

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

Chung-Shien Lee <sup>1,2</sup>Matthew Milone<sup>3</sup>Nagashree Seetharamu <sup>2</sup>

<sup>1</sup>Department of Clinical Health Professions, St. John's University, Queens, NY, USA; <sup>2</sup>Division of Medical Oncology and Hematology, Northwell Health Cancer Institute, Lake Success, NY, USA; <sup>3</sup>Pharmacy Department, Long Island Jewish Medical Center, New Hyde Park, NY, USA

**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 in 17 in men and women, respectively.<sup>1</sup> 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<sup>1,2</sup> at 15%.

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).<sup>1</sup> NSCLC accounts for approximately 85% of all lung cancer cases.<sup>3</sup> 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.<sup>4</sup>

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

Correspondence: Nagashree Seetharamu  
Email nseetharamu@northwell.edu

months.<sup>5</sup> 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.<sup>6</sup> 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.<sup>6</sup> 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,  $p < 0.001$ ).<sup>7</sup> 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.<sup>8,9</sup>

*EGFR* is a cell-surface tyrosine kinase receptor belonging to the erbB 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.<sup>10</sup> 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.<sup>10</sup> Downstream pathways include: *Ras/Raf*/(*Ras*/*MAPK*), (*PI3K/AKT*), and *STAT*, all leading to rapid cell survival, proliferation, and cellular migration.<sup>10</sup> 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%.<sup>11</sup> 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.<sup>12</sup>

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.<sup>6–9,13–32</sup> 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.<sup>33,34</sup> 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.<sup>35</sup> 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.<sup>22,23,25,26</sup> Afatinib had marginal improvement in PFS but no difference in OS when compared to gefitinib.<sup>22,23</sup> Dacomitinib, on the other hand showed significant improvement in PFS as well as OS predominantly in the Asian population.<sup>25,26</sup> 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.<sup>36</sup> 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.<sup>37</sup> 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*.<sup>37</sup> Clinical trials of osimertinib began in 2013 and showed impressive anti-tumor activity

**Table I** Select Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors Trials

Trial	Phase	N	Patient Population	Intervention	Median Follow-Up (Median, Months)	PFS (Median, Months)	OS (Median, Months)	ORR (%)
<b>IPASS</b> <sup>6,13</sup>	3	1217 261 (EGFR+)	Treatment naïve 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
<b>WJTOG-3405</b> <sup>14,15</sup>	3	172	Chemotherapy naïve patients with stage IIIB/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
<b>First-SIGNAL</b> <sup>16</sup>	3	42	Stage IIIB/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
<b>NEJ002</b> <sup>7</sup>	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
<b>EURTAC</b> <sup>17</sup>	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<0.0001	19.3 vs 19.5; HR=1.04 (0.65–1.68); p=0.87	53 vs 15
<b>OPTIMAL</b> <sup>8,9</sup>	3	154	EGFR mutated stage IIIB/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
<b>ENSURE</b> <sup>18</sup>	3	217	EGFR mutated stage IIIB/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
<b>LUX-LUNG1</b> <sup>19</sup>	2B/3	585	EGFR mutated Stage IIIB/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

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Trial	Phase	N	Patient Population	Intervention	Median Follow-Up (Median, Months)	PFS (Median, Months)	OS (Median, Months)	ORR (%)
<b>LUX-LUNG3</b> <sup>20</sup>	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
<b>LUX-LUNG6</b> <sup>21</sup>	3	364	Treatment naïve 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
<b>LUX-LUNG7</b> <sup>22,23</sup>	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
<b>LUX-LUNG8</b> <sup>24</sup>	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
<b>ARCHER 1050</b> <sup>25,26</sup>	3	452	Treatment naïve 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
<b>ARCHER 1009</b> <sup>27</sup>	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
<b>AURA3</b> <sup>28</sup>	3	419	T790M-positive advanced NSCLC with disease progression after 1 <sup>st</sup> 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
<b>FLAURA</b> <sup>29</sup>	3	556	Treatment naïve 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
<b>ICOGEN</b> <sup>30</sup>	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)

Table 1 (Continued).

Trial	Phase	N	Patient Population	Intervention	Median Follow-Up (Median, Months)	PFS (Median, Months)	OS (Median, Months)	ORR (%)
<b>CONVINCE</b> <sup>31</sup>	3	285	EGFR mutated stage IIIB/IV NSCLC	Icotinib 125 mg three times daily vs 3 week cycles of chemotherapy (75 mg/m <sup>2</sup> cisplatin plus 500 mg/m <sup>2</sup> 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.

in *EGFR*-mutated (*EGFR*-m) NSCLC, which had progressed on first generation *EGFR* TKI.<sup>28</sup> 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)=0.3, 95% CI, 0.23 to 0.41, p<0.001), and an ORR was significantly better with osimertinib (71% vs 31%; odds ratio for objective response, 5.39; 95% CI, 3.47 to 8.48, p<0.001). The results of this study lead to osimertinib's FDA approval in November 2015 for the treatment of patients with metastatic *EGFR*-m NSCLC with an acquired T790M mutation as detected by an FDA-approved test after tumor progression on an earlier generation *EGFR*-TKI.<sup>28</sup>

In the TREM study, the efficacy of osimertinib was assessed in both T790M-positive and T790M-negative patients. Patients with progression on at least one other *EGFR*-TKI were assigned to receive treatment with osimertinib 80 mg once daily until radiologic progression or death with the primary endpoint being ORR. One hundred and ninety-nine patients were included with 120 (60%) being T790M positive. Of those that were

T790M positive, ORR was 60% (95% CI, 51 to 69%) and DoR was 11.8 months compared to 28% (95% CI, 15 to 41%) and 10.7 months for those that were 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.<sup>38</sup>

## 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.<sup>29</sup> 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.<sup>29</sup> An updated

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;  $p=0.046$ ).<sup>39</sup> This led 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.<sup>33</sup>

## 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.<sup>40</sup> CNS metastases are especially prevalent in patients with *EGFR*-m lung cancer.<sup>41</sup> 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.<sup>41</sup> 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.<sup>42</sup> 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  $T_{max}$  of 13 minutes (range 5–30min).<sup>43</sup> 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.<sup>28,44,45</sup> 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.<sup>46</sup> 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).<sup>47</sup> Multiple case reports have been published describing CNS efficacy of osimertinib.<sup>48</sup>

## 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.<sup>49</sup> 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.<sup>50,51</sup>

The ADJUVANT/CTONG 1104 study investigated gefitinib's use in completely resected *EGFR*-m NSCLC.<sup>52</sup> 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.<sup>53</sup>

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 with the most common adverse events being diarrhea, paronychia, and dry skin.<sup>50</sup>

## 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.<sup>10</sup> 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%).<sup>10</sup> 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*-TKI.<sup>54</sup> Preclinical studies suggested that osimertinib has activity against *EGFR* exon 20 insertion mutations but in patients, responses are rare with standard 80 mg dosing.<sup>55–57</sup>

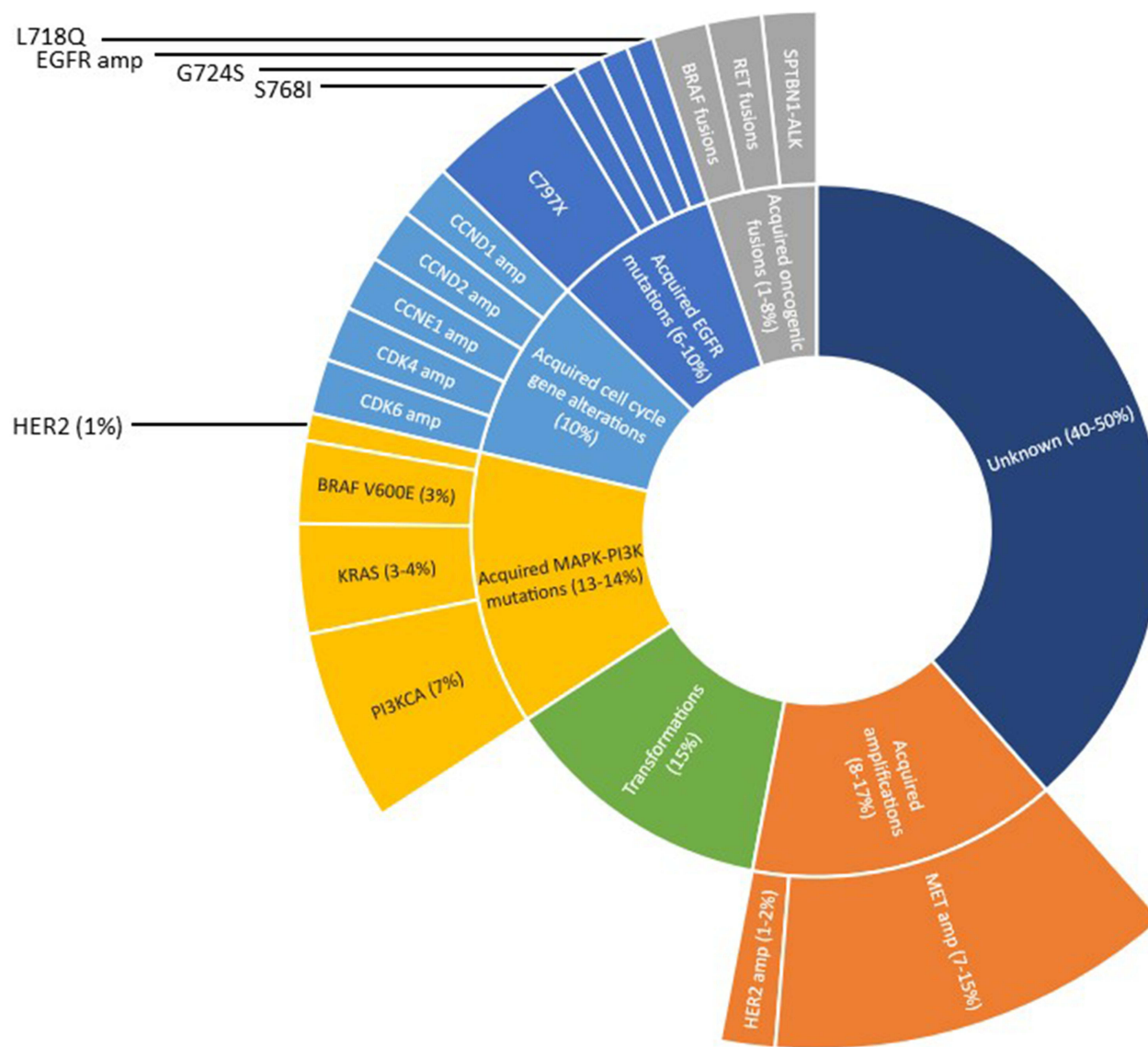
The Phase 2 ECOG-ACRIN 5162 study analyzed osimertinib 160 mg in advanced NSCLC patients with *EGFR* exon 20 insertions in 20 patients. The ORR was 25%, median PFS was 9.7 months (95% CI, 4.07 to NA), and median DoR was 5.7 months (95% CI, 4.73 to NA). The investigators of the study concluded that osimertinib 160 mg is well-tolerated and that there is clinical benefit in this subset of patients warranting further studies.<sup>58</sup>

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).<sup>59</sup> 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 *EGFR*m 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.<sup>60</sup> 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.

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.<sup>60</sup> In the FLAURA study, mechanisms of resistance observed in patients that had disease progression while on osimertinib were: loss of T790M (68%), *EGFR*



**Figure 1** First line resistance to osimertinib; data from Leonetti et al.<sup>61</sup>

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.<sup>60</sup>

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.<sup>61</sup> 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*.<sup>61</sup> Figure 1 summarizes resistance mechanisms to osimertinib when used as first-line therapy.<sup>61</sup>

## 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.<sup>29,39</sup> 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.<sup>50</sup> With osimertinib commonly used as first line treatment for *EGFRm* advanced or metastatic NSCLC patients, the



**Table 2** Select Ongoing and Future Clinical Trials for Osimertinib

Protocol Name	Phase	Patient Population	Treatment Regimen	Target Sample Size (n)	Primary Outcomes	Secondary Outcomes
NCT04413201 (AFAMOSI) <sup>63</sup>	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 <sup>64</sup>	I	Treatment naïve EGFR mutated metastatic NSCLC with BM (I–IO)	Osimertinib + SRS	40	MTD	PFS, OS, CNS ORR, ORR
NCT03667820 <sup>65</sup>	II	Treatment naïve EGFR mutated metastatic NSCLC	Osimertinib + SABR	37	PFS	OS, DOR, ORR, safety, time to subsequent SABR
NCT04391283 <sup>66</sup>	IV	Treatment naïve EGFR mutated metastatic NSCLC	Osimertinib	500	TTD	PFS, ORR, DCR, OS, safety
NCT04438902 <sup>67</sup>	II	Progression on osimertinib with EGFR T790M mutated NSCLC	Osimertinib + anlotinib	30	PFS	ORR, DCR, safety
NCT03969823 (WARRIOR) <sup>68</sup>	II	Treatment naïve EGFR mutated metastatic NSCLC	Osimertinib	148	Proportion of acquired resistance mechanisms	Safety, PFS, OS, ORR
NCT04563871 (BLOSSOM) <sup>69</sup>	II	Progression on EGFR TKI with LM with EGFR mutated NSCLC	Osimertinib	80	OS	LM ORR, LM DOR, LM DCR, LM PFS
NCT03497767 (OUTRUN) <sup>70</sup>	II	Treatment naïve EGFR mutated metastatic NSCLC with BM	Osimertinib + SRS	80	IC PFS	Use of WBRT, brain failure, OS
NCT03122717 <sup>71</sup>	I/II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + gefitinib	64	Safety	ORR, PFS, OS
NCT03778229 (SAVANNAH) <sup>72</sup>	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 <sup>73</sup>	IV	Progression on first generation EGFR TKI with T790M mutated NSCLC	Osimertinib + aspirin	330	PFS	OS
NCT03858491 (OSIBOOST) <sup>74</sup>	I	Treatment naïve EGFR mutated metastatic NSCLC	Osimertinib + cobicistat	26	Osimertinib AUC	Safety
NCT03940703 (INSIGHT 2 Study) <sup>75</sup>	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) <sup>76</sup>	III	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + pemetrexed + cisplatin or carboplatin	586	PFS	OS, ORR, DOR, DCR
NCT03392246 <sup>77</sup>	II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + selumetinib	25	Best OR	PFS, OS, safety

(Continued)

Table 2 (Continued).

Protocol Name	Phase	Patient Population	Treatment Regimen	Target Sample Size (n)	Primary Outcomes	Secondary Outcomes
NCT03891615 <sup>78</sup>	I	Progression on osimertinib with EGFR mutated metastatic NSCLC	Osimertinib + niraparib	30	MTD	Toxicity, ORR, PFS
NCT04184921 <sup>79</sup>	IV	Progression on osimertinib with EGFR mutated metastatic NSCLC	Osimertinib + aspirin	350	PFS	OS, ORR, TTP
NCT03532698 <sup>80</sup>	III	Progression on osimertinib with EGFR T790M mutated metastatic NSCLC	Osimertinib + aspirin	100	ORR	DCR, TTP, DOR
NCT04233021 (ORBITAL) <sup>81</sup>	II	EGFR mutated metastatic NSCLC with BM or LM	Osimertinib	113	ORR	OS, PFS, safety, QOL
NCT03769103 <sup>82</sup>	II	Treatment naïve EGFR mutated metastatic NSCLC with BM	Osimertinib + SRS	76	IC PFS	IC ORR, time to WBRT, OS, QOL
NCT04591002 <sup>83</sup>	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 <sup>84</sup>	II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + ramucirumab	150	PFS	ORR, DCR, OS, safety
NCT04001777 <sup>85</sup>	I	EGFR mutated metastatic NSCLC	APG-1252 + osimertinib	60	MTD, RP2D	Efficacy
NCT03810807 <sup>86</sup>	I	Treatment naïve EGFR mutated metastatic NSCLC	Dacomitinib + osimertinib	22	MTD, best ORR	N/A
NCT03255083 <sup>87</sup>	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 <sup>88</sup>	I/II	Progression on osimertinib with EGFR mutated locally advanced or metastatic NSCLC	Quaratusugene ozeplasmid (GPX-001) + osimertinib	100	MTD, PFS2	ORR, OS, DOT, safety
NCT03434418 <sup>89</sup>	II	Treatment naïve uncommon EGFR mutated locally advanced or metastatic NSCLC (exon 18 G719X, exon 20 S768I, or exon 21 L861Q)	Osimertinib	37	ORR	PFS, safety, OS
NCT02803203 <sup>90</sup>	I/II	Treatment naïve EGFR mutated metastatic NSCLC	Bevacizumab + osimertinib	50	MTD, PFS	N/A
NCT03521154 (LAURA) <sup>91</sup>	III	EGFR mutated stage III unresectable NSCLC	Osimertinib following chemoradiation	200	PFS	CNS PFS, OS, ORR, DOR, DCR, safety
NCT03433469 <sup>92</sup>	II	Surgically resectable, EGFR mutated Stage I–IIIA NSCLC	Osimertinib (neoadjuvant)	27	MPR	ORR, DFS, OS, DOR, safety

(Continued)

Table 2 (Continued).

Protocol Name	Phase	Patient Population	Treatment Regimen	Target Sample Size (n)	Primary Outcomes	Secondary Outcomes
NCT03989115 <sup>93</sup>	I/II	Progression on osimertinib with EGFR mutated locally advanced or metastatic NSCLC	RMC-4630 + osimertinib	168	Safety, DLT	PK, ORR, DOR
NCT03133546 (BOOSTER) <sup>94</sup>	II	Progression on first generation EGFR TKI with T790M mutated NSCLC	Bevacizumab + osimertinib	155	PFS	ORR, OS, safety
NCT04085315 <sup>95</sup>	I	Progression on osimertinib with EGFR mutated metastatic NSCLC	Alisertib + osimertinib	36	Safety	ORR, DOR, DCR, PFS, OS, CNS DCR
NCT03414814 <sup>96</sup>	II	Progression on chemotherapy with EGFR Exon 20 mutation locally advanced or metastatic NSCLC	Osimertinib	28	ORR	Safety, PFS, OS, DOR
NCT04351555 (NeoADAURA) <sup>97</sup>	III	EGFR mutated resectable NSCLC	Osimertinib + pemetrexed + cisplatin or carboplatin	328	MPR	PCR, EFS, OS, DFS, QOL
NCT03567642 <sup>98</sup>	I	Treatment naïve EGFR mutated metastatic NSCLC with concurrent RBI and TP53 alterations	Osimertinib + platinum chemotherapy + etoposide	20	MTD	N/A
NCT04479306 <sup>99</sup>	I	Progression on osimertinib with EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + alisertib or sapanisertib	40	DLT, RP2D, safety	ORR, PFS
NCT02496663 <sup>100</sup>	I	Progression on EGFR TKI with EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + necitumumab	100	MTD, safety	ORR, PFS, DCR, PK
NCT03831932 <sup>101</sup>	I	Progression on EGFR TKI with EGFR mutated locally advanced or metastatic NSCLC	Telaglenastat + osimertinib	18	RP2D	DLT, PFS, OS
NCT02954523 <sup>102</sup>	I/II	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + dasatinib	10	Safety	PK, PD, PFS, OS, DOR
NCT04425681 (OWBLM) <sup>103</sup>	II	EGFR mutated advanced or metastatic NSCLC with leptomeningeal metastasis	Osimertinib + bevacizumab	20	CNS PFS, ORR	CNS OS, PFS, safety
NCT04148898 <sup>104</sup>	II	EGFR mutated advanced or metastatic NSCLC with leptomeningeal metastasis	Osimertinib + bevacizumab	80	CNS PFS, ORR	CNS OS, PFS, safety
NCT02736513 <sup>105</sup>	II	Treatment naïve or previously treated advanced EGFR mutated metastatic NSCLC with asymptomatic BM	Osimertinib	40	IC ORR	IC DCR, time to IC response, IC PFS
NCT04606771 <sup>106</sup>	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 <sup>107</sup>	II	Treatment naïve EGFR mutated (cfDNA in plasma) locally advanced or metastatic NSCLC	Osimertinib + carboplatin + pemetrexed	571	PFS	ORR
NCT04141644 <sup>108</sup>	IB	EGFR mutated locally advanced or metastatic NSCLC stable on osimertinib	Osimertinib + ipilimumab	26	Safety	ORR, PFS, OS
NCT04181060 <sup>109</sup>	III	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + bevacizumab	300	PFS	OS, best ORR, CNS PFS, safety
NCT03455829 <sup>110</sup>	IB/II	Treatment naïve EGFR mutated metastatic NSCLC	Lerociclib + osimertinib	30	DLT, RP2D, safety, PFS	ORR, PK, OS
NCT04335292 (OCELOT) <sup>111</sup>	II	Previously treated with osimertinib and second line platinum and pemetrexed	Osimertinib	200	ORR	PFS, DOR, DCR, OS, TTF, QOL
NCT02503722 <sup>112</sup>	I	Progression on osimertinib with EGFR mutated advanced or metastatic NSCLC	Sapanisertib + osimertinib	36	Safety	PK, PD, ORR, DCR, PFS
NCT04545710 <sup>113</sup>	II	Progression on osimertinib with EGFR mutated advanced or metastatic NSCLC	Osimertinib + abemaciclib	18	PFS	N/A
NCT02520778 <sup>114</sup>	I	Progression on EGFR TKI with EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + navitoclax	50	Safety	PK, ORR,
NCT02824952 <sup>115</sup>	II	Treatment naïve stage IIIA/B EGFR mutated NSCLC	Osimertinib (neoadjuvant)	40	ORR	PFS, tumor volume
NCT02917993 <sup>116</sup>	I/II	Progression on EGFR TKI with EGFR mutated locally advanced or metastatic NSCLC	Itacitinib + osimertinib	59	Safety, DLT, ORR	PK, PFS, OS
NCT04029350 <sup>117</sup>	II	Progression on EGFR TKI with EGFR and T790M mutation locally advanced or metastatic NSCLC	Anlotinib + osimertinib	53	PFS	OS, ORR, DCR, safety
NCT02789345 <sup>118</sup>	I	Progression on EGFR TKI with EGFR T790M mutated advanced NSCLC	Osimertinib + ramucirumab or necitumumab	74	Safety	PK, PD, ORR, DCR, DOR, PFS, OS
NCT03784599 (TRAEMOS) <sup>119</sup>	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 <sup>120</sup>	II	Treatment naïve EGFR mutated metastatic NSCLC with BMs	Osimertinib + bevacizumab	112	PFS	OS, safety, ORR, IC ORR,
NCT03410043 (NORTHSTAR) <sup>121</sup>	II	EGFR mutated locally advanced or metastatic NSCLC	Osimertinib + LCT	143	PFS	OS, safety
NCT04285671 <sup>122</sup>	I/II	Progression on osimertinib with EGFR mutated advanced or metastatic NSCLC	Necitumumab + trastuzumab + osimertinib	26	R2PD, safety, ORR	PFS, DOR, OS QOL

(Continued)

Table 2 (Continued).

Protocol Name	Phase	Patient Population	Treatment Regimen	Target Sample Size (n)	Primary Outcomes	Secondary Outcomes
NCT04487080 (MARIPOSA) <sup>123</sup>	III	Treatment naïve EGFR mutated locally advanced or metastatic NSCLC	Amivantamab + lazertinib vs lazertinib	1000	PFS	OS, ORR, DOR, IC PFS, safety
NCT04338243 <sup>124</sup>	I/II	Progression on EGFR TKI with EGFR mutated advanced NSCLC	Glumetinib + osimertinib	70	ORR	DOR, OS
NCT03755102 <sup>125</sup>	I	Progression on osimertinib with EGFR mutated advanced or metastatic NSCLC	Dacomitinib + osimertinib	24	ORR	PFS, OS
NCT03807778 <sup>126</sup>	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 <sup>127</sup>	II	Treatment naïve EGFR mutated metastatic NSCLC with BM	Osimertinib + SRS	76	CNS PFS	CNS OS, time to SRS/WBRT, OS, QOL
NCT04129502 <sup>128</sup>	III	Treatment naïve EGFR mutated, exon 20 locally advanced or metastatic NSCLC	Osimertinib	318	PFS	ORR, OS, DOR, DCR, QOL
NCT02716116 <sup>129</sup>	I/II	EGFR/HER2 mutated locally advanced or metastatic NSCLC (also includes exon 20)	Osimertinib	306	ORR	PK, PD, DOR, DCR, PFS, OS
NCT03755102 <sup>130</sup>	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.

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.<sup>62</sup> 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, quaratusugene ozeplasmid, alisertib, sapanisertib, necitumumab, telaglenastat, sapanisertib, abemaciclib and itacitinib.<sup>63–130</sup>

Osimertinib's benefit against chemotherapy was proven in the AURA3 study with a better overall ORR than the

platinum-pemetrexed combination.<sup>28</sup> Currently being studied is the combination of osimertinib with carboplatin and pemetrexed in individuals diagnosed with metastatic lung cancer with an *EGFR* mutation.<sup>76,111</sup> 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 *EGFR* *m*cDNA 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/m<sup>2</sup> 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.<sup>107</sup>



*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 1b 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 anti-tumor activity with *MET*-amplified, *EGFR* mutation-positive, advanced NSCLC for patients who had disease progression on a previous *EGFR*-TKI.<sup>131</sup> The combination of osimertinib and tepotinib, another *MET* inhibitor is currently being investigated in the INSIGHT 2 trial.<sup>75</sup>

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 anti-tumor 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.<sup>132</sup>

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 Astra-Zeneca in the last year. The authors report no other conflicts of interest in this work.

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