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Comparison of Osimertinib Mono and Combination Therapy in Treating EGFR-mutated Non-small Cell Lung Cancers

Yali Xie[1,a,*]

[1]*Sichuan Kelun-Biotech Biopharmaceutical Co. Ltd, Department of Biostatistics, Chengdu, China*
a. kkkarenxieee@outlook.com
**corresponding author*

Abstract: Osimertinib, a third-generation epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), has become a cornerstone in the treatment of EGFR-mutated (EGFRm) non-small cell lung cancer (NSCLC), with notable efficacy against common EGFR mutations, the T790M resistance mutation, and in treating brain metastases. Despite its benefits, resistance to Osimertinib monotherapy, especially due to secondary mutations such as C797S, poses a major clinical challenge. This study compares the outcomes of Osimertinib as monotherapy versus combination approaches, assessing the potential of additional agents to enhance treatment efficacy and counteract resistance. Findings from recent clinical trials suggest that combining Osimertinib with chemotherapy or other therapeutic agents may improve patient outcomes, supporting further investigation into optimized combination strategies for managing EGFRm NSCLC.

Keywords: Osimertinib, EGFR-TKI, NSCLC, mono therapy, combination therapy

1. Introduction

Worldwide new cases and dead cases are respectively estimated to be 19.974 million and 9.744 million in 2022, as reported recently by Freddie Bray of the International Agency for Research on Cancer under the World Health Organization [1,2]. Among them, there were 2.481 million (12.4%) new cases of lung cancer. It is also the case that lung cancer has once again become the world's top cancer after being overtaken by breast cancer in 2020. As a major part of lung cancer (85%), non-small cell lung cancer (NSCLC) originates in larger cells, such as airway epithelial cells or mucus-producing cells [2].

NSCLC patients may usually undergo progression in case of epidermal growth factor receptor (EGFR) mutations. As a result, the advent of targeted therapies, such as EGFR tyrosine kinase inhibitors (EGFR-TKIs), has transformed the treatment landscape. In patients with lung cancer, the therapeutic regimens have been changed owing to the correlation between biomarkers and EGFR-TKIs, especially in those with EGFR-mutated (EGFRm) NSCLC, resulting in high remission rates and improved patient outcomes [3,4]. Nowadays, patients with EGFRm NSCLC have more treatment options and can experience improved prognostic outcomes with the advancement of targeted therapies, especially the emergence of third-generation EGFR-TKIs. For example, Osimertinib, Ametinib and Volmetinib, have the characteristics of irreversibly binding EGFR mutation sites, which eventually overcome the common T790M resistance mutation of earlier agents. These drugs

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have also shown efficacy against brain metastases because they effectively penetrate the blood-brain barrier [5-7].

Before the approval of EGFR-TKIs for postoperative intervention of patients with early EGFRm NSCLC, platinum-based chemotherapy was the standard postoperative adjuvant therapy, yet with slight therapeutic benefits. The absolute 5-year survival rate was only improved by about 5% [8,9]. EGFR-TKI has made remarkable achievements in the postoperative adjuvant treatment of early EGFRm NSCLC, among which the third generation EGFR-TKI Oechtinib was the first to announce the ADAURA study results of its adjuvant treatment of early EGFRm NSCLC patients. Based on its overwhelming DFS benefit and favorable safety profile, Osimertinib was approved by the Food and Drug Administration and National Medical Products Administration (NMPA) respectively in December 2020 and April 2021 for stage IB-IIIA EGFRm NSCLC after operation [10]. Based on Evidence studies, the first-generation Ectinib domestically obtained an approval by NMPA in June 2021 as an adjuvant option for postoperative patients with stage II-IIIA EGFRm NSCLC [11].

As a result, the latest-generation Osimertinib has currently been the first-line standard regimen in EGFRm NSCLC as it may be effective in remarkably prolonging progression-free survival (PFS) and effectively treating brain metastases [12]. However, the main issue with Osimertinib monotherapy is the development of resistance, particularly with the C797S mutation, which limits its long-term efficacy and has led to the exploration of combination therapies to delay or overcome resistance.

Emerging evidence suggests that combination therapy-Osimertinib used alongside other treatment modalities such as chemotherapy or other targeted agents-may further enhance therapeutic outcomes by overcoming resistance mechanisms like the C797S mutation [13]. The author evaluated the efficacy, including PFS and overall survival (OS), as well as safety of Osimertinib monotherapy compared to Osimertinib-based combination therapies to determine the most effective approach for treating EGFRm NSCLC.

This review intends to shed light on the differences between Osimertinib mono and combination therapies from the aspects of the efficacy, PFS, OS, and safety profile. This study is expected to determine which approach offers superior outcomes for treating EGFRm NSCLC, focusing on the potential benefits of combination strategies in overcoming resistance and enhancing long-term prognosis.

2. Osimertinib Monotherapy

Osimertinib is the world's first third representative EGFR-TKI targeting patients with EGFR mutated NSCLC. It can effectively inhibit EGFR sensitive mutations (exon deletion mutation 19 and exon L858R point mutation 21) and EGFR T790M drug-resistant mutations and has excellent performance in suppressing brain metastases [14].

Concerning the mechanism of action, Osimertinib can inhibit EGFR tyrosine kinase activity. Highly expressed EGFR can be found frequently in various types of tumors, and its mutation or overexpression leads to infinite cell proliferation and tumor formation. By competitively binding the active site of EGFR with ATP, Osimertinib prevents its phosphorylation, thereby retarding tumor cell behaviors, such as growth and proliferation [15,16].

2.1. The clinical achievement of Osimertinib monotherapy in treating NSCLC

As documented in pre-clinical study [17], in relative to earlier-generation drugs, Osimertinib demonstrates a superior capacity to penetrate the blood-brain barrier, exhibiting a substantial therapeutic impact on brain metastases. Moreover, various clinical studies, such as the AURA series study [18-20], FLAURA study [21] and BLOOM study [22], have confirmed the advantage of Osimertinib in the control of intracranial lesions.

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Specifically, in FLAURA's study, Osimertinib treatment showed a "brain protection" effect: Among the total central nervous system (CNS) analysis set (cFAS, i.e., CNS metastases found in patients at baseline), the 18-month PFS rate of BMS patients in the Osimertinib and Control (gefitinib or erlotinib) groups was 58% and 40%, respectively. Also, in cFAS population, the Complete Response(CR) rate in the Osimertinib group reached 41% [21,23].

The ADAURA study offers additional data of critical clinical data to support the function of Osimertinib in the adjuvant treatment of early NSCLC. Osimertinib can significantly prolong the disease-free survival (DFS) and obviously enhance the OS of patients. The 5-year OS rate of ADAURA study was as high as 88%, which further consolidated the status of Osimertinib as the standard therapy for treating participants with EGFR-positive stage Ib-IIIA NSCLC after operation [10,24].

Clinical studies on Osimertinib monotherapy are summarized in **Table 1**, which details key trials evaluating its efficacy in treating NSCLC. These studies demonstrate significant improvements in PFS and OS, particularly in participants with brain metastases. In AURA3 study, the median of CNS-PFS in treatment is 11.7 months while it is only 5.6 months in another arm with platinum-pemetrexed. The data highlight Osimertinib's role as a preferred first-line treatment.

Table 1: The Results of Clinical Trials in Osimertinib Monotherapy

Study Name (registered number)	Phase	Population	Treatment Arm (T)	Control Arm (C)	Results (T vs C)
AURA[18] (NCT01802632)	Phase1/2	Phase1: - Phase2: Advanced lung cancer with progression after prior EGFR-TKI therapy; EGFR T790M status determined in expansion cohorts EGFRT790M-positive, locally advanced or metastatic (stage IIIB/IV) NSCLC with progression on prior EGFR-TKI therapy; includes patients with stable, asymptomatic CNS metastases	Osimertinib	-	ORR-Overall: 51% (45%, 58%) ORR-Confirmed EGFR T790M: 61% (52%,70%) mPFS-EGFR T790M-positive:9.6(8.3, NE) mPFS-EGFR T790M-negative:2.8(2.1,4.3) *DCO: 20140801
AURA2[19] (NCT02094261)	Phase2		Osimertinib	-	ORR: 70% (64%,77%) *DCO: 20151101

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Table 1: (continued).

AURA3[20] (NCT02151981)	Phase3	T790M-positive advanced NSCLC with progression after first-line EGFR-TKI therapy	Osimertinib	Platinum-pemetrexed	CNS ORR: 70% (51%, 85%) vs.31% (11%, 59%) OR: 5.13 (1.44,20.64; P = 0.015) CNS mPFS: 11.7 vs.5.6 (HR: 0.32(0.15, 0.69); P = 0.004) *DCO: 20160415
ADAURA[10] (NCT02511106)	Phase3	Completely resected EGFR mutation-positive NSCLC (stage IB-IIIA)	Osimertinib	Placebo	DFS: HR (0.27(0.21,0.34) 4yrs DFS rate: 73% vs. 38% *DCO: 20220411
FLAURA [21] (NCT02296125)	Phase3	Previously untreated EGFR mutation-positive (exon 19 deletion or L858R) advanced NSCLC	Osimertinib	standard EGFR-TKI (Gefitinib or Erlotinib)	mPFS: 18.9 vs 10.2 (HR: 0.46(0.37,0.57); P<0.001) ORR: 80% vs. 76% (OR: 1.27(0.85,1.90); P=0.24) *DCO:20170612

Note HR: hazard ratio; yrs: years; OR: odds ratio; NE: not evaluate; NR: not reached; DCO: data cut-off date; vs.:versus. Data sourced from referenced published clinical trials.

When interpreting the advantages of Osimertinib monotherapy in NSCLC, we can understand that it can intervene brain metastases effectively by penetrating the blood-brain barrier. Osimertinib is superior to earlier-generation agents in penetrating the blood-brain barrier and accessing intracranial lesions, especially useful for delaying brain metastases. The FLAURA study showed that the mPFS of participants with advanced mEGFR NSCLC treated with Osimertinib monotherapy was 18.9 months [21], which was significantly better than that of first-generation EGFR-TKI. In addition, Osimertinib can shrink tumor lesions, effectively control disease progression, and improve the quality of life of patients when intervening brain metastases.

In general, Osimertinib has proven highly effective as a first-line choice for advanced mEGFR NSCLC, significantly improving PFS, OS, and CNS-PFS.

2.2. The safety and toxicity of Osimertinib monotherapy

Common adverse effects of Osimertinib with monotherapy include rash, nausea and vomiting, diarrhea, fatigue, and muscle and joint pain. However, adverse events of grade 3 or higher were less

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frequent with Osimertinib than with standard EGFR-TKIs (34% vs. 45%), such as gefitinib or erlotinib in FLAURA study [21]. Despite a frequent presence, these adverse reactions can usually be effectively controlled through appropriate management and medical intervention [25].

Osimertinib showed a better safety profile in terms of tolerability compared to earlier EGFR-TKIs. The adverse effects of Osimertinib are usually mild and in most cases can be alleviated over time. As for skin reactions, Osimertinib outperforms earlier-generation agents such as Gefitinib and Erotinib, which are more likely to cause severe skin reactions and interstitial lung disease. In addition, Osimertinib has shown a lower rate of disease progression and higher patient tolerance in patients with NSCLC, especially in mEGFR patients [26,27].

2.3. Resistance of Osimertinib monotherapy

With the gradual popularization of the clinical application of novel EGFR-TKIs (i.e., the third generation), an era of "the last third-generation EGFR drugs" has come to benefit lung cancer management. How to solve the follow-up treatment after the third-generation drug resistance is an urgent clinical problem. Osimertinib monotherapy resistance can arise from on-target mechanisms, which involve mutations directly in the EGFR gene, such as the C797S mutation. Osimertinib forms a covalent bond with EGFR at cysteine 797 (C797) residues situated within the ATP-binding fissure. Osimertinib may fail to bind to EGFR in the case of C797S mutation, making the C797 residue a critical site for acquired resistance to Osimertinib. Indeed, EGFR C797S mutation is observed in approximately 10-26% of patients who develop resistance to second-line Osimertinib therapy. Other gene mutations that can cause Osimertinib resistance have a lower incidence than C797S, including G796X, solvent frontier mutations L792X, L718X, and G724S [28].

Nevertheless, the cumulative incidence of these mutations is significantly lower compared to the T790M mutation responsible for Osimertinib resistance (50%-60%). Osimertinib "on-target" resistance appears to be less common in first line compared to second-line therapy using Osimertinib. Only 7% of patients in the FLAURA study [21] had the EGFR C797X mutation, and as expected, no T790M mutation was found in ocitini-resistant tumors [29].

Osimertinib monotherapy faces significant challenges of resistance, particularly in the presence of EGFR C797S mutation, which compromises the drug's efficacy in 10-26% of second-line treatments. Other less frequent mutations contributing to resistance (off-target resistance), include HER2 amplification, RAS-MAPK pathway activation, MET amplification, and small cell transformation, allowing tumor cells to bypass EGFR inhibition. These alternative pathways highlight the complexity of resistance mechanisms and the necessity for in-depth digging and validation into novel combination therapies or targeted approaches to effectively manage patients once resistance develops [30].

3. Osimertinib Combination Therapy

Osimertinib has played an essential therapeutic role in NSCLC, particularly in participants with EGFR mutations. Faced with various primary and acquired resistances to the proposed third-generation agents, Osimertinib combination therapy is a major development direction. Through the combination of TKI or immunotherapy drugs, more NSCLC patients can benefit from delaying or overcoming drug resistance. Osimertinib not only performed well in monotherapy, but also demonstrated significant advantages in combination therapy.

3.1. Combination Therapy Scheme Selection

With the growing understanding of resistance mechanisms to Osimertinib, combination therapies have emerged as promising approaches to enhance treatment efficacy and overcome resistance. These

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third generation can be used jointly with other targeted agents or chemotherapy, offering the potential to tackle both on-target and off-target resistance. These strategies aim to delay resistance development and improve PFS. The efficacy of such combinations has been deciphered in several trials clinically, which focused on optimizing outcomes for participants with advanced EGFRm NSCLC.

3.1.1. Early - and third-generation EGFR-TKI combination

A resistance management strategy involves the use of both early- and latest-generation EGFR-TKIs, which, when combined, may overcome or delay the development of "on-target" resistance. For instance, in EGFRm NSCLC, Osimertinib and early-generation agent jointly can counteract the antibiotic-associated C797S mutation. Niederst et al. showed that when encountering T790M and C797S mutations of EGFR in trans (residing on different EGFR alleles) at the same time, the use of a first-generation EGFR-TKI (which targets C797S) alongside a third-generation agent (which targets T790M) could reestablish the inhibition of the EGFR signaling pathway [31].

3.1.2. Combination with chemotherapy

The advantage of Osimertinib combination therapy lies in its synergistic effect with chemotherapy agents, which further prolongs PFS in patients. In the FLAURA2 study, the Osimertinib + chemotherapy group had a median CNS-PFS of 30.2 months and a significantly higher complete response rate than in the Osimertinib monotherapy group. This combination treatment regimen not only reduced the risk of disease progression or patient death, but also extended overall survival [25]. However, combination therapy may also increase certain toxicity and side effects, which need to be weighed and selected by doctors according to the specific situation of the patient .For example, the FLAURA2 results showed that the incidence of grade ≥3 adverse events was 64% and 27% in the Osimertinib combination and monotherapy groups, respectively, most of which were typical chemotherapy-related toxic events[25,32]. Other clinical studies on Osimertinib combination therapy are also summarized in Table 2. The mPFS is longer than that of monotherapy studies in Table1, almost 20 months or even longer as FLOWERS and OPAL study reported. But in Table 1, the mPFS in monotherapy was shorter than 20 months, such as 18.9 months in FLAURA study.

Table 2: The results of Clinical Trials in Osimertinib Combination Therapy

Study Name (Registered number)	Phase	Population	Treatment Arm(T)	Control Arm(C)	Results (T vs C)
FLAURA2[25] (NCT04035486)	Phase3	EGFRm(exon 19 deletion or L858R) advanced NSCLC, treatment-naive for advanced disease	Osimertinib with chemotherapy	Osimertinib	PFS: 25.5 (24.7, NE) vs. 16.7 (14.1,21.3) (HR:0.62(0.49,0.79); P<0.001) CNS-PFS: 0.47 (0.33–0.66) ORR:83% vs. 76% *DCO:20230403

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Table 2: (continued).

FLOWERS [33] (NCT05163249)	Phase2	Treatment-naive stage IIIB-IV NSCLC with de novo MET alteration (MET amplification and/or overexpression) and EGFR mutation	Osimertinib with Savolitinib	Osimertinib	ORR: 90.5% vs. 60.9% mPFS: 19.6 vs. 9.3 (HR:0.59(0.19,1.81)) *DCO:20240528
OPAL [34] (jRCTs031180226)	Phase2	previously untreated EGFRm advanced non-squamous NSCLC	、Osimertinib with Cisplatin	Osimertinib with Carboplatin	ORR: 90.9% (84.0%,97.8%) vs. 90.9% (84.0%,97.8%) mPFS: 29.5 (18.2, NE) vs. NR (27.2, NE) *DCO:20220831

Note HR: hazard ratio; OR: odds ratio; NE: not evaluate; NR: not reached; DCO: data cut-off date; vs. versus. Data sourced from referenced published clinical trials.

4. Prospects

Osimertinib has shown excellent efficacy in advanced mEGFR NSCLC patients as a first-line strategy. FLAURA study has documented significantly superior effects of Osimertinib on improving PFS, OS and CNS-PFS to earlier EGFR-TKIs [21]. The FLAURA2 study further explored the efficacy of Osimertinib combined with chemotherapy and showed a significant increase in mPFS of about 9 months in the combination group, suggesting that Osimertinib combined with chemotherapy may be a new first-line treatment option [25]. In addition, the benefit of Osimertinib combined with chemotherapy was more pronounced in L858R mutation and CNS metastasis subgroups.

With the wide application of Osimertinib, the problem of drug resistance has been highly concerned by researchers. Research progress has shown a complicated resistance mechanism of Osimertinib, involving EGFR-dependent and -independent pathways. In response to the problem of drug resistance, multiple treatment strategies are being explored, such as combination medication, next-generation EGFR-TKIs, immunotherapy, etc. The ongoing clinical studies of combination therapy are also very impressive in terms of efficacy and other data.

Wentao Tian et al. published research in Cancer Med in August 2024, combined data from the FLAURA2 and FLAURA studies. Their report pointed out that Osimertinib combined with chemotherapy was less cost-effective than Osimertinib alone for untreated participants with advanced mEGFR NSCLC on the basis of the U.S. health care system, However, better cost-effectiveness was found in patients with L858R mutation and without baseline CNS metastasis [35].

Active studies are ongoing to address resistance mechanisms of Osimertinib, multiple strategies, including next-generation EGFR-TKIs, combination therapies, and immunotherapy. Early clinical studies have shown promising results. However, cost-effectiveness analyses suggest that while Osimertinib monotherapy may be more cost-effective overall, and combination therapy can offer greater benefits in specific subgroups like L858R-mutant and CNS metastasis patients. These findings pave the way for more personalized approaches to treatment.

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5. Conclusion

Osimertinib has demonstrated significant efficacy when applied alone as a monotherapy and jointly in combination therapy for patients with NSCLC, mainly in those with brain metastases. Its roles in extending PFS and OS, especially when combined with chemotherapy, underscore its potential in first line and resistant settings. As further clinical trials are conducted, there is strong potential to optimize Osimertinib-based treatment strategies, offering NSCLC patients more effective, personalized options and improved prognoses in the future.

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