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CASE SERIES

# Characterization of Patients with *EGFR* Mutation-Positive NSCLC Following Emergence of the Osimertinib Resistance Mutations, L718Q or G724S: A Multicenter Retrospective Observational Study in France

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**Purpose:** The third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), osimertinib, is an effective first-line therapy for patients with common *EGFR* mutation-positive non-small cell lung cancer (NSCLC). However, almost all patients become resistant to treatment. In some patients, emergence of tertiary *EGFR* mutations is implicated as a resistance mechanism. This study describes patients with NSCLC who acquired the rare *EGFR* mutations, L718Q or G724S, following EGFR TKI treatment.

**Patients and Methods:** This was a retrospective, observational study undertaken in France from Feb–Nov 2021, in patients with *EGFR* mutation-positive NSCLC with an acquired L718Q or G724S mutation. Primary objectives were description of tumor characteristics, progression, and progression under treatment.

**Results:** Nine eligible patients were identified. Acquired resistance to initial EGFR TKI treatment was associated with T790M emergence in six patients, who then received osimertinib monotherapy. Overall, eight patients received osimertinib monotherapy treatment at some point (average treatment duration: 18.3 months). Following the emergence of L718Q or G724S, patients received chemotherapy (n = 4; two of whom subsequently received afatinib), nivolumab (n = 2), afatinib (n = 2), or immunochemotherapy (n = 1). In the four patients who received afatinib after identification of L718Q or G724S, 2 achieved a partial response, one had stable disease and one had progressive disease. Treatment duration was 1.6–31.7 months. In patients with controlled disease (n = 3), progression-free survival was 6.1–31.7 months. Two of these patients had previously received osimertinib.

**Conclusion:** Currently, there is no consensus regarding the treatment of *EGFR* mutation-positive NSCLC following emergence of the osimertinib resistance mutations, L718Q or G724S. Afatinib appears to be a promising treatment option in this setting.

**Keywords:** osimertinib, afatinib, real-world evidence, tertiary *EGFR* mutations

## Introduction

Activating mutations in the epidermal growth factor receptor (*EGFR)* gene are present in approximately 10–15% of Caucasian patients with advanced non-small cell lung cancer (NSCLC) of adenocarcinoma histology (11% in France),[1] rising to about 50% in Asian patients.[2] First-line standard of care for these patients comprises monotherapy with an EGFR tyrosine kinase inhibitor (TKI). Three generations of EGFR TKI are available which have different mechanisms of action; the first-generation reversible EGFR TKIs (erlotinib and gefitinib), the second-generation ErbB family blockers



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(afatinib and dacomitinib), and the third-generation irreversible EGFR TKI, osimertinib.[2] Head-to-head prospective trials have demonstrated the superiority of second- and third-generation TKIs over first-generation EGFR TKIs.[3–5] Based on the Phase III FLAURA trial,[4,6] which demonstrated overall survival (OS) benefit with osimertinib versus erlotinib/gefitinib and favorable tolerability, osimertinib is often used as treatment of choice for *EGFR* mutation-positive NSCLC. However, disease progression is ultimately inevitable.[7]

Most randomized clinical trials of EGFR TKIs have been restricted to patients with so called "common" *EGFR* mutations, comprising deletions of exon 19 (Del19) and L858R in exon 21; these two mutations represent a large majority of the *EGFR* mutations detected.[8] Consequently, few prospective data are available to inform treatment decisions for the estimated 7–23% of *EGFR* mutation-positive NSCLC tumors that harbor uncommon *EGFR* mutations.[9]

Uncommon *EGFR* mutations are highly heterogeneous. In silico and in vitro observations indicate that the sensitivity of uncommon *EGFR* mutations to different EGFR TKIs varies widely, with second-generation EGFR TKIs generally exhibiting a broader inhibitory profile than first- or third-generation agents.[10,11] Recently a classification system was proposed that categorizes uncommon *EGFR* mutations into four different groups according to their impact on the tertiary structure of the receptor.[12] These categories are as follows: classical-like mutations; T790M-like mutations (which are resistant to first- and second-generation EGFR TKIs); exon 20 loop insertion mutations; and P-loop αC-helix compressing (PACC) mutations. PACC mutations are considered to be sensitive to second-generation EGFR TKIs but are resistant to osimertinib because they interfere with the binding of the TKI to the receptor.[12]

While mechanisms of resistance to osimertinib are highly heterogeneous and can involve EGFR-independent phenomena (in ~75% of cases) such as MET amplification and transformation to SCLC, the emergence of tertiary *EGFR*-dependent resistance mutations, such as C797X (a PACC mutation), is implicated in some patients (10–25%).[7,13] Although C797X is the most common osimertinib resistance mutation (occurring in ~7–29% of cases),[14] other such mutations have been identified, including L718Q and G724S, which are also PACC mutations. Emergence of L718Q is thought to account for ~2% of cases of acquired resistance to first-line treatment with osimertinib.[15,16] Likewise, case studies have documented the emergence of G724S, although the prevalence of this resistance mutation is uncertain due to a current lack of data.[15]

In the current study, nine patients with *EGFR* mutation-positive NSCLC who acquired *EGFR* L718Q or G724S mutations following EGFR TKI treatment were identified; here, we describe their clinical characteristics and outcomes, including four patients who received afatinib after osimertinib.

# Patients and Methods

## Study Design and Patients

This retrospective, single country, multicenter, non-interventional observational study based on real-world data collection was undertaken at five sites of the Groupe Français de Pneumo-Cancérologie in France. All patients included in the study had *EGFR* mutation-positive NSCLC, had received EGFR TKI treatment, and had acquired either an L718Q or G724S mutation at some point during their treatment course.

From February 2021 to November 2021, potential study participants were identified during follow-up consultations or contacted by a study investigator to obtain informed consent for inclusion in the study. Deceased patients were identified by the principal investigator at each site, who oversaw consent for the collection of personal data. Participation in other clinical studies was permitted. Patients who required consent from a guardian or for whom relevant data were unavailable were excluded.

Patient characteristics, demographics, details of treatment, type of *EGFR* mutation, and clinical outcomes were obtained from clinical record forms and follow-up medical consultations.

## Objectives and Assessments

The primary objective was description of tumor characteristics, progression, and progression under treatment.

Secondary objectives were description of the clinical and socio-demographic characteristics of patients; duration of osimertinib treatment (time from initiation to discontinuation); mode of clinical and site progression; and treatment after progression; progression-free survival (PFS) of post-osimertinib treatment(s).

## Statistical Analysis

Prespecified statistical analyses were conducted by Centre Hospitalier Intercommunal de Créteil for Clinical Research and Biostatistics. Qualitative and quantitative data are presented using descriptive statistics.

## Compliance with Ethics Guidelines

The study was designed and conducted in accordance with local laws and regulations, and with the Declaration of Helsinki. The study protocol was approved by the institutional review boards of the participating centers.

Data were collected in accordance with the French National Data Protection Authority (Commission Nationale de l'Informatique et des Libertés [CNIL]) guidance on processing of retrospective personal data in health research (MR-004, Méthodologies de Référence, CNIL, published July 16, 2018). Patients who were still alive at the time of writing provided written informed consent to be included and consented to publication. For deceased patients, the Groupe Français de Pneumo-Cancérologie followed Commission Nationale Informatique & Libertés MR-004 reference methodology regarding the processing of personal data.

# Results

## Patient Characteristics and Demographics

A total of nine eligible patients were identified (five women; four men; Table 1). The cohort consisted of six Caucasian and three Asian patients; four non-smokers and five former smokers. The mean age at diagnosis was 64.1 years (median [range]: 64.5 [54–77] years). At the time of diagnosis, six patients had metastatic NSCLC, one had stage III NSCLC, and two had stage II NSCLC; all patients had Eastern Cooperative Oncology Group performance status 0 or 1.

At the initiation of systemic treatment, all patients had stage IV adenocarcinoma. The sites of metastasis were bone (n = 6), lung (n = 4), brain (n = 3), adrenal (n = 1), and pleura (n = 1). Four patients had an *EGFR* L858R mutation, with

**Table 1** Patient Characteristics and Demographics

| | | | At Diagnosis | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Case (M/F)** | **Tobacco (Pack/ Years)** | **Ethnicity** | **Age (Years)** | **Stage at Diagnosis** | **ECOG PS** | **Somatic *EGFR* Alteration** | **Treatment Lines (n)** | **Rare *EGFR* Alteration** | **Time of Rare *EGFR* Discovery** |
| 1 (M) | Yes (5) | Caucasian | 77 | II | N/A | Exon 21 L861 | 5 | G724S | After L3 |
| 2 (M) | Yes (N/A) | Caucasian | 67 | II | 1 | Exon 19 Del | 4 | L718Q | After L2 |
| 3 (M) | No | Caucasian | 61 | III | 0 | Exon 21 L858R | 5 | L718Q | After L3 |
| 4 (F) | No | Asian | 58 | IV | 0 | Exon 21 L858R + T790M | 6 | L718Q | After L3 |
| 5 (M) | Yes (1) | Caucasian | 65 | IV | 1 | Exon 19[a] | 5 | L718Q | After L2 |
| 6 (F) | No | Asian | 60 | IV | 0 | Exon 21 L858R | 4 | L718Q | After L3 |
| 7 (F) | No | Asian | 50 | IV | 0 | Exon 19 Del | 6 | L718Q | After L3 |
| 8 (M) | Yes (N/A) | Caucasian | 68 | IV | 0 | Exon 21 L858R | 5 | L718Q | After L4 |
| 9 (F) | Yes (N/A) | Caucasian | 44 | IV | 1 | Exon 19 Del | 4 | G724S | After L3 |

**Notes**: [a]Complex variant of exon 19 (c2240_2257de18; p.Leu747_Pro753delinsSer).

**Abbreviations**: ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epithelial growth factor; L, treatment line; M/F, male/female; N/A, not available.

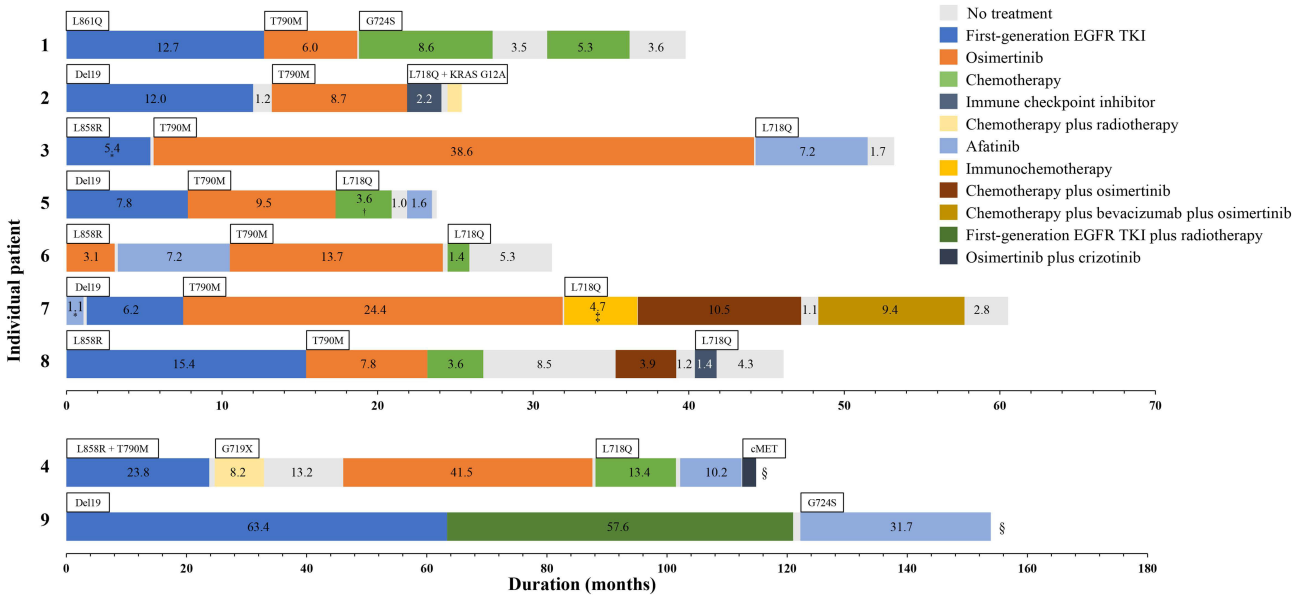


**Figure 1** Treatment sequence from the start of EGFR TKI therapy and emergence of EGFR mutations in each patient. *Discontinued due to toxicity; †Carboplatin, pemetrexed, and bevacizumab ‡Carboplatin, paclitaxel, bevacizumab, and atezolizumab; §Patient is still alive.

one having a concomitant *de novo* T790M mutation. Four patients had an *EGFR* Del19 mutation and one had an *EGFR* L861Q mutation. At the time of cut-off, six patients had died. Average follow-up was 71 months (range: 24–169).

## Treatment Sequence

The sequence of treatments and the occurrence of *EGFR* mutations for each patient is presented in Figure 1.

All patients received treatment with several EGFR TKIs. The first EGFR TKI received was erlotinib or gefitinib in seven patients, afatinib in one patient and osimertinib in one patient. In six patients, acquired resistance to initial treatment with an EGFR TKI was associated with the emergence of T790M. All six of these patients received osimertinib following detection of T790M. In total, eight of the patients received osimertinib at some point during their treatment path. The average duration of treatment with osimertinib was 19.2 months (range: 6.0–41.5 months). Seven patients had a L718Q or G724S mutation emerges after osimertinib treatment. In one case, a G724S mutation emerged during treatment with erlotinib. L718Q/G724S mutations were detected via tissue rebiopsy in five patients, via liquid biopsy in three patients, and unknown in one patient.

Following the detection of L718Q or G724S, the initial treatment option was chemotherapy (n = 4), immunotherapy (nivolumab; n = 2), afatinib (n = 2), and immunochemotherapy (n = 1; Table 2). In total, four patients received afatinib at some point after a L718Q or G724S resistance mutation was identified. In these patients, the duration of afatinib treatment was 31.7, 10.2, 7.2, and 1.6 months. Best responses were partial response (PR), stable disease (SD), and progressive disease, respectively. In the three patients who exhibited disease control, PFS was 31.7, 6.1, and 7.0, months, respectively. Time on treatment for the two patients who received nivolumab was 2.2 and 1.4 months, respectively. Time on treatment in the four patients who received chemotherapy as first treatment after the detection of L718Q or G724S was 13.4, 8.6, 3.6, and 1.4 months, respectively.

## Outcomes in Patients Who Received Afatinib

### Patient 3

A 61-year-old Caucasian male non-smoker who was initially diagnosed on August 8, 2013 with stage III NSCLC (T2N2M0). He underwent an upper right lobectomy and lobe-specific nodal dissection with adjuvant cisplatin and navelbine until December 2, 2013. Following disease recurrence in 2016, the patient was diagnosed with *EGFR* mutation-positive NSCLC (L858R). The patient initiated gefitinib therapy (250 mg/day) on September 9, 2016 and

**Table 2** Treatment Options/Outcomes Following Emergence of L718Q or G724S and Survival Since Start and Finish of Osimertinib

| Patient | First Treatment, Best Response, Time on Treatment (Months) | Second Treatment, Best Response, Time on Treatment (Months) | Third Treatment, Best Response, Time on Treatment (Months) | OS from Start of Osimertinib Monotherapy (Months) | OS from end of Osimertinib Monotherapy (Months) |
|---|---|---|---|---|---|
| 1 | Carboplatin/pemetrexed<br>PR<br>8.6 | Paclitaxel<br>SD<br>5.3 | – | 26.8 | 20.9 |
| 2 | Nivolumab<br>SD<br>2.2 | Gemcitabine + radiotherapy<br>PD<br>0.9 | – | 12.0 | 3.4 |
| 3 | Afatinib<br>SD<br>7.2 | – | – | 47.5 | 8.9 |
| 4 | Carboplatin/pemetrexed<br>PR<br>13.4 | Afatinib<br>PR<br>10.2 | Osimertinib + crizotinib<br>N/A[a]<br>2.3[a] | 68.6 | 27.2 |
| 5 | Carboplatin/pemetrexed + bevacizumab<br>PR<br>3.6 | Afatinib<br>PD<br>1.6 | – | 15.8 | 6.4 |
| 6 | Carboplatin/pemetrexed<br>PD<br>1.4 | – | – | 20.6[b] | 6.9 |
| 7 | Carboplatin/paclitaxel + bevacizumab + atezolizumab<br>PR<br>4.7 | Chemotherapy + osimertinib<br>PR<br>10.5 | Paclitaxel + bevacizumab + osimertinib<br>N/A<br>9.4 | 52.9 | 28.5 |
| 8 | Nivolumab<br>PD<br>1.4 | – | – | 30.5 | 22.8 |
| 9 | Afatinib<br>PR<br>31.7[a] | – | – | N/A | N/A |

**Notes**: [a]Patient still alive and undergoing treatment; [b]From final osimertinib monotherapy treatment.
**Abbreviations**: N/A, not applicable; PD, progressive disease; PR, partial response; OS, overall survival; SD, stable disease.

achieved a best response of PR. The patient remained on treatment for 5.4 months before discontinuing on February 20, 2017 due to liver toxicity. Following liquid rebiopsy, T790M was detected and the patient initiated osimertinib (80 mg/day) on February 24, 2017. The patient achieved PR with PFS of 38.6 months. Treatment was discontinued on May 11, 2020, due to disease progression. At this point, L718Q was detected. The patient initiated afatinib treatment (40 mg/day) on May 13, 2020. No dose reductions were required. The patient achieved SD and remained on treatment for 7.2 months before discontinuing on December 18, 2020, due to disease progression. The patient died on February 6, 2021. From the initiation of afatinib, the patient survived for 8.9 months.

### Patient 4

A 58-year-old Asian female non-smoker who was initially diagnosed on November 9, 2011, with stage IV NSCLC (T2N0M1c) of the right upper lobe with lung and bone metastases. The tumor was *EGFR* mutation positive (L858R and T790M). The patient initiated gefitinib treatment (250 mg/day) on November 22, 2011, and achieved PR with PFS of 23.8 months. Treatment was discontinued on November 15, 2013, due to disease progression. At this point, G719X was detected. The patient then received chemotherapy and thoracic radiotherapy, achieving a PR and PFS of 8.2 months. Following disease progression, the patient initiated osimertinib (80 mg/day) on September 18, 2015, and remained on treatment for 41.5 months. Treatment was discontinued on March 1, 2019 due to disease progression in the brain. The *EGFR* L718Q resistance mutation was detected. At this point the patient received platinum-doublet chemotherapy (pemetrexed plus carboplatin) and maintenance chemotherapy. She achieved a PR but discontinued treatment due to progression of the primary tumor and lung metastases. Treatment with afatinib was initiated on May 14, 2020, and resulted in a PR with PFS of 6.1 months. Treatment was discontinued on March 20, 2021, due to the emergence of new pulmonary lesions. Following rebiopsy, amplification of cMET and EGFR L858R/T790M were detected. Combination treatment with osimertinib and crizotinib was initiated on March 25, 2021. The patient was still alive on June 3, 2021. From the initiation of afatinib, the patient survived for 12.7 months.

### Patient 5

A 65-year-old Caucasian male smoker who was initially diagnosed on December 23, 2016, with stage IV NSCLC (T4N3M1c). The primary tumor was in the left lower lobe and metastases were detected in the liver, adrenal gland, brain, bone, and pleura. Tumor biopsy analysis identified an *EGFR* Del19 mutation. The patient initiated erlotinib treatment (150 mg/day) on January 5, 2017, and achieved a PR with PFS of 7.8 months. Treatment was terminated on August 30, 2017, due to pleural, pericardial, and pulmonary progression. Liquid biopsy detected T790M. Treatment with osimertinib (80 mg/day) was initiated on September 1, 2017, and continued until June 15, 2018. Treatment was discontinued due to hepatic, bone, and pulmonary progression. Progression was attributable to the emergence of L718Q that was detected at this point. The patient was treated with carboplatin/pemetrexed plus bevacizumab and maintenance chemotherapy and achieved PR. Progression was detected on October 2, 2018. A further liquid biopsy detected L718Q and T790M. The patient started afatinib treatment (40 mg/day) on October 30, 2018, and continued to December 18, 2018. However, the patient did not respond to treatment and died on December 25, 2018. From the initiation of afatinib, the patient had survived for 1.9 months.

### Patient 9

A 44-year-old Caucasian female smoker who was initially diagnosed on December 19, 2007, with stage IV NSCLC (T2N2M1b). The primary tumor was in the right lower lobe and lung metastases were detected. Initially the patient was treated with platinum-based chemotherapy between March 10 and December 12, 2008. PFS was unknown. Following detection of an *EGFR* Del19 mutation, the patient initiated treatment with erlotinib on January 20, 2009. The patient achieved PR and remained on erlotinib monotherapy until April 30, 2014, when a new lesion was detected in the brain, which was treated with radiotherapy. Erlotinib treatment was continued and there were two further occurrences of brain progression on October 8, 2015, and September 8, 2016. Again, the brain lesion was successfully treated with radiotherapy on both occasions. Erlotinib therapy was finally discontinued on February 14, 2019, due to emergence of new pulmonary lesions. In total, the patient was treated with erlotinib for 122.1 months. At the time of progression, tumor rebiopsy identified G724S. Afatinib treatment was started on March 22, 2019. The patient achieved PR and was still alive and in remission on November 9, 2021. From the initiation of afatinib, the patient had survived for 31.7 months.

## Discussion

In this retrospective study, we reviewed clinical records for patients with *EGFR* mutation-positive NSCLC who acquired the tertiary PACC mutations, L718Q or G724S, during treatment with EGFR TKIs. Our findings are consistent with previous reports and demonstrate that these rare mutations represent a mechanism of acquired resistance to osimertinib in some patients.[15] The mutations emerged following treatment with osimertinib monotherapy in seven of the nine patients.

The characteristics of the nine identified patients were generally consistent with those typical of *EGFR* mutation-positive NSCLC. All patients had adenocarcinoma and most were non- or ex-smokers.

There does not appear to be any link between the type of activating *EGFR* mutation and the emergence of L718Q or G724S. Four patients had a Del19 mutation, four patients had the L858R mutation, and one patient had an uncommon exon 21 mutation at diagnosis. These findings contradict an earlier in silico study that predicted that G724S would only block osimertinib in the context of a Del19 mutation.[17] Another interesting observation was that, following treatment with osimertinib, L718Q or G724S were usually detected in isolation and T790M was not present at the point of acquired resistance. This observation has implications for post-osimertinib treatment options and indicates that other EGFR TKIs, like afatinib, could be utilized in these patients. Other studies have noted that L718Q usually emerges in isolation.[18]

Given the rarity of L718Q and G724S mutations, few clinical data are available to inform treatment decisions. Accordingly, the nine patients in our study received a spectrum of treatments following detection of these mutations, including platinum doublet chemotherapy, immune checkpoint inhibitors either as monotherapy or combined with chemotherapy, and afatinib. Preclinical biochemical, cellular, and structural analyses indicate that afatinib retains inhibitory activity against these mutations in vitro and in vivo.[19] In this study, we identified four patients who received afatinib following failure of osimertinib. Three of these patients achieved PFS of at least 6 months. The fourth patient progressed quickly, presumably reflecting the co-occurrence of L718Q and T790M at the start of afatinib treatment.

Mechanisms of resistance to osimertinib are highly heterogenous, and numerous treatment modalities are being assessed post-osimertinib.[16,20] The data presented herein add to a growing body of evidence that suggests that afatinib could be a suitable treatment option post osimertinib in the small number of patients where resistance is driven by G724S or L718Q mutations. A recent report of a database of >1000 patients with uncommon *EGFR* mutations included 13 patients with G724S (69% previously treated with osimertinib) and three patients with L718Q (all previously treated with osimertinib).[21] In these patients, the objective response rate following afatinib treatment was 17% and 67%, respectfully. All 16 patients achieved at least SD. Furthermore, a recent retrospective analysis in China identified seven patients with L718Q or L718V mutations who received afatinib following failure of osimertinib. In these patients, the objective response rate was 42%, the disease control rate was 86% and median PFS was 2.6 months (range: 1–6). Of note, immunotherapy and TKIs other than afatinib were ineffective in patients with L718Q or L718V and acquired resistance to osimertinib.[22] Another retrospective analysis showed similar results in patients with G724S. In 23 patients treated with afatinib (n = 8) or other treatments (alternative EGFR TKI, chemotherapy, or best supportive care [n = 15]), PFS was significantly higher in the afatinib group (median: 4.5 vs 1.7 months; P = 0.037) including in those patients who previously received osimertinib (median: 6.2 vs 1.0 months; P = 0.005). The disease control rate with afatinib was 100%.[23] In addition to these studies, several published patient cases have reported activity of afatinib after the emergence of G724S[24–28] or L718Q.[29,30] Of these seven cases, five were treated with a first-generation EGFR TKI followed by osimertinib and one received osimertinib following chemotherapy. Of interest, at the point of resistance to osimertinib, tumor re-evaluation indicated the disappearance of T790M, but with an activating mutation still detectable as well as G724S or L718Q. PRs with afatinib were observed in four patients and SD in three. In one case, the patient received afatinib in combination with osimertinib[27] and in another afatinib was combined with bevacizumab.[28] In cases where tumor clonality was assessed following treatment with afatinib, the G724S clone was abrogated or reduced.[24,27,28] These cases demonstrate the importance of monitoring tumor clonality across lines of treatment in order to select appropriate therapy.

Although patient numbers were small, other treatment modalities demonstrated clinical activity following the emergence of L718Q or G724S. Of the four patients who received platinum-doublet chemotherapy as initial treatment following detection of L718Q or G724S, three patients achieved PR. Another patient received an immunochemotherapy combination as initial treatment post mutation detection and also achieved PR. However, neither of the two patients who received nivolumab monotherapy responded. These findings suggest that chemotherapy or immunochemotherapy are potential treatment options post osimertinib in patients with *EGFR* mutation-positive NSCLC especially, for example, if T790M is still detectable Another retrospective study has also indicated that chemotherapy could be an effective treatment option beyond osimertinib in patients where a targetable mechanism of resistance has not been identified.[31]

As a retrospective analysis, this study had several unavoidable limitations, such as selection bias, notification bias, and information bias. Another limitation was that disease progression was defined by investigators according to their usual clinical practice. Due to low numbers, PFS and OS Kaplan–Meier curves were not produced; survival outcomes were assessed in individual patients and analyzed descriptively. The small number of patients preclude definitive conclusions and further data are required. The findings are hypothesis generating only.

To conclude, this study provides further evidence that the rare *EGFR* mutations, L718Q and G724S, are responsible for acquired resistance to osimertinib in a small number of patients with *EGFR* mutation-positive NSCLC. Based on our real-world observations, there is no consensus among physicians regarding how these patients should be treated; several different treatment modalities were employed. This reflects the rarity of the mutations and paucity of clinical data. Our observations are consistent with preclinical findings and indicate that L718Q and G724S are sensitive to afatinib, provided there is not a concomitant T790M mutation. Therefore, afatinib appears to be a promising treatment option in this setting.

## Abbreviations

CNIL, Commission Nationale de l'Informatique et des Libertés; Del19, deletions of exon 19; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; OS, overall survival; PACC, P-loop αC-helix compressing; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

## Data Sharing Statement

The raw data supporting the conclusions of this article will be made available by the corresponding author, without undue reservation.

## Ethics Statement

The protocol was approved by the Local Ethics Committee of the Intercommunal Hospital Center of Créteil (CHIC) on December 9, 2020. Patients who were still alive at the time of writing provided written informed consent to be included and consent for publication. For deceased patients, the Groupe Français de Pneumo-Cancérologie followed Commission Nationale Informatique & Libertés MR-004 reference methodology regarding the processing of personal data.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

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