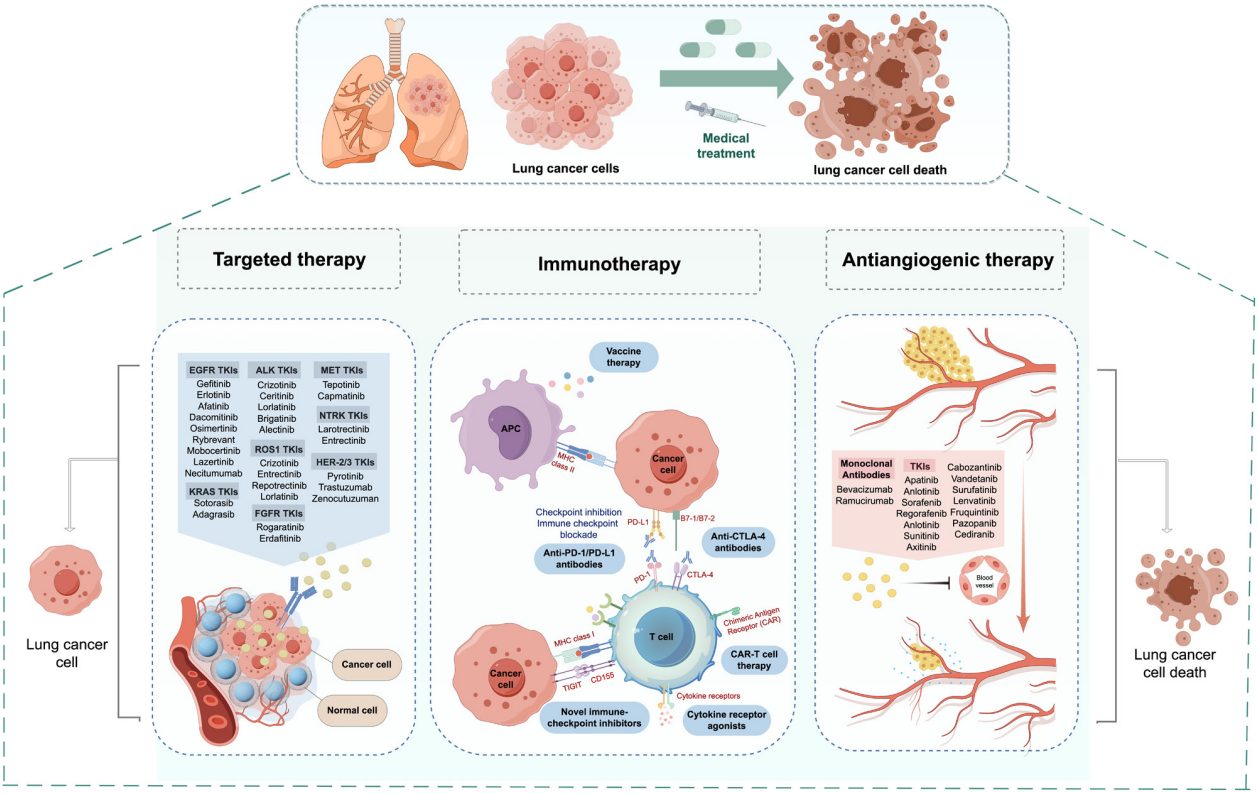

Figure 1. Breakthroughs in the treatment of non-small cell lung cancer in the past two decades. TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; MET, mesenchymal-epithelial transition factor; KRAS, kirsten rat sarcoma viral oncogene homolog; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; NTRK, neurotrophic tyrosine receptor kinase; HER-2/3, human epidermal growth factor receptor 2/3; FGFR, fibroblast growth factor receptor; APC, antigen-presenting cell; MHC, major histocompatibility complex; PD-1/PD-L1, programmed cell death protein 1/programmed death-ligand 1; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CAR-T, chimeric antigen receptor T-cell; TIGIT, T-cell immune receptor with Ig and ITIM domains.

In addition to bevacizumab, anlotinib is another antiangiogenic drug widely used in clinical settings. The mechanism of action of anlotinib is dissimilar in some respects to bevacizumab and it is the only antiangiogenic drug that is effective as a single drug treatment at present, although it is a late-line drug (18). In clinical practice, antiangiogenic drugs need to be used in combination with other treatments in most cases and have the disadvantages of relatively high toxicity and lack of established biomarkers. Considering these factors, antiangiogenic targeted therapy represents an innovation, although it is not as significant as targeted therapy and immunotherapy.

In addition to considering the disease stage, pathologic type, driver gene mutation status and expression of immunotherapy predictors of the patient, treatment selection for NSCLC must also consider patient frailty and comorbidities. Frail patients and those with significant comorbidities, such as cardiovascular disease or diabetes, often have limited tolerance for standard therapies, necessitating a more tailored approach. Tools such as ECOG performance status and the Charlson Comorbidity Index can guide clinicians in optimizing treatment regimens, which may include dose reduction, alternative drug choices or supportive care strategies. For instance, in clinical practice, for elderly patients (aged >70 years), with comorbidities, such as severe hepatic or renal dysfunction, poor performance status (PS score ≥2), lack of sensitive driver gene mutations and with programmed death-ligand 1 (PD-L1) expression <50%, single-agent chemotherapy (administered intravenously or orally) is often used as a first-line treatment instead of standard platinum-based doublet chemotherapy with or without immunotherapy (19). Such personalized approaches are critical in improving outcomes while minimizing treatment-related adverse effects.

4. Progress and prospects of treatment for NSCLC

Targeted therapy. In previous years, the field of targeted therapy for lung cancer has witnessed significant advancements. Various targets, such as EGFR, mesenchymal-epithelial transition factor (MET), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), the proto-oncogene RET, Kirsten rat sarcoma viral oncogene homolog G12C (KRAS G12C) and HER2, have been identified and corresponding drugs are continuously being developed or improved. In addition to well-known mutations such as EGFR, ALK and ROS1 fusions, researchers are paying increasing attention to rare mutations and the development of drugs targeting these mutations (12,20,21).

For patients with typical EGFR mutations, osimertinib remains the standard first-line therapy; however, combination therapies such as osimertinib with chemotherapy or amivantamab (a bispecific antibody targeting EGFR and c-MET) plus lazertinib (a third-generation EGFR TKI), have exhibited improved progression-free survival (PFS), although with increased toxicity (22). For EGFR exon 20 insertion mutations,

amivantamab plus chemotherapy is a first-line option (23). Sunvozertinib, a novel EGFR TKI, was approved in China and shows promise for exon 20 insertions, Thr790Met and uncommon mutations (24). For patients with ALK rearrangements, the third-generation ALK-TKI, lorlatinib, has exhibited exceptional efficacy in treatment-naïve patients and demonstrates strong central nervous system (CNS) activity. In recent years, both crizotinib, repotrectinib and entrectinib were proven to be effective in treating ROS1 fusion-positive NSCLC (25-27). The objective response rate (ORR) of entrectinib in patients with ROS1 fusion-positive reached 67.1%, with a CNS response rate of 79.2% (26). For patients with RET fusion-positive NSCLC, selpercatinib and pralsetinib demonstrated improved prognosis (28,29); however, it is crucial to monitor for pulmonary infections while using RET inhibitors.

In lung cancer, the BRAF and HER2 genes are involved in regulating the cell cycle. Mutations in the BRAF gene, particularly the BRAF V600E mutation, have been extensively studied and are known to be closely associated with the initiation and progression of various cancers. The BRAF protein is a key signaling molecule regulating cell proliferation and survival. Its activation leads to the activation of the downstream MAPK signaling pathway, promoting cell cycle progression and enhancing cellular proliferation capacity (30). BRAF mutations have become a research hotspot in the past 2 years, especially after the approval of combination targeted therapies. Using dabrafenib in combination with trametinib has become a new paradigm in treating BRAF V600E-mutated NSCLC (26). In addition, the combination of encorafenib with binimetinib is also a viable option for patients with advanced NSCLC carrying the BRAF V600E mutation (31). For patients carrying MET Exon 14 skipping mutations, capmatinib, tepotinib and savolitinib were demonstrated to be effective therapeutic options (32).

The role of the HER2 gene is crucial in lung cancer. HER2 is a receptor tyrosine kinase and its overexpression or mutation can lead to aberrant increases in proliferative signaling. Upon activation, HER2 not only promotes cell cycle progression but also interacts with the BRAF signaling pathway, which further aids tumor development and metastasis (33). In the case of HER2-mutated NSCLC, both trastuzumab and pyrotinib have demonstrated effective treatment performance (34). Additionally, other drugs such as the antibody-drug conjugates (ADCs), DS8201 and RC48, have shown promising results (34,35).

For patients harboring KRAS G12C mutations, results from the CodeBreaK 100 study revealed that previously treated patients with NSCLC and with the KRAS G12C mutation had an ORR of 40.7% with a median PFS (mPFS) and a median overall survival (mOS) of 6.3 and 12.5 months, respectively, following treatment with sotorasib (36). On this basis, CodeBreak 200 second-line comparison of the difference in efficacy between sotorasib and docetaxel in patients with KRAS G12C mutations revealed an mPFS of 5.6 vs. 4.5 months, respectively. Concurrently, OS did not reach a statistical difference. Although the CodeBreaK 200 trial met its primary endpoint, the mPFS benefit in the sotorasib arm was 5 weeks, less than the imaging follow-up interval. Thus, the Food and Drug Administration panel ultimately concluded that the primary study endpoint of CodeBreaK 200 could not be reliably interpreted given the inherent error in assessing PFS during the imaging follow-up interval (37). The efficacy of another small molecule KRAS G12C inhibitor, adagrasib, was evaluated in the KRYSTAL-1 study as a second-line treatment for KRAS G12C-mutated NSCLC, with an ORR of 42.9%, mPFS of 6.5 months and mOS of 12.6 months. The same study revealed some efficacy of adagrasib against intracranial lesions (38). At present, sotorasib and adagrasib are approved as second-line treatment. Ongoing studies are exploring their efficacy as first-line combinations with chemotherapy and immunotherapy. KRAS G12C is currently a hot research topic and, in addition to sotorasib and adagrasib, new drugs such as JDQ443, D-1553 and JAB-21822 are in early clinical trial stages and breakthroughs in their efficacy are anticipated (39,40).

NTRK fusion is a driver mutation in various tumors and can be detected in multiple types of cancer, including NSCLC with an incidence rate of 0.1-3.3% (41). NTRK inhibitors, larotrectinib and entrectinib, exhibited favorable systemic and intracranial efficacy (42,43). MET exon 14 skipping mutations, an important driver gene in NSCLC, have an incidence rate of 3-4%. Several MET-TKIs, such as savolitinib, are approved treatments for various cancers, including NSCLC, with MET exon 14 skipping mutations (44). In addition to the aforementioned rare targets in NSCLC, research on other targets such as neuregulin 1 (NRG1), cytoplasmic linker protein 1-leukocyte receptor tyrosine kinase fusion and KRAS G12D is also progressing rapidly (45-47). These targets may also result in breakthroughs and contribute to advancing precision treatment for NSCLC. Current and clinically available targeted agents for NSCLC and other investigational agents are summarized in Table I.

In the treatment of lung cancer, drug resistance is a major obstacle leading to therapeutic failure and tumor recurrence, particularly in targeted therapies where diverse resistance mechanisms may be active. In EGFR-mutated lung cancer, the most common resistance mechanisms include secondary T790M mutations, C797S mutations and bypass pathway activation (such as MET or HER2 amplification). In patients with ALK fusion-positive, resistance can arise from secondary mutations (such as L1196M and G1269A) or bypass pathway activation (such as EGFR, KIT or MET amplification). For KRAS-mutated cancers, resistance mechanisms involve secondary mutations or activation of other signaling pathways (such as PI3K, MAPK or HER2 amplification) (48). Additionally, resistance to immunotherapy is often linked to changes in the TME or immune escape, such as loss of antigen presentation. During treatment, some patients with NSCLC may also undergo phenotypic transformation into SCLC, which further contributes to resistance. Tumor cells may also evade drug effects by enhancing DNA damage repair mechanisms (49). Overcoming these resistance mechanisms encounters the following challenges: i) Difficulty in identifying heterogeneity; the resistance mechanisms within different patients and their tumors are highly heterogeneous and need to be monitored dynamically relying on highly sensitive gene sequencing technology; ii) lack of efficient drugs; for example, the efficacy of existing third-generation TKIs for the C797S mutation is insufficient and the development of fourth-generation TKIs is still in the early stage; iii)

Table I. Summary of drugs currently available in the clinic and under investigation for treatable driver gene targets in non-small cell lung cancer.

Gene	Target point	Available drugs	Clinical trial drugs	Clinical trial numbers
EGFR	Exon 19 deletion	Erlotinib (first generation)	HSK40118	NCT06050980
	Exon 21 L858R mutation	Gefitinib (first generation)	JNJ6372	NCT02609776
	Exon 20 T790M mutation	Icotinib (first generation)	DAJH-1050766	CTR20221031
		Afatinib (second generation)	U31402	NCT04965766
		Dacomitinib (second generation)		
		Osimertinib (third generation)		
		Furmonertinib (third generation)		
		Almonertinib (third generation)		
		Befotertinib (third generation)		
	Exon 20 insertion mutation	Mobocertinib (TAK788)	Furmonertinib	NCT05607550
		Amivantamab (JNJ6372)	PLB1004	NCT06015503
		Sunvozertinib (DZD9008)	YK029A	NCT05767892
			FWD1509	NCT05068024
	Exon 18 G719X point mutation	Afatinib (second generation)	Mefatinib	CTR2000029058
	Exon 21 L861Q point mutation	Osimertinib (third generation)	HTMC0503	CTR20212743
	Exon 20 S768I point mutation		Sutetinib	NCT05168566
ALK	EML4-ALK	Crizotinib (first generation)	TGRX-326	NCT06082635
		Alectinib (second generation)	CT3505	NCT05257512
		Ceritinib (second generation)	TL139	CTR20202551
		Brigatinib (second generation)		
		Ensartinib (second generation)		
		Iruplinalkib (second generation)		
		Lorlatinib (third generation)		
ROS1	CD74-ROS1	Crizotinib	TPX-0005	NCT03093116
		Entrectinib	AB-106	NCT04395677
BRAF	V600E	Dabrafenib + Trametinib	ABM-1310	NCT05501912
		Encorafnib + Binimetinib	KIN2787	NCT04913285
MET	METex14	Tepotinib	Glesatinib	NCT02954991
		Capmatinib	APL-101	NCT03175224
		Savolitinib	Cabozantinib	NCT03911193
		Glumetinib		
		Bozitinib		
RET	Rearrangement	Selpercatinib	SY-5007	NCT06031558
		Pralsetinib	HS-10365	NCT06147570
			APS03118	CTR20222441
KRAS	G12C	Sotorasib	D1553	NCT06300177
		Adagrasib	Divarasib	NCT06497556
			GH35	CTR20222296
			HJ891	CTR20212195
			Olomorasib	NCT06119581
HER2	HER2 amplification	DS8201	PLB1004	NCT0601550
	Exon 20 insertions		FS-1502	NCT03944499
NTRK	1-3	Larotrectinib	TL118	CTR20191622
		Entrectinib	HG030	CTR20202020
			VC004	NCT06658353

EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; ROS1, ROS proto-oncogene 1, receptor tyrosine kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; MET, mesenchymal-epithelial transition factor; RET, rearranged during transfection proto-oncogene; KRAS, kirsten rat sarcoma viral oncogene; HER2, human epidermal growth factor receptor 2; NTRK, neurotrophic tyrosine receptor kinase; NCT, national clinical trial; CTR, Chinese Clinical Trial Registry.

difficulty in optimizing the combination strategy; although the combination of chemotherapy, radiotherapy and targeting agents can delay resistance, the accumulation of toxicity has reduced its application (50). Future directions include the development of specialized inhibitors targeting drug-resistant mutations (such as fourth-generation EGFR-TKIs and KRAS multi-mutant targeted drugs), the advancement of liquid biopsy technology to monitor the dynamic changes of drug-resistant genes and the precise design of combination therapies with controllable toxicity.

Overall, recent advancements in targeted therapy for NSCLC have led to the development of treatments targeting mutations such as EGFR, MET, BRAF, RET, KRAS G12C and HER2. For EGFR mutations, osimertinib remains as standard treatment, with combination therapies exhibiting improved PFS. Amivantamab is a first-line option for EGFR exon 20 insertions. Lorlatinib is effective for ALK-rearranged NSCLC, and drugs such as crizotinib and entrectinib are used for ROS1-positive cases. Selpercatinib and pralsetinib are effective for RET fusions. BRAF mutations are treated with dabrafenib plus trametinib, while MET exon 14 mutations are targeted by capmatinib and tepotinib. HER2 mutations are addressed with trastuzumab, pyrotinib and ADCs such as DS8201. KRAS G12C mutations respond to sotorasib and adagrasib, with studies exploring their use in first-line combinations. NTRK fusions are treated with larotrectinib and entrectinib. Despite these advancements, resistance mechanisms remain a major challenge, including secondary mutations and bypass pathways, highlighting the need for new inhibitors, improved liquid biopsies and optimized combination therapies.

Immunotherapy. Immunotherapy primarily works by stimulating the immune system to enhance immune cell recognition and antitumor activities, enabling the immune system to attack and eliminate tumor cells. Tumor immunotherapy encompasses various approaches, including the use of ICIs, adoptive cell therapy, cancer vaccines, monoclonal antibodies, oncolytic virus therapy, cytokine therapy, Toll-like receptor agonists and chimeric antigen receptor T-cell (CAR-T) therapy, leveraging the immune system of the body to target and destroy cancer cells (51). Among these, ICIs such as programmed cell death protein 1 (PD-1), PD-L1 and cytotoxic t-lymphocyte-associated protein 4 (CTLA-4) antibodies (ipilimumab and tremelimumab) demonstrated advanced and widespread clinical research and utilization in lung cancer. For NSCLC without actionable mutations, ICIs targeting PD-1/PD-L1 and CTLA-4 are the standard treatment. For high PD-L1 expression (≥50%), anti-PD-1 or anti-PD-L1 monotherapy, or their combination with chemotherapy, are established as effective. For intermediate PD-L1 expression (1-49%), the standard treatment combines ICIs with chemotherapy. In cases with low PD-L1 expression (<1%), combinations of anti-PD-1/PD-L1 and anti-CTLA-4 inhibitors are commonly used (52). ICI monotherapy has exhibited limited efficacy in patients with EGFR, ALK, RET, ROS1 and NTRK mutations. However, KRAS G12C mutations are associated with a stronger response to ICI therapy. In addition, re-treatment with ICIs may be considered for patients who initially responded but have not been treated for an extended period, specifically >6 months (53). In recent years, inhibitors targeting other immune checkpoints in addition to PD-1/PD-L1, have demonstrated potential in the treatment of NSCLC, offering a promising new direction for therapy. CTLA-4 inhibitors, such as ipilimumab, did not achieve significant advancements in the treatment of various solid tumors, including NSCLC, however, the combination of CTLA-4 inhibitors with PD-1/PD-L1 inhibitors revealed some progress in NSCLC treatment. In the CheckMate 227 trial, the combination of ipilimumab with nivolumab significantly improved PFS and OS compared with chemotherapy (54). However, the KEYNOTE-598 study found that in patients with high PD-L1 expression, combining CTLA-4 inhibitors with pembrolizumab did not provide significant benefits over monotherapy and was associated with higher side effects (55). This finding highlights the need for further exploration to identify suitable patient populations for such combinations. Previous research has increasingly focused on some novel ICIs, including T-cell immunoreceptors with Ig and ITIM domains (TIGIT), lymphocyte-activation gene 3 (LAG-3) and T-cell immunoglobulin and mucin-domain containing-3 (TIM-3) targets. In the CITYSCAPE trial, TIGIT inhibitors (such as tiragolumab) combined with atezolizumab significantly improved the PFS and remission rate in PD-L1-positive patients, and other drugs (including vibostolimab and ociperlimab) also exhibited potential in this area (56). The soluble LAG-3 protein, eftilagimod α, showed positive results in treating NSCLC in combination with immunotherapy and chemotherapy by enhancing the function of T cells and antigen-presenting cells (57). TIM-3 target inhibitors (such as sabatolimab) demonstrated enhanced antitumor immune responses in preclinical research (58). Novel ICIs and dual-immunization strategies have shown promising results in selected patients. However, efficacy and safety vary from person to person, thereby the beneficiary populations should be further clarified. Moreover, optimization of treatment regimens is needed to improve efficacy and reduce the risk of adverse events in advanced NSCLC.

Tumor-specific vaccine therapy aims to stimulate the host immune system to generate tumor antigen-specific effector T cells and memory T cells by introducing tumor antigens, thereby initiating or amplifying adaptive antitumor immune responses. Although NSCLC vaccines demonstrated promising results in preliminary phase II clinical studies, there are still challenges in their administration, including limited penetration into tumors, weakened immune responses and resistance (51). Current vaccine research primarily focuses on antigen-specific vaccines and whole-cell vaccines. Antigen-specific vaccines include peptide/protein vaccines, DNA vaccines, and vector vaccines, while whole-cell vaccines comprise allogeneic vaccines and autologous dendritic cell vaccines. Adaptive cell therapy utilizes immune cells from patients that have tumor-reactive properties. These cells are cultured, genetically engineered and reinfused into the patients to recognize and target cancer cells. The most commonly used approaches in this field are CAR-T, tumor-infiltrating lymphocyte (TIL), T-cell receptor and natural killer cell therapies (51,59,60). The remission rate of CAR-T therapy in hematological malignancies can reach 80-90% (51). However, the efficacy of CAR-T therapy in NSCLC still requires further exploration.

ICIs have reshaped the treatment landscape of advanced NSCLC however, only ~20% of patients achieve durable

responses to immunotherapy and some patients may experience severe adverse reactions or are unresponsive. Therefore, identifying biomarkers that can predict the efficacy and prognosis of immunotherapy is of paramount importance. The only validated predictive biomarker is PD-L1, but its predictive value is not absolute. With a deeper understanding of molecular biology, genomic sequencing technologies, and the immune microenvironment, the identification of new molecular characteristics has led to the discovery of additional potential biomarkers. PD-L1 expression is a key biomarker for predicting the efficacy of immunotherapy; however, even without PD-L1 expression, some cases can achieve favorable responses to immunotherapy. The heterogeneity of tumors in terms of time and space can partially explain this phenomenon. In this regard, TILs are currently a hot topic (61). Studies have found that analyzing tumor infiltration characteristics at diagnosis can predict the efficacy of immunotherapy and guide treatment decisions. Human leukocyte antigen class I (HLA-I) exhibits polymorphism in patients with NSCLC (62). For example, a study by Chowell *et al* (63) revealed that the HLA B44 supertype is associated with improved OS, while the HLA B62 supertype is associated with low OS. Currently, several systematic reviews confirmed the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in various types of cancer and this easily obtainable and cost-effective index may become the next widely used predictive biomarker for ICIs based on PD-L1 (64).

Tumor mutational burden (TMB) refers to the number of somatic mutations in the tumor genome after excluding germline mutations. These mutations can generate neoantigens that can be recognized by the immune system, leading to antitumor immune responses. Therefore, an elevated TMB value (≥10 mut/Mb) may be a predictive factor for the efficacy of ICIs (65). Additionally, studies indicated that the gut microbiome can regulate adaptive and innate immunity, influencing the antitumor immune response in the TME. However, despite the significant benefits of immunotherapy, patients with NSCLC inevitably experience disease progression due to resistance to the therapy. Resistance to ICIs arises from immune escape, the TME and tumor heterogeneity, which together limit long-lasting efficacy and exacerbate treatment challenges (66). Resistance to ICIs is manifested through: i) Antigen loss or downregulation of immune recognition such as reduced PD-L1 expression in cancer cells or mutated major histocompatibility complex molecules, which weaken T-cell recognition (67); ii) immunosuppressive TME-regulatory T cells, myeloid-derived suppressor cells and M2-type macrophages which are increased, and factors such as TGF-β, IL-10 and VEGF are upregulated (68); and iii) genetic and functional heterogeneity through which subpopulations of drug-resistant T cells expand under pressure of therapeutic selection (69). Addressing ICI resistance faces several challenges including: i) The lack of reliable methods for early identification of resistance mechanisms; and ii) the limited efficacy of existing TGF-β or colony stimulating factor 1 receptor inhibitors due to the complexity of TME dynamic regulation. Response strategies include combination-targeted TME therapies (such as TGF-β inhibitors in combination with PD-1 inhibitors), exploration of antitumor vaccines to restore antigen-presenting function and development of multi-targeted immunomodulatory agents to address the treatment of patients with drug resistance (15,66,70).

In summary, immunotherapy has transformed advanced NSCLC treatment, primarily through ICIs targeting PD-1/PD-L1 and CTLA-4. For patients with high PD-L1 expression, monotherapy or combination with chemotherapy is effective, while intermediate and low PD-L1 cases often require combined ICI therapies. KRAS G12C mutations exhibit stronger responses, but ICIs are less effective in EGFR, ALK and other mutations. New ICIs targeting TIGIT, LAG-3 and TIM-3 are emerging, alongside combination therapies to improve efficacy. However, resistance mechanisms such as immune escape and tumor heterogeneity remain major challenges. Ongoing research is focused on identifying reliable biomarkers and developing strategies to overcome these resistance issues.

ADCs. Traditional lung cancer treatments such as chemotherapy, targeted therapy and immunotherapy face challenges of systemic toxicity and drug resistance, while the emergence and rapid development of ADCs have brought new hope to patients with NSCLC. ADC drugs combine the targeting properties of monoclonal antibodies with the potent cytotoxicity of chemotherapeutic drugs, using antibodies to specifically recognize targeted antigens on the surface of tumor cells, and then delivering the cytotoxic agent precisely inside the tumor cells (71). This 'targeted bomb' mode of action not only improves the tumor-killing ability of the drug but also minimizes the damage to normal cells. With the continuous advancement of ADC technology, including the improvement of linker technology, optimization of antibody selection and toxin design, ADC drug research in lung cancer is gaining more and more attention.

For lung cancers carrying specific biomarkers such as HER2 or TROP2, ADC drugs such as DS-8201 (detrastuzumab, HER2 ADC, T-DXd) and DS-1062 (datopotamab deruxtecan, TROP2 ADC, dato-DXd) demonstrated high antitumor activity, offering new therapeutic options for patients who previously experienced treatment failure (72,73).

As a HER2-targeted ADC drug, trastuzumab deruxtecan achieved positive results in pivotal clinical trials such as DESTINY-Lung01, DESTINY-Lung02 and DESTINY-Lung05 (74-76). Trastuzumab deruxtecan was approved for marketing in the United States, Europe and China, becoming the world's first ADC drug for the treatment of adult patients with unresectable locally advanced or metastatic NSCLC with HER2-activating mutations.

Telisotuzumab vedotin was revealed to be effective in pretreated patients (who had received ≤2 lines of prior systemic therapies, including ≤1 line cytotoxic chemotherapy, immunotherapy, and targeted therapy if eligible) with c-Met-positive NSCLC, especially those with high MET protein expression and EGFR wild-type NSCLC (77).

In EGFR-mutated NSCLC, patritumab deruxtecan (HER3-DXd) demonstrated efficacy in patients who progressed after EGFR TKI treatment (78). Additionally, BL-B01D1, a bispecific ADC targeting both EGFR and HER3, is showing early promise in a clinical trial (79).

ADC drug development also faces some difficulties, such as the optimization of the drug-antibody ratio, the stability and release characteristics of the linker, the complexity of the TME, and the double-edged sword represented by the bystander effect (71). Current clinical studies focus on the design and optimization of ADCs and investigators are exploring ways to improve the efficacy and safety of ADCs. Researchers have been summarizing clinical trial data in real time, allowing them to speculate about the design direction of future ADCs. They anticipate developing ADCs that will have more promising clinical applications. In addition, as the understanding of the molecular biology of NSCLC deepens, future ADCs may incorporate new targets and therapeutic strategies to further improve therapeutic efficacy. In short, the research of ADC drugs not only fills the gap in the field of lung cancer treatment, but also represents the future direction of precision tumor therapy.

ADCs offer a promising solution to the challenges of traditional lung cancer treatments by targeting tumor cells more precisely with minimal damage to healthy tissue. Drugs, such trastuzumab deruxtecan (HER2) and DS-1062 (TROP2) have strong activity in biomarker-positive NSCLC, while others including telisotuzumab vedotin (MET-positive) and patritumab deruxtecan (EGFR-mutant) are also promising. Despite some challenges in ADC optimization, they represent a key future direction in lung cancer therapy.

Challenges in NSCLC combination therapies. Recent advances in combination therapies for advanced-stage NSCLC highlighted the potential of integrating different therapeutic modalities to enhance treatment efficacy. For example, the combination of ICIs with chemotherapy demonstrated improved survival outcomes in patients with high TMB (80). Similarly, targeted therapies such as EGFR inhibitors are being combined with anti-angiogenic agents or chemotherapy to overcome resistance mechanisms and extend PFS (81). Novel approaches integrating immunotherapy with radiotherapy or epigenetic modulators are also being explored in preclinical and clinical settings, aiming to exploit synergistic effects (70). Despite these promising advances, significant challenges remain in optimizing these combination strategies for widespread clinical use.

The development of combination therapies for advanced-stage NSCLC faces significant challenges, including the complexity of biological mechanisms, the risk of inducing new resistance pathways and the difficulty of managing cumulative toxicity (70). Clinically, the lack of robust predictive biomarkers complicates patient selection, while trial designs for multi-drug regimens remain challenging due to the need to separate the contributions of each component (80). Additionally, combination therapies can significantly increase the economic burden, and their limited accessibility in resource-constrained settings poses a challenge to their worldwide adoption and application (82). Addressing these challenges will require a multidisciplinary approach, combining advances in molecular biology, innovative trial methodologies and collaborative frameworks to ensure the efficacy, safety and affordability of combination strategies.

5. Discussion

The treatment landscape for advanced NSCLC has witnessed notable advancements in recent years. The introduction of ICIs, targeted therapies and personalized medicine approaches has significantly improved outcomes for patients with NSCLC. These novel therapeutic modalities have expanded treatment options, offering greater efficacy and reduced toxicity compared with conventional chemotherapy regimens.

Despite these advancements, challenges remain, including the development of resistance to targeted therapies, the identification of predictive biomarkers for treatment response and the optimization of combination strategies to overcome resistance mechanisms. Additionally, the exploration of novel immunotherapeutic approaches such as cytokine receptor agonists, tumor vaccines, CAR-T-cell therapy and new ICIs hold promise for further improving patient outcomes.

Multiple challenges are encountered in the treatment of advanced NSCLC, including drug resistance, therapeutic toxicity, high cost and underrepresentation of minorities in clinical trials. These issues not only affect patient outcomes but also limit the development and application of new therapies. Drug resistance is a major obstacle in the treatment of advanced NSCLC. Although the emergence of targeted therapies and immunotherapies has provided new hope, several patients still develop drug resistance after receiving treatment, which increases the risk of disease progression (83). In addition, toxicity of treatment is a problem that cannot be ignored; especially in elderly patients or patients with comorbidities, treatment-related adverse effects may be more severe (84). The high cost of treatment is also an important factor influencing the willingness of patients to undergo treatment. The extremely high cost of several novel drugs and therapies renders them unaffordable for some patients, which in turn affects their treatment choices and survival prognosis (85). At the same time, the underrepresentation of minorities in clinical trials further exacerbates this problem. Research has revealed that the participation of minorities in cancer clinical trials is markedly lower than their proportion of cancer incidence, which leaves treatment programs for these groups without adequate clinical data to support them (86). To address these challenges, steps must be taken to improve the design and conduct of clinical trials, to make them more inclusive and patient-centered. Clinical trial participation rates can be improved by optimizing trial enrollment criteria, decreasing participation thresholds and increasing recruitment of minorities, thereby providing more patients with effective treatment options (87). Concurrently, new strategies are needed to expand treatment options and comprehensive approaches are needed to ensure sustainability and global accessibility of innovations. The scientific community needs to strengthen collaboration to stimulate innovative solutions in order to advance the field of NSCLC treatment (88).

Immunotherapy, with ICIs as the representative, greatly improve the prognosis of patients who are negative for driver mutations. Currently, the most common immunotherapy combinations involve the use of immunotherapies with chemotherapy. Additionally, immunotherapy drugs have the potential to be combined with several different medications, including anti-angiogenic drugs, targeted therapies, Janus kinase inhibitors, poly ADP-ribose polymerase inhibitors, ADCs, TIGIT monoclonal antibodies, VEGFR inhibitors and bispecific antibodies. However, predicting the efficacy and prognosis of immunotherapy remains a challenge. Promising biomarkers

such as TILs, HLA-I polymorphism, NLR and the gut microbiome are being investigated to improve patient selection and guide treatment decisions. In addition, it is necessary to explore the best treatment modality of immunotherapy combined with other drugs to maximize the benefits of immunotherapy.

6. Conclusion

In summary, recent advances in NSCLC treatment, including ICIs, targeted therapies and ADCs, have significantly improved patient outcomes. However, several challenges remain such as drug resistance, limited efficacy in certain patient subgroups, and the need for reliable predictive biomarkers. Emerging therapies such as ADCs are promising but require further investigation to assess long-term efficacy and safety. Moving forward, research should focus on optimizing combination therapies, overcoming resistance and identifying new therapeutic targets, with a deeper understanding of NSCLC biology being key to future innovations.

7. Expert opinion

Looking ahead, the future of NSCLC treatment is promising, with ongoing research efforts focused on unraveling the complexities of tumor biology, identifying novel therapeutic targets and developing innovative treatment strategies. The advent of precision medicine, liquid biopsy techniques and immunotherapy-based combination regimens herald a new era in NSCLC management, offering hope for improved survival and quality of life for patients with advanced disease. In the future, there will be an increasing number of targeted drugs and combination treatment strategies, leading to the advancement of precision treatment for lung cancer. With the increasing availability of targeted therapy drugs, the re-biopsy of resistant tumors and identification of rare mutations will facilitate the continuation of personalized treatment for patients who develop resistance to targeted therapy, thereby prolonging patient survival and transitioning lung cancer into a manageable chronic condition. The maturation of kinase inhibitor technology is evident and the field is projected to concentrate on drug developments and broadening the scope of existing drugs over the next decade. The emergence of next-generation kinase inhibitors to supplant earlier medications has been observed in various signaling pathways. For example, in the EGFR and ALK pathways, fourth-generation drugs are already in preclinical development. Furthermore, exploring different treatment modalities, such as combination therapies with different mechanisms of action, adjuvant use of kinase inhibitors, and neoadjuvant therapies, is another area of research.

8. Review article highlights

The highlights of the present review article are summarized as follows: i) Advances in oncology have revolutionized lung cancer treatment with breakthroughs in targeted therapies and immunotherapy, emphasizing personalized approaches; ii) over the past two decades, breakthroughs in NSCLC treatment, including targeted therapies, immunotherapy and personalized strategies, have significantly improved patient survival and quality of life, while also emphasizing the need for tailored approaches based on disease stage, driver mutations and patient comorbidities; iii) recent advancements in targeted therapy for lung cancer have focused on identifying rare mutations and developing corresponding drugs, with ongoing updates enhancing treatment options; iv) ADCs have emerged as a promising class of drugs, combining targeted delivery with potent cytotoxic effects and representing a significant step forward in precision treatment strategies; and v) immunotherapy has transformed treatment paradigms, although challenges remain in predicting responses and managing side effects.

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Authors' contributions

ZW, GC, JZ, and JW contributed to drafting the manuscript, while ZW and YZ critically reviewed it. All authors were involved in significant aspects of the present study, including conception, study design, research acquisition, analysis, and interpretation. All authors have participated in drafting, revising, or critically reviewing the manuscript, read and approved the final version for publication, agreed on the selected journal, and accepted accountability for all aspects of the work. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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