Su et al. Journal of Hematology & Oncology (2025) 18:35
https://doi.org/10.1186/s13045-025-01679-1

Journal of
Hematology & Oncology

REVIEW

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# Recent advances in therapeutic strategies for non-small cell lung cancer

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## Abstract

The development of targeted therapy with small-molecule tyrosine kinase inhibitors and immunotherapy with immune checkpoints inhibitors has ushered in the era of precision medicine in treating lung cancer, which remains the leading cause of cancer-related deaths worldwide. Both targeted therapy and immunotherapy have significantly improved the survival of patients with metastatic non-small-cell lung cancer (NSCLC). Additionally, recent groundbreaking studies have demonstrated their efficacy in both the perioperative setting and following concurrent chemoradiotherapy in early-stage NSCLC. Despite significant advancements in first-line treatment options, disease progression remains inevitable for most patients with advanced NSCLC, necessitating the exploration and optimization of subsequent therapeutic strategies. Emerging novel agents are expanding treatment options in the first-line setting and beyond. Recently, emerging bispecific antibodies have shown enhanced efficacy. For instance, amivantamab has been approved as a treatment for epidermal growth factor receptor (EGFR)-mutant NSCLC, including those with EGFR exon 20 insertion mutations. Additionally, antibody–drug conjugates (ADCs), including HER2-targeting trastuzumab deruxtecan, TROP2-targeting ADCs, HER3-targeting patritumab deruxtecan, and MET-targeting telisotuzumab vedotin, have demonstrated promising outcomes in several clinical trials. This review summarizes the recent advancements and challenges associated with the evolving NSCLC therapeutic landscape.

**Keywords** Biomarkers, Non-small-cell lung cancer, NSCLC, Antibody–drug conjugates, Bispecific antibodies, Targeted therapy, Immune checkpoint inhibitors

## Background

Lung cancer remains the leading cause of cancer-related deaths worldwide, with non-small-cell lung cancer (NSCLC) accounting for more than 85% of cases [1]. Approximately 20 years ago, the discovery of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and subsequent biomarker studies that identified the role of EGFR mutations in cancer etiology marked the beginning of the precision medicine era in lung cancer [2, 3]. Since then, numerous oncogenic driver mutations have been identified in lung cancer patients [4], and the use of TKIs in treating lung cancer has expanded significantly (Fig. 1). Additionally, the NSCLC treatment landscape changed with the introduction of immune checkpoint inhibitors (ICIs) that target the programmed death-1 (PD-1)/programmed death-ligand 1 (PD-L1) axis and the B7 family protein/

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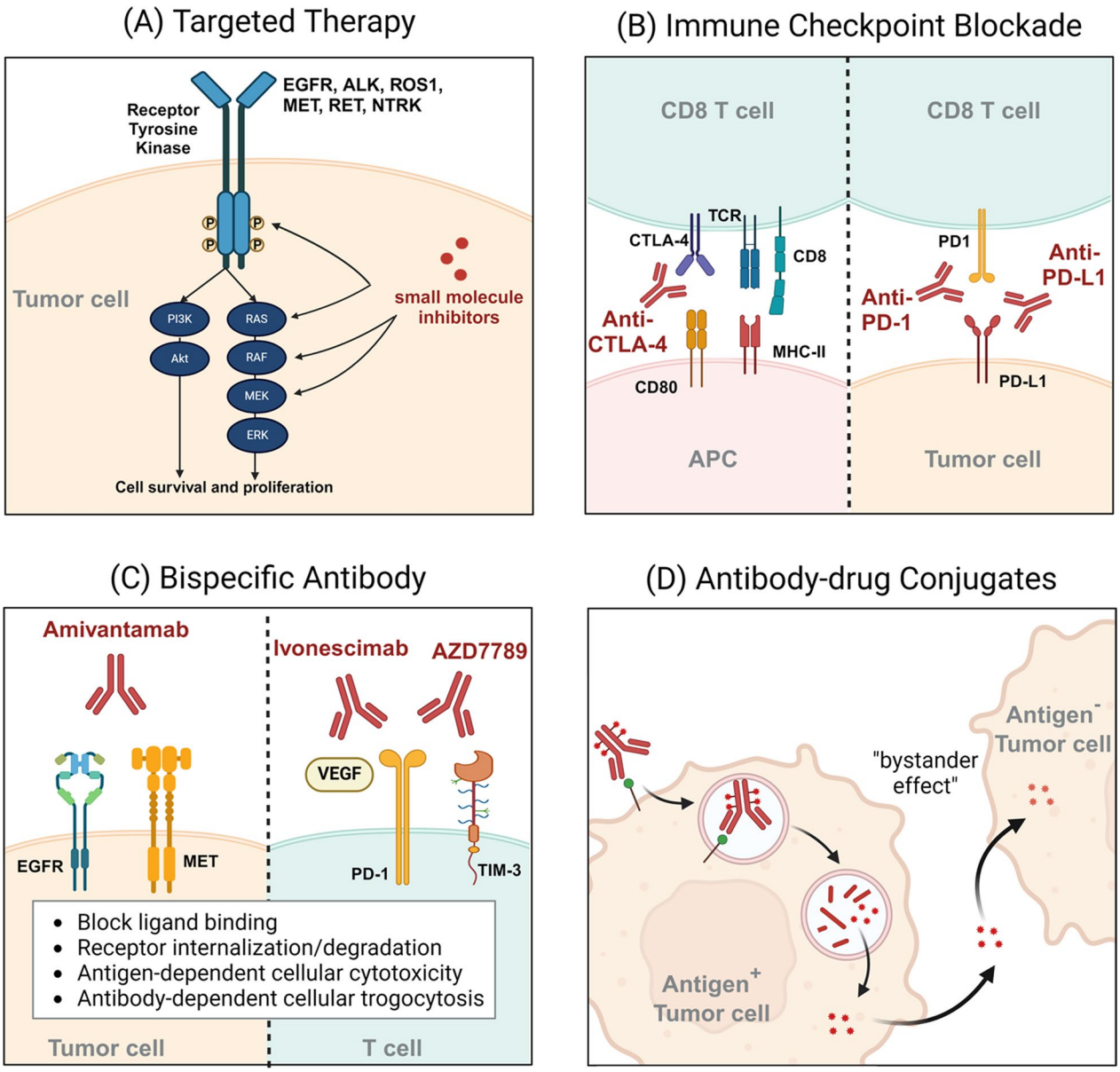


**Fig. 1** Major categories of therapeutic treatments for NSCLC. **A** Targeted therapies inhibit oncogenic receptor tyrosine kinases and their downstream signaling pathways, thereby suppressing tumor survival signals. **B** Immune checkpoint inhibitors, such as those targeting PD-1/PD-L1, B7/CTLA-4, and related pathways, restore T-cell function by reversing exhaustion, enhancing cytotoxic activity, and modulating the tumor immune microenvironment. **C** Bispecific and bifunctional antibodies simultaneously target molecules such as EGFR and MET, PD-1 and VEGF, or PD-1 and TIM-3, thereby reducing ligand-receptor interactions, promoting receptor degradation, and inducing antibody-mediated cellular cytotoxicity. **D** Antibody–drug conjugates deliver precise chemotherapeutic agents via cancer-specific antigen-targeting antibodies, enabling a bystander effect to eliminate neighboring cancer cells

cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) axis. Over the last few years, ICIs have become the backbone of NSCLC treatment for patients without oncogenic driver mutations in both the early and metastatic settings [5]. However, treatment options in the second line and beyond remain limited, with various novel compounds such as antibody–drug conjugates (ADCs) [6] and bispecific antibodies [7] currently under investigation (Fig. 1). Despite NSCLC's molecular heterogeneity, these innovations and the complex drug development landscape are biomarker agnostic. Efforts to identify prognostic and predictive biomarkers of response are a cornerstone for continuing progress in precision

medicine. In this review, we examine recent advancements in therapeutic strategies and biomarkers for NSCLC.

## Recent advances in targeted therapy

### Common EGFR-mutant NSCLC

#### *Metastatic disease*

Treatment with EGFR-TKIs, including gefitinib and erlotinib (first generation) and afatinib and dacomitinib (second generation), has shown superior responses compared to chemotherapy for EGFR-mutant NSCLC with the classic sensitizing mutation *EGFR L858R* and *EGFR* exon 19 deletion [8, 9]. The phase 3 AURA3 study established osimertinib (a third-generation irreversible TKI) as an effective second-line therapy for patients with acquired T790M mutations, the most common acquired resistance to first- and second-generation TKIs [10]. To improve first-line treatment, the phase 3 FLAURA study compared osimertinib to first-generation TKIs, and showed significant improvement in progression-free survival (PFS) (18.9 vs 10.2 months, $P=0.02$) and overall survival (OS) (38.6 vs 31.8 months, $P=0.046$), and superior central nervous system (CNS) clinical activity with not reached (NR) CNS PFS (NR vs 13.9 months, $P=0.014$)$P=$[11–13]. These findings established osimertinib as the standard-of-care first-line treatment for patients with common *EGFR*-mutant NSCLC. However, patients inevitably develop acquired resistance to osimertinib, leading to disease progression. Broadly, mechanisms of resistance can be grouped into 3 categories: on-target *EGFR*-dependent, off-target *EGFR*-independent, and histological transformation. An understanding of these mechanisms is important when considering new treatment strategies for treatment-naïve patients and those who progress after initial treatment with osimertinib.

Mesenchymal-epithelial transition (MET) amplification is the most common off-target independent mechanism of resistance [14]. Currently, emerging clinical trials are evaluating the efficacy of combination therapies in this context. As an example, the single-arm phase 2 INSIGHT2 study evaluated the addition of the MET inhibitor tepotinib to osimertinib in patients with NSCLC with EGFR mutations who progressed on osimertinib because of MET amplification acquired resistance [15]. The objective response rate (ORR), the primary endpoint, was 50.0% (95% confidence interval [CI] 39.7–60.3) in 49 evaluable patients, with a median duration of response (DOR) of 8.5 months (95% CI 6.1–not estimable [NE]). The PFS in the overall study population was 5.6 months (95% CI 4.2–8.1) with a median OS of 17.8 months (95% CI 11.1–NE), showing promising clinical activity [15]. Similarly, amivantamab, a novel bispecific antibody targeting both EGFR and MET, showed promising efficacy in osimertinib-resistant and treatment-naïve NSCLC with classic EGFR mutations [16, 17]. In 2024, the United States Food and Drug Administration (FDA) approved the combination of platinum-based chemotherapy and amivantamab for patients with NSCLC with classic EGFR mutations whose disease has progressed on EGFR TKI treatment [18] and the combination of lazertinib and amivantamab for patients with previously untreated EGFR-mutant NSCLC [19]. Another bispecific antibody targeting both PD-1 and vascular endothelial growth factor (VEGF), ivonescimab, also showed promising efficacy in common EGFR-mutant NSCLC with acquired resistance to osimertinib [20, 21].

To address acquired resistance to osimertinib and improve first-line treatment efficacy, the phase 3 FLAURA2 study investigated the addition of platinum-based chemotherapy to osimertinib in comparison to standard-of-care osimertinib monotherapy [22]. The combination therapy showed a significant improvement in PFS compared to osimertinib alone (29.4 vs 19.9 months; hazard ratio [HR]: 0.62; 95% CI 0.48–0.80; $P=0.0002$); however, OS is still immature [22]. The PFS benefit appeared across all predefined subgroups, including age, sex, race, smoking status, and type of *EGFR* mutation, and the benefit was more profound among patients with brain metastases at baseline (24.9 vs 13.8 months) [22]. Despite the clinical benefit, the combination led to a higher rate of treatment-related adverse events (AEs) than the monotherapy (grade $\geq 3$: 54% vs 11%; serious AEs: 19% vs 5%), which needs to be considered. Even so, the FDA approved the combination of osimertinib and platinum-based chemotherapy in the first-line setting. Subsequent post-hoc analysis revealed that the presence of baseline circulating tumor DNA (ctDNA) is a poor prognostic biomarker but could predict the higher therapeutic benefit for the combination of osimertinib and chemotherapy when compared to osimertinib monotherapy [23]. More studies are warranted to define the optimal biomarker for stratifying patients to receive different treatment modalities—including osimertinib monotherapy, the osimertinib and chemotherapy combination, or lazertinib combined with amivantamab—as well as to identify the resistance mechanisms and optimal second-line therapy for patients who received first-line combination osimertinib and chemotherapy.

#### *Resectable early-stage disease*

Based on the clinical benefit of EGFR TKIs in metastatic settings, their role also was evaluated in early-stage EGFR-mutant NSCLC. In the adjuvant settings, the phase 3 ADAURA study investigated osimertinib for 3 years

compared to placebo following adjuvant platinum-based chemotherapy in resectable NSCLC. This study met its primary endpoint of disease-free survival (DFS) (median DFS: 65.8 vs 21.9 months; HR: 0.23; 95%; CI 0.18–0.30; $P < 0.001$) and showed an OS benefit (5-year OS: 85% vs 73%; HR: 0.49; 95% CI 0.33–0.73; $P < 0.001$) [24, 25]. More importantly, adjuvant osimertinib led to a lower rate of CNS recurrence (HR: 0.24; 95% CI 0.14–0.42) [24]. Based on the study result, the FDA approved osimertinib for adjuvant therapy for patients with early-stage NSCLC and common EGFR mutations after tumor resection, paving the way for targeted therapy against actionable mutations in adjuvant settings. However, many patients in the treatment arm experienced disease recurrence immediately after completing the 3-year course of osimertinib, accompanied by a subsequent loss of CNS control [26]. This raises the important question of how long patients should be treated with osimertinib. Given the long-term AEs associated with osimertinib, particularly cardiac risk [27], there is a need for predictive biomarkers to determine the optimal treatment duration.

A post-hoc analysis of the ADAURA study data focusing on molecular residual disease (MRD) was reported recently at the 2024 American Society of Clinical Oncology (ASCO) annual meeting. The analysis first identified a patient-specific panel for detecting MRD. The baseline MRD rates were 0%, 8%, and 13% among patients with stages IB, II, and III NSCLC, respectively. The incidence of baseline MRD was higher among patients who did not receive adjuvant chemotherapy. Among patients without baseline-detected MRD, more MRD events were identified in those receiving placebo (69%) than those receiving adjuvant osimertinib (25%). For patients with baseline-detected MRD, 100% of those receiving placebo relapsed during the first 3 years and 80% of those receiving osimertinib experienced disease recurrence, with 2 cases occurring during treatment and 2 after treatment [28]. These results suggest that the presence of MRD might be an indicator for extended treatment with osimertinib in the adjuvant setting.

On the other hand, studying osimertinib in the neoadjuvant setting showed underwhelming results. Aredo et al. evaluated the efficacy of neoadjuvant osimertinib up to 8 weeks prior to surgical resection of stage I-IIIA EGFR-mutant NSCLC [29]. In this phase 2 study, the major pathological response (MPR) rate was approximately 15% with no observed pathologic complete response (pCR) and a median DFS of 32.4 months (95% CI 25.9-NR) [29]. These results indicate the importance of its combination with chemotherapy; the ongoing phase 3 NeoADAURA study is comparing the treatment efficacy of neoadjuvant combination osimertinib and chemotherapy with neoadjuvant osimertinib or chemotherapy alone (NCT04351555). Further biomarker analysis revealed that co-occurring RBM10 mutations may interfere with treatment response, and YAP1 activation could drive tumor growth, presenting potential targets for combination therapy [29].

#### *Unresectable early-stage disease*

Following the PACIFIC trial, durvalumab has become the standard of care for patients with stage III unresectable NSCLC receiving concurrent chemoradiation without progression; however, patients with EGFR-mutant NSCLC still derive less benefit from consolidative durvalumab [30]. A retrospective study involving patients with stage III NSCLC indicated that the presence of an EGFR mutation is a poor prognostic factor [31]. Subsequent analysis revealed that among patients with stage III unresectable NSCLC, durvalumab did not provide a survival benefit, whereas EGFR-TKI consolidation resulted in significant benefits [32, 33]. In the phase 3 LAURA trial, which enrolled patients with stage III unresectable EGFR-mutant NSCLC, those who received osimertinib had a PFS of 39.1 months (95% CI 31.5-NR) —significantly longer than the control group's PFS of 5.6 months (95% CI 3.7–7.4, $P < 0.001$) [34]. Currently, the use of osimertinib in the consolidative setting after chemoradiotherapy is under FDA review.

Taken together, the findings from the LAURA and ADAURA trials highlight the fact that targeted therapy improves the outcome of early-stage EGFR-mutant NSCLC. Future studies are warranted to identify biomarkers for de-escalating treatment and balancing survival, quality of life, and medical costs. Current therapeutic strategies for patients with common EGFR mutations are summarized in Fig. 2.

### KRAS-mutant NSCLC

KRAS mutation is the most prevalent oncogenic driver mutation in NSCLC, accounting for 30% of cases, with the most frequent mutations occurring in codons 12 and 13 [35]. Developing targeted therapy for KRAS has been challenging due to the molecule's round and smooth surface and its high affinity for guanosine triphosphate (GTP) [35]. Two FDA-approved KRAS inhibitors, sotorasib and adagrasib, were developed to target the inactive conformation of the KRAS protein [36, 37]. The single-arm phase 2 clinical trials of sotorasib [38] and adagrasib [39] established their efficacy in patients with pretreated KRAS G12C-mutant NSCLC and also identified KEAP1 as a poor prognostic co-occurring mutation. At the 2-year follow-up of the KRYSTAL-1 study of adagrasib, patients with co-occurring TP53 mutations had the longest OS of 18.7 months (95% CI 11.3–27.0), followed by those with CDKN2A

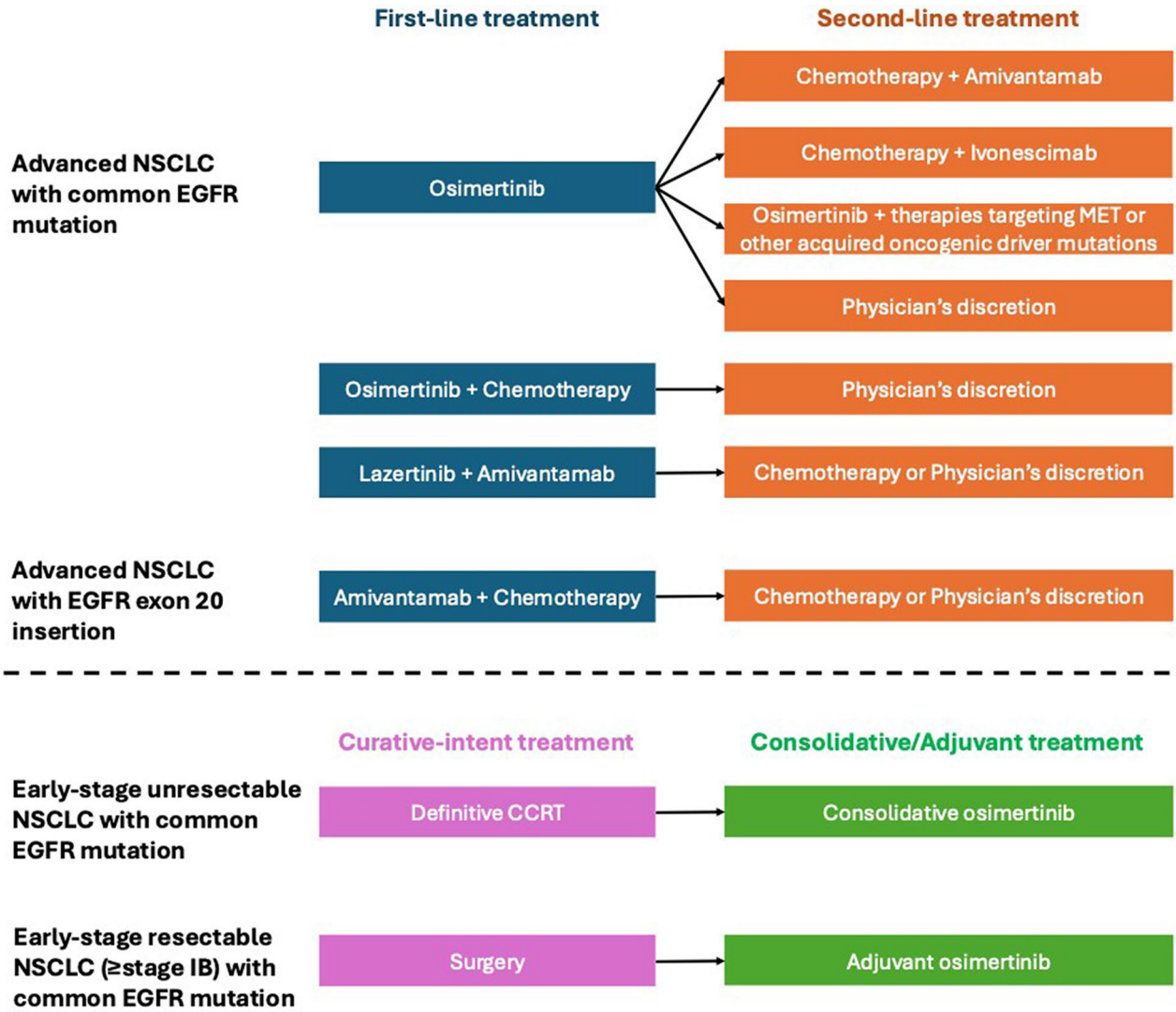


**Fig. 2** Proposed therapeutic strategies for patients with common EGFR mutation. ADC, antibody–drug conjugate; CCRT, concurrent chemoradiotherapy; MET, mesenchymal-epithelial transition

mutations (13.0 months; 95% CI 1.6–20.8), STK11 mutations (9.2 months; 95% CI 5.0–12.7), and KEAP1 mutations (5.7 months; 95% CI 3.6–9.2) [40]. Despite their success in the phase 3 clinical trials CodeBreak 200 [41] and KRYSTAL-12 [42], the PFS for both drugs was only around 6 months, indicating a need for further investigation into combination therapies.

The CodeBreak 100/101 study investigated the efficacy of combining sotorasib with pembrolizumab or atezolizumab in KRAS G12C inhibitor-naïve patients with KRAS G12C-mutant NSCLC, revealing that over 30% of patients experienced ≥ grade 3 hepatitis [43]. Another multicenter retrospective study enrolling patients with advanced KRAS G12C-mutant NSCLC also demonstrated a threefold higher risk of severe hepatitis with sequential use of PD-1 inhibitors and sotorasib [44]. These findings limit the use of the sotorasib-pembrolizumab combination.

In contrast, the phase 2 KRYSTAL-7 trial demonstrated that the combination of adagrasib and pembrolizumab provided an ORR of 63% and a disease control rate (DCR) of 84% among treatment-naïve patients with KRAS G12C-mutant NSCLC and PD-L1 expression higher than 50%, with treatment-related hepatic events occurring in less than 10% of patients [45]. An ongoing phase 3 trial is comparing concurrent adagrasib and pembrolizumab vs pembrolizumab monotherapy for treatment-naïve patients with KRAS

G12C-mutated NSCLC and PD-L1 expression ≥ 50% (NCT04613596).

Since the combination of sotorasib and ICIs is associated with a higher risk of AEs, another combination strategy is combining sotorasib with platinum doublet chemotherapy. The phase 1b CodeBreak 101 study evaluated the combination of chemotherapy and sotorasib, reporting an ORR of 65% in treatment-naïve and 54% in pretreated patients with KRAS G12C-mutant NSCLC, without additional AEs [46]. Currently, the ongoing phase 3 CodeBreak 202 trial aims to compare this combination with chemoimmunotherapy in treatment-naïve patients with KRAS G12C-mutated NSCLC (NCT05920356).

In addition to the development of combination therapy based on sotorasib and adagrasib, multiple KRAS G12C inhibitors are being investigated. For instance, divarasib (GDC-6036) has demonstrated more favorable therapeutic efficacy in patients with KRAS G12C-mutant NSCLC. In the NSCLC cohort of the phase 1 study evaluating divarasib's efficacy, the ORR was 53.4% and the median PFS was 13.1 months [47]. The ongoing phase 3 KRASCENDO 1 study will compare the efficacy of divarasib with sotorasib and adagrasib in patients with pretreated KRAS G12C-mutant NSCLC (NCT06497556). Broadly, new agents and strategies targeting KRAS G12C and other mutations for treating KRAS-mutant NSCLC and other cancers are being vigorously investigated, leading to the expansion of the potential options to improve patient outcomes [48].

#### ALK fusion-positive NSCLC

Since the identification of the anaplastic lymphoma kinase (ALK) fusion protein, several ALK TKIs have been developed [49]. Second-generation ALK TKIs have become the mainstay of treatment due to their significantly extended PFS and higher intracranial response rates [49]. The third-generation ALK TKI, lorlatinib, has also been proven to be an effective second-line treatment for patients with acquired resistance to second-generation ALK TKIs [50]. However, sequential use of second- to third-generation ALK TKIs can induce compound mutations, leading to lorlatinib resistance [51]. The resistance mediated by compound mutations might be addressed by fourth-generation ALK TKIs, such as NVL-655 [52] and TPX-0131 [53, 54]. In the phase 1/2 ALVOKE-1 study using NVL-655, the ORR was 38% (39/103) in the overall population, including 37% (16/43) among patients who had received at least 3 prior lines of ALK TKIs, including second- and third-generation ALK TKIs. More importantly, the ORR was 58% (15/26) in patients harboring compound mutations, which supports the role of NVL-655 in this patient population [55]. NVL-655 also exhibited an intracranial response rate of 50% (1/2) among patients who were lorlatinib naïve and 15% (2/13) among patients who received prior lorlatinib therapy [55].

The phase 3 CROWN study evaluated the efficacy of first-line lorlatinib [56]. In the updated long-term report, the ORR was 81% (95% CI 73–87%), and the median PFS remains unreached after 5 years [56]. Notably, upon acquired resistance, no ALK kinase domain mutations emerged, which might explain the extremely long PFS and imply lower tumor heterogeneity [56]. This observation potentially supports the first-line use of lorlatinib rather than its sequential use. The FDA has approved lorlatinib as a first-line treatment option for ALK-positive NSCLC.

Similar to EGFR-mutant NSCLC, there is an increasing focus on clinical trials for early-stage ALK-positive NSCLC. The phase 3 ALINA study aims to compare the treatment efficacy between adjuvant alectinib and chemotherapy [57]. In this study, DFS remains unreached in patients with stage II-IIIA or stage IB-IIIA disease (the intention-to-treat population); the DFS in both patient groups was significantly longer than in those receiving placebo [57]. Additionally, the incidence of distant recurrence was significantly decreased (2.3% vs 17.3%) in the alectinib group [57]. Despite the excellent treatment outcomes and FDA approval of alectinib as an adjuvant therapy, several questions remain that require further investigation. These include the optimal treatment duration, AE management, and OS benefit.

#### ROS1 fusion-positive NSCLC

The c-ROS1 proto-oncogene is a member of the human receptor tyrosine kinase family and was first identified as a fusion variant, SLC34A2-ROS1 and CD74-ROS1, in NSCLC cell lines [58]. Since ROS1 shares a high degree of amino acid sequence homology in the kinase domain with ALK [59], several ALK-TKIs have demonstrated efficacy in treating patients with ROS1 fusion-positive NSCLC, including crizotinib [60, 61], lorlatinib [62, 63], and entrectinib [64, 65]. Despite the promising response to targeted therapy, disease progression is inevitable, with the solvent-front mutation G2032R emerging as the most prevalent acquired resistance mechanism in patients with ROS1 fusion-positive NSCLC [66]. While the solvent mutation G1202R in the ALK kinase protein can be treated with the third-generation ALK TKI lorlatinib [67], the response rate with lorlatinib for patients with the acquired ROS1 G2032R mutation was 0% [62].

Repotrectinib, a next-generation TKI targeting both ROS1 and TRK, has demonstrated clinical activity and manageable safety in patients with ROS1 fusion-positive NSCLC in the pivotal phase 1/2 TRIDENT-1 trial (NCT03093116). Among TKI-naïve ROS1 fusion-positive

NSCLC patients, the response rate was 79% (95% CI 68–88%), the DOR was 34.1 months (95% CI 25.6-NE), and the median PFS was 35.7 months (95% CI 27.4-NE). For patients previously treated with ROS1 TKIs, the response rate was 38% (95% CI 25–52%), the DOR was 14.8 months (95% CI 7.6-NE), and the median PFS was 9.0 months (95% CI 6.8–19.6) [68]. Notably, for patients with the acquired G2032R mutation, the response rate with repotrectinib was 59% (95% CI 33–82%), which is significantly better than the historical data with lorlatinib. Additionally, most AEs were manageable, with only 3% of patients discontinuing repotrectinib due to them [68]. These data suggest that repotrectinib can be an outstanding choice for first-line therapy and can effectively overcome the common acquired resistance mechanism in ROS1 fusion-positive NSCLC. Based on these results, repotrectinib was approved by the FDA for ROS1 fusion-positive NSCLC in 2024.

Foritinib is another potential ROS1 tyrosine kinase inhibitor (TKI) that has demonstrated promising tumor-suppressive effects in preclinical studies using nude mice bearing BaF3/CD74-ROS1$^{G2032R}$ xenografts [69]. In a phase 2 single-arm study evaluating the therapeutic efficacy of foritinib, the ORR was 94% (16/17) in ROS1 inhibitor-naïve patients and 40% (10/25) in patients who had previously received a ROS1 inhibitor [70]. In an exploratory analysis of patients with CNS metastases at baseline, the ORR was 100% (5/5) in ROS1 inhibitor-naïve patients and 40% (6/15) in previously treated patients [70]. These findings support foritinib as a promising first-line treatment for ROS1 fusion-positive NSCLC. Further investigation is warranted, particularly in patients with acquired G2032R resistance mutations.

#### NTRK fusion-positive NSCLC

Despite the excellent treatment responses demonstrated by entrectinib and repotrectinib for patients with neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumors [71–74], disease progression remains inevitable, as the solvent-front mutation is a major acquired resistance mechanism [74]. Since repotrectinib could target both ROS1 and NTRK, patients with NTRK fusion-positive solid tumors were also enrolled in the pivotal phase 1/2 TRIDENT-1 study. Among patients with TKI-naïve NTRK fusion-positive NSCLC, the response rate to repotrectinib was 58% (95% CI 41–73%), the 12-month DOR was 86% (95% CI 71–100%), and the 12-month PFS was 56% (95% CI 40–72%). For patients previously treated with NTRK TKIs, the response rate was 50% (95% CI 35–65%), the 12-month DOR was 39% (95% CI 16–62%), and the 12-month PFS was 22% (95% CI 8–36%) [75].

The response rate to repotrectinib was similar to patients who received entrectinib or larotrectinib as first-line therapy. More importantly, for patients with acquired solvent mutations, the response rate to repotrectinib was 60% (95% CI 39–79%), the 12-month DOR was 33% (95% CI 7–58%), and the 12-month PFS was 21% (95% CI 4–39%) [75]. Approximately 7% of patients discontinued repotrectinib due to treatment-related AEs. These results indicate that repotrectinib is a very promising second-line therapy for NTRK fusion-positive solid tumors.

#### MET exon 14 skipping NSCLC

The MET exon 14 skipping mutation results in the loss of the juxtamembrane domain of the MET protein, leading to a loss of self-regulatory function and the constitutive activation of oncogenic signaling [76]. There are 2 FDA-approved MET TKIs, capmatinib and tepotinib, that are effective for this subgroup of patients [77–79]. Recently, another MET TKI, savolitinib, was evaluated in a phase 3b study, demonstrating an ORR of 58.6% (95% CI 47.6–69.1), a PFS of 13.8 months (95% CI 9.7-NR), and a 12-month OS of 77.9% (95% CI 67.5–85.3), with tolerable AEs [80]. The response rate was consistent across all types of exon 14 skipping subtypes, including base substitution, insertion/deletion, splice site alteration, and whole exon deletion [80]. An alternative approach for MET exon 14 skipping is amivantamab, which is a bispecific antibody.

#### HER2-mutant NSCLC

About 3–5% of patients with NSCLC have a human epidermal growth factor receptor 2 (HER2) mutation; more than 80% of these mutations are due to an exon 20 insertion [81]. Poziotinib was evaluated in the ZENITH20 study, demonstrating an ORR of 30% and a PFS of 5.6 months in patients with HER2-mutant NSCLC who received at least 2 prior therapies [82]. The treatment outcome was similar with treatment-naïve patients with HER2-mutated NSCLC [83]. Additionally, the ORR was consistent regardless of the types and sequences of prior treatments, including anti-HER2 antibodies and ADCs, suggesting that poziotinib might be a potential salvage therapy option [82]. However, the relatively low intracranial response rate (22.2%) [84], aggressive toxicity profiles, and high dose interruption rate limited its clinical application.

Emerging small molecules targeting HER2 mutation were recently reported at the International Association for the Study of Lung Cancer (IASLC) 2024 World Conference on Lung Cancer (WCLC). The phase 1a/1b BEAMION LUNG-1 study evaluated the treatment efficacy of zongertinib (BI1810631), a small-molecule HER2 TKI, demonstrating an ORR of 73.9% with minimal

toxicity (less than 10% experienced grade ≥ 3 AEs) [85]. The updated analysis from the phase 1a cohort further revealed encouraging survival results, with median PFS of 13.8 months (2.3-NR) and 12.3 months (7.6–17.2) among patients with a twice-a-day escalation dosage and a once-a-day escalation dosage, respectively [86]. Subsequent analysis from the phase 1b cohort further demonstrated comparable ORRs (72.4% vs 78.2%) between patients who received 120 mg and 240 mg of zongertinib, with similar and manageable AE profiles [87]. These data suggest that zongertinib could be another potential promising treatment option in the future. The ongoing phase 3 BEAMION LUNG-2 study will compare zongertinib with the standard of care as a first-line treatment for patients with HER2-mutated NSCLC (NCT06151574).

Another promising small-molecule inhibitor is BAY 2927088, a reversible TKI that potently targets activating HER2 mutations in preclinical models [88]. In the expansion cohort of the phase 1/2 SOHO-01 study, which enrolled pretreated patients with HER2-mutated NSCLC, BAY 2927088 demonstrated rapid and durable responses, with an ORR of 72.1% and a median PFS of 7.5 months [89]. The outcomes were even more favorable among patients with HER2 YVMA insertions, showing an ORR of 90.0% and a median PFS of 9.9 months [89]. These data support the ongoing phase 3 SOHO-02 trial, which compares BAY 2927088 with the standard of care as a first-line treatment for patients with HER2-mutated NSCLC (NCT06452277). In addition to small-molecule targeted therapy, an alternative approach for HER2 mutation is the ADC trastuzumab deruxtecan (further discussed in "Traztuzumab deruxtecan" section). Table 1 summarizes the clinical efficacy of targeted therapy in representative trials.

#### Clinical activity of targeted therapies for CNS metastases in NSCLC harboring driver mutations

Some patients with metastatic NSCLC have CNS metastases that exhibit resistance to standard cytotoxic chemotherapy due to the blood–brain barrier (BBB), which restricts the penetration of systemically administered agents into the CNS and brain lesions. Molecularly targeted therapies serve as crucial treatment options for CNS metastases, particularly in patients harboring specific driver mutations. Certain targeted therapies have demonstrated improved CNS penetration, enabling them to overcome the BBB and reach metastatic brain lesions [90]. Targeted therapies including osimertinib, alectinib, lorlatinib, and others are well known with strong CNS bioavailability. However, the optimal strategy of targeted therapy for CNS metastases in NSCLC harboring driver mutations is still evolving and is a key clinical question of interest to thoracic oncologists.

In metastatic EGFR-mutated NSCLC, the results from the FLAURA study demonstrated that osimertinib has clinical efficacy for CNS metastasis. The combination of osimertinib with platinum pemetrexed showed superior CNS efficacy compared to osimertinib monotherapy, delaying CNS progression (HR 0.58, 95% CI 0.43–1.04) and improving the intracranial complete response rate (59% vs. 43%) in the FLAURA2 study [91].

For patients with metastatic ALK fusion-positive NSCLC, alectinib and lorlatinib demonstrated superior CNS activity and significantly delayed CNS progression compared to crizotinib in subgroup analyses of 2 phase 3 studies, including the ALEX [92] and the CROWN studies [93]. The next-generation ALK inhibitor NVL-655 also demonstrated a promising intracranial response rate of 50% in the lorlatinib naïve subgroup and 15% in the lorlatinib-pretreated subgroup [55].

For metastatic ROS1 fusion-positive NSCLC, lorlatinib achieved an intracranial response rate of 64% among TKI-naïve patients and 50% among crizotinib-pretreated patients [62]. An updated integrated analysis of 3 phase 1/2 studies—ALKA-372–001, STARTRK-1, and STARTRK-2—demonstrated a promising intracranial response rate of 79.2% with entrectinib [94]. Additionally, entrectinib has shown potential as a salvage therapy for patients with ROS1 fusion-positive NSCLC who experience CNS-only progression following crizotinib treatment [95]. The next-generation ROS1 TKI repotrectinib has also exhibited a favorable intracranial response rate, with 89% in TKI-naïve patients and 38% in TKI-pretreated patients [68]. These data support the role of entrectinib and repotrectinib in achieving optimal CNS control in ROS1 fusion-positive NSCLC.

On the other hand, the clinical activity of KRAS G12C inhibitors in CNS metastases appears to be limited compared to EGFR and ALK inhibitors. In the CodeBreaK 200 phase 3 study, sotorasib exhibited promising clinical activity in a small subset of patients with CNS metastases ($n = 40$ in the sotorasib arm, $n = 29$ in the docetaxel arm). The median time to CNS recurrence was 9.6 months with sotorasib versus 5.4 months with docetaxel (HR 0.84, $P = 0.37$) [96]. In a preclinical mouse model bearing intracranial KRAS G12C-mutant NSCLC xenografts, adagrasib demonstrated good CNS penetration, with increased drug concentrations in plasma, cerebrospinal fluid, and brain tissue, correlating with antitumor activity [97]. In the KRYSTAL-1 phase 1/2 study, adagrasib achieved an intracranial ORR of 42% in patients with CNS metastases [98].

**Table 1** Representative clinical trials for targeted therapies in NSCLC

| Study | Patients | Treatment | ORR (%) | mPFS or mDFS (months) | HR for mPFS/mDFS | mOS (months) | HR for mOS | ≥ G3 AE (%) | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| FLAURA | Treatment-naïve EGFR-mutant advanced NSCLC | Osimertinib | 80 | 18.9 | 0.46 [0.37–0.57] | 38.6 | 0.80 [0.64–1.00] | 34 | [11–13] |
| | | SoC (erlotnib or gefitinib) | 76 | 10.2 | | 31.8 | | 45 | |
| FLAURA2 | Treatment-naïve EGFR-mutant advanced NSCLC | Osimertinib + CT | 83 | 29.4 | 0.62 [0.48–0.80] | $^{\$}$79% | 0.90 [0.65–1.24] | 54 | [22] |
| | | Osimertinib | 76 | 19.9 | | $^{\$}$73% | | 11 | |
| MARIPOSA | Treatment-naïve EGFR-mutant advanced NSCLC | Lazertinib + amivantamab | 86 | 23.7 | 0.70 [0.58–0.85] | $^{\$}$74% | 0.80 [0.61–1.05] | 75 | [17] |
| | | Osimertinib | 85 | 16.6 | | $^{\$}$69% | | 43 | |
| INSIGHT2 | Osimertinib-resistant EGFR-mutant NSCLC | Osimertinib + tepotinib | 50 | 5.6 | | 17.8 | | | [15] |
| CHRYSALIS | Osimertinib-resistant EGFR-mutant NSCLC (combinational cohort) | Lazertinib + amivantamab | 36 | 4.9 | | | | 4 | [137] |
| CHRYSALIS-2 | NSCLC with uncommon EGFR mutations | | | | | | | | [141] |
| | Total population | Lazertinib + amivantamab | 52 | 11 | | | | | |
| | Treatment-naïve | Lazertinib + amivantamab | 57 | 19.5 | | | | | |
| | TKI-pretreated | Lazertinib + amivantamab | 48 | 7.8 | | | | | |
| PALMOMA-3 | Osimertinib- and chemotherapy-pretreated EGFR-mutant advanced NSCLC | Lazertinib + amivantamab (s.c.) | 27 | 6.1 | 0.84 [0.64–1.10] | NR | 0.62 [0.42–0.92] | 52 | [142] |
| | | Lazertinib + amivantamab (i.v.) | 27 | 4.3 | | NR | | 56 | |
| HARMONi-A | Osimertinib-resistant EGFR-mutant NSCLC | Ivonescimab + CT | 50.6 | 7.1 | | | | 61.5 | [20] |
| | | Placebo + CT | 35.4 | 4.8 | | | | 49.1 | |
| ADAURA | Resectable early-stage EGFR-mutant NSCLC (≥ stage IB) | Osimertinib | | 68.5 | | *85% | | | [24] |
| | | Placebo | | 21.9 | | *73% | | | |
| LAURA | Unresectable early-stage EGFR-mutant NSCLC | Osimertinib | | 39.1 | | | | | [34] |
| | | Placebo | | 5.6 | | | | | |
| CodeBreaK100 | $KRAS^{G12C}$-mutant advanced NSCLC refractory to CT and PD-1/PD-L1 Ab | Sotorasib | 37.1 | 6.8 | | 12.5 | | 19.8 | [36] |
| KRYSTAL-1 | $KRAS^{G12C}$-mutant advanced NSCLC refractory to CT and PD-1/PD-L1 Ab | Adagrasib | 42.9 | 6.5 | | 12.6 | | 44.8 | [37] |

**Table 1** (continued)

| Study | Patients | Treatment | ORR (%) | mPFS or mDFS (months) | HR for mPFS/mDFS | mOS (months) | HR for mOS | ≥ G3 AE (%) | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| CodeBreak200 | $KRAS^{G12C}$-mutant advanced NSCLC refractory to CT and PD-1/PD-L1 Ab | Sotorasib<br>Docetaxel | 28.1<br>13.2 | 5.6<br>4.5 | | 10.6<br>11.3 | | 33<br>40 | [41] |
| KRYSTAL-12 | $KRAS^{G12C}$-mutant advanced NSCLC refractory to CT and PD-1/PD-L1 Ab | Adagrasib<br>Docetaxel | 31.9<br>9.2 | 5.5<br>3.8 | | | | 47<br>45.7 | [42] |
| CodeBreak100/101 | KRAS G12C inhibitor-naïve $KRAS^{G12C}$-mutant advanced NSCLC | Sotorasib + atezolizumab (lead-in) | 20 | | | 8.1 | | 30 | [43] |
| | | Sotorasib + atezolizumab (concurrent) | 20 | | | 11.5 | | 60 | |
| | | Sotorasib + pembrolizumab (lead-in) | 37 | | | NR | | 53 | |
| | | Sotorasib + pembrolizumab (concurrent) | 32 | | | 14.1 | | 79 | |
| CodeBreak 101 | KRAS G12C inhibitor-naïve $KRAS^{G12C}$-mutant advanced NSCLC | | | | | | | | [46] |
| | First-line | Sotorasib + CT | 65 | 10.8 | | | | 49 | |
| | Second-line | Sotorasib + CT | 54 | 8.3 | | | | 57 | |
| KRYSTAL-7 | Treatment-naïve $KRAS^{G12C}$-mutant advanced NSCLC with PD-L1 ≥ 50% | Adagrasib + pembrolizumab | 63 | NR | | | | 5 | [45] |
| GO42144 | $KRAS^{G12C}$-mutant advanced NSCLC | Divarasib | 56.4 | 13.1 | | | | 18 | [47] |
| CROWN | Treatment-naïve ALK-rearranged advanced NSCLC | Lorlatinib<br>Crizotinib | 76<br>58 | NR<br>9.3 | 0.28<br>[0.19–0.41] | NR<br>NR | 0.72<br>[0.41–1.25] | 58<br>47 | [56] |
| ALVOKE-1 | Pre-treated ALK-rearranged advanced NSCLC | | | | | | | | [55] |
| | Total population | NVL-655 | 38 | | | | | | |
| | ≥ 3 prior ALK-TKI | NVL-655 | 37 | | | | | | |
| | Lorlatinib-naïve | NVL-655 | 53 | | | | | | |
| | Prior lorlatinib | NVL-655 | 76 | | | | | | |
| | G1202R mutation | NVL-655 | 49 | | | | | | |
| | Compound mutation | NVL-655 | 58 | | | | | | |

**Table 1** (continued)

| Study | Patients | Treatment | ORR (%) | mPFS or mDFS (months) | HR for mPFS/ mDFS | mOS (months) | HR for mOS | ≥ G3 AE (%) | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| ALINA | Resectable early-stage ALK-rearranged NSCLC | | | | | | | | [57] |
| | Stage II-IIIA | Alectinib | | NR | 0.24 [0.13–0.45] | | | 29.7 | |
| | | CT | | 44.4 | | | | 30.8 | |
| | Stage IB-IIIA | Alectinib | | NR | 0.24 [0.13–0.43] | $^{\$}$98.4% | 0.22 [0.08–0.58] | | |
| | | CT | | 41.3 | | $^{\$}$85.8% | | | |
| Profile1001 | ROS1-rearranged advanced NSCLC | Crizotinib | 72 | 19.2 | | 51.4 | | 36 | [60, 61] |
| Phase 2 study of lorlatinib | ROS1-rearranged advanced NSCLC | | | | | | | | [62, 63] |
| | TKI-naïve | Lorlatinib | 81 | NR | | | | 43 | |
| | Crizotinib-pretreated | Lorlatinib | 46 | 13.9 | | | | | |
| Integrated analysis of ALKA-372–001, STARTRK-1, and STARTRK-2 | ROS1-rearranged advanced NSCLC | Entrectinib | 77 | 19.0 | | | | 34 | [64, 65, 72, 73] |
| | NTRK-rearranged advanced NSCLC | Entrectinib | 57 | 11.0 | | 21.0 | | | |
| Integrated analysis of 3 phase1/2 studies | NTRK-rearranged advanced NSCLC | Larotrectinib | 79 | 28.3 | | 44.4 | | 39 | [71, 74] |
| TRIDENT-1 | ROS1-rearranged advanced NSCLC | | | | | | | | [68, 75] |
| | TKI-naïve | Repotrectinib (TPX-0005) | 79 | | | | | | |
| | Prior ROS1 TKI | Repotrectinib (TPX-0005) | 38 | 35.7 | | | | | |
| | G2032R mutation | Repotrectinib (TPX-0005) | 59 | 9.0 | | | | | |
| | NTRK-rearranged advanced NSCLC | | | | | | | | |
| | TKI-naïve | Repotrectinib (TPX-0005) | 58 | $^{\#}$50% | | | | | |
| | Prior NTRK TKI | Repotrectinib (TPX-0005) | 50 | $^{\#}$22% | | | | | |
| | Solvent-front mutation | Repotrectinib (TPX-0005) | 60 | $^{\#}$21% | | | | | |
| SAF001 | ROS1-rearranged advanced NSCLC | | | | | | | | [70] |
| | TKI-naïve | Foritinib | 94 | | | | | | |
| | TKI-naïve with CNS mets | Foritinib | 100 | | | | | | |
| | Prior ROS1 TKI | Foritinib | 40 | | | | | | |
| | Prior ROS1 TKI with CNS mets | Foritinib | 40 | | | | | | |

**Table 1** (continued)

| Study | Patients | Treatment | ORR (%) | mPFS or mDFS (months) | HR for mPFS/ mDFS | mOS (months) | HR for mOS | ≥ G3 AE (%) | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| GEOMETRY mono-1 | Advanced NSCLC with MET exon 14 skipping | | | | | | | | [77, 79] |
| | Cohort 4 (previously treated) | Capmatinib | 41 | 5.4 | | 46.4 | | 75 | |
| | Cohort 5b (treatment naïve) | Capmatinib | 68 | 12.4 | | 66.9 | | 75 | |
| VISION cohort A | Advanced NSCLC with MET exon 14 skipping | | | | | | | | [78] |
| | Tissue-biopsy | Tepotinib | 62 | 11.0 | | | | | |
| | Liquid-biopsy | Tepotinib | 56 | 8.5 | | | | | |
| Phase 3b study of savolitinib | Advanced NSCLC with MET exon 14 skipping | Savolitinib | 58.6 | 13.8 | | | | | [80] |
| ZENITH-20 | HER2-mutant advanced NSCLC | | | | | | | | [82, 83] |
| | Cohort 2 (≥ 2 prior treatment) | Poziotinib | 39 | 5.6 | | | | | |
| | Cohort 4 (treatment naïve) | Poziotinib | 30 | 5.6 | | | | | |
| BEAMION Lung-1 | HER2-mutant advanced NSCLC | | | | | | | | [86, 87] |
| | Cohort 1a | Zongertinib twice-a-day escalation<br>Zongertinib once-a-day escalation | | 13.8<br>12.3 | | | | 9.6 | |
| | Cohort 1b | Zongertinib 120 mg<br>Zongertinib 240 mg | 72.4<br>78.2 | | | | | 15.2 | |
| SOHO-1 | HER2-mutant advanced NSCLC | | | | | | | | [88, 89] |
| | Total population<br>YVMA insertions | BAY 2927088<br>BAY 2927088 | 72.1<br>90 | 7.5<br>9.9 | | | | 40.9 | |
| Phase 1/1b study of telisotuzumab vedotin | EGFR-mutant advanced NSCLC with acquired resistance to osimertinib | Osimertinib + telisotuzumab vedotin | 50 | 7.4 | | | | 32 | [186] |

Ab, antibodies; CT, chemotherapy; G3 AE, grade 3 adverse event; HR, hazard ratio; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; SoC, standard of care; TKI, tyrosine kinase inhibitor

[#] 1-year progression-free survival

[$] 2-year overall survival rate

*5-year overall survival rate

## Recent advances in immunotherapy

### Perioperative immunotherapy for early-stage lung cancer

The implementation of neoadjuvant or adjuvant immunotherapy has been shown to improve DFS among

**Table 2** Summary of clinical trials focusing on perioperative immunotherapy combinations

| Clinical trial | CheckMate-816 (Arm C) | CheckMate-816 (Arm A, terminated prematurely) | CheckMate-77 T | AEGEAN | KEYNOTE -671 | NEOTORCH |
|---|---|---|---|---|---|---|
| Phase | 3 | 3 | 3 | 3 | 3 | 3 |
| Stage | IB-IIIA | IB-IIIA | II-IIIB | II-IIIB | II-IIIB | II-III |
| No. patients | 358 | 215 | 452 | 800 | 786 | 404 |
| Experimental arm | Nivolumab + CT 3 cycles | Nivolumab 3 cycles + ipilimumab at cycle 1 | Nivolumab + CT 4 cycles | Durvalumab + CT 4 cycles | Pembrolizumab + CT 4 cycles | Toripalimab + CT 3 cycles |
| Control arm | CT alone | CT alone | CT alone | CT alone | CT alone | CT alone |
| Primary endpoint | EFS, pCR, OS | EFS, pCR, OS | EFS | MPR, EFS | EFS | MPR, EFS |
| MPR (%) | 36.9 vs 8.9 | 28.3 vs 14.8 | 35.4 vs 12.1 | 33.3 vs 12.3 | 30.2 vs 11.0 | 48.5 vs 8.4 |
| pCR (%) | 24.0 vs 2.2 | 20.4 vs 4.6 | 25.3 vs 4.7 | 17.2 vs 4.3 | 18.1 vs 4.0 | 24.8 vs 1.0 |
| Median EFS | NR (31.6-NR) vs 21.1 (14.8–42.1) | 54.8 (24.4-NR) vs 20.9 (14.2-NR) | NR (28.9-NR) vs 18.4 (13.6–28.1) | NR (31.9-NR) vs 25.9 (18.9-NR) | 47.2 (32.9-NR) vs 18.3 (14.8–22.1) | NR (NR-NR) vs 15.1 (10.6–21.9) |
| 2-year OS | 82.7% | 82.0% | | | 80.9% | 81.2% |

CT, chemotherapy; EFS, event-free survival; pCR, pathologic complete response; OS, overall survival; MPR, major pathological response; NR, not reached. The references are listed in the related description.

patients with early-stage NSCLC [99]. The combination of nivolumab and chemotherapy has demonstrated improved DFS and OS in patients with early-stage NSCLC without EGFR mutations or ALK rearrangements, with pCR serving as the most important predictive biomarker for better DFS and OS [100]. Similar findings were observed in clinical trials utilizing nivolumab in combination therapy, including CheckMate 77 T [101] and NADIM2 [102], and in trials using other ICIs, such as durvalumab in the AEGEAN trial [103], pembrolizumab in the KEYNOTE-671 trial [104], and toripalimab in the NEOTORCH trial [105] (Table 2). Currently, the ongoing IMPower030 trial aims to evaluate the outcome of neoadjuvant atezolizumab combined with chemotherapy [106]. An important question remains regarding which subgroups of patients should receive adjuvant immunotherapy. In the CheckMate 816 study, DFS was similar between the combination therapy and chemotherapy monotherapy arms when stratified by the presence of pCR [100]. In contrast, the KEYNOTE-671 study showed improved DFS in patients who did not achieve pCR when receiving adjuvant pembrolizumab [104]. Recently, a cross-trial comparison between CheckMate 816 and CheckMate 77 T demonstrated superior DFS in the CheckMate 77 T study, with the survival benefit primarily observed in patients who did not achieve pCR [107]. These findings suggest the need for refined selection criteria for determining which patients may benefit from adjuvant immunotherapy.

In the exploratory analysis of the CheckMate-816 trial, patients with PD-L1 expression ≥ 1% exhibited a higher pCR rate (32.6% vs 16.7%), better 3-year event-free survival (EFS) rate (72% vs 42%), and improved 3-year OS rate (85% vs 71%) than those with PD-L1 expression < 1% [108]. The combination of nivolumab and ipilimumab also demonstrated promising neoadjuvant efficacy in the CheckMate-816 study despite early closure of the immunotherapy combination arm [109]. In post-hoc analysis, high expression of a 4-gene signature, including CD8A, STAT1, LAG3, and CD274, was associated with better EFS in patients receiving the neoadjuvant nivolumab-ipilimumab combination [109].

Among patients with early-stage NSCLC, those with N2 lymph node involvement represent the most complicated subgroup; they typically require multidisciplinary management [110–112]. In the exploratory analysis of the phase 3 AEGEAN trial, the HR for EFS was 0.63 (95% CI 0.43–0.90) among patients with N2 disease treated with neoadjuvant durvalumab and chemotherapy, consistent with the modified intent-to-treat population (HR: 0.68). The DFS benefit was similar in both single-station and multi-station disease (HR: 0.61 and 0.69, respectively) [113].

Similarly, in the phase 3 CheckMate-77 T trial, the HR for EFS was comparable between patients with stage III NSCLC with N2 disease and those without N2 disease (HR: 0.46 and 0.60, respectively) treated with a combination of neoadjuvant nivolumab and chemotherapy. Additionally, a similar HR for EFS was observed between patients with single-station and multi-station N2 disease (HR: 0.40 and 0.23, respectively) [114]. These studies demonstrate that the combination of neoadjuvant

immunotherapy and chemotherapy could potentially address this challenging patient population that was difficult to treat during the chemotherapy era, establishing a new standard of care. The ongoing clinical trial will evaluate the efficacy of neoadjuvant durvalumab in combination with monalizumab, an anti-NKG2A monoclonal antibody; oleclumab, an anti-CD73 monoclonal antibody; or danvatirsen, an anti-STAT3 antisense oligonucleotide (NEOCOAST study, NCT03794544) [115]; it will also evaluate the efficacy of combining chemotherapy with dual immunotherapy—durvalumab plus monalizumab or durvalumab plus oleclumab—and combining chemotherapy with volrustomig, a bispecific antibody targeting both PD-1 and CTLA-4 (NEOCOAST-2, NCT05061550) [116].

Subsequent studies have mainly focused on the role of predictive biomarkers in the treatment efficacies of neoadjuvant therapy. The presence of an oncogenic driver mutation is typically a poor prognostic factor for immunotherapy. In the subgroup analysis of patients with EGFR-mutant NSCLC enrolled in the AEGEAN trial, EFS was similar between those who received neoadjuvant durvalumab plus chemotherapy and those who received neoadjuvant chemotherapy alone [117]. These data suggest that neoadjuvant chemoimmunotherapy may not be suitable for these patients, and the role of targeted therapy should be further evaluated.

In the 4-year follow-up of the CheckMate-816 trial, the survival benefit of the treatment persisted across different chemotherapy backbones. Additionally, ctDNA showed potential as a predictive biomarker. In the study, 43 patients in each group had detectable baseline ctDNA, and the clearance rate after neoadjuvant treatment was higher in the combination group (56% vs 35%). The clearance of ctDNA was also associated with better OS in both groups, indicating its predictive role for improved survival outcomes [118]. Similarly, in the exploratory ctDNA analysis of the AEGEAN trial, neoadjuvant durvalumab and chemotherapy resulted in a greater reduction in median variant allele fraction (VAF) compared to chemotherapy monotherapy [119]. All patients who achieved pCR and over 90% of patients who achieved MPR had ctDNA clearance by cycle 4 [119]. ctDNA clearance with neoadjuvant chemoimmunotherapy could be a potential early-response biomarker to identify patients who benefit from treatment before tumor resection.

There has been a similar finding in the adjuvant setting. The phase 3 Impower010 trial evaluated the treatment efficacy of adjuvant atezolizumab, which is FDA approved to treat early-stage PD-L1-positive NSCLC [120, 121]. Among the tumor mutational burden (TMB)-evaluable population, patients with low TMB had poor DFS compared to those with high TMB, and adjuvant atezolizumab improved DFS in both patients with high and low TMB [122], suggesting the TMB is more likely a prognostic biomarker. In the post-hoc analysis, the presence of the KRAS mutation did not affect the DFS benefit from adjuvant atezolizumab [123]. Using a generalized random forest model to evaluate RNA-sequencing data, a gene signature associated with TGFβ-mediated cancer-associated fibroblasts (CAFs) was identified as the greatest variable for predicting the benefit of atezolizumab compared to the control arm [124]. Patients with a high TGFβ CAF gene signature expression had worse DFS than those with low TGFβ CAF gene signature expression in the control group, indicating that this marker is a poor prognostic factor [124]. In contrast, patients in the atezolizumab group had similar survival outcomes regardless of high or low TGFβ CAF gene signature expression, indicating an improved outcome following the administration of atezolizumab [124]. Further prospective validation of these findings is warranted.

### Consolidative immunotherapy for unresectable early-stage lung cancer

Consolidative durvalumab has demonstrated significant clinical benefit in patients with unresectable early-stage NSCLC who did not experience disease progression following chemoradiotherapy, with a 5-year OS rate of 42.9% and a PFS rate of 33.1% [125]. However, subgroup analyses indicate that the survival benefit is primarily observed in patients with PD-L1 expression [125], leaving the optimal therapeutic strategy for those without PD-L1 expression after chemoradiotherapy under debate. The subsequent PACIFIC-2 trial further investigated the efficacy of concurrent durvalumab with chemoradiotherapy followed by consolidative durvalumab [126]. Unfortunately, this trial did not demonstrate a significant clinical benefit, and approximately one-quarter of patients experienced AEs that led to the discontinuation of durvalumab [126]. The ongoing phase 3 CheckMate73L study is evaluating the efficacy of concurrent nivolumab and chemoradiotherapy followed by consolidative nivolumab, with or without ipilimumab, in comparison to the standard of care involving concurrent chemoradiotherapy followed by consolidative durvalumab [127]. However, this study also revealed no PFS benefit when adding nivolumab concurrently with definitive chemoradiotherapy [128]. In addition to exploring concurrent immunotherapy, the phase 2 COAST study has shown promising efficacy with the combination of durvalumab and either monalizumab (an anti-NKG2A antibody) or oleclumab (an anti-CD73 antibody) as consolidative therapy, compared to durvalumab monotherapy [129]. Based on these findings, the ongoing phase 3 PACIFIC-9 study

aims to validate the clinical benefits of these combination therapies [130].

#### Systemic immunotherapy for metastatic lung cancer

The implementation of immunotherapy has demonstrated an OS benefit compared to chemotherapy [131, 132]. However, the response rate for ICI monotherapy remains between 20 and 40% [131, 132], highlighting the importance of combination therapy to improve treatment outcomes. TIGIT is an immune checkpoint molecule with a high affinity for its ligand poliovirus receptor (PVR), which inhibits T-cell activation through direct PVR signaling and inhibition of CD226 signaling [133].

Despite the success of a phase 2 study showing improved PFS among patients receiving the combination of atezolizumab and the anti-TIGIT tiragolumab compared to atezolizumab alone [134], the phase 3 SKYSCRAPER-1 trial did not meet its primary endpoint of PFS benefit. Another anti-TIGIT agent was investigated in the phase 2 ARC-7 trial, in which treatment-naïve patients with PD-L1-high-expressing metastatic NSCLC were randomized into 3 groups to receive either anti-PD-1 zimberelimab alone, zimberelimab plus the anti-TIGIT domvanalimab, or zimberelimab plus domvanalimab and the anti-adenosine receptor etrumadenant [135]. Those receiving zimberelimab plus domvanalimab, with or without etrumadenant, exhibited longer PFS compared to those receiving zimberelimab monotherapy, with tolerable AEs [135]. Ongoing phase 3 studies include ARC-10 (NCT04736173), evaluating the treatment efficacy of zimberelimab plus domvanalimab vs pembrolizumab; STAR-121 (NCT05502273), combining domvanalimab and zimberelimab plus chemotherapy [136]; and SPLFIO-174, combining cemiplimab, a PD-1 inhibitor, with either S095018 (anti-TIM3 antibody), S095024 (anti-CD73 antibody), or S095029 (anti-NKG2A antibody), to treat patients with metastatic NSCLC (NCT06162572).

### Recent advances in bispecific antibodies

Bispecific antibodies, designed to simultaneously bind 2 antigens or epitopes, have emerged as a major anticancer therapeutic strategy over the past 2 decades. Owing to advances in protein engineering technologies and considerable preclinical research efforts, bispecific antibodies are constantly being developed and optimized to improve their efficacy and mitigate toxicity [7].

#### Amivantamab

MET amplification has been identified as a key resistance mechanism in patients with EGFR-mutant NSCLC who receive first-line osimertinib, as well as in those with acquired T790M mutations treated with second-line osimertinib [14]. Additionally, the presence of de novo MET amplification compromises the therapeutic efficacy of EGFR-TKIs, further supporting the rationale for targeting MET in the upfront treatment setting [137]. Amivantamab, an EGFR- and MET-targeting agent developed via the DuoBody platform, is the only bispecific antibody approved for NSCLC treatment [138]. Based on the results of the phase 1 CHRYSALIS study, amivantamab is FDA approved as an effective second-line treatment for NSCLC patients with exon 20 insertion [138]. The subsequent phase 3 PAPILLON trial, which evaluated the treatment efficacy of chemotherapy with or without amivantamab, demonstrated that the combination therapy provided a significantly higher response rate (73%; 95% CI 65–80%) and longer PFS (11.4 months; 95% CI 9.8–13.7 months) than chemotherapy alone [139]. Consequently, this combination therapy has been FDA approved as a first-line treatment strategy for NSCLC patients with EGFR exon 20 insertion.

Amivantamab also provides promising efficacy in NSCLC patients with common EGFR mutations. In the phase 3 MARIPOSA study, which enrolled patients with treatment-naïve EGFR-mutant NSCLC, the combination of lazertinib and amivantamab demonstrated significantly better PFS (23.7 months; 95% CI 19.1–27.7 months) compared to those receiving osimertinib (16.6 months; 95% CI 14.8–18.5 months) or lazertinib alone (18.5 months; 95% CI 14.8–20.1 months) [17]. The HR for PFS was 0.68 (95% CI 0.56–0.83, $P<0.001$) among patients receiving the combination of lazertinib and amivantamab compared to those receiving osimertinib, with better OS (HR: 0.80, 95% CI 0.61–1.05) [17]. The combination of lazertinib and amivantamab-vmjw was approved by the FDA for the first-line treatment of locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations.

In a secondary analysis of the MARIPOSA trial focusing on high-risk patient subpopulations, the combination of lazertinib and amivantamab provided a PFS benefit over osimertinib among patients with brain metastasis (HR: 0.69; 95% CI 0.53–0.92; $P=0.010$), liver metastasis (HR: 0.58; 95% CI 0.37–0.91; $P=0.017$), TP53 co-mutation (HR: 0.65; 95% CI 0.48–0.87; $P=0.003$), and detectable ctDNA (HR: 0.68; 95% CI: 0.53–0.86; $P=0.002$) [140]. Brain metastasis is the major prognostic factor for patients with EGFR-mutant NSCLC; an investigator-initiated phase 2 trial further demonstrated a good response in intracranial lesions (40%; 95% CI 20–64%) and leptomeningeal carcinomatosis (33%; 95% CI 15–57%), which could support the broadening of enrollment criteria in future clinical trials [141].

Additionally, in the analysis of cohort C of the CHRYSALIS-2 study, the ORR and PFS were 52% (95% CI 42–62%) and 11.1 months (95% CI 7.8–17.8), respectively, among patients with NSCLC with uncommon EGFR mutations treated with the combination of lazertinib and amivantamab [142]. In the subgroup of treatment-naïve patients with NSCLC, the ORR and PFS were 57% (95% CI 42–71%) and 19.5 months (95% CI 11.2-NR), respectively [142]. Notably, in the subgroup of patients with TKI-pretreated NSCLC, the ORR and PFS were 48% (95% CI 35–62%) and 7.8 months (95% CI 5.4–11.1), respectively, indicating that this combination could also serve as a salvage therapy in patients with NSCLC with uncommon EGFR mutations [142].

Given that intravenous amivantamab induces a high incidence of infusion-related reactions, evaluating different dosage modalities is important. In the phase 3 PALOMA-3 study, patients with osimertinib- and chemotherapy-pretreated EGFR-mutant NSCLC were stratified to receive either subcutaneous or intravenous amivantamab in combination with lazertinib [143]. The subcutaneous administration of amivantamab demonstrated pharmacokinetics and an ORR non-inferior to the intravenous route. Moreover, subcutaneous dosing provided a numerically longer DOR (11.2 vs 8.3 months) and PFS (6.1 vs 4.3 months) and significantly longer OS (HR: 0.62; 95% CI 0.42–0.92; $P=0.002$) [143]. Importantly, the incidence of infusion-related reactions (13% vs 66%) and venous thromboembolism (9% vs 14%) were significantly decreased with subcutaneous amivantamab [143]. This study supports a more convenient and safer dosing route, which is currently under FDA review.

Since MET is a target of amivantamab, its therapeutic efficacy in MET-altered lung cancer was also evaluated in the CHRYSALIS study cohort MET-2, providing an ORR of 33%, a PFS of 5.4 months (95% CI 4.3–7.0), and an OS of 15.8 months (95% CI 13.1–21.8) [144]. The ORR was 50% (8/16) among treatment-naïve patients, 46% (13/28) among pretreated patients without exposure to MET TKIs, and 21% (11/53) among MET TKI-pretreated patients [144]. This result indicates that amivantamab can target MET-exon-14-skipping NSCLC in both treatment-naïve patients and those with acquired resistance to prior MET therapies despite a relative lower response rate in the MET TKI-pretreated population [144].

#### Ivonescimab

The implementation of immunotherapy for patients with EGFR-mutant NSCLC remains a significant challenge. A meta-analysis of 3 phase 3 clinical trials that administered ICIs as second-line treatments demonstrated that patients with EGFR mutations do not respond effectively to these inhibitors [145]. Similarly, the retrospective IMMUNOTARGET study revealed a response rate of only 12% for patients with EGFR mutations [146].

Subsequently, 2 phase 3 clinical trials, CheckMate-722 [147] and Keynote-789 [148], attempted to combine ICIs with chemotherapy for patients with EGFR-mutant NSCLC who had acquired resistance to EGFR TKIs. Unfortunately, both trials failed to show clinical benefits. Previously, the combination of ICIs, chemotherapy, and antiangiogenic therapy emerged as a potential treatment strategy, as demonstrated by subgroup analysis of patients with EGFR mutation in the IMpower150 trial [149]; this trial showed clinical benefit over chemotherapy alone. This finding was further supported by the ORIENT-31 trial using sintilimab, a PD-1 inhibitor, in combination with chemotherapy and antiangiogenic therapy [150], and the ATTLAS trial using atezolizumab in combination with chemotherapy and antiangiogenic therapy [151]. Taken together, the combination of chemotherapy and ICIs did not provide sufficient efficacy in treating patients with EGFR-mutant NSCLC who acquired resistance to osimertinib. Instead, the combination of chemotherapy, ICIs, and antiangiogenic therapy could be an alternative option.

A regimen with a similar concept was also reported at ASCO 2024. A newly developed bispecific antibody, ivonescimab, which targets both PD-1 and VEGF, showed promising treatment efficacy in patients with EGFR-mutant NSCLC [20]. Patients who received a combination of chemotherapy and ivonescimab had a PFS of 7.1 months (95% CI 5.9–8.7 months), significantly longer than those who received chemotherapy alone (HR: 0.46; 95% CI 0.34–0.62) [20]. These results further support the efficacy of combining chemotherapy with agents targeting PD-1/PD-L1 and VEGF for patients with EGFR-mutant NSCLC with acquired resistance to osimertinib. However, additional clinical trials are warranted to compare ivonescimab with other established antiangiogenic agents, such as bevacizumab or ramucirumab, and ICIs when combined with chemotherapy.

In addition to the post-osimertinib setting, the ongoing HARMONi-2 trial is evaluating the efficacy of ivonescimab monotherapy in patients with metastatic NSCLC and PD-L1 of higher than 50%. The median PFS for patients treated with ivonescimab was 11.14 months, which was significantly longer than those receiving pembrolizumab. Additionally, higher ORR (50.0% vs 38.5%) and DCR (89.9% vs 70.5%) were observed in the ivonescimab group [152]. These findings are consistent with previous phase 2 single-arm studies evaluating the efficacy of combining atezolizumab and bevacizumab as a first-line therapy in patients with NSCLC with high PD-L1 expression [153]. These data further support the

rationale for combining PD-1/PD-L1 inhibition with antiangiogenic therapies.

#### Bispecific antibodies targeting dual immune checkpoints

Multiple bispecific antibodies targeting PD-1/PD-L1 and CTLA-4 are being investigated. MEDI5752 (volrustomig) is a PD-1 and CTLA-4 bispecific antibody [154]. In the NSCLC cohort of a phase 1/2 first-in-human trial investigating the response and safety profile of volrustomig, patients receiving 1500 mg of MEDI5752 combined with chemotherapy showed significantly better PFS and OS than those receiving pembrolizumab and chemotherapy, especially in patients with PD-L1 expression below 1%. The ORR was similar between patients receiving 1500 mg or 750 mg of MEDI5752 every 3 weeks, with fewer AEs in the 750 mg group for a more flexible dosage strategy [155]. There are ongoing phase 2 and 3 studies investigating MEDI5752-based combination therapy in patients with either metastatic disease or surgically resectable early-stage NSCLC. AK104 is an IgG1 scaffold Fc-engineered humanized antibody that also targets PD-1 and CTLA-4. In cohort A of the phase 1b/2 AK104-202 trial, AK104 demonstrated an OS of 19.61 months in patients with chemotherapy-pretreated, immunotherapy-naïve NSCLC [156]. This result supported the ongoing clinical trials evaluating AK104, either alone or in combination with chemotherapy, for patients with locally advanced or metastatic NSCLC.

KN046, a bispecific antibody that targets CTLA-4 and PD-L1, could activate T cells in the tumor microenvironment of PD-L1-expressing tumors [157]. KN046 monotherapy showed encouraging preliminary efficacy with acceptable AEs among patients with NSCLC who failed first-line chemotherapy [158], ICIs [159], or EGFR TKIs [160] in phase 2 studies. The subsequent phase 2 KN406-202 trial further revealed that the combination of chemotherapy and KN046 demonstrated efficacy (ORR of 46%, PFS of 5.8 months, and OS of 26.6 months) and acceptable AEs in patients with NSCLC [161], which supports the rationale for a phase 3 clinical trial.

Emerging bispecific antibodies targeting other immune checkpoints are being evaluated for treating NSCLC. For example, sabestomig (AZD7789), a bispecific antibody targeting PD-1 and T-cell immunoglobulin mucin-3 (TIM-3), could potentially activate T-effector cells, increase tumor phagocytosis, and enhance antigen presentation [162]. A phase 1 study demonstrated its safety profile and efficacy signal in patients with immunotherapy-resistant NSCLC [162]. Table 3 summarizes the clinical efficacy of bispecific antibodies in representative trials.

## Recent advances in antibody–drug conjugates

#### Traztuzumab deruxtecan

Trastuzumab deruxtecan is a HER2-targeted ADC consisting of a humanized anti-HER2 monoclonal antibody, cleavable linker, and membrane-permeable payload [163]. In the Destiny-Lung01 study, trastuzumab deruxtecan demonstrated durable anticancer activity in patients with previously treated HER2-mutant NSCLC, with an ORR of 55%, median PFS of 8.2 months, and OS of 17.8 months [164]. Although the safety profile was generally manageable, 25% of patients discontinued treatment due to drug-related AEs, including pneumonitis and interstitial lung disease [164]. In the phase 2 DESTINY-Lung02 study, which assessed the efficacy and safety of trastuzumab deruxtecan at doses of 5.4 mg/kg and 6.4 mg/kg among patients with HER2-mutant NSCLC, the ORR and PFS were similar between the 2 dosage groups. More importantly, the 5.4 mg/kg group experienced fewer AEs, particularly drug-related interstitial lung disease [165]. The pooled analysis of DESTINY-Lung01 and DESTINY-Lung02 also revealed that trastuzumab deruxtecan monotherapy demonstrated intracranial confirmed ORRs of 50% (5.4 mg/kg) and 30% (6.4 mg/kg), and median intracranial confirmed DORs of 9.5 months (5.4 mg/kg) and 4.4 months (6.4 mg/kg) [166]. These results support the use of 5.4 mg/kg as the appropriate treatment dosage for trastuzumab deruxtecan.

#### Datopotamab deruxtecan

Trophoblast cell surface antigen 2 (TROP2) is a cell surface glycoprotein that is upregulated in various malignant tumors and plays a role in oncogenic signaling pathway transduction [167]. Due to its rare expression in normal cells, TROP2 has become an attractive target for ADC design [167]. Datopotamab deruxtecan is a TROP2-targeting ADC that has demonstrated encouraging antitumor activity, with an ORR of 28% and a DOR of 10.5 months at a dose of 6 mg/kg among patients with solid tumors including NSCLC in the TROPION-PanTumor01 study [168]. Updated results from the NSCLC cohort in the TROPION-PanTumor01 study further demonstrate its promising efficacy, with an ORR of 21–25%, a DCR of 67–80%, and a PFS of 4.3–8.2 months in patients with NSCLC who were pretreated with chemotherapy and immunotherapy, across different dosage groups [169].

Interestingly, in another updated analysis of the NSCLC cohort treated with datopotamab deruxtecan, patients with actionable driver mutations exhibited an ORR of 35% and a DOR of 9.5 months [170]. This result was further confirmed by the phase 2 TROPION-Lung05 trial, which demonstrated that datopotamab deruxtecan could benefit patients with NSCLC with actionable driver

**Table 3** Representative clinical trials using bispecific antibodies to treat NSCLC

| Study | Patients | Treatment | ORR (%) | mPFS (months) | HR for mPFS | mOS (months) | HR for mOS | ≥G3 AE (%) | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| MARIPOSA | Treatment-naïve EGFR-mutant advanced NSCLC | Lazertinib + amivantamab<br>Osimertinib | 86<br>85 | 23.7<br>16.6 | 0.70<br>[0.58–0.85] | $^{\$}$74%<br>$^{\$}$69% | 0.80<br>[0.61–1.05] | 75<br>43 | [17] |
| CHRYSALIS | Osimertinib-resistant EGFR-mutant advanced NSCLC (combinational cohort) | Lazertinib + amivantamab | 36 | 4.9 | | | | 4 | [138, 144] |
| | Advanced NSCLC with EGFR exon 20 insertion (cohort D) | Amivantamab | 39 | 8.3 | | | | 35 | |
| | Advanced NSCLC with MET exon 14 skipping (cohort MET-2) | Amivantamab | 33 | 5.4 | | 15.8 | | 42 | |
| CHRYSALIS-2 | Advanced NSCLC with uncommon EGFR mutations (cohort C) | | | | | | | | [142] |
| | Total population | Lazertinib + amivantamab | 52 | 11 | | | | | |
| | Treatment-naïve | Lazertinib + amivantamab | 57 | 19.5 | | | | | |
| | TKI-pretreated | Lazertinib + amivantamab | 48 | 7.8 | | | | | |
| PAPILLON | Treatment-naïve advanced NSCLC with EGFR exon 20 insertion | Amivantamab + CT<br>CT | 73<br>47 | 11.4<br>6.7 | 0.40<br>[0.30–0.53] | NR<br>24.4 | 0.67<br>[0.42–1.09] | 75<br>54 | [139] |
| PALMOMA-3 | Osimertinib- and chemotherapy-pretreated EGFR-mutant advanced NSCLC | Lazertinib + amivantamab (s.c.)<br>Lazertinib + amivantamab (i.v.) | 27<br>27 | 6.1<br>4.3 | 0.84<br>[0.64–1.10] | NR<br>NR | 0.62<br>[0.42–0.92] | 52<br>56 | [143] |
| HARMONi-a | Osimertinib-pretreated EGFR-mutant advanced NSCLC | Ivonescimab + CT<br>CT | 50.6<br>35.4 | 7.1<br>4.8 | 0.46<br>[0.34–0.62] | | | 61.5<br>49.1 | [20] |
| HARMONi-2 | Advanced NSCLC with PD-L1 ≥ 50% | Ivonescimab<br>Pembrolizumab | 50<br>38.5 | 11.14<br>5.82 | 0.51<br>[0.38–0.69] | | | 29.4<br>15.6 | [152] |

**Table 3** (continued)

| Study | Patients | Treatment | ORR (%) | mPFS (months) | HR for mPFS | mOS (months) | HR for mOS | ≥G3 AE (%) | Refs. |
|---|---|---|---|---|---|---|---|---|---|
| First-in-human study of MEDI5752 | Advanced non-squamous NSCLC | | | | | | | | [155] |
| | Randomized cohort | MEDI5752 1500 mg + CT | 50 | 15.1 | | NR | | 80 | |
| | Randomized cohort | Pembrolizumab + CT | 47.6 | 8.9 | | 16.5 | | 61 | |
| | Single-arm cohort | MEDI5752 750 mg + CT | 40.8 | | | | | 50 | |
| | Advanced non-squamous NSCLC with PD-L1 < 1% | | | | | | | | |
| | Randomized cohort | MEDI5752 1500 mg + CT | 55.6 | 13.4 | | | | | |
| | Randomized cohort | Pembrolizumab + CT | 30 | 9.0 | | | | | |
| | Single-arm cohort | MEDI5752 750 mg + CT | 48 | | | | | | |
| AK104-202 | CT-pretreated advanced NSCLC | | | | | | | | [156] |
| | ICI-naïve | Cadonilimab (AK104) | 10 | 1.97 | | 19.61 | | 10 | |
| | Primary resistance to IO | Cadonilimab (AK104) | 0 | 1.87 | | 4.93 | | 0 | |
| | Acquired resistance to IO | Cadonilimab (AK104) | 0 | 1.84 | | 13.16 | | 18.8 | |
| KN046-201 cohort A and B | Advanced NSCLC | | | | | | | | [158–160] |
| | Cohort A/B: Resistance to CT | KN046 | 14.1 | 3.7 | | 19.8 | | 42.2 | |
| | *Cohort C: Resistance to IO | KN046 | 3.2 | 2.8 | | 13.3 | | 22.6 | |
| | Cohort D: Resistance to TKI | KN046 | 26.9 | 5.52 | | 12.68 | | 53.8 | |
| KN406-202 | Treatment-naïve advanced NSCLC | KN046 + CT | 46 | 5.8 | | 26.6 | | 66.7 | [161] |

CT, chemotherapy; G3 AE, grade 3 adverse event; HR, hazard ratio; ICI, immune checkpoint inhibitor; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

*Combined with data from KN046-CHN-001.

mutations, including EGFR mutation and ALK rearrangement [171]. The updated survival analysis focusing on patients with brain metastasis also revealed promising intracranial activity, with an intracranial ORR of 22% and a DCR of 72% [172]. The PFS for patients with brain metastasis was also similar to those without brain metastasis [172]. These study results indicate that datopotamab deruxtecan could potentially be a salvage therapy for patients with and without oncogenic driver mutations.

The subsequent phase 3 TROPION-Lung01 study compared the treatment efficacy of datopotamab deruxtecan with docetaxel among NSCLC patients who were pretreated with chemoimmunotherapy in the absence of driver mutations, and with targeted therapy and chemotherapy if driver mutations were identified [173]. In this mixed population, datopotamab deruxtecan provided superior PFS compared to docetaxel (4.4 vs 3.7 months; $P = 0.004$), particularly among patients with non-squamous histology (5.6 vs 3.7 months) [173]. This is the first ADC to demonstrate superior efficacy in heavily pretreated NSCLC patients.

Following the results of the phase 3 TROPION-Lung01 study, the ICARUS-Lung01 study utilized sequential tumor biopsy and blood sampling to identify predictive

biomarkers for response to datopotamab deruxtecan [174]. Although patients with a wide range of TROP2 expression may benefit from datopotamab deruxtecan, those with a TROP2 H-score higher than 100 had the longest PFS compared to other subgroups. An analysis of driver alterations did not reveal any association with treatment response [174].

Based on bulk RNA-sequencing analysis, the activation of DNA repair pathways and the suppression of immune-related pathways after 1–2 cycles of datopotamab deruxtecan were associated with treatment resistance [174]. Ongoing analyses include genomic analysis at progression, spatial distribution of TROP2 using artificial intelligence (AI) digital pathology, modulation of the tumor immune microenvironment, internalization of datopotamab deruxtecan, and the evaluation of circulating tumor cells and DNA [174].

In addition to being used as monotherapy, there are several studies evaluating the efficacy of combining pembrolizumab and datopotamab deruxtecan. In the phase 1b TROPION-Lung02 study, which enrolled patients who had received ≤ 2 prior lines of therapy, patients treated with datopotamab deruxtecan plus pembrolizumab, with or without platinum chemotherapy, exhibited response rates of 38–49%, with the DOR not yet reached [175]. Among patients receiving first-line therapy, the ORR was 50–57%, with the DOR also not reached [175]. Similarly, in the phase 1b TROPION-Lung04 study, which enrolled patients with previously treated or treatment-naïve NSCLC and without actional driver mutations, patients who received datopotamab deruxtecan plus pembrolizumab, with or without platinum chemotherapy, have promising ORRs of 50–77% and durable response [176]. These findings support subsequent phase 3 studies: AVANZAR (NCT05687266); TROPION-Lung07 (NCT0555732), focusing on patients with PD-L1 < 50%; and TROPION-Lung08 (NCT05215340), focusing on patients with PD-L1 > 50%.

#### Sacituzumab govitecan

Sacituzumab govitecan is another TROP2-targeting ADC that has been FDA approved as a second-line therapy for triple-negative breast cancer and uroepithelial carcinoma. The expansion cohort of the IMMU-132–01 phase 1/2 basket trial demonstrated that sacituzumab govitecan provided well-tolerated and durable responses among patients with heavily treated NSCLC, with a clinical benefit rate of 43% and DOR of 6 months [177]. The subsequent phase 2 EVOKE-02 study also demonstrated that the combination of sacituzumab govitecan and pembrolizumab exhibited encouraging antitumor activity, with an ORR of 67% in patients with PD-L1 > 50% and an ORR of 44% among patients with PD-L1 < 50%, along with tolerable AEs [178]. This study supports the rationale for the ongoing phase 3 EVOKE-3 study, evaluating sacituzumab govitecan plus pembrolizumab vs pembrolizumab monotherapy in patients with PD-L1 expression > 50%. Another ongoing phase 3 trial, Velocity-Lung (Substudy-1), aims to evaluate the treatment efficacy of zimberelimab and domvanalimab in combination with sacituzumab govitecan or etrumadenant.

Recently, the phase 3 EVOKE-01 study, which compared the treatment efficacy of sacituzumab govitecan to docetaxel, failed to demonstrate superiority over docetaxel as a second-line therapy for NSCLC patients who had acquired resistance to first-line anti-PD-1 therapy [179]. However, a prespecified subgroup analysis showed a significant improvement in OS (11.8 vs 8.3 months; HR: 0.75; 95% CI 0.58–0.97) among patients who did not respond to their last anti-PD-1 therapy [179]. These findings may inform the design of future clinical trials.

#### Sacituzumab tirumotecan

Sacituzumab tirumotecan is a TROP2-targeting ADC that utilizes a novel linker to conjugate its payload, a belotecan-derived topoisomerase I inhibitor [180]. The linker is designed to be cleaved by both extracellular pH changes and intracellular enzymes, enabling the efficient release of the membrane-permeable payload, which exerts a bystander effect [180]. In a phase 2 study evaluating the efficacy of sacituzumab tirumotecan monotherapy, the treatment demonstrated an ORR of 43.6% and a PFS of 7.2 months in pretreated patients with NSCLC with diverse genomic profiles [181]. The phase 2 OptiTROP-Lung01 study reported the treatment efficacy of combining sacituzumab tirumotecan and KL-A167, a PD-L1 inhibitor, in different dosage combinations [182]. This study demonstrated promising efficacy among treatment-naïve patients with NSCLC, with an ORR of 77.6% in the overall population. There is consistent efficacy across all PD-L1 expression levels and different histology subtypes [182]. Currently, there are 3 ongoing phase 3 clinical trials: 1 focused on treatment-naïve NSCLC patients with PD-L1 expression > 50% (NCT06170788); another evaluating the combination as maintenance therapy among patients with metastatic squamous NSCLC (NCT06422143); and a third in the postoperative setting for patients who did not achieve pCR (NCT06312137).

#### Patritumab deruxtecan

Human epidermal growth factor receptor 3 (HER3), also known as receptor tyrosine-protein kinase erbB-3

**Table 4** Representative clinical trials using ADCs to treat patients with NSCLC

| Study | Patients | Treatment | ORR (%) | mPFS (months) | HR for mPFS | mOS (months) | HR for mOS | ≥ G3 AE (%) | Ref |
|---|---|---|---|---|---|---|---|---|---|
| Destiny-Lung01 | Previously treated HER2-mutant advanced NSCLC | Traztuzumab deruxtecan | 55 | 8.2 | | 17.8 | | 46 | [164] |
| Destiny-Lung02 | Previously treated HER2-mutant advanced NSCLC | Traztuzumab deruxtecan 5.4 mg/kg | 49 | 9.9 | | 19.5 | | 38.6 | [165] |
| | | Traztuzumab deruxtecan 6.4 mg/kg | 56 | 15.4 | | NE | | | |
| TROPION-PanTumor01 | Previously treated advanced solid tumor | | | | | | | | [168–170] |
| | NSCLC cohort | Datopotamab deruxtecan 4 mg/kg<br>Datopotamab deruxtecan 6 mg/kg<br>Datopotamab deruxtecan 8 mg/kg | 22<br>26<br>23.8 | 4.3<br>6.9<br>5.2 | | 12.9<br>11.4<br>10.5 | | 30<br>54<br>58.8 | |
| | Subgroup with AGA | Datopotamab deruxtecan | 35 | | | | | | |
| TROPION-Lung05 | Previously treated advanced NSCLC with actional driver alterations | | | | | | | | [171, 172] |
| | Total population<br>EGFR mutation<br>ALK rearrangement<br>Brain metastasis | Datopotamab deruxtecan<br>Datopotamab deruxtecan<br>Datopotamab deruxtecan<br>Datopotamab deruxtecan | 49<br>34<br>8<br>[$]22 | 5.4<br>5.8<br>4.3 | | | | 47 | |
| TROPION-Lung01 | Previously treated advanced NSCLC | Datopotamab deruxtecan<br>Docetaxel | | 4.4<br>3.7 | 0.75 [0.62–0.91] | 12.4<br>11.0 | 0.90 [0.72–1.13] | 25<br>41 | [173] |
| TROPION-Lung02 | Advanced NSCLC with ≤ 2 prior lines of therapy | | | | | | | | [175] |
| | Total population | Datopotamab deruxtecan + ICI<br>Datopotamab deruxtecan + ICI + CT | 38<br>49 | | | | | 31<br>58 | |
| | First-line | Datopotamab deruxtecan + ICI<br>Datopotamab deruxtecan + ICI + CT | 50<br>57 | | | | | | |

**Table 4** (continued)

| Study | Patients | Treatment | ORR (%) | mPFS (months) | HR for mPFS | mOS (months) | HR for mOS | ≥ G3 AE (%) | Ref |
|---|---|---|---|---|---|---|---|---|---|
| TROPION-Lung04 | Treatment-naïve advanced NSCLC without actional driver alterations | Datopotamab deruxtecan + ICI<br>Datopotamab deruxtecan + ICI + CT | 50<br>76.9 | | | | | 31.6<br>57.1 | [176] |
| IMMU-132–01 | Previously treated advanced NSCLC | Sacituzumab govitecan | 17 | 5.2 | | 9.5 | | | [177] |
| EVOKE-02 | Treatment-naïve advanced NSCLC | | | | | | | | [178] |
| | PD-L1 ≥ 50% (cohort A)<br>PD-L1 < 50% (cohort B) | Sacituzumab govitecan<br>Sacituzumab govitecan | 67<br>44 | 13.1 | | | | 40 | |
| EVOKE-01 | Advanced NSCLC with acquired resistance to anti-PD1 | Sacituzumab govitecan<br>Docetaxel | 13.7<br>18.1 | 4.1<br>3.9 | 0.92 [0.77–1.11] | 11.1<br>8.9 | 0.84 [0.68–1.04] | 66.6<br>75.7 | [179] |
| Phase 2 study of sacituzumab tirumotecan | Previously treated advanced NSCLC | | | | | | | | [181] |
| | Total population<br>EGFR-mutant<br>EGFR-wild type<br>Non-squamous<br>Squamous | Sacituzumab tirumotecan<br>Sacituzumab tirumotecan<br>Sacituzumab tirumotecan<br>Sacituzumab tirumotecan<br>Sacituzumab tirumotecan | 43.6<br>60.0<br>26.3<br>22.2<br>30.0 | 7.2<br>11.5<br>5.3<br>5.8<br>5.1 | | 22.6<br>22.7<br>14.1<br>16.2<br>12.8 | | 69.8 | |
| OptiTROP-Lung01 | Treatment-naïve NSCLC | | | | | | | | [182] |
| | Cohort 1A | SKB264 5 mg/kg + KL-A167 1200 mg | 48.6 | 15.4 | | | | | |
| | Cohort 1B<br>Non-squamous<br>Squamous<br>PD-L1 < 1%<br>PD-L1 1–49%<br>PD-L1 ≥ 50% | SKB264 5 mg/kg + KL-A167 900 mg | 77.6<br>72.7<br>84.0<br>63.2<br>81.3<br>87.0 | *84.6%<br>*93.8%<br>*73.5%<br>*82.2%<br>*76.6%<br>*91.3% | | | | | |
| HERTHENA-Lung01 | EGFR-mutant advanced NSCLC with acquired resistance to TKI and platinum-based CT | | | | | | | | [184] |
| | Total population<br>Post 3rd generation EGFR-TKI | Patritumab deruxtecan<br>Patritumab deruxtecan | 28.4<br>28.2 | 5.5<br>5.5 | | 11.9<br>11.8 | | 45.3 | |

**Table 4** (continued)

| Study | Patients | Treatment | ORR (%) | mPFS (months) | HR for mPFS | mOS (months) | HR for mOS | ≥ G3 AE (%) | Ref |
|---|---|---|---|---|---|---|---|---|---|
| Phase 1/1b study of telisotuzumab vedotin | EGFR-mutant advanced NSCLC with acquired resistance to osimertinib | Osimertinib + telisotuzumab vedotin | 50 | 7.4 | | | | 32 | [186, 187] |
| LUMINOSITY | Advanced NSCLC with ≤ 2 prior lines of therapy | | | | | | | | [188] |
| | c-Met OE NSQ EGFR WT<br>c-Met high<br>c-Met intermediate | Telisotuzumab vedotin<br>Telisotuzumab vedotin<br>Telisotuzumab vedotin | 28.6<br>34.6<br>22.9 | 5.7<br>5.5<br>6.0 | | 14.5<br>14.6<br>14.2 | | | |
| | c-Met OE NSQ EGFR mutant<br>c-Met high<br>c-Met intermediate | Telisotuzumab vedotin<br>Telisotuzumab vedotin<br>Telisotuzumab vedotin | 11.6<br>16.7<br>0 | | | | | | |
| | c-Met OE SQ | Telisotuzumab vedotin | 11.1 | | | | | | |

CT, chemotherapy; G3 AE, grade 3 adverse event; HR, hazard ratio; ICI, immune checkpoint inhibitor; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small cell lung cancer; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

(ERBB3), is widely expressed on the cell surface of NSCLC, reported in 83% of tumors, and associated with a higher incidence of distant metastasis and shorter DFS [183]. In the HERTHENA-Lung01 study, which enrolled patients with advanced-stage EGFR-mutant NSCLC who had disease progression after EGFR TKIs and platinum-based chemotherapy, patritumab deruxtecan (5.6 mg/kg) demonstrated clinically meaningful and durable efficacy with an ORR of 29.8% and acceptable AEs [184]. The efficacy was observed across various resistance mechanisms. Additionally, patritumab deruxtecan showed good intracranial activity, with an intracranial confirmed ORR of 33.3% and a DCR of 76.7% [184]. Patritumab deruxtecan has emerged as a promising salvage therapy for patients with EGFR-mutant NSCLC and acquired resistance to EGFR TKI and chemotherapy [184]. The ongoing phase 3 HERTHENA-Lung02 study compares patritumab deruxtecan with docetaxel (NCT05338970). Since HER3 expression did not show a significant difference between responders and nonresponders [184], a future study on predictive biomarkers is warranted.

#### Telisotuzumab vedotin

The c-MET protein is a transmembrane receptor tyrosine kinase that is activated upon binding with hepatocyte growth factor [185]. Overexpression of the c-MET protein has been identified in approximately 50% of NSCLC cases [185], making it a promising target for ADC design. Phase 1/1b trials have demonstrated the efficacy of combining osimertinib and telisotuzumab vedotin, a c-MET-targeting ADC, in patients with EGFR-mutant, c-MET-overexpressing NSCLC who had acquired resistance to osimertinib, showing an ORR of 50% and a DCR of 76% [186]. The subsequent phase 2 LUMINOSITY study further investigated the therapeutic efficacy of telisotuzumab vedotin monotherapy. In stage 1, the ORR was 36.5% in the non-squamous EGFR wild-type cohort (52.2% in the c-MET-high group and 24.1% in the c-MET-intermediate group) but was modest in the non-squamous EGFR mutant (11.6%) and squamous (11.1%) cohorts [187]. The significant discrepancy between patients with and without EGFR mutation indicates the importance of osimertinib-based combination therapy for patients with EGFR mutation and c-MET overexpression [187].

In stage 2 of the LUMINOSITY trial, the clinical benefit of telisotuzumab vedotin was evaluated on patients with c-MET–overexpressing non-squamous EGFR wild-type advanced NSCLC; it showed encouraging efficacy, with an ORR of 28.6%, a median DOR of 8.3 months, and

tolerable AEs. The ORR was consistent across patients with different levels of c-MET expression [188]. This result highlighted that telisotuzumab vedotin could be a potential therapeutic strategy in the future. The ongoing phase 3 clinical trial will investigate its treatment efficacy among patients with MET protein overexpression. Table 4 summarizes the clinical efficacy of ADCs in representative trials.

## Conclusions

With the advent of targeted therapies and ICIs, we have reshaped the treatment paradigm not only for metastatic NSCLC, but also for early-stage NSCLC. Combination chemotherapy and anti-PD-(L)1 antibodies offer a new standard of care for perioperative treatment of resectable early-stage NSCLC. Adjuvant osimertinib and alectinib have demonstrated promising clinical benefits for early-stage NSCLC with EGFR mutations or ALK rearrangement, respectively. For unresectable locally advanced NSCLC, ICIs and targeted therapy (e.g., EGFR TKIs) have become viable therapeutic treatment strategies after chemoradiotherapy. Newly developed bispecific antibodies have further revolutionized the therapeutic landscape. Amivantamab, either as monotherapy or in combination with lazertinib or chemotherapy, offers novel treatment options for patients with treatment-naïve and osimertinib-resistant NSCLC with common EGFR mutations, as well as those with EGFR exon 20 insertions. Ivonescimab also presents a promising therapeutic approach for patients with osimertinib-resistant NSCLC with common EGFR mutations and serves as a first-line treatment for those with high PD-L1 expression. In addition, newly developed ADCs are promisingly effective, including HER2-targeting trastuzumab deruxtecan, TROP2-targeting ADCs, HER3-targeting patritumab deruxtecan, and MET-targeting telisotuzumab vedotin.

The changing landscape of NSCLC treatment provides numerous therapeutic options, but determining how to incorporate them into clinical practice to improve patient outcomes remains challenging. Future studies are necessary to identify and validate new therapeutic approaches and predictive biomarkers for each treatment strategy, and to determine the optimal sequencing and integration of these therapies.

### Abbreviations

| | |
|---|---|
| ADC | Antibody–drug conjugate |
| AE | Adverse event |
| AI | Artificial intelligence |
| ALK | Anaplastic lymphoma kinase |
| ASCO | American Society of Clinical Oncology |
| CAF | Cancer-associated fibroblast |
| CCRT | Concurrent chemoradiotherapy |
| CI | Confidence interval |
| CNS | Central nervous system |
| ctDNA | Circulating tumor DNA |
| CTLA-4 | Cytotoxic T-lymphocyte–associated antigen 4 |
| DCR | Disease control rate |
| DFS | Disease-free survival |
| DOR | Duration of response |
| EGFR | Epidermal growth factor receptor |
| EFS | Event-free survival |
| ERBB3 | Receptor tyrosine-protein kinase erbB-3 |
| FDA | US Food and Drug Administration |
| FISH | Fluorescence in situ hybridization |
| GTP | Guanosine triphosphate |
| HER2 | Human epidermal growth factor receptor 2 |
| HER3 | Human epidermal growth factor receptor 3 |
| HR | Hazard ratio |
| ICIs | Immune checkpoint inhibitors |
| IHC | Immunohistochemistry |
| MET | Mesenchymal-epithelial transition |
| MPR | Major pathological response |
| MRD | Molecular residual disease |
| NE | Not estimable |
| NR | Not reached |
| NSCLC | Non-small cell lung cancer |
| NTRK | Neurotrophic tyrosine receptor kinase |
| ORR | Objective response rate |
| OS | Overall survival |
| pCR | Pathologic complete response |
| PD-1 | Programmed death-1 |
| PD-L1 | Programmed death-ligand 1 |
| PFS | Progression-free survival |
| PVR | Poliovirus receptor |
| TIM-3 | T cell immunoglobulin mucin-3 |
| TKIs | Tyrosine kinase inhibitors |
| TMB | Tumor mutational burden |
| TROP2 | Trophoblast cell surface antigen 2 |
| VAF | Variant allele fraction |
| VEGF | Vascular endothelial growth factor |
| WCLC | World Conference on Lung Cancer |

### Acknowledgements

The authors would like to thank Angela Dahlberg, editor in the Division of Medical Oncology, The Ohio State University Comprehensive Cancer Center, for editing the manuscript.

### Author contributions

All the authors were involved in the conceptualization and preparation of the manuscript, and approved the final manuscript.

### Funding

The present study did not receive funding.

### Availability of data and materials

No datasets were generated or analysed during the current study.

## Declarations

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

Received: 18 November 2024 Accepted: 17 February 2025
Published: 27 March 2025

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