

Review Article

Current treatment strategies for *EGFR*-mutated non-small cell lung cancer: from first line to beyond osimertinib resistance

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Abstract

Osimertinib, a third-generation EGFR TKI, is the standard therapy for previously untreated *EGFR*-mutated non-small cell lung cancer patients following the landmark FLAURA study. However, resistance inevitably hinders patient prognosis, increasing the need for new therapeutic strategies beyond osimertinib. Frontline osimertinib-based combination strategies (platinum-based chemotherapy and angiogenesis inhibitors) are currently being tested primarily to prevent initial resistance. In the later-line setting after osimertinib, many next-line therapeutic candidates have been actively examined in clinical trials. Notably, several drugs with novel mechanisms of action, such as antibody–drug conjugates and EGFR–MET bispecific antibodies, have shown promising efficacy despite the resistance mechanisms and are close to clinical application. In addition, genotype-based target strategies have been investigated for a better understanding of osimertinib resistance mechanisms based on molecular profiling tests at relapse. The C797S mutation and *MET* gene alterations are commonly identified following osimertinib resistance, for which targeting strategies are actively tested. This review describes current pharmacotherapeutic strategies for *EGFR*-mutated non-small cell lung cancer based on the results of clinical trials and the latest published data, broadly grouped into two sections: 1) EGFR TKIs-based combination therapy in the front-line setting and 2) novel therapeutic strategies after osimertinib resistance.

Key words: lung cancer, EGF receptor, tyrosine kinase inhibitors, precision medicine

Introduction

Epidermal growth factor receptor (*EGFR*) mutation was the first driver oncogene identified in lung cancer (1). The development of EGFR tyrosine kinase inhibitors (TKIs) targeting activating *EGFR* mutations has led to a paradigm shift in pharmacotherapy for patients with advanced non-small cell lung cancer (NSCLC). Several other driver oncogenes have been discovered in NSCLC, and the

corresponding molecular targeting agents are preferentially used in clinical practice (2).

EGFR TKIs are the major first-line (1L) therapy for patients with advanced NSCLC with activating *EGFR* mutations. Substantial evidence for EGFR TKI has historically been established in randomized controlled trials, demonstrating superior efficacy to conventional platinum-based chemotherapy. Gefitinib (3,4), erlotinib (5–7) and

afatinib (8,9) have shown survival benefits over standard-of-care platinum-based chemotherapy in the 1L setting, with better response and significantly improved progression-free survival (PFS). Subsequently, studies were conducted for a head-to-head comparison of EGFR TKIs. Second-generation (2G) TKIs, afatinib and dacomitinib, were compared with the first-generation (1G) TKI, gefitinib, in randomized controlled trials, demonstrating prolonged PFS (10,11); however, both were more toxic than gefitinib (10–13).

Osimertinib is an irreversible third-generation (3G) EGFR TKI that selectively inhibits sensitizing *EGFR* and T790M resistance mutations (14). In the phase III AURA3 trial, osimertinib showed better efficacy over platinum-based chemotherapy for T790M-positive NSCLC patients previously treated with prior-generation EGFR TKIs approved as salvage therapy in this setting (15). Later, the phase III FLAURA trial demonstrated significantly prolonged PFS in the osimertinib arm compared with the gefitinib or erlotinib arm [18.9 vs. 10.2 months; hazard ratio (HR), 0.46; 95% confidence interval (CI), 0.37–0.57] in the 1L setting (16); therefore, osimertinib was also approved as a 1L regimen for *EGFR*-mutated advanced NSCLC. Furthermore, constant superiority in overall survival (OS) was observed in the osimertinib arm until the final OS analysis (38.6 vs. 31.8 months; HR, 0.80; 95% CI, 0.64–1.00) despite crossover to osimertinib being permitted in the comparator TKI arm upon T790M emergence at disease progression (17). In addition, osimertinib had a higher response rate to central nervous system (CNS) lesions and showed a reduced risk of CNS progression (18,19). Regarding toxicity, osimertinib was relatively well tolerated, with a comparable rate of grade ≥ 3 adverse events to the comparator EGFR TKIs, and no serious safety concerns were observed (16,17). This evidence supports the validity of choosing 1L treatment for *EGFR*-mutated advanced NSCLC patients, boosting osimertinib to a forefront agent in this setting.

Despite the robust evidence established by the AURA3 and FLAURA trials, most patients eventually develop osimertinib resistance. However, the next-line therapy for osimertinib resistance is yet to be confirmed. Therefore, it is necessary to establish effective and novel therapeutic strategies for this population. To date, various treatment strategies have been investigated in the clinic to address osimertinib resistance and improve patient prognosis. This review focuses on current therapeutic strategies for *EGFR*-mutated NSCLC, EGFR TKI-based combination strategies to outperform osimertinib monotherapy and the next-line novel drug candidates following 1L osimertinib, based on data from ongoing clinical trials and published literature.

EGFR TKI-based combination strategy

Osimertinib monotherapy prolonged PFS and OS in a 1L setting (16,17); however, there is room for improvement in survival outcomes. A strategy to either prevent or postpone resistance acquisition to 1L EGFR TKI is desired, offering a combination strategy of EGFR TKI with other anticancer agents. Furthermore, the organ-specific efficacy properties might also allow for a combination strategy after 1L EGFR TKI resistance. This section describes the current status of frontline combination strategies for *EGFR*-mutated advanced NSCLC patients.

Combining EGFR TKI with platinum-based chemotherapy

Intratumoral and intrapatient molecular heterogeneity within *EGFR*-mutated NSCLC may be associated with intrinsic resistance to EGFR TKI. It has been assumed that EGFR TKI monotherapy cannot

treat innate TKI-resistant cancer cells (20). In theory, a combination of cytotoxic chemotherapeutic agents with different mechanisms of action could regulate intratumor heterogeneity and delay resistance to EGFR TKIs (21,22). Therefore, combination strategies of EGFR TKI and platinum-based chemotherapy have been investigated.

This combination strategy for *EGFR*-mutated advanced NSCLC patients was examined before the launch of osimertinib. Therapeutic schemes, including the timing of platinum-based chemotherapy, vary across trials. The phase III IMPRESS trial assessed continuing gefitinib combined with cisplatin plus pemetrexed compared with chemotherapy alone when the disease progressed with 1L gefitinib. It failed to demonstrate the PFS benefit of continuing gefitinib [median PFS, 5.4 vs. 5.4 months; HR (95% CI), 0.86 (0.65–1.13)] (23), and OS was inferior in the continuing group [median OS, 13.4 vs. 19.5 months; HR (95% CI), 1.44 (1.07–1.94)] (24), showing the disadvantage of continuing gefitinib with cisplatin plus pemetrexed at disease progression on 1L gefitinib.

In contrast, a concurrent combination of gefitinib with platinum-based chemotherapy as a 1L regimen is an effective approach. In the phase III NEJ009 trial, gefitinib in combination with carboplatin plus pemetrexed (CGP) was compared with gefitinib alone in a 1L setting (25). PFS was significantly prolonged in the CGP group (median, 20.9 vs. 11.9 months; HR, 0.49; 95% CI, 0.39–0.62) (25), and OS was also extended in the CGP group (median, 49.0 vs. 38.5 months, HR, 0.82; 95% CI, 0.64–1.06) (26). Another phase III trial conducted in India to compare CGP and gefitinib alone in a 1L setting showed significantly improved PFS (median, 16 vs. 8 months; HR, 0.51; 95% CI, 0.39–0.66) and OS (median, not reached vs. 20.5 months; HR, 0.45; 95% CI, 0.31–0.65) (27). These results supported that the CGP regimen would be an effective 1L approach for *EGFR*-mutated advanced NSCLC patients.

Following the approval of 1L osimertinib, these combination strategies were investigated by replacing gefitinib with osimertinib. A combination strategy following osimertinib resistance in a scheme analogous to that in the IMPRESS trial is being investigated based on the higher CNS activity of osimertinib. In the phase III COMPEL trial (NCT04765059), patients with non-CNS progression after initial response to 1L osimertinib were randomized to platinum-pemetrexed plus osimertinib or placebo groups. The primary endpoint will be PFS, stratified by the presence or absence of stable CNS metastases (28). The randomized phase II TORG1938/EPONA trial (jRCTs071200029) being conducted in Japan is evaluating the efficacy of platinum-pemetrexed with or without continuation of osimertinib. In this trial, the feasibility of platinum-pemetrexed plus osimertinib for non-CNS progression after initial response to osimertinib in patients with brain metastatic *EGFR*-mutated NSCLC is being investigated with PFS as the primary endpoint (29). These trials will elucidate the plausibility of the beyond progressive disease (PD) combination strategy during the progression of extracranial lesions after 1L osimertinib.

The concurrent strategy of osimertinib plus platinum-based chemotherapy is also being tested. The phase II OPAL trial evaluated the safety and efficacy of osimertinib plus platinum-pemetrexed in the 1L setting, reporting an objective response rate (ORR) of 90.9% (95% CI, 84.0–97.8), median PFS of 31.0 months (95% CI, 26.8 months-not reached) and an acceptable safety profile (30). Moreover, the phase III FLAURA2 trial (NCT04035486) is investigating the efficacy of 1L osimertinib with or without platinum-pemetrexed chemotherapy for *EGFR*-mutated locally advanced or metastatic NSCLC with 587 patients (31). In the 30 patients who participated in the safety run-in component of the trial, no specific pattern of toxicities was reported in the combination therapy group

(32). The initial data cutoff for the primary endpoint of PFS was April 3, 2023. Another treatment scheme involving the insertion of platinum pemetrexed during EGFR TKI therapy is also under investigation. The JCOG1404/WJOG8214L (UMIN000020242) is a randomized phase III trial that compares 1L osimertinib (or gefitinib) and inserted cisplatin plus pemetrexed with osimertinib (or gefitinib) alone for patients with advanced *EGFR*-mutated NSCLC (33). In the experimental group, gefitinib or osimertinib was administered on days 1–56. After a drug-free period of 2 weeks, three cycles of cisplatin and pemetrexed were administered on days 71, 92 and 113. Gefitinib or osimertinib was reinitiated on day 134 and continued until the disease progressed. The investigators hypothesized that initiating platinum doublet chemotherapy after the initial response to EGFR TKIs might prevent the emergence of acquired resistance to EGFR TKIs and increase patient survival. Unlike the FLAURA2 trial, OS is the primary endpoint of the JCOG1404/WJOG8214L trial. Patient enrollment was completed, and the results are expected to be published shortly. These trials provide instructive information regarding the optimal timing for combining 1L of osimertinib with platinum-based chemotherapy.

Overall, the combination strategy of EGFR TKI and platinum-based chemotherapy is feasible because the CGP regimen has shown survival benefits as a 1L regimen in randomized phase III trials. However, increased toxicities associated with the addition of chemotherapy should be considered (23–27).

To date, the superiority of combination regimens over osimertinib monotherapy is questionable; therefore, progress in ongoing randomized trials comparing osimertinib plus chemotherapy with osimertinib will draw further clinical interest.

Combining EGFR TKI with VEGF inhibitor

Combination therapies using EGFR TKI and angiogenesis inhibitors have also been extensively investigated. EGFR activation and VEGF expression are reportedly closely interrelated (34). These have common downstream pathways, and signaling from both can stimulate their shared pathway and act in a protumorigenic manner (35–38). Therefore, EGFR-VEGF dual inhibition is considered a rational strategy in *EGFR*-mutated NSCLC.

Several clinical studies have reported that adding the anti-VEGF antibody, bevacizumab, to the 1G EGFR TKI, erlotinib, prolonged PFS but not OS. A randomized phase II JO25567 trial first reported improved PFS of erlotinib plus bevacizumab over erlotinib alone in previously untreated *EGFR*-mutated NSCLC patients (median PFS, 16.0 vs. 9.7 months; HR, 0.54; 95% CI, 0.36–0.79) (39). The efficacy of this combination therapy was validated in subsequent phase III trials. The NEJ026 and ARTEMIS/CTONG1509 trials successfully demonstrated the prolonged PFS with erlotinib plus bevacizumab over erlotinib (NEJ026: median PFS, 16.9 vs. 13.3 months; HR, 0.605; 95% CI, 0.417–0.877 (40)) (ARTEMIS/CTONG1509: median PFS, 17.9 vs. 11.2 months, HR: 0.55; 95% CI, 0.41–0.73 (41)). In addition, subgroup analysis in both trials for types of *EGFR* mutations showed a PFS benefit in patients with exon19 deletion and patients with the L858R mutation, a population known to have a reduced response to EGFR TKIs.

The RELAY trial is a global, placebo-controlled, double-blinded phase III trial conducted to assess the efficacy of erlotinib plus the anti-VEGFR 2 antibody, ramucirumab, compared with erlotinib plus placebo in previously untreated advanced NSCLC patients with activating *EGFR* mutations (42). A total of 449 patients, of whom 336 East Asian, were enrolled. PFS, as the primary endpoint, was

significantly improved with erlotinib plus ramucirumab compared with erlotinib plus placebo (median, 19.4 vs. 12.4 months; HR, 0.59; 95% CI, 0.46–0.76). A PFS benefit was consistently observed, irrespective of the *EGFR* mutation (exon19 deletion or L858R). Moreover, the frequency of acquiring the T790M mutation upon disease progression was similar in the two groups, suggesting that adding ramucirumab did not affect T790M emergence.

In summary, the EGFR-VEGF dual-inhibition strategy confers a PFS benefit for patients with advanced *EGFR*-mutated NSCLC in a 1L setting. It was also expected to be effective in patients with the L858R mutation based on the results of the subgroup analysis. However, these combinations have yet to improve OS (43,44). Patients receiving a combination regimen have a higher incidence of grade ≥ 3 treatment-related adverse events (40–42,45), and adverse events specific to angiogenesis inhibitors should be considered.

Currently, combination therapy with osimertinib, bevacizumab or ramucirumab in a 1L setting is being investigated. A phase I/II trial by Yu et al. evaluated osimertinib plus bevacizumab in the 1L setting with 49 patients. The study met the primary endpoint with a 12-month PFS rate of 76% (95% CI, 65–90%), an overall response rate of 80% (95% CI, 67–91%) and a CNS response rate of 100% (6 of 6; 95% CI, 50–100% (46)). However, the randomized phase II WJOG9717L trial, which investigated osimertinib with or without bevacizumab in previously untreated *EGFR*-mutated NSCLC, failed to show improved PFS with the combination regimen (combination vs. osimertinib alone: median PFS, 22.1 vs. 20.1 months; HR, 0.862; 95% CI, 0.531–1.397 (47)).

Awaiting the feasibility of this combination, it will be necessary to await the results of ongoing randomized trials. Clinical trials of osimertinib-based combination regimens are summarized in Table 1.

Novel therapeutic strategy beyond osimertinib

Several mechanisms underlying acquired resistance to osimertinib have been identified. They can be broadly classified into *EGFR*-dependent (on-target) and *EGFR*-independent (off-target) resistance mechanisms. In on-target resistance, cell proliferation and tumor growth are driven by sustained activation of *EGFR* signaling, including secondary *EGFR* mutations, amplification, mutation loss and ligand overexpression. Conversely, in off-target resistance, tumor growth depends on pathways other than *EGFR* signaling, such as alternative pathway kinase activation, downstream signaling pathway activation, histological transformation and cell cycle gene alterations (Fig. 1) (48–52).

Available data regarding the resistance mechanisms to osimertinib, based on plasma and/or tissue biomarker analyses, have been compiled from several clinical and observational studies, including the AURA3 and FLAURA trials. Based on these studies, the frequency and description of osimertinib resistance mechanisms are summarized in Fig. 2 (53–61). *EGFR* C797S and *MET* amplifications are relatively common after the 1L and later-line osimertinib therapies and are considered important therapeutic targets. Other resistance mechanisms have been identified, including alterations in the RAS/MAPK and PIK3/AKT pathways, cell cycle gene alterations, oncogenic fusions and histological transformations (53–61).

Along with the growing understanding of osimertinib resistance mechanisms, next-line novel therapeutic agents are being developed and intensively examined in clinical trials. Progress in ongoing clinical trials has shown promising efficacy of several

Table 1. Summary of clinical trials on osimertinib-based combination strategy

| Agent | Trial number (Trial name) | Phase | Number of patients | Arm | Year | Status |
|--|---------------------------------|-------|--------------------|--|------|--------------------------------------|
| EGFR TKI + platinum-based chemotherapy | NCT04410796 | II | 571 | Osimertinib | 2020 | Recruiting |
| | NCT04695925 (TOP) | III | 291 | Osimertinib + CBDCA + PEM Osimertinib | 2021 | Not yet recruiting |
| | NCT04769388 (FLAME) | II | 150 | Osimertinib + CBDCA + PEM * concurrent TP53 mutation Osimertinib | 2021 | Recruiting |
| | NCT04765059 (COMPEL) | III | 204 | * 3 weeks after 1 L osimertinib without PD Osimertinib + CBDCA/CDDP + PEM Placebo + CBDCA/CDDP + PEM | 2021 | Recruiting |
| | jRCTs071200029 (TORG1938/EPONA) | II | 92 | * PD after 1 L osimertinib Osimertinib + CBDCA/CDDP + PEM CBDCA/CDDP + PEM | 2020 | Recruiting |
| | NCT05281406 (PACE-LUNG) | II | 50 | * PD after osimertinib Osimertinib + CBDCA/CDDP + PEM | 2022 | Recruiting |
| | NCT05507606 | II | 50 | * ctDNA EGFRm after 3w 1 L osimertinib Osimertinib + bevacizumab + CBDCA + PEM * concurrent TP53 mutation | 2022 | Recruiting |
| | NCT04035486 (FLAURA2) | III | 587 | Osimertinib | 2019 | Active, not recruiting |
| | NCT04335292 (OCELOT) | II | 200 | Osimertinib + CBDCA/CDDP + PEM | 2020 | Recruiting |
| | NCT05493501 | III | 420 | Osimertinib → CBDCA/CDDP + PEM → osimertinib Aumoleritinib Aumoleritinib + CBDCA/CDDP + PEM Osimertinib | 2022 | Recruiting |
| EGFR TKI + VEGF inhibitor | UMIN000020242 | III | 500 | Osimertinib (gefitinib) | 2015 | Active, not recruiting |
| | (JCOG1404/WJOG8214L, AGAIN) | | | Osimertinib (gefitinib) → CDDP + PEM → osimertinib (gefitinib) | | |
| | NCT02971501 | II | 112 | Osimertinib | 2016 | Active, not recruiting |
| Bevacizumab | NCT04181060 | III | 300 | Osimertinib + bevacizumab Osimertinib | 2019 | Recruiting |
| | NCT04988607 (FLAIR) | II | 90 | Osimertinib + bevacizumab | 2021 | Not yet recruiting |
| | NCT03909334 | II | 150 | Osimertinib + bevacizumab * patients with EGFR L858R only Osimertinib | 2019 | Recruiting |
| Ramucirumab | JapicCTI-184146 (TORG1833) | II | 120 | Osimertinib + ramucirumab Osimertinib | 2018 | Progressing Recruitment completed |
| | NCT04487080 (MARIPOSA) | III | 1074 | Osimertinib + ramucirumab Amivantamab + lazertinib Osimertinib + placebo Lazertinib + placebo | 2020 | Active, not recruiting |

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CBDCA, carboplatin; CDDP, cisplatin; PEM, pemetrexed; PD, progressive disease.

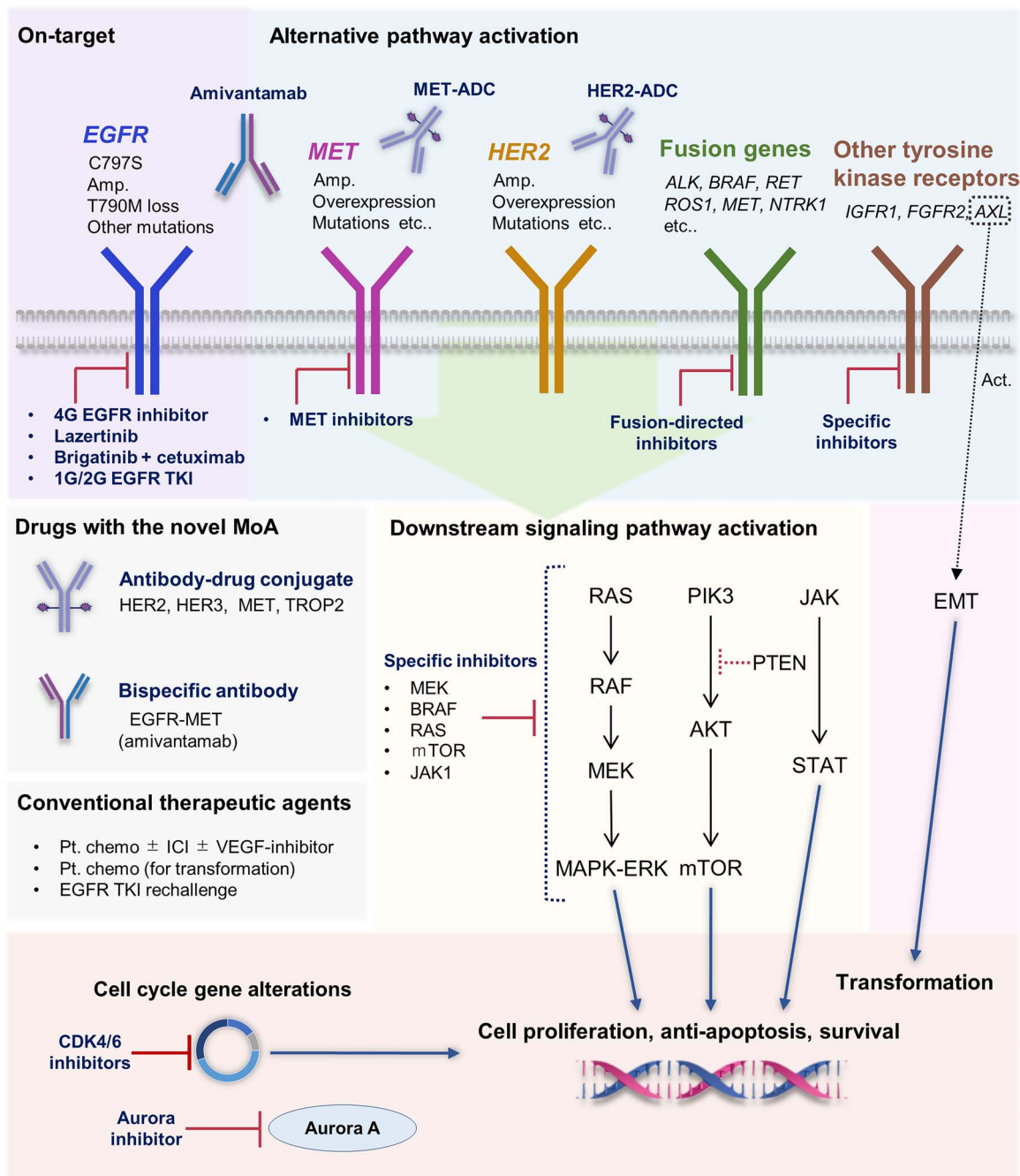


Figure 1. Overview of osimertinib resistance mechanisms and corresponding treatment options. Diverse targeting strategies might be available depending on the resistance mechanism. Abbreviations: 4G, fourth generation; 1G, first generation; 2G, second generation; TKI, tyrosine kinase inhibitor; MoA, mechanism of action; ADC, antibody–drug conjugate; amp., amplification; Pt. chemo, platinum-based chemotherapy; ICI, immune checkpoint inhibitor.

novel agents such as a HER3-directed antibody–drug conjugate (ADC) and an EGFR-MET bispecific antibody in osimertinib-resistant patients (62). Importantly, these agents reportedly exhibit antitumor activity regardless of resistance mechanisms and are nearing clinical application. Other genotype-based strategies, focusing on *EGFR* C797S and *MET* gene alterations, are also being examined, highlighting the importance of molecular testing at relapse. This section provides an overview of the current status of novel therapeutic strategies following osimertinib resistance.

Antibody–drug conjugate

ADC is a novel drug class belonging to the immunotherapeutic agent category, which is rapidly emerging in oncology and especially lung cancer (63). ADCs are designed to bind a cytotoxic payload through a linker to a specific monoclonal antibody directed against a tumor antigen. Internalization occurs once the monoclonal antibody binds to the targeted antigen, resulting in linker degeneration and release of the cytotoxic payload, thereby exerting an antitumor effect (64,65). ADCs targeting HER2, HER3, TROP-2 and MET have potential applicability in NSCLC patients (66). These agents are

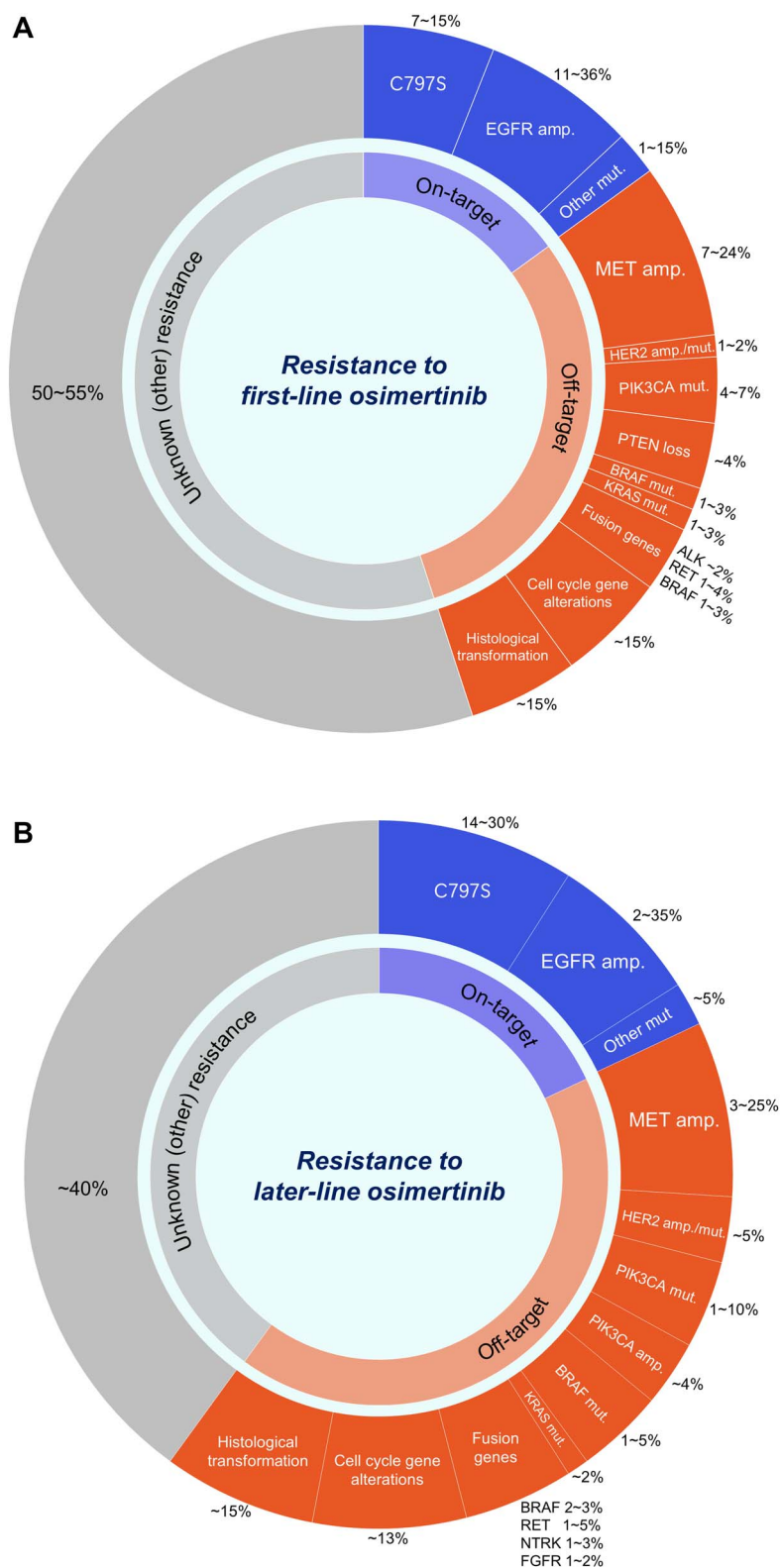


Figure 2. Breakdown of frequency and types of major resistance mechanisms to first-line (A) and later-line (B) osimertinib treatment based on previous reports (53-61). Note: different molecular aberrations might have been identified in the same patient. Abbreviations: amp., amplification; mut., mutation.

being investigated in clinical trials, which include patients after they develop osimertinib resistance (MET-directed ADCs will be described in a later section).

A HER3-directed ADC, patritumab deruxtecan (U3-1402) (HER3-DXd), has the closest clinical application in osimertinib-resistant patients. HER3 is not implicated in oncogenicity, although it

is involved in *EGFR/HER2*-mediated resistance through conjugation with *MET* and has recently been regarded as an important therapeutic target (67). A phase I dose escalation/expansion HER3-DXd study for *EGFR*-mutated NSCLC patients previously treated with *EGFR* TKIs, including osimertinib, was conducted (U31402-A-U102, NCT03260491). The participants were heavily pre-treated [median number of prior treatment lines: 4 (1–9)], with 89% of them receiving osimertinib. In the pooled population of patients treated with 5.6 mg/kg HER3-DXd using the recommended dose for expansion, the confirmed ORR was 39%. Median PFS was 8.2 months for osimertinib pretreated patients (68). Importantly, responses to HER3-DXd were observed notwithstanding different *EGFR* TKI resistance mechanisms not directly associated with *HER3*, such as *EGFR* C797S, *MET*, *HER2* amplification and *BRAF* fusion (68). The phase II HERTHENA-Lung01 trial (NCT04619004) for HER3-DXd in patients with *EGFR*-mutated NSCLC previously treated with at least one *EGFR* TKI and a platinum-based chemotherapy regimen is ongoing. Similarly, the phase III HERTHENA-Lung02 trial (NCT05338970) is comparing HER3-DXd and platinum-based chemotherapy in *EGFR*-mutated NSCLC after progression using a 3G *EGFR* TKI. Furthermore, the efficacy of combining HER3-DXd and osimertinib for *EGFR*-mutated NSCLC with osimertinib progression is currently being evaluated in a phase I trial (NCT04676477).

HER2-directed ADCs, trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) are being investigated in NSCLC patients with *HER2* gene alterations. The phase II TRAEMOS trial (NCT03784599) evaluated the efficacy of T-DM1 in combination with osimertinib for *EGFR*-mutated NSCLC patients previously treated with *EGFR* TKIs, including osimertinib who acquired *HER2* overexpression and/or amplification with re-biopsy at relapse. However, the reported ORR and median PFS were 13% and 2.8 months, respectively, indicating the limited efficacy of this approach. Therefore, the trial was terminated early (69). On the other hand, T-DXd has demonstrated attractive antitumor efficacy for previously treated *HER2* positive (overexpression or mutations) NSCLC (not including *EGFR*-mutated patients) with an ORR of 55% and a median PFS and OS of 8.2 and 17.8 months, respectively (DESTINY-Lung01, NCT03505710 (70)). An ongoing phase Ib trial (NCT04042701) is investigating T-DXd in combination with pembrolizumab in *HER2*-expressing or *HER2*-mutated patients, including those with *EGFR*-mutated NSCLC who were previously treated with *EGFR* TKIs.

TROP-2 is an intracellular calcium signaling transducer and an attractive target for ADC. Datopotamab deruxtecan (Dato-DXd), a TROP-2 targeting ADC, has demonstrated satisfactory therapeutic efficacy in patients with NSCLC in a phase I trial (TROPION-PanTumor01, NCT03401385 (71)) and is further being investigated for *EGFR*-mutated patients who were previously treated with osimertinib in the TROPION-Lung05 (NCT04484142) and TROPION-Lung01 (NCT04656652) trials.

Preliminary data on the efficacy of ADCs in the clinical trials described above underscore the viability of this approach in osimertinib-resistant populations. Despite their impressive efficacy, the reported negligible occurrence of interstitial lung disease (ILD) should be considered. In the DESTINY-Lung01 trial, 24 of 91 patients (26%) developed T-DXd-related ILD, including four (6.6%) grade 3 and two (2.2%) grade 5 patients (70). A systematic review of advanced *HER2*-positive solid tumor patients reported an incidence

of T-DXd-related ILD of 11.40%, which was exceptionally high at 24.77% in NSCLC patients (72). Insufficient data are available; however, the frequency of ILD related to HER3-DXd (68) and Dato-DXd (71) was reported to be 5–10.6% and 8% in phase I trials, respectively. The definite mechanism is unknown, as it is assumed that these pulmonary toxicities may be associated with the cytotoxic payload carried by ADCs. Safety data for more patients are required in ongoing clinical trials.

In summary, positive preliminary data on ADCs in *EGFR*-mutated NSCLC after osimertinib resistance were provided. HER3-DXd has been evaluated extensively in clinical trials. If the promising efficacy of ADCs is demonstrated in the above clinical trials, it could change the treatment paradigm for *EGFR*-mutated NSCLC in TKI-resistant populations.

MET-targeting strategy

The *MET* oncogene encodes the receptor tyrosine kinase, c-Met, whose dysregulation is an oncogenic driver. *MET* signaling mediates osimertinib resistance by bypassing *EGFR* downstream signaling pathways such as PI3K/AKT, JAK/STAT3 and RAS/MAPK/ERK (73). Among the various genomic statuses of the *MET* oncogene, *MET* amplification is a common resistance mechanism to osimertinib, detectable in 6–24% of cases (53–61). *MET* gene alterations are considered an important therapeutic target after osimertinib resistance, and several potential therapeutic candidates have been developed and examined in clinical trials.

***MET* tyrosine kinase inhibitor.** Clinical trials of *MET* TKIs for osimertinib-resistant patients are ongoing; the efficacy of savolitinib, tepotinib and capmatinib as single agents or combined with osimertinib in patients who acquired resistance to osimertinib has been evaluated.

The phase Ib TATTON trial (NCT02143466) investigated the efficacy of savolitinib and osimertinib for *EGFR*-mutated NSCLC patients previously treated with *EGFR* TKIs. The recently published data of the interim analysis revealed the acceptable safety profile and encouraging antitumor activity of this approach; an ORR of 30% and a median PFS of 5.4 months were obtained in patients previously treated with 3G *EGFR* TKI, reaching 64–67% and 9–11 months, respectively, in 3G *EGFR* TKI-naïve patients based on the study's different cohorts (74). In the phase II SAVANNAH trial (NCT03778229), savolitinib in combination with osimertinib in *EGFR*-mutated NSCLC patients with *MET*-driven (amplification and/or overexpression) resistance mechanisms acquired after osimertinib is being evaluated. Preliminary data showed an ORR of 32% and a median PFS of 5.3 months in the overall population (75). Notably, the population with higher *MET* levels with amplification and/or overexpression had an ORR of 49% and a median PFS of 7.1 months, compared with an ORR of 9% and a median PFS of 2.8 months in the population without higher *MET* levels (75). In the phase II ORCHARD trial, *MET*-amplified patients are assigned to the osimertinib plus savolitinib arm (76), and the recent interim analysis results showed an ORR of 41% (77). The phase III SACHI trial (NCT05015608) compared osimertinib plus savolitinib with platinum-based chemotherapy in patients with *MET* amplification acquired after 1L *EGFR* TKI therapy. In addition, the phase III SAF-FRON trial (NCT05261399) compared osimertinib plus savolitinib with platinum-based chemotherapy in *MET*-amplified and/or *MET*-overexpressed patients previously treated with osimertinib.

Tepotinib is also being investigated in several clinical trials. The phase Ib/II INSIGHT trial evaluated the efficacy and safety of tepotinib combined with gefitinib. In the phase II part with randomization against platinum-based chemotherapy, tepotinib plus gefitinib was assessed in *EGFR*-mutated NSCLC patients with *MET* amplification and/or overexpression previously treated with 1G- or 2G-*EGFR* TKIs. The survival outcomes were comparable in both arms; however, the median PFS and OS were longer in the tepotinib plus gefitinib arm than in the chemotherapy arm in a prespecified subgroup analysis of the high *MET*-expressing group (78). The phase II INSIGHT2 trial (NCT03940703) compared the combination of tepotinib plus osimertinib with tepotinib alone in patients previously treated with 1L of osimertinib. The initial results were recently reported; the ORR was high at 55% for tepotinib plus osimertinib compared with 8.3% for tepotinib alone (79). The combination of capmatinib and osimertinib is also being investigated in clinical trials [phase II A Lung-MAP trial (NCT05642572), phase III GEOMETRY-E trial (NCT04816214)].

EGFR-MET bispecific antibody. Amivantamab is a fully humanized bispecific antibody targeting *EGFR* mutations and *MET* mutation/s/amplifications. Amivantamab inhibits ligand binding of *EGFR* and *MET*, further inhibits downstream signaling pathways and has been reported to have antibody-dependent cellular cytotoxicity; therefore, it is expected to have a wider range of effects (80). Specifically, it has antitumor activity against various activating and resistant *EGFR* mutations (del19, L858R, T790M, C797S and exon20 insertion) (81,82) and might have potential clinical use for osimertinib-resistant patients.

The multiarm phase I CHRYSALIS trial (NCT02609776) investigated the combination of amivantamab and lazertinib (a potent brain-penetrant 3G *EGFR* TKI) immediately after osimertinib resistance in 45 patients with NSCLC with activating *EGFR* mutations. The ORR was 36%, and overall patients' median PFS was 4.9 months (83). Notably, this combination approach had an ORR of 47% in patients with *EGFR/MET*-driven resistances and an ORR of 29% in patients without these resistances (83). In the recently reported CHRYSALIS-2 trial (NCT04077463) results, combining amivantamab with lazertinib showed antitumor activity for *EGFR*-mutated NSCLC patients who had disease progression with 1 or 2L osimertinib followed by platinum-based chemotherapy (including heavily pretreated patients) with an ORR of 33% and median PFS of 5.1 months (84). A combination of amivantamab and lazertinib is being investigated in phase III trials for *EGFR*-mutated patients. The MARIPOSA study (NCT04487080), a randomized phase III trial, compares the combination of amivantamab and lazertinib with osimertinib monotherapy in the 1L setting. In addition, the MARIPOSA-2 study (NCT04988295), a randomized, open-label, phase III trial, compared lazertinib, amivantamab, carboplatin and pemetrexed with carboplatin, amivantamab and pemetrexed in *EGFR*-mutated NSCLC patients following disease progression during or after osimertinib treatment. Regarding the toxicity of amivantamab, skin and mucous membrane disorders and edema associated with *EGFR* and *MET* inhibition have been frequently reported (85). Besides, it should be noted that infusion site reactions frequently occur at initial administration (85,86).

MET-directed ADC. Telisotuzumab vedotin (Teliso-V) is a *MET*-directed ADC composed of ABT-700, an anti-c-Met monoclonal antibody, and monomethyl auristatin E, a potent microtubule inhibitor as a cytotoxic payload (87). Teliso-V has shown antitumor activity in solid tumors with *MET* gene alterations (88,89) and

has been investigated in clinical trials in patients after they acquire osimertinib resistance.

In a phase II trial (NCT03539536), the ORR of Teliso-V monotherapy was reported to be 13.3% in *EGFR*- and c-Met-positive nonsquamous NSCLC patients (90). The combination of Teliso-V and *EGFR* TKIs is also being tested in an ongoing phase I/II trial (NCT02099058), which involves patients who acquired c-Met overexpression following 1L osimertinib. The safety and efficacy of Teliso-V monotherapy or in combination with osimertinib, erlotinib, or nivolumab are currently being evaluated. In the reported interim analysis results, the combination of Teliso-V and osimertinib showed an ORR of 58% in patients previously treated with 1L osimertinib (91). Moreover, an ongoing randomized phase III trial (NCT04928846) compares Teliso-V and docetaxel in previously treated c-Met-overexpressing NSCLC patients, including *EGFR*-mutated patients.

In summary, in patients after osimertinib resistance, the *MET*-targeting strategy would be feasible. *MET* TKIs have shown a certain efficacy in early-phase clinical trials and are further being evaluated in phase III trials. Drugs with novel mechanisms of action are also promising for acquired *MET* gene alterations. Specifically, amivantamab in combination with lazertinib has broader antitumor activity and has demonstrated impressive efficacy in patients without *EGFR/MET*-driven resistances and in heavily pretreated patients. It should be noted, however, that the evaluation criteria for *MET* gene alterations is yet to be standardized and differs among trials. Amplification might be underestimated in liquid biopsy analysis with plasma specimens.

C797S-targeting strategy

Among on-target resistance mechanisms to osimertinib, the C797S mutation is common and emerging in 7–15 and 14–30% of cases resistant to 1L- and later-line osimertinib therapy, respectively (53–61). The C797S mutation occurs in exon 20 and is responsible for drug resistance by breaking the covalent bond between osimertinib and the mutant *EGFR* site (92). C797S imparts cross-resistance to other irreversible 3G *EGFR* TKIs by inhibiting binding to the active *EGFR* site (92–95).

C797S may have different drug susceptibilities depending on the acquired allelic status. When C797S occurs on a chromosome other than T790M (trans), it retains sensitivity to 1G- and 3G-TKI combination therapy (95). Preclinical data and some case reports have shown the efficacy of osimertinib in combination with gefitinib or erlotinib for *EGFR*-mutated NSCLC harboring T790M in trans with C797S mutation (96–98). In contrast, if C797S and T790M occur on the same chromosome (cis), they lose activity against any conventional *EGFR* TKIs (95–97). As a potential approach to C797S in cis, the efficacy of combining brigatinib, an *EGFR*-ALK dual inhibitor, with anti-*EGFR* antibodies has been reported. Preclinical data have demonstrated that combining brigatinib with cetuximab or panitumumab has antitumor activity against triple mutant cells with C797S in cis and T790M and activates *EGFR* mutation (98–100). A phase I/III trial conducted to ascertain the safety and efficacy of brigatinib combined with panitumumab in patients who acquired C797S after osimertinib treatment is ongoing (jRCT2031200231).

As another promising therapeutic agent against C797S mutation, a next-generation *EGFR* allosteric inhibitor is being developed (101). *EGFR* allosteric inhibitors that belong to fourth-generation (4G) *EGFR* inhibitors bind to *EGFR* far from the ATP-binding site, thereby selectively altering *EGFR* conformation and bypassing the

C797S-mediated resistance mechanism (92,102). These agents have shown antitumor activity alone or combined with osimertinib *in vivo/in vitro* studies (ongoing clinical trials on 4G EGFR inhibitors are summarized in Table 2). EAI-045 is the first EGFR allosteric inhibitor targeting T790M and C797S mutations (103). EAI-045 exhibited limited activity *in vivo* as a single agent; however, the marked tumor regression for the triple mutant (L858R/T790M/C797S) Ba/F3 cell line was observed when combined with cetuximab (102). Several novel 4G EGFR inhibitors have shown antitumor activity in *in vivo/in vitro* research. JBJ-04-125-02 is a more potent EGFR allosteric inhibitor that selectively targets L858R and inhibits triple mutant (L858R/T790M/C797S) EGFR signaling. JBJ-04-125-02, combined with osimertinib, offered increased cell death, more effective inhibition of cell proliferation and increased efficacy compared with either single agent alone (104). Comparing the EAI-045 and JBJ-04-125-02, CH7233163, a potent and selective 4G EGFR inhibitor, showed activity against triple EGFR mutants with del19/T790M/C797S (105). Furthermore, some agents are being evaluated as candidates in clinical trials. BLU-701 is a new, highly selective and potent oral EGFR inhibitor that has demonstrated *in vivo* antitumor activity against sensitizing EGFR mutations (del19 or L858R) and double mutations with C797S (del19/C797S or L858R/C797S) (106). The phase III HARMONY trial (NCT05153408) evaluates the safety and efficacy of BLU-701 in EGFR-mutated NSCLC patients previously treated with EGFR TKIs, including osimertinib. The effectiveness of BLU-701 in patients with C797X mutations will be evaluated in a phase II expansion cohort study. BLU-945 is a selective and potent 4G EGFR inhibitor with activity against triple-resistant mutations (del19 or L858R/T790M/C797S) (107,108). A combination of BLU-945 with either gefitinib or osimertinib exhibited increased antitumor activity compared with BLU-945 alone for del19/T790M/C797S in a patient-derived xenograft model (109). The phase III SYMPHONY trial (NCT04862780) also evaluates the safety and efficacy of BLU-945, either a single agent or combined with osimertinib in NSCLC patients with activating EGFR mutations previously treated with EGFR TKIs including osimertinib. The efficacy of BLU-945 in patients with the C797S mutation will be evaluated in a phase II expansion cohort. Other 4G EGFR inhibitors, such as JIN-A02 (NCT05394831) and BBT-176 (NCT04820023), will also be assessed in phase III trials.

In summary, C797S mutation is a crucial on-target resistance mechanism that can be potentially targeted after osimertinib resistance. Treatment with brigatinib and EGFR antibodies is being evaluated based on the cis/trans strategy for the C797S mutation. Moreover, there are sufficient preclinical data for the efficacy of 4G EGFR inhibitors for C797S, and 4G EGFR inhibitors are currently being investigated in early-phase clinical trials.

Other specific inhibitors

Molecular aberrations other than C797S and MET gene alterations have also been identified following osimertinib resistance. Changes in downstream signaling pathways (i.e. RAS/MAPK/ERK, PI3K/AKT and JAK/STAT3), oncogenic fusion genes, alterations in other tyrosine kinase receptors and cell cycle genes are regarded as resistance mechanisms to osimertinib (Fig. 1) that are potentially targetable. However, each of these is a rare fraction detected in <10% of cases (53–61). Specific inhibitors targeting these mechanisms are currently being investigated in early-phase clinical trials. The ongoing clinical

trials of these agents are summarized in Table 2. It is still being undetermined whether these specific inhibitors will be implemented in practice, as limited evidence has suggested their efficacy; therefore, the progress of clinical trials of individual agents should be monitored closely.

Chemoimmunotherapy combination

Immune oncology combinatorial treatment (chemo-IO) with a VEGF inhibitor may be a possible treatment option in the clinic following 1L osimertinib resistance. The potential applicability of chemo-IO for EGFR-mutated patients was first reported in a subgroup analysis of EGFR- and ALK-positive patients in the IMpower150 trial, showing survival benefits in terms of both PFS and OS in the atezolizumab, bevacizumab, paclitaxel and carboplatin groups compared with the bevacizumab, paclitaxel and carboplatin groups (110,111).

The chemo-IO ± VEGF inhibitor strategy for patients with EGFR mutations is being investigated in ongoing prospective trials. The CheckMate 722 (NCT02864251) and KEYNOTE-789 (NCT03515837) trials investigated chemo-IO in patients previously treated with EGFR TKIs. Both trials were recently reported to have failed to show the PFS benefit of chemo-IO over platinum chemotherapy (112,113). On the other hand, the ORIENT-31 trial (NCT03802240) that is investigating combination therapy of sintilimab (anti-PD-1 antibody), IBI305 (a bevacizumab biosimilar), and platinum-based chemotherapy in EGFR TKI-treated patients demonstrated significantly improved PFS in the sintilimab + IBI305 + chemotherapy arm compared with chemotherapy alone [median PFS, 6.9 vs. 4.3 months; HR (95% CI), 0.464 (0.337–0.639); $P < 0.0001$] (114). These results suggest a potential role for VEGF inhibitors combined with chemo-IO for EGFR-mutated patients.

Discussion and conclusion

This review discussed potential treatment strategies for EGFR-mutated advanced NSCLC based on clinical trials. Osimertinib monotherapy is currently the preferred therapeutic option in this population based on favorable efficacy and safety data from the AURA3 and FLAURA trials. However, since resistance to osimertinib would hinder persistent effectiveness for patients, strategies beyond osimertinib in 1L and later-line settings need to be provided.

In the 1L setting, strategies combining EGFR TKI and platinum-based chemotherapy or VEGF inhibitors are being investigated to surpass osimertinib monotherapy. In addition, the beyond PD osimertinib-based combination strategy is also being investigated, expecting to control CNS involvements. An encouraging data on combination strategies from clinical trials before the FLAURA era supports the feasibility of combining osimertinib with these anticancer agents. The results of the ongoing randomized trials of osimertinib-based combination therapy could set a new landmark in 1L therapy for EGFR-mutated NSCLC soon.

In later-line settings after osimertinib resistance, various novel therapeutic strategies have been challenged to address acquired resistance, linked to information on resistance mechanisms, with molecular profile testing gaining a better understanding in recent years. Drugs with a novel class of action, such as ADCs and EGFR-MET bispecific antibodies, have also shown specific clinical activity in osimertinib-resistant patients regardless of the resistance mechanism.

Table 2. Summary of clinical trial after osimertinib resistance

| Agent | Trial number (Trial name) | Phase | Number of patients | Arm | Year | Status |
|--|-------------------------------|-------|--------------------|--|------|------------------------|
| Fourth-generation EGFR allosteric inhibitor | | | | | | |
| BLU-701 | NCT05153408 (HARMONY) | I/II | 160 | BLU-701 | 2021 | Recruiting |
| | | | | BLU-701 + osimertinib | | |
| | | | | BLU-701 + CBDCA + PEM | | |
| BLU-945 | NCT04862780 (SYMPHONY) | I/II | 190 | BLU-945 | 2021 | Recruiting |
| | | | | BLU-945 + osimertinib | | |
| BBT-176 | NCT04820023 | I/II | 168 | BBT-176 | 2021 | Recruiting |
| JIN-A02 | NCT05394831 | I/II | 95 | JIN-A02 | 2022 | Not yet recruiting |
| MET inhibitor | | | | | | |
| Savolitinib | NCT02143466 (TATTON) | Ib | 344 | Savolitinib + osimertinib | 2014 | Active, not recruiting |
| | NCT03778229 (SAVANNAH) | II | 360 | Savolitinib + osimertinib | 2018 | Recruiting |
| | | | | Saboltinib + placebo | | |
| | NCT05015608 (SACHI) | III | 250 | Savolitinib + osimertinib | 2021 | Recruiting |
| | | | | CDDP/CBDCA + PEM | | |
| | NCT05261399 (SAFFRON) | III | 324 | Savolitinib + osimertinib | 2022 | Recruiting |
| | | | | CDDP/CBDCA + PEM | | |
| Teportinib | NCT03940703 (INSIGHT2) | II | 120 | Teportinib + osimertinib | 2019 | Active, not recruiting |
| | | | | Teportinib | | |
| Capmatinib | NCT05642572 (A Lung-MAP) | II | 66 | Capmatinib + osimertinib + ramucirumab | 2022 | Not yet recruiting |
| | | | | Capmatinib + osimertinib | | |
| | NCT04816214 (GEOMETRY-E) | III | 245 | Capmatinib + osimertinib | 2021 | Active, not recruiting |
| | | | | CDDP/CBDCA + PEM | | |
| Other specific inhibitor | | | | | | |
| Selumetinib (MEK1/2 inhibitor) | NCT02143466 (TATTON) | Ib | 344 | Selumetinib + osimertinib | 2014 | Active, not recruiting |
| DS-1205c (AXL inhibitor) | NCT03255083 | I | 13 | DS-1205c + osimertinib | 2017 | Terminated |
| ERAS-007 (ERK1/2 inhibitor) | NCT04959981 (HERKULES-2) | I/II | 200 | ERAS-601 + osimertinib | 2021 | Active, not recruiting |
| Sapanisertib (mTOR inhibitor) | NCT02503722 | I | 36 | Sapanisertib + osimertinib | 2015 | Active, not recruiting |
| TQ-B3525 (PIK α / β inhibitor) | NCT05284994 | I/II | 160 | TQ-B3525 + osimertinib | 2022 | Recruiting |
| Itacitinib (JAK1 inhibitor) | NCT02917993 | I/II | 59 | Itacitinib + osimertinib | 2016 | Active, not recruiting |
| Abemaciclib (CDK4/6 inhibitor) | NCT04545710 | II | 18 | Abemaciclib + osimertinib | 2020 | Recruiting |
| Alisertib (AURKA inhibitor) | NCT04479306 | I | 48 | Alisertib + osimertinib | 2020 | Active, not recruiting |
| Antibody–drug conjugate | | | | | | |
| Trastuzumab deruxtecan (T-Dxd) (HER2-ADC) | NCT04042701 | Ib | 115 | T-DXd + pembrolizumab (part 2 dose expansion cohort) | 2019 | Recruiting |
| Patritumab deruxtecan (HER3-ADC) | NCT03260491 | I | 264 | HER3-DXd | 2017 | Recruiting |
| | NCT04676477 | I | 252 | HER3-DXd + osimertinib | 2020 | Recruiting |
| | NCT04619004 (HERTHENA-Lung01) | II | 420 | HER3-DXd (fixed dose or up-titration) | 2020 | Recruiting |
| | | | | HER3-DXd | | |
| | NCT05338970 (HERTHENA-Lung02) | III | 560 | CDDP/CBDCA + PEM | 2022 | Recruiting |

(Continued)

Table 2. Continued

| Agent | Trial number (Trial name) | Phase | Number of patients | Arm | Year | Status |
|---|------------------------------|-------|---|--|------------|------------------------|
| Dapotamab deruxtecan (Dato-Dxd) (TROP2-ADC) | NCT04484142 (TROPION-Lung05) | II | 137 | Dato-DXd | 2020 | Active, not recruiting |
| | NCT04656652 (TROPION-Lung01) | III | 590 | Dato-DXd Docetaxel | 2020 | Recruiting |
| Telisotuzumab vedotin (Teliso-V) (MET-ADC) | NCT02099058 | I | 260 | Teliso-V | 2014 | Recruiting |
| | | | | Teliso-V + erlotinib Teliso-V + nivolumab | | |
| | NCT04928846 | III | 698 | Teliso-V | 2021 | Recruiting |
| | | | | Teliso-V + osimertinib Docetaxel | | |
| EGFR-MET bispecific antibody Amivantamab | NCT02609776 (CHRYSA LIS) | I | 780 | Amivantamab + lazertinib | 2015 | Recruiting |
| | | I/IIb | 460 | Lazertinib Amivantamab + lazertinib | | |
| | NCT04988295 (MARIPOSA-2) | III | 600 | Amivantamab + Lazertinib + CBDCA + PEM | 2021 | Recruiting |
| | | | | Amivantamab + Lazertinib + CBDCA + PEM CBDCA + PEM Amivantamab + CBDCA + PEM | | |
| Immune checkpoint inhibitor ICI + chemotherapy | NCT02864251 (Checkmate 722) | III | 367 | Nivolumab + CDDP/CBDCA + PEM | 2016 | Completed |
| | | | | CDDP/CBDCA + PEM | | |
| | NCT03515837 (KEYNOTE-789) | III | 492 | Pembrolizumab + CDDP/CBDCA + PEM | 2018 | Active, not recruiting |
| | | | | CDDP/CBDCA + PEM | | |
| NCT03802240 (ORIENT-31) | III | 600 | Sintilimab + IBI305 + CDDP + PEM | 2019 | Recruiting | |
| | | | Sintilimab + placebo + CDDP + PEM Placebo + placebo + CDDP + PEM | | | |
| Multiple study treatment (platform study) | NCT03944772 (ORCHARD) | II | 250 | Osimertinib + savolitinib | 2019 | Recruiting |
| | | | | Osimertinib + gefitinib | | |
| | | | | Osimertinib + necitumumab | | |
| | | | | CBDCA + PEM + durvalumab | | |
| | | | | Osimertinib + alectinib | | |
| | | | | Osimertinib + selpercatinib | | |
| | | | | CDDP/CBDCA + etoposide + durvalumab Osimertinib + CDDP/CBDCA + PEM Osimertinib + selumetinib Osimertinib + Dato-DXd | | |

Abbreviations: CBDCA, carboplatin; PEM, pemetrexed; CDDP, cisplatin; ADC, antibody–drug conjugate; ICI, immune checkpoint inhibitor.

The C797S mutation and *MET* amplification are important therapeutic targets in this setting. Several agents targeting a relatively rare fraction of resistance mechanisms are currently being investigated in early-phase clinical trials. Chemo-IO plus VEGF inhibitors may be an option for 1L osimertinib-resistant patients. However, most of these therapies still need to be investigated in clinical trials and are unavailable in practice. Therefore, performing a re-biopsy at relapse is necessary to expand the possibilities of available trial platforms for individual patients, which would facilitate enrollment in ongoing clinical trials.

In conclusion, the pharmacotherapeutic management of *EGFR*-mutated advanced NSCLC has been rapidly updated to a new phase with the advent of genomic medicine. Upfront combination strategies aimed at preventing or postponing the emergence of resistance are currently being evaluated. Strategies using antibody agents with novel mechanisms of action during a relapse should be implemented clinically. In addition, there is a growing need for repeated proactive re-biopsies for molecular profile testing. A greater understanding of osimertinib resistance mechanisms will contribute to further progress in the ongoing clinical trials discussed in this review, establishing new therapeutic evidence in this setting. Ultimately, this will maximize survival outcomes in patients with relapsed disease.

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