Osimertinib in EGFR-Mutated Lung Cancer: A Review of the Existing and Emerging Clinical Data

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Abstract: The use of epidermal growth factor receptor (EGFR) inhibitors such as osimertinib has improved outcomes and quality of life for patients with EGFR-mutated non-small cell lung cancer (NSCLC). Osimertinib has become the preferred EGFR tyrosine kinase inhibitor (TKIs) for patients with these mutations after demonstrating superior efficacy compared to first generation EGFR TKIs, such as erlotinib and gefitinib. More recently osimertinib has also shown to be beneficial in patients with resectable NSCLC harboring EGFR mutations irrespective of whether they received adjuvant chemotherapy or not. The drug is now FDA approved in this setting. With osimertinib being used more commonly in earlier stage and front-line settings, we are more likely to see patients who develop resistance to this drug. The aim of this review is to provide a comprehensive review of the data with osimertinib in EGFR mutation positive NSCLC, potential resistance mechanisms and an overview of key ongoing clinical trials.

Keywords: non-small cell lung cancer, epidermal growth factor receptor, tyrosine kinase inhibitor, osimertinib

Introduction

Lung cancer is one of the most prevalent cancers developed in men and women throughout the world. Lung cancer remains the leading cause of cancer related mortality, accounting for 23% in males and 22% in females. Lifetime probability of developing lung cancer is estimated to be 1 in 15 and 1 and 17 in men and women, respectively. The overall five-year survival rate for lung cancer has been decreasing over the last few decades, yet it still remains the second highest of all cancer diagnosis’ at 15%.1,2

Lung cancer is categorized into two large types: small-cell lung carcinoma and non-small cell lung carcinoma (NSCLC) (which encompasses histologies such as adenocarcinoma, squamous cell carcinoma, and large cell carcinoma).1 NSCLC accounts for approximately 85% of all lung cancer cases.3 Adenocarcinoma, is the most prevalent histological subtype originating from mucus-secreting cells, in both smokers and non-smokers. Adenocarcinoma is a heterogeneous disease further stratified by molecular driver mutations as detailed below. Epidermal growth factor receptor (EGFR) was one of the first discovered actionable driver mutations.4

Treatment for NSCLC has been evolving over the last few decades. The landmark trial in 2003, analyzed four chemotherapy platinum-based doublets in patients with untreated advanced NSCLC and concluded no survival difference between the regimens analyzed with median overall survival (OS) in all arms being less than 12
months. The paradigm-changing IPASS study by Mok et al, published in 2009 demonstrated superior efficacy of gefitinib, an oral tyrosine kinase inhibitor (TKI) over platinum doublet chemotherapy in front-line setting for treatment of NSCLC in never or former light-smokers of Asian ethnicity. Exploratory analysis of efficacy based on EGFR mutation showed that the progression-free survival (PFS) was 9.8 for patients who were treated with gefitinib vs 6.4 months for those who were treated with carboplatin and paclitaxel (hazard ratio [HR] 0.48, p<0.001). PFS was higher in patients treated with chemotherapy compared to those treated with gefitinib in EGFR wild-type cohort highlighting the importance of EGFR mutation testing in NSCLC. This led to further investigation of the use of EGFR TKIs in patients with EGFR mutated advanced NSCLC. NEJ002 was a randomized Phase 3 trial comparing gefitinib to carboplatin and paclitaxel in this patient population. Gefitinib demonstrated an improvement in PFS with a median of 10.8 months compared to 5.4 months in the chemotherapy group (HR=0.32, p<0.001). In a similar study design, OPTIMAL compared erlotinib to carboplatin and paclitaxel and also demonstrated a PFS improvement with an EGFR TKI compared to chemotherapy (13.1 vs 4.6 months; HR=0.16, p<0.0001). Both of these studies did not show a statistically significant improvement in OS.

EGFR is a cell-surface tyrosine kinase receptor belonging to the erB family which includes erbB1 (EGFR), erbB2 (HER2), erbB3, and erbB4. Ligand binding is necessary to activate a wild-type EGFR, inducing a conformational change to its active state. Receptor activation subsequently results in autophosphorylation of tyrosine residues within the tail of the EGFR, forming a large protein complex that can induce downstream signaling. Downstream pathways include: Ras/Raf/(Ras/MAPK), (PI3K/AKT), and STAT, all leading to rapid cell survival, proliferation, and cellular migration. In NSCLC with EGFR mutations, there is constant ligand-independent activation and proliferation within the rapidly dividing cells. Mutations within the EGFR gene occur in approximately 15% of NSCLC adenocarcinomas, and in Asian populations, the incidence has been reported at roughly 62%. Genetic mutations of EGFR typically involve single nucleotide variation (SNV), insertion, deletion, and copy number variations. Genetic variations are frequently seen in exons 18–21, with therapeutic response to TKI noted primarily in NSCLC with exon 19 and 21 mutations. The most common mutations within EGFR are the deletion of amino acids at 747–750 of exon 19 (19Del) and L858R of exon 21, discovered in 33.1% and 40.9% of the patient population, respectively.

Multiple TKIs have shown activity in EGFR mutation positive NSCLC. The agents are categorized as first generation reversible agents (gefitinib, icotinib and erlotinib), second generation irreversible agents (afatinib and dacomitinib) and third generation agents with activity against secondary resistance mutation (osimertinib) and are summarized in Table 1. Gefitinib, erlotinib, afatinib, dacomitinib and osimertinib are all approved by United States Food and Drug Administration (US FDA) for use in front-line setting for EGFR mutation-positive NSCLC.

Head-to-head comparison between first generation TKIs, gefitinib and erlotinib was performed in a phase 3 study and both drugs were noted to have similar efficacy and toxicity. Second generation agents, afatinib and dacomitinib have been shown to have superior efficacy than gefitinib in LUX-Lung-7 and the ARCHER-1050 studies respectively. Afatinib had marginal improvement in PFS but no difference in OS when compared to gefitinib. Dacomitinib, on the other hand showed significant improvement in PFS as well as OS predominantly in the Asian population. However, both these agents had significantly increased toxicity compared to gefitinib.

Osimertinib in Previously-Treated EGFR-Mutation Positive NSCLC Patients

Acquired resistance to first or second generation EGFR-TKIs is common and occurs approximately 10 months from initiation of therapy. The T790M substitution within exon 20, is a leading contributor for resistance to first- and second-generation EGFR inhibitors in NSCLC. T790M mutations within exon 20 result in 60% of acquired resistance to EGFR-TKIs. Osimertinib is an oral, third generation EGFR-TKI, that was formulated to inhibit EGFR with preferential activity against both sensitizing and T790M resistance mutations. Osimertinib provides benefit in patients with T790M mutations by irreversibly targeting cysteine-797 residue in the ATP binding site of EGFR kinase via a covalent bond formation. This results in selective inhibition of mutant EGFR including T790M at a concentration that is nine-fold lower than wild-type EGFR. Clinical trials of osimertinib began in 2013 and showed impressive anti-tumor activity.
| Trial       | Phase | N   | Patient Population                                                                 | Intervention                                                                 | Median Follow-Up (Median, Months) | PFS (Median, Months) | OS (Median, Months) | ORR (%) |
|------------|-------|-----|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------|---------------------|---------------------|---------|
| IPASS6,13  | 3     | 1217261 (EGFR+)                     | Treatment naive patients in East Asia with advanced adenocarcinoma and who were nonsmokers or former light smokers | Gefitinib 250 mg/ day vs carboplatin plus paclitaxel | 17.0 | EGFR+ group: 9.5 vs 6.3; HR=0.48 (0.36–0.64); p<0.001 EGFR- group: 1.5 vs 5.5; HR=2.85 (2.05–3.98); p<0.001 | 18.8 vs 17.4; HR=0.90 (0.79–1.02); p=0.109 | 71.2 vs 47.3 |
| WJTOG-3405 | 14,15 | 172 | Chemotherapy naïve patients with stage III/IV NSCLC or post-operative recurrence harboring EGFR mutations | Gefitinib 250 mg/ day or cisplatin plus docetaxel | 59.1 | 9.2 vs 6.3; HR=0.49 (0.34–0.71); p<0.0001 | 34.8 vs 37.3; HR=1.252 (0.883–1.775) | 62.1 vs 32.2 |
| First-SIGNAL | 16   | 42  | Stage III/IV adenocarcinoma                                                        | Gefitinib 250 mg/ day vs gemcitabine plus cisplatin | 35  | 5.8 vs 6.4; HR=1.198 (0.944–1.520); p=0.138 | 22.3 vs 22.9; HR=0.932 (0.716–1.213); p=0.604 | 84.6 vs 37.5 |
| NEJ00216   | 3     | 230 | Treatment naïve EGFR mutated advanced NSCLC                                       | Gefitinib 250 mg/ day vs carboplatin plus paclitaxel | 704 days | 10.8 vs 5.4; HR=0.322 (0.236–0.438); p<0.001 | 27.7 vs 26.6; HR=0.887 (0.634–1.241); p=0.483 | 73.7 vs 30.7 |
| EURTAC17   | 3     | 173 | Treatment naïve EGFR mutated advanced NSCLC                                       | Erlotinib 150 mg/ day vs 3-week cycles of standard IV chemotherapy | 18.9 vs 14.4 | 9.7 vs 5.2; HR=0.37 (0.25–0.54); p<0.001 | 19.3 vs 19.5; HR=1.04 (0.65–1.68); p=0.87 | 53 vs 15 |
| OPTIMAL8,9 | 3     | 154 | EGFR mutated stage III/IV NSCLC                                                    | Erlotinib 150 mg/ day vs gemcitabine plus carboplatin | 25.9 | 13.1 vs 4.6; HR=0.16 (0.10–0.26); p<0.0001 | 22.8 vs 27.2; HR=1.19 (0.83–1.71); p=0.2663 | 83 vs 36 |
| ENSURE18   | 3     | 217 | EGFR mutated stage III/IV NSCLC                                                    | Erlotinib 150 mg/ day vs gemcitabine and cisplatin up to 4 cycles | 28.9 vs 27.1 | 11.0 vs 5.5; HR=0.34 (0.22–0.51); p<0.0001 | 26.3 vs 25.5; HR=0.91 (0.63–1.31); p=0.607 | 62.7 vs 33.6 |
| LUX-LUNGI19 | 2B/3  | 585 | EGFR mutated Stage III/IV NSCLC who had received 1 or 2 previous chemotherapy regimens and had disease progression after 12 weeks of treatment with erlotinib or gefitinib | Afatinib 40 mg/ day vs placebo | NR | 3.3 vs 1.1; HR=0.38 (0.31–0.48); p<0.0001 | 10.8 vs 12.0; HR=1.08 (0.86–1.35); p=0.74 | NR |

(Continued)
| Trial         | Phase | N   | Patient Population                        | Intervention                                                                 | Median Follow-Up (Median, Months) | PFS (Median, Months)                           | OS (Median, Months)                           | ORR (%) |
|--------------|-------|-----|-------------------------------------------|-----------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------|-----------------------------------------------|---------|
| LUX-LUNG3    | 3     | 345 | EGFR mutated stage IIIb/IV NSCLC          | Afatinib 40 mg/day vs up to 6 cycles of cisplatin plus pemetrexed chemotherapy | 16.4                             | 11.1 vs 6.9; HR=0.58 (0.43–0.78); p=0.001   | 28.2 vs 28.2; HR=0.88 (0.66–1.17); p=0.39    | 56.1 vs 22.6 |
| LUX-LUNG6    | 3     | 364 | Treatment naive EGFR mutated advanced NSCLC | Afatinib 40 mg/day vs gemcitabine and cisplatin for up to 6 cycles          | 16.6                             | 11.0 vs 5.6; HR=0.28 (0.20–0.39); p<0.0001  | 23.1 vs 23.5; HR=0.93 (0.72–1.22); p=0.61     | 66.9 vs 23.0 |
| LUX-LUNG7    | 2B    | 319 | EGFR mutated stage IIIb/IV NSCLC          | Afatinib 40 mg/day vs gefitinib 250 mg/day                                   | 42.6                             | 11.0 vs 10.9; HR=0.73 (0.57–0.95); p=0.017  | 27.9 vs 24.5; HR=0.86 (0.66–1.12); p=0.258   | 70 vs 56 |
| LUX-LUNG8    | 3     | 795 | Stage IIIb/IV SCLC after progression of >4 cycles of platinum-based chemotherapy | Afatinib 40 mg/day vs erlotinib 150 mg/day                                   | 18.4                             | 2.4 vs 1.9; HR=0.82 (0.68–1.00); p=0.0427   | 7.9 vs 6.8; HR=0.81 (0.69–0.95); p=0.0077    | 22 vs 11 |
| ARCHER 1050  | 3     | 452 | Treatment naive EGFR mutated advanced NSCLC | Dacomitinib 45 mg/day vs gefitinib 250 mg/day                               | 31.1                             | 14.7 vs 9.2; HR=0.59 (0.47–0.74); p<0.0001  | 34.1 vs 26.8; HR=0.760 (0.582–0.993)          | 74.9 vs 71.6 |
| ARCHER 1009  | 3     | 878 | Locally advanced or metastatic NSCLC, progression after 1–2 previous regimens of chemotherapy | Dacomitinib 45 mg/day vs erlotinib 150 mg/day                               | 7.1                              | 2.6 vs 2.6; HR=0.941 (0.802–1.104); p=0.229 | 7.9 vs 8.4; HR=1.079 (0.914–1.274); p=0.817  | 11.0 vs 8.0 |
| AURA3        | 3     | 419 | T790M-positive advanced NSCLC with disease progression after 1st line EGFR TKI therapy | Osimertinib 80 mg/day vs pemetrexed plus either carboplatin or cisplatin    | 8.3                              | 10.1 vs 4.4; HR=0.30 (0.23–0.41); p<0.001   | NR                                             | 71 vs 31 |
| FLAURA       | 3     | 556 | Treatment naive EGFR mutated advanced NSCLC | Osimertinib 80 mg/day vs standard EGFR TKI either gefitinib 250 mg/day or erlotinib 150 mg/day | 29                               | 18.9 vs 10.2; HR=0.46 (0.37–0.57); p<0.001  | 38.6 vs 31.8; HR=0.80 (0.64–1.00); p=0.046    | 80 vs 76 |
| ICOGEN       | 3     | 399 | Previously treated with one or more platinum-based chemotherapy regimens with no response | Icotinib 125 mg three times daily vs gefitinib 250 mg once daily            | 24                               | 4.6 vs 3.4; HR=0.84 (0.67–1.05); p=0.13     | 13.3 vs 13.9; HR=1.02 (0.82–1.27); p=0.57    | 27.6 vs 27.2 |

(Continued)
in EGFR-mutated (EGFR-m) NSCLC, which had progressed on first generation EGFR TKI. The subsequent phase 3 AURA3 study further solidified the role of osimertinib in NSCLC patients who had developed T790M resistance mutation on first generation TKI by showing significantly improved efficacy in comparison to platinum-pemetrexed regimen in this patient population. Patients enrolled in the study were assigned in a 2:1 ratio to receive either oral osimertinib (80 mg once daily) or intravenous pemetrexed (500 mg per square meter of body-surface area) plus either carboplatin (AUC 5) or cisplatin (75 mg per square meter) every 3 weeks for 6 cycles; primary endpoint was investigator-assessed progression free survival. Results showed a longer PFS with osimertinib than combination chemotherapy (10.1 months vs 4.4 months; hazard ratio (HR)=0.61, 95% CI, 0.43–0.87; p=0.006) and DoR was 11.2 vs 7.9 months for T790M-negative (p=0.229). PFS was 10.8 months for T790M positive vs 5.1 months for T790M negative (HR 0.62, p=0.007). OS was 22.5 months vs 13.4 months (HR 0.55, p=0.002) for T790M positive against negative. This study further emphasized osimertinib’s role when treating patients positive for T790M NSCLC but also suggested that there is benefit from osimertinib in patients who had progressive cancers that were T790M-negative.

Osimertinib as Frontline Treatment for EGFR-Mutated NSCLC

Given the promising results of the AURA3 trial, the FLAURA trial was conducted to investigate osimertinib’s use in the front line setting of recurrent or metastatic EGFR-m, treatment naïve NSCLC. Patients enrolled into the study were randomly assigned in a 1:1 ratio to receive either osimertinib 80 mg once daily or a first-generation EGFR-TKI (gefitinib 250 mg daily or erlotinib 150 mg daily). Patients with brain metastases were also included in this trial. The study met its primary endpoint of investigator-assessed PFS, which was reported as 18.9 months in the osimertinib arm compared to 10.2 months in the control (HR for disease progression or death 0.46, 95% CI, 0.37 to 0.57; p<0.001). ORR was not different between the two groups, but duration of response was considerably longer in osimertinib arm at 17.2 months compared to 8.5 months on the first generation TKI arm.

| Trial | Phase | N | Patient Population | Intervention | Median Follow-Up (Median, Months) | PFS (Median, Months) | OS (Median, Months) | ORR (%) |
|-------|-------|---|-------------------|--------------|---------------------------------|---------------------|---------------------|---------|
| CONVINCEN21 | 3 | 285 | EGFR mutated stage IIIb/IV NSCLC | Icotinib 125 mg three times daily vs 3 week cycles of chemotherapy (75 mg/mg cisplatin plus 500 mg/m² pemetrexed on Day 1) | 39.6 | 11.2 vs 7.9; HR=0.61 (0.43–0.87); p=0.006 | 30.5 vs 32.1; p=0.8854 | NR |

Abbreviations: EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; NR, Not reported; ORR, overall response rate; OS, overall survival; PFS, progression free survival; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitors.
follow up confirmed a benefit in OS with osimertinib as well, 38.6 months in the osimertinib arm vs 31.8 months in the other arm (HR=0.80; 95% CI, 0.64 to 1.00; p=0.046). This lead to the FDA granting osimertinib an approval in 2018 as first-line therapy for patients with metastatic NSCLC whose tumors have EGFR exon 19 deletion or exon 21 L858R mutation.33

**Osimertinib in Patients with Central Nervous System (CNS) Metastases**

Presence of CNS metastases is commonly observed in lung cancer patients with some studies reporting up to 65% lifetime incidence of brain metastases or leptomeningeal metastases (LMs) in patients with NSCLC.40 CNS metastases are especially prevalent in patients with EGFR-m lung cancer.41 TKIs have shown benefit in patients diagnosed with EGFR-m NSCLC and LMs, resulting in a median OS of 10 months versus 3.3 months in patients who did not receive TKIs.42 When it comes to earlier generation TKIs, their concentration within the cerebrospinal fluid is less than that found in the blood which in turn results in treatment failure due to pharmacokinetic limitations.42 Osimertinib, on the other hand, effectively penetrates the blood-brain barrier, resulting in higher brain exposure than the previously tested EGFR-TKIs. A positron emission tomography (PET) study with radioisotope labeled osimertinib showed that the drug rapidly distributed within the brain, with a higher uptake into the grey compared to the white matter with a $T_{\text{max}}$ of 13 minutes (range 5–30min).43 In patients with CNS metastases evaluable-for-response, which was defined as one measurable CNS lesion in the AURA, AURA3 and FLAURA trials, collective CNS response rate was 71.6%, control rate 93%, and PFS 11.7 months.28,44,45 A Phase 1 (BLOOM) study analyzed the activity of osimertinib in patients with EGFR-m NSCLC and LMs. Osimertinib was given at a dose of 160 mg once daily until disease progression or there was unmanageable drug-related toxicity. Within the trial, there was a total of 41 patients who were assessed for pre-defined endpoints of ORR, DoR, PFS, OS, pharmacokinetics (PK), and safety. Data from the trial showed an investigator assessed median duration of response (DoR) of 8.3 months (95% CI, 5.6 to 16.5), and an ORR of 41% (95% CI, 26% to 58%) and neuroradiologic blinded committee review median DOR 15.2 months (95% CI, 7.5 to 17.5) and ORR of 62% (95% CI, 45% to 78%), with adverse event rates similar to those found in previous osimertinib trials.46 The APOLLO study looked at the efficacy and safety of osimertinib for real-world patients with EGFR-T790M NSCLC and CNS metastases via circulating biomarkers for response to therapy. In the study, 38 patients were enrolled with a median follow-up of 8.2 months and demonstrated a median PFS of 8.4 months (95% CI, 5.8 to 10.9) and ORR of 39.4% (95% CI, 22.9 to 57.9).47 Multiple case reports have been published describing CNS efficacy of osimertinib.48

**Osimertinib as Adjuvant Therapy Post-Surgical Resection in Early Stage EGFR-m NSCLC**

Approximately 30% of patients with NSCLC present in early stage and are eligible to undergo curative surgical resection. Understandably, prognosis is highly dependent on stage at diagnosis with 5-year OS rate ranging from 60 to 74% for stage I, 47 to 55% for stage II, and 38% for stage IIIA.49 Although the use of chemotherapy in the adjuvant setting is the standard of care for stage II or III NSCLC, disease recurrence frequently occurs. An estimated 45% of patients diagnosed with stage IB, and 76% of patients diagnosed with stage III, succumb to disease recurrence despite adjuvant chemotherapy.50,51

The ADJUVANT/CTONG 1104 study investigated gefitinib’s use in completely resected EGFR-m NSCLC.52 This was a phase 3, open-label trial that randomized 222 patients in a 1:1 fashion to receive either gefitinib for two years or intravenous chemotherapy. Baseline demographics were similar amongst the two groups. Fifty-nine percent of patients in this study were female, three-quarter of patients were never smokers and 52% of patients had an exon 19 deletion. The primary endpoint was disease-free survival (DFS) and the median DFS was significantly longer with gefitinib compared to intravenous chemotherapy ([28.7 months 95% CI, 24.9 to 32.5] vs 18.0 months [95% CI, 13.6 to 22.3]; [HR=0.60, 95% CI 0.42 to 0.87; p=0.0054]). This ultimately did not translate to OS benefit (75.5 vs 62.8 months; HR=0.92; 95% CI, 0.62 to 1.36; p=0.674) and recurrence in the CNS was common.53

The ADAURA study investigated osimertinib’s use in resected EGFR-m NSCLC. This was a double-blind, phase 3, randomized control trial, assigning patients in a 1:1 ratio to osimertinib 80 mg once daily or placebo for 3 years with screening and randomization occurring after surgery.
The primary endpoint of this study was DFS and OS was a secondary endpoint. At 24 months after randomization, 90% of the patients with stage II to IIIA disease in the osimertinib group (95% CI, 84 to 93) and 44% of those in the placebo group (95% CI, 37 to 51) were alive and disease-free (HR for disease recurrence or death, 0.17; 99.06% CI, 0.11 to 0.26; p<0.001). The overall trial population had 89% of patients in the osimertinib group and 52% in the placebo group alive and disease-free at 24 months (HR for disease recurrence or death 0.20; 99.12% CI, 0.14 to 0.30; p<0.001). Osimertinib’s benefit was seen across all subgroups, but OS data has not yet matured. Recurrence of CNS related disease occurred in 2% and 11%, respectively. Safety outcomes reported in the trial were similar to those found in other osimertinib trials and second-generation EGFR-TKIs are not affected by this mutation and second-line treatment with these medications are being analyzed to overcome this resistance. However, if the T790M mutation is present concurrently with the C797S mutation, a combination of osimertinib and an earlier generation EGFR-TKI is required to overcome both resistance mechanisms.

In the phase 1 AURA trial, there as a subpopulation of patients who clinically worsened while on osimertinib and the C797S mutation was present in 40% of these patients. In the FLAURA study, mechanisms of resistance observed in patients that had disease progression while on osimertinib were: loss of T790M (68%), EGFR

Efficacy of Osimertinib in NSCLC Harboring Relatively Less Common EGFR Mutations

EGFR exon 20 insertion mutation is the third most common type of EGFR mutation after exon 19 deletions and L858R. EGFR-mutant tumors due to exon 20 insertions are observed in 4 to 10% of lung cancer diagnosis’ and are commonly discovered in women, non-smokers, Asian populations with adenocarcinoma. Having EGFR-mutant NSCLC due to exon 20 insertions differentiates from other EGFR mutations due to an in-frame base pair insertion within exon 20, increasing resistance to first- and second-generation EGFR-TKIs, which yields very low response rates (3–8%). This is because exon 20 insertions result in steric hindrance of the drug-binding pocket leading to increased ability of the receptor to bind ATP and decreased affinity to currently available EGFR-TKIs. Preclinical studies suggested that osimertinib has activity against EGFR exon 20 insertion mutations but in patients, responses are rare with standard 80 mg dosing. The Phase 2 ECOG-ACRIN 5162 study analyzed osimertinib 160 mg in advanced NSCLC patients with EGFR exon 20 insertions in 20 patients. The ORR was 25%, median PFS was 9.7 months (95% CI, 4.07 to NA), and median DoR was 5.7 months (95% CI, 4.73 to NA). The investigators of the study concluded that osimertinib 160 mg is well-tolerated and that there is clinical benefit in this subset of patients warranting further studies.

Other uncommon EGFR mutations consist of G719X, L861Q, S768I and L747S. An open-label phase 2 study investigated osimertinib’s use in uncommon EGFR mutations, which included any EGFR mutation other than exon 19 deletion, L858R, T790M, or exon 20 insertion. ORR was 50% (95% CI, 33% to 67%) and median PFS was 8.2 months (95% CI, 5.9 to 10.5) in all 36 patients. The most common mutation was G719X, which was present in 53% of patients and an ORR of 53% (95% CI, 28% to 77%) was seen in these patients with a median PFS of 8.2 months (95% CI, 6.2 to 10.2). L861Q was seen in 25% of patients with an ORR of 78% (95% CI, 44% to 100% and median PFS of 15.2 months (95% CI, 1.3 to 29.1). S768I was seen in 22% of patients with an ORR of 38% (95% CI, 0% to 81% and median PFS of 12.3 months (95% CI, 0 to 28.8). Although data is still insufficient, this data demonstrates osimertinib as a potential option in patients with uncommon EGFR mutations.

Mechanisms of Resistance to Osimertinib

Resistance to EGFR-TKI invariably occurs at some point during the disease course. For patients who progress on first and second generation TKI, development of secondary T790M mutation is the most commonly noted cause against, which osimertinib has excellent activity as detailed above. However, since osimertinib is now the preferred front-line agent for EGFRm NSCLC, new pathways for resistance are being unraveled. Common mechanisms discovered thus far include secondary resistance mechanisms that interact with osimertinib’s binding to its primary site of action such as development of C797S mutation and activation of alternative signaling pathways independent of osimertinib’s binding site. First and second-generation EGFR-TKIs are not affected by this mutation and second-line treatment with these medications are being analyzed to overcome this resistance. However, if the T790M mutation is present concurrently with the C797S mutation, a combination of osimertinib and an earlier generation EGFR-TKI is required to overcome both resistance mechanisms.
mutations (C797S, G724S, L718Q) (22%), and in the other cases: MET amplifications, HER2 amplifications, PI3KCA mutations, KRAS or BRAF mutations, RET fusions, FGFR3 fusions, and BRAF fusions.60

Mutations within the L792, and L718 residues of EGFR have also been discovered as resistance mechanisms to osimertinib. L792 mutations are not independent of other mutations and frequently coexist with other EGFR mutations, occurring in cis with T790M and in trans with G796/C797.61 Also responsible for resistance to osimertinib is within the L718 residue, most commonly being L718Q, which is located within the ATP-binding site of the EGFR kinase domain, altering the binding of osimertinib to EGFR.61 Figure 1 summarizes resistance mechanisms to osimertinib when used as first-line therapy.61

**Conclusion and Future Directions**

Osimertinib has demonstrated its superiority over first generation EGFR TKIs with better PFS and OS in patients with EGFRm advanced or metastatic NSCLC.29,39 Recently, the ADAURA study demonstrated a 80% reduction in the risk of recurrence or death with osimertinib use in the adjuvant setting in patient with EGFRm NSCLC.50 With osimertinib commonly used as first line treatment for EGFRm advanced or metastatic NSCLC patients, the
| Protocol Name (Abbreviation) | Phase | Patient Population | Treatment Regimen | Treatment Target Sample Size (n) | Primary Outcomes | Secondary Outcomes |
|----------------------------|-------|--------------------|------------------|---------------------------------|-----------------|-------------------|
| NCT04413201 (AFAMOSI) 63  | IV    | Treatment naïve EGFR mutated, T790M negative, advanced or metastatic non-squamous NSCLC | Afatinib followed by osimertinib vs osimertinib | 126 | Time to EGFR-TKI failure at 24 months | PFS, OS, ORR, DCR, safety, QOL |
| NCT03535363 64           | I     | Treatment naïve EGFR mutated metastatic NSCLC with BM (1–10) | Osimertinib + SRS | 40 | MTD | PFS, OS, CNS ORR, ORR |
| NCT03667820 65           | II    | Treatment naïve EGFR mutated metastatic NSCLC | Osimertinib + SABR | 37 | PFS | OS, DOR, ORR, safety, time to subsequent SABR |
| NCT04391283 66           | IV    | Treatment naïve EGFR mutated metastatic NSCLC | Osimertinib | 500 | TTD | PFS, ORR, DCR, OS, safety |
| NCT04438902 67           | II    | Progression on osimertinib with EGFR T790M mutated NSCLC | Osimertinib + anlotinib | 30 | PFS | ORR, DCR, safety |
| NCT03969823 (WARRIOR) 68 | II    | Treatment naïve EGFR mutated metastatic NSCLC | Osimertinib | 148 | Proportion of acquired resistance mechanisms | Safety, PFS, OS, ORR |
| NCT04563871 (BLOSSOM) 69 | II    | Progression on EGFR TKI with LM with EGFR mutated NSCLC | Osimertinib | 80 | OS | LM ORR, LM DOR, LM DCR, LM PFS |
| NCT03497767 (OUTRUN) 70  | II    | Treatment naïve EGFR mutated metastatic NSCLC with BM | Osimertinib + SRS | 80 | IC PFS | Use of WBRT, brain failure, OS |
| NCT03122717 71           | I/II  | Treatment naïve EGFR mutated locally advanced or metastatic NSCLC | Osimertinib + gefitinib | 64 | Safety | ORR, PFS, OS |
| NCT03778229 (SAVANNAH) 72| II    | Progression on osimertinib with EGFR mutated and MET mutated locally advanced or metastatic NSCLC | Osimertinib + savolitinib | 259 | ORR | PFS, OS, DOR, QOL, safety |
| NCT03543683 73           | IV    | Progression on first generation EGFR TKI with T790M mutated NSCLC | Osimertinib + aspirin | 330 | PFS | OS |
| NCT03858491 (OSIBOOST) 74| I     | Treatment naïve EGFR mutated metastatic NSCLC | Osimertinib + cobicistat | 26 | Osimertinib AUC | Safety |
| NCT03940703 (INSIGHT 2 Study) 75 | II    | MET Amplified, EGFR mutated advanced or metastatic NSCLC having acquired resistance to prior EGFR TKI | Tepotinib + osimertinib | 120 | Safety, ORR | DOR, DCR, PFS, OS, QOL |
| NCT04035486 (FLAURA2) 76 | III   | Treatment naïve EGFR mutated locally advanced or metastatic NSCLC | Osimertinib + pemetrexed + cisplatin or carboplatin | 586 | PFS | OS, ORR, DOR, DCR |
| NCT03392246 77           | II    | Treatment naïve EGFR mutated locally advanced or metastatic NSCLC | Osimertinib + selumetinib | 25 | Best OR | PFS, OS, safety |

(Continued)
| Protocol Name | Phase | Patient Population | Treatment Regimen | Target Sample Size (n) | Primary Outcomes | Secondary Outcomes |
|---------------|-------|--------------------|-------------------|-----------------------|------------------|--------------------|
| NCT03891615   | I     | Progression on osimertinib with EGFR mutated metastatic NSCLC | Osimertinib + niraparib | 30 | MTD | Toxicity, ORR, PFS |
| NCT04184921   | IV    | Progression on osimertinib with EGFR mutated metastatic NSCLC | Osimertinib + aspirin | 350 | PFS | OS, ORR, TTP |
| NCT03532698   | III   | Progression on osimertinib with EGFR T790M mutated metastatic NSCLC | Osimertinib + aspirin | 100 | ORR | DCR, TTP, DOR |
| NCT04233021   | II    | EGFR mutated metastatic NSCLC with BM or LM | Osimertinib | 113 | ORR | OS, PFS, safety, QOL |
| NCT03769103   | II    | Treatment naive EGFR mutated metastatic NSCLC with BM | Osimertinib + SRS | 76 | IC PFS | IC ORR, time to WBRT, OS, QOL |
| NCT04591002   | II    | Progression of remaining GGN after curative resection for EGFR mutated stage I adenocarcinoma | Osimertinib (adjuvant) | 56 | Regression rate | Avoidance of subsequent treatments, rate of treatment failure, safety |
| NCT03909334   | II    | Treatment naive EGFR mutated locally advanced or metastatic NSCLC | Osimertinib + ramucirumab | 150 | PFS | ORR, DCR, OS, safety |
| NCT04001777   | I     | EGFR mutated metastatic NSCLC | APG-1252 + osimertinib | 60 | MTD, RP2D | Efficacy |
| NCT03810807   | I     | Treatment naive EGFR mutated metastatic NSCLC | Dacomitinib + osimertinib | 22 | MTD, best ORR | N/A |
| NCT03255083   | I     | Progression on EGFR TKI with EGFR mutated locally advanced or metastatic NSCLC | DS-1205c + osimertinib | 13 | Safety | PD, PK, ORR, DCR, PFS, OS |
| NCT04486833   | II/I  | Progression on osimertinib with EGFR mutated locally advanced or metastatic NSCLC | Quaratusugene ozeplasmid (GPX-001) + osimertinib | 100 | MTD, PFS2 | ORR, OS, DOT, safety |
| NCT03434418   | II    | Treatment naive uncommon EGFR mutated locally advanced or metastatic NSCLC (exon 18 G719X, exon 20 5768I, or exon 21 L861Q) | Osimertinib | 37 | ORR | PFS, safety, OS |
| NCT02803203   | I/I   | Treatment naive EGFR mutated metastatic NSCLC | Bevacizumab + osimertinib | 50 | MTD, PFS | N/A |
| NCT03521154   | III   | EGFR mutated stage III unresectable NSCLC | Osimertinib following chemoradiation | 200 | PFS | CNS PFS, OS, ORR, DOR, DCR, safety |
| NCT03433469   | II    | Surgically resectable, EGFR mutated Stage I–IIIA NSCLC | Osimertinib (neoadjuvant) | 27 | MPR | ORR, DFS, OS, DOR, safety |

(Continued)
| Protocol Name          | Phase | Patient Population                                                                 | Treatment Regimen                  | Target Sample Size (n) | Primary Outcomes | Secondary Outcomes |
|------------------------|-------|-----------------------------------------------------------------------------------|------------------------------------|------------------------|------------------|--------------------|
| NCT03989115            | I/II  | Progression on osimertinib with EGFR mutated locally advanced or metastatic NSCLC | RMC-4630 + osimertinib             | 168                    | Safety, DLT      | PK, ORR, DOR       |
| NCT03133546 (BOOSTER)  | II    | Progression on first generation EGFR TKI with T790M mutated NSCLC                 | Bevacizumab + osimertinib          | 155                    | PFS              | ORR, OS, safety    |
| NCT04085315            | I     | Progression on osimertinib with EGFR mutated metastatic NSCLC                      | Alisertib + osimertinib           | 36                     | Safety           | ORR, DOR, DCR, PK, DCS, DOR |
| NCT03414814            | II    | Progression on chemotherapy with EGFR Exon 20 mutation locally advanced or metastatic NSCLC | Osimertinib                       | 28                     | ORR              | Safety, PFS, OS, DOR |
| NCT04351555 (NeoADAURA)| III   | EGFR mutated resectable NSCLC                                                      | Osimertinib + pemetrexed + cisplatin or carboplatin | 328                    | MPR              | PCR, EFS, OS, DFS, QOL |
| NCT03567642            | I     | Treatment naive EGFR mutated metastatic NSCLC with concurrent RB1 and TP53 alterations | Osimertinib + platinum chemotherapy + etoposide | 20                     | MTD              | N/A                |
| NCT04479306            | I     | Progression on osimertinib with EGFR mutated locally advanced or metastatic NSCLC | Osimertinib + alisertib or sapanisertib | 40                     | DLT, RP2D, safety | ORR, PFS           |
| NCT02496663            | I     | Progression on EGFR TKI with EGFR mutated locally advanced or metastatic NSCLC     | Osimertinib + necitumumab         | 100                    | MTD, safety      | ORR, PFS, DCR, PK  |
| NCT03831932            | I     | Progression on EGFR TKI with EGFR mutated locally advanced or metastatic NSCLC     | Telaglenastat + osimertinib       | 18                     | RP2D             | DLT, PFS, OS       |
| NCT02954523            | I/II  | Treatment naive EGFR mutated locally advanced or metastatic NSCLC                  | Osimertinib + dasatinib           | 10                     | Safety           | PK, PD, PFS, OS, DOR |
| NCT04425681 (OWBLM)    | II    | EGFR mutated advanced or metastatic NSCLC with leptomeningeal metastasis          | Osimertinib + bevacizumab         | 20                     | CNS PFS, ORR     | CNS OS, PFS, safety |
| NCT04148898            | II    | EGFR mutated advanced or metastatic NSCLC with leptomeningeal metastasis          | Osimertinib + bevacizumab         | 80                     | CNS PFS, ORR     | CNS OS, PFS, safety |
| NCT02736512            | II    | Treatment naive or previously treated advanced EGFR mutated metastatic NSCLC with asymptomatic BM | Osimertinib                       | 40                     | IC ORR           | IC DCR, time to IC response, IC PFS |
| NCT04606771            | II    | Progression on osimertinib with EGFR mutated and MET amplified advanced NSCLC      | Savolitinib + osimertinib         | 56                     | ORR              | PFS, DOR, TSA, OS, PK |

(Continued)
Table 2 (Continued).

| Protocol Name | Phase | Patient Population                                                                 | Treatment Regimen                              | Target Sample Size (n) | Primary Outcomes | Secondary Outcomes          |
|---------------|-------|-------------------------------------------------------------------------------------|-------------------------------------------------|-----------------------|------------------|-------------------------------|
| NCT04410796   | II    | Treatment naïve EGFR mutated (cfDNA in plasma) locally advanced or metastatic NSCLC | Osimertinib + carboplatin + pemetrexed          | 571                   | PFS              | ORR                           |
| NCT04141644   | IB    | EGFR mutated locally advanced or metastatic NSCLC stable on osimertinib            | Osimertinib + ipilimumab                        | 26                    | Safety            | ORR, PFS, OS                 |
| NCT04181060   | III   | Treatment naïve EGFR mutated locally advanced or metastatic NSCLC                  | Osimertinib + bevacizumab                      | 300                   | PFS              | OS, best ORR, CNS PFS, safety |
| NCT03455829   | II/II | Treatment naïve EGFR mutated metastatic NSCLC                                      | Lerociclib + osimertinib                       | 30                    | Safety            | ORR, PK, OS                  |
| NCT04335292   | II    | Previously treated with osimertinib and second line platinum and pemetrexed        | Osimertinib                                    | 200                   | ORR              | PFS, DOR, DCR, OS, TTF, QOL  |
| NCT02503722   | I     | Progression on osimertinib with EGFR mutated advanced or metastatic NSCLC         | Sapanisertib + osimertinib                     | 36                    | Safety            | PK, PD, ORR, DCR, PFS        |
| NCT04545710   | II    | Progression on osimertinib with EGFR mutated advanced or metastatic NSCLC         | Osimertinib + abemaciclib                      | 18                    | PFS              | N/A                           |
| NCT02520778   | I     | Progression on EGFR TKI with EGFR mutated locally advanced or metastatic NSCLC    | Osimertinib + navitoclax                       | 50                    | Safety            | PK, ORR,                      |
| NCT02824952   | II    | Treatment naïve stage IIIA/B EGFR mutated NSCLC                                   | Osimertinib (neoadjuvant)                      | 40                    | ORR              | PFS, tumor volume            |
| NCT02917993   | I/II  | Progression on EGFR TKI with EGFR mutated locally advanced or metastatic NSCLC    | Itacitinib + osimertinib                       | 59                    | Safety, DLT, ORR | PK, PFS, OS                  |
| NCT04029350   | II    | Progression on EGFR TKI with EGFR and T790M mutation locally advanced or metastatic NSCLC | Anlotinib + osimertinib                       | 53                    | PFS              | OS, ORR, DCR, safety          |
| NCT02789345   | I     | Progression on EGFR TKI with EGFR T790M mutated advanced NSCLC                    | Osimertinib + ramucirumab or necitumab         | 74                    | Safety            | PK, PD, ORR, DCR, DOR, PFS, OS |
| NCT03784599   | II    | Progression on EGFR TKI with EGFR and HER2 mutation locally advanced or metastatic NSCLC | Trastuzumab-emtansine + osimertinib           | 58                    | Safety, ORR      | PFS, DCR, OS                 |
| NCT02971501   | II    | Treatment naïve EGFR mutated metastatic NSCLC with BMs                             | Osimertinib + bevacizumab                     | 112                   | PFS              | OS, safety, ORR, IC ORR      |
| NCT03410043   | II    | EGFR mutated locally advanced or metastatic NSCLC                                 | Osimertinib + LCT                             | 143                   | PFS              | OS, safety                   |
| NCT04285671   | I/II  | Progression on osimertinib with EGFR mutated advanced or metastatic NSCLC         | Necitumab + trastuzumab + osimertinib         | 26                    | R2PD, safety, ORR | PFS, DOR, OS QOL             |

(Continued)
clinical question of how to overcome disease progression while on osimertinib comes in to play. One of the more paramount clinical scenarios being studied is how to properly overcome acquired resistance to osimertinib. The specific configuration of T790M and C797S in the trans position is resistant to third-generation EGFR-TKIs, but is sensitive to a combination therapy with third-generation EGFR-TKIs. To help overcome acquired resistance to osimertinib, combination therapies are being studied to give patients another option if treatment failure with osimertinib develops. Table 2 summarizes the many ongoing clinical trials with osimertinib including combination therapy with anlotinib, savolitinib, aspirin, cobicistat, tepotinib, niraparib, quaransuugene ozeplasmid, alisertib, sapanisertib, necitumumab, telaglenastat, sapanisertib, abemaciclib and itacitinib.

Osimertinib’s benefit against chemotherapy was proven in the AURA3 study with a better overall ORR than the platinum-pemetrexed combination. Currently being studied is the combination of osimertinib with carboplatin and pemetrexed in individuals diagnosed with metastatic lung cancer with an EGFR mutation. Hypothesized with this combination therapy is the ability to help further suppress cancer progression in these patients and limit the development of resistance. A phase 2, open-label, randomized study is underway analyzing osimertinib alone vs combination with pemetrexed and carboplatin in patients with detectable EGFRm cfDNA after being already started on osimertinib. Patients will be receiving either osimertinib 80 mg daily or osimertinib 80 mg daily with carboplatin AUC of 5 IV every 3 weeks and pemetrexed 500 mg/m² IV every 3 weeks for a total of 4 cycles. Primary outcome of this study is assessing PFS from the duration of time when randomization was conducted to when disease progression was observed. A secondary endpoint will be intracranial PFS, analyzing from time of randomization to disease progression within the CNS or death.

### Table 2 (Continued).

| Protocol Name                        | Phase | Patient Population                                      | Treatment Regimen                  | Target Sample Size (n) | Primary Outcomes | Secondary Outcomes |
|--------------------------------------|-------|--------------------------------------------------------|------------------------------------|------------------------|------------------|--------------------|
| NCT04487080 (MARIPOSA)              | III   | Treatment naive EGFR mutated locally advanced or metastatic NSCLC | Amivantamab + lazertinib vs lazertinib | 1000                   | PFS              | OS, ORR, DOR, IC PFS, safety |
| NCT04338243                          | I/II  | Progression on EGFR TKI with EGFR mutated advanced NSCLC | Glumetinib + osimertinib          | 70                     | ORR              | DOR, OS            |
| NCT03755102                          | I     | Progression on osimertinib with EGFR mutated advanced or metastatic NSCLC | Dacomitinib + osimertinib         | 24                     | ORR              | PFS, OS            |
| NCT03807778                          | I/II  | EGFR mutated, exon 20 locally advanced or metastatic NSCLC who have progressed on EGFR-TKI | Osimertinib                        | 63                     | Safety           | PK, PD, ORR, DOR, DCR, PFS, OS, QOL |
| NCT03769103                          | II    | Treatment naive EGFR mutated metastatic NSCLC with BM | Osimertinib + SRS                  | 76                     | CNS PFS          | CNS OS, time to SRS/WBRT, OS, QOL |
| NCT04129502                          | III   | Treatment naive EGFR mutated, exon 20 locally advanced or metastatic NSCLC | Osimertinib                        | 318                    | PFS              | ORR, OS, DOR, DCR, QOL |
| NCT02716116                          | I/II  | EGFR/HER2 mutated locally advanced or metastatic NSCLC (also includes exon 20) | Osimertinib                        | 306                    | ORR              | PK, PD, DOR, DCR, PFS, OS |
| NCT03755102                          | I     | Progression on osimertinib with EGFR mutated advanced or metastatic NSCLC | Dacomitinib + osimertinib         | 24                     | ORR              | PFS, OS            |

**Abbreviations:** BM, brain metastases; CNS, central nervous system; DCR, disease control rate; DFS, disease free survival; DOR, duration of response; EGFR, epidermal growth factor receptor; EFS, event-free survival; GGN, ground-glass opacity nodule; IC, intracranial; LCT, local consolidation therapy; LM, leptomeningeal metastases; MET, mesenchymal-epithelial transition factor; MPR, major pathological response; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PCR, pathological complete response; PD, pharmacodynamics; PK, pharmacokinetics; PFS, progression-free survival; QOL, quality of life; RP2D, recommended phase 2 dose; SABR, stereotactic ablative radiation; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; TSA, tumor size assessment; TTP, time to progression; TTD, time to discontinuation; TTF, time to treatment Failure; WBRT, whole brain radiotherapy.
MET driven acquired resistance is becoming more prevalent in patients diagnosed with NSCLC. Preclinical data have analyzed osimertinib’s role in combination with a MET TKI for treatment of EGFR mutation-positive lung cancer with MET acquired resistance. In a multicenter, phase Ib study, patients were enrolled with locally advanced or metastatic, MET-amplified, EGFR mutation-positive NSCLC who had disease progression on EGFR-TKIs. Patients received osimertinib 80 mg and savolitinib (MET inhibitor) 600 mg daily (patients weighing more than 55 kg received 300 mg of savolitinib). Among 69 patients within the study that had previous third-generation EGFR-TKI exposure, ORR was 30% Safety profile observed were adverse events of grade \( \geq 3 \) occurring in 57% of patients with most common being increases in aspartate aminotransferase, and neutropenia. Investigators concluded that this combination is associated with an acceptable risk-benefit profile and encouraging antitumor activity with MET-amplified, EGFR mutation-positive, advanced NSCLC for patients who had disease progression on a previous EGFR-TKI.\(^{131}\) The combination of osimertinib and tepotinib, another MET inhibitor is currently being investigated in the INSIGHT 2 trial.\(^{75}\)

Another therapeutic combination being studied is osimertinib and bevacizumab in patients with CNS metastases (specifically LMs). Bevacizumab is a recombinant humanized monoclonal antibody against VEGF, where in animal studies, plays a key role in LMs. Theorized is that inhibition of both EGFR and VEGF signaling pathways could enhance the antitumor efficacy and further prevent resistance to EGFR-TKIs. Recently in a phase 2 study, the addition of bevacizumab to osimertinib was not shown to be beneficial in previously treated EGFR TKIs patients with the T790M mutation.\(^{132}\)

Osimertinib provides substantial benefit for a robust patient population suffering from a diagnosis with NSCLC. Its unique receptor binding properties are novel within the EGFR-TKI class. As study results progress further and expand osimertinib’s use across different clinical settings, it is of importance to keep the clinical benefit relevant and not allow further resistance mechanisms to develop.

**Disclosure**

Dr Chung-Shien Lee is an Advisory Board participant for G1 Therapeutics. Nagashree Seetharamu has served on the advisory boards for Genentech, Amgen, Takeda and AstraZeneca in the last year. The authors report no other conflicts of interest in this work.

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